Title Page

Protocol Title:		A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache
Short Protocol Title:		A Phase 4 Randomized Controlled Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Medication Overuse Headache
Protocol Number:		20170703
Investigational Product:		Erenumab
Trade Name:		AIMOVIG®
Sponsor	Name of Sponsor:	Amgen Inc.
	Address:	One Amgen Center Drive Thousand Oaks, CA 91320
	Telephone Number:	805-447-1000
Protocol Approver	Name:	[redacted]
	Function:	Global Development Lead
Key Sponsor Contact	Name:	[redacted]
	Address:	One Amgen Center Drive Thousand Oaks, CA 91320
	Telephone Number:	[redacted]
	Email Address:	[redacted]
EudraCT Number:		2018-003342-16
NCT Number:		**NCT03971071**
Protocol Date:		Document Version Date

	Original	20 September 2018
	Amendment 1 (v2.0)	19 April 2019
	Amendment 2 (v3.0)	**27 May 2020**
Version/Date:	Data Element Standards Version 6.1	

Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1- 800-77-AMGEN; Canadian sites, 1-866-50-AMGEN; for all other countries, insert the local toll-free Medical Information number; Amgen's general number in the US, 1-805-447-1000.

Investigator's Agreement:

I have read the attached protocol entitled A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache, dated **27 May 2020**, and agree to abide by all provisions set forth therein.

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

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

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

_____

Signature

_____ _____

Name of Investigator Date (DD Month YYYY)

Table of Contents

List of Tables

List of Figures

1. Protocol Synopsis

Protocol Title: A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache

Short Protocol Title: A Phase 4 Randomized Controlled Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Medication Overuse Headache

Study Phase: 4

Indication: Preventive treatment of migraine in adults

Rationale

In a prior study, erenumab 70 mg and 140 mg administered subcutaneously (SC) every 4 weeks were superior to placebo in controlling monthly migraine days (MMD) in a chronic migraine (CM) population. A subgroup analysis revealed that CM subjects who met thresholds for medication overuse (CM-MO subjects) at baseline experienced significant reductions of their monthly headache days (MHD) and were able to revert medication overuse status more often than placebo-treated subjects. This benefit seemed to be heightened when the subgroup analysis was further refined to include CM-MO subjects with a history of at least 1 prior treatment failure due to lack of efficacy or tolerability issues. Based on these observations and the significant unmet medical need medication overuse headache (MOH) represents, Study 20170703 is being conducted to better understand the efficacy of erenumab in a dedicated MOH population.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared with placebo on achieving MOH remission during the double-blind treatment period (DBTP)	• Absence of MOH at month 6 as defined by mean monthly acute headache medication days (AHMD) < 10 days over months 4, 5, and 6 **(week 13 through 24)** OR mean monthly headache days (MHD) < 14 days over months 4, 5, and 6 **(week 13 through 24)** of the DBTP where AHMD include any eDiary day in which an acute headache medication intake is reported
Primary Estimand	
The estimand for the primary efficacy endpoint consists of: • The target population, which includes subjects diagnosed with CM and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month • The endpoint, which is the absence of MOH at month 6 as defined by mean monthly AHMD < 10 days over months 4, 5, and 6 **(week 13 through 24)** OR mean MHD < 14 days over months 4, 5, and 6 **(week 13 through 24)** of the DBTP • The intercurrent event, **which is** adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of investigational product (IP), regardless of adherence to treatment. • The summary measure, which is the odds ratio of absence of MOH between each erenumab dose group (ie, 70 mg or 140 mg) and the placebo group	
Secondary	
• To evaluate the effect of erenumab compared with placebo in reducing acute headache medication days (AHMD) during the DBTP	• Change from baseline in mean monthly AHMD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP
The estimand for the secondary objective on AHMD consists of: • The target population, which includes subjects diagnosed with CM and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month. • The endpoint, which is the change from baseline in mean monthly AHMD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP • The intercurrent event**, which** is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of investigational product (IP) and have at least 1 change from baseline in MHD, regardless of adherence to treatment. • The summary measure, which is the difference in mean of the endpoint between each erenumab dose group (ie, 70 mg and 140 mg) and the placebo group	
• To evaluate the effect of erenumab compared with placebo	• Sustained MOH remission during DBTP, as defined by absence of MOH at months 3 **(week 12)** and

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

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

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

Hypotheses

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

Overall Design

Study 20170703 is a phase 4, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of erenumab against placebo in subjects with CM who have a history of at least 1 preventive treatment failure and are diagnosed with MOH.

Up to 20% of the total population will be composed by subjects with regular opioid medication use (ie, > 4 days/month). Subjects in this cohort will be randomized and evaluated separately in an exploratory fashion for the efficacy and safety of erenumab against placebo in reducing opioid medication intake.

Number of Subjects

Approximately 687 subjects (549 subjects in the nonopioid-treated cohort and up to 138 subjects in the opioid-treated cohort) will be randomized in a 1:1:1 fashion to either placebo, erenumab 70 mg SC every 4 weeks, or erenumab 140 mg SC every 4 weeks.

Summary of Subject Eligibility Criteria

Adults ≥ 18 years with a documented history of migraine without aura and/or migraine with aura and MOH according to the International Headache Society (IHS) Classification (International Classification of Headache Disorders, 3rd Edition [ICHD-3]) for ≥ 12 months at screening.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.4.

Treatments

Subjects will receive 2 SC injections (in the upper arm, upper thigh, or abdomen) on day 1 and every 4 weeks until week 24 (DBTP). Subjects randomized to the erenumab 70 mg group will get 1 injection of active (erenumab 70 mg/mL) and 1 injection of placebo, subjects in the erenumab 140 mg group will receive 2 injections of active, and subjects randomized to placebo will receive 2 injections of placebo. Subjects who successfully complete the DBTP of the study will be given the option to continue in an open-label treatment period (OLTP) of 28-week duration. Subjects who received placebo during the DBTP will be allocated to either erenumab 70 mg or 140 mg in a 1:1 fashion. Subjects who received erenumab during the DBTP will receive the same erenumab dose in OLTP. The same treatment allocation procedure will be done within the opioid-treated and nonopioid-treated cohorts for placebo-treated subjects as defined at the initial randomization.

Procedures

After signing informed consent, subjects will enter an up to 7-week screening period**,** which is composed of an initial screening period up to 3 weeks followed by a 4-week baseline period. Subjects will be randomized/enrolled into the 24-week DBTP and will begin to receive double-blind investigational product SC every 4 weeks. Subjects who successfully complete the DBTP will have the opportunity to enter a 28-week OLTP. Subjects will use an electronic diary (eDiary) everyday throughout the baseline period, DBTP, and during the last quarter of the OLTP (defined as starting at the week 40 visit through week 52/End of Study [EOS]) to report information about their migraine and nonmigraine headaches, other migraine-related symptoms, and acute headache medication use. Subjects will have scheduled in-clinic study visits throughout the study.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

Statistical Considerations

The primary analysis will be performed when the last subject in the nonopioid-treated cohort completes the week 24 assessments or discontinues the DBTP. The final analysis for the study will be performed after all subjects (nonopioid-treated and opioid-treated cohorts) complete the study through the OLTP last visit or discontinue from the study.

Formal statistical analyses using statistical models and hypothesis testing will be performed for the nonopioid-treated cohort only.

For the primary and other dichotomous efficacy endpoints, a stratified Cochran-Mantel-Haenszel test will be used after the missing data is imputed as nonresponse. Continuous secondary endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The mean change from baseline for each treatment group, the treatment difference, 95% CI, and p-value will be reported.

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

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

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

Primary and secondary endpoints in erenumab 70 mg versus placebo**:**

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

Patient-reported outcome-related secondary endpoints for the non-European Union (EU) region:

7. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)

8. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)
9. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)
10. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)

OR

Patient-reported outcome-related secondary endpoints for the EU region**:**

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

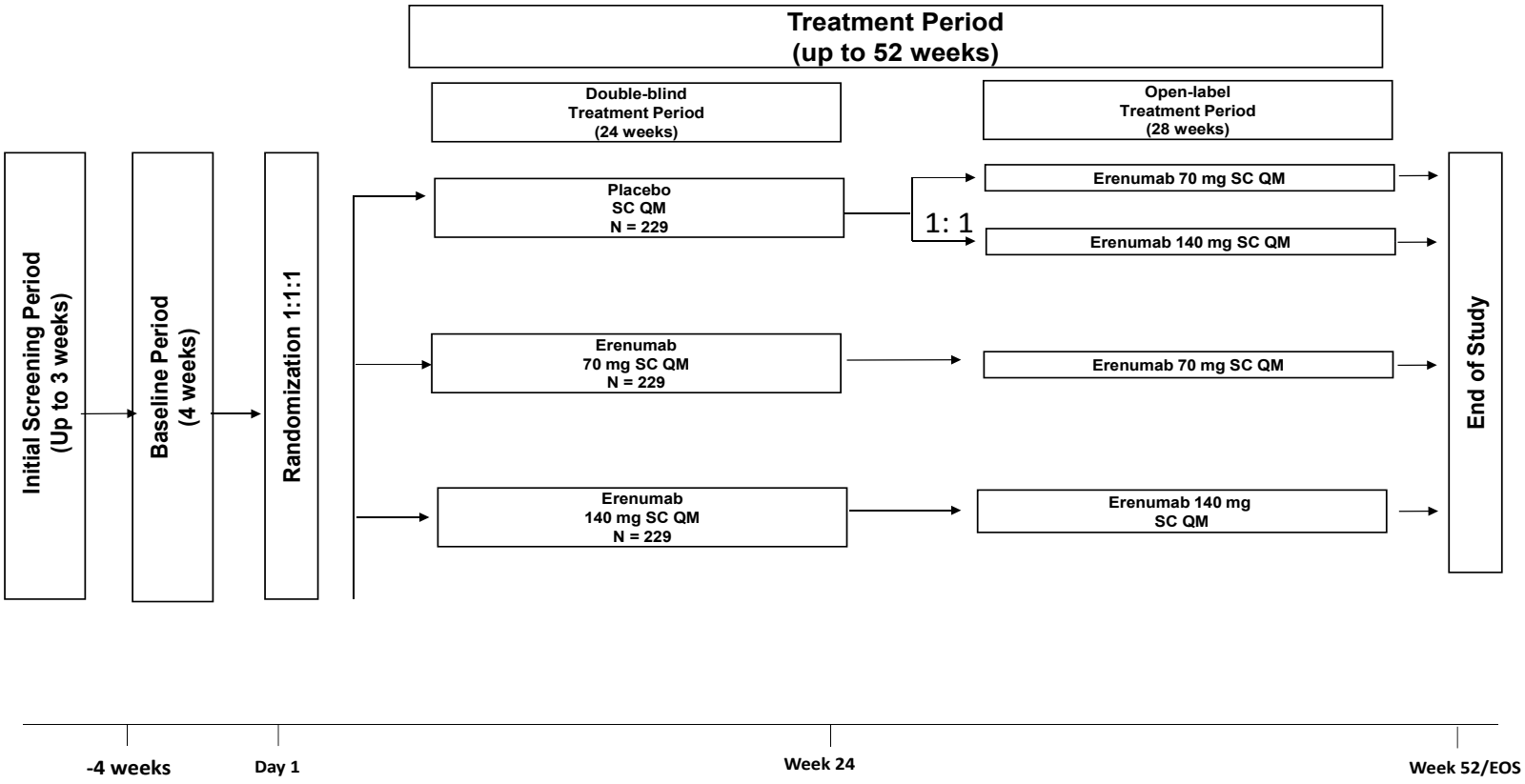
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



SC = subcutaneous; QM = monthly; EOS = End of Study

2.2 Schedule of Activities

Table 2-1. Schedule of Activities - Study Visits Through Double-blind Treatment Period

	Screening Period		Treatment Period							
	Initial Screening Period	Baseline Period[a]	Double-blind Treatment Period (24 Weeks)							
PROCEDURE	(up to 3 weeks before Baseline)	(4 weeks before Day 1)	Day 1[b]	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET[c]	Notes
Clinic Visit	X	X	X	X	X	X	X	X	X	
Informed consent	X									
IRT call	X		X	X	X	X	X	X	X	
Part 1 inclusion and exclusion criteria	X									
Demographics	X									
Physical examination	X								X	
Physical measurements	X		X							
Medical history	X									
Neurological medical history	X									
Cardiovascular medical history	X									
Cardiac risk factors	X									
Headache and migraine frequency history	X									
Migraine prevention medication history	X									
Vital signs	X		X	X	X	X	X	X	X	Pre-randomization on Day 1; BP, HR, RR, and temperature

Footnotes after last page of table.

Table 2-1. Schedule of Activities - Study Visits Through Double-blind Treatment Period

	Screening Period		Treatment Period							
	Initial Screening Period	Baseline Period[a]	Double-blind Treatment Period (24 Weeks)							
PROCEDURE	**(up to 3 weeks before Baseline)**	**(4 weeks before Day 1)**	**Day 1[b]**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24/ ET[c]**	**Notes**
Electrocardiogram	X									
Part 2 inclusion and exclusion criteria			X							Pre-randomization on Day 1
Randomization			X							
Adverse events			X	X	X	X	X	X	X	Post-randomization on Day 1
Serious adverse events	X	X	X	X	X	X	X	X	X	
Adverse device effects[d]			X	X	X	X	X	X	X	
Product complaints			X	X	X	X	X	X	X	
Concomitant therapies review	X		X	X	X	X	X	X	X	
LABORATORY ASSESSMENTS[e]										
Urine pregnancy test (females of childbearing potential only)[f]	X		X	X	X	X	X	X	X	A highly sensitive test at screening and at Day 1 pre-randomization of initiation of investigational product
Urine drug testing	X	X	X	X	X	X	X	X	X	Post-randomization on Day 1; Central laboratory
Hematology	X	X (to be performed at the discretion of the investigator)								Central laboratory After screening, hematology testing will be at the discretion of the investigator

Footnotes after last page of table.

Table 2-1. Schedule of Activities - Study Visits Through Double-blind Treatment

	Screening Period		Treatment Period							
	Initial Screening Period	Baseline Period[a]	Double-blind Treatment Period (24 Weeks)							
PROCEDURE	**(up to 3 weeks before Baseline)**	**(4 weeks before Day 1)**	**Day 1[b]**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24/ ET[c]**	**Notes**
Chemistry	X	X (to be performed at the discretion of the investigator)								Central laboratory After screening, chemistry testing will be at the discretion of the investigator
HIV, Hepatitis B and C screening	X									Central laboratory
BIOMARKER DEVELOPMENT										
Blood sample			X			X			X	
PHARMACOGENETIC ASSESSMENTS										
Pharmacogenetic sampling (optional)[g]			X							Post-randomization on Day 1; central laboratory
STUDY TREATMENT										
Amgen investigational product			X	X	X	X	X	X		Pre-filled syringes
CLINICAL OUTCOME ASSESSMENTS/PATIENT-REPORTED OUTCOMES										
Assign eDiary to subject		X								
Subject brings eDiary to center for use during visit or to return			X	X	X	X	X	X	X	Sites retain eDiary at week 24/ET visit
eDiary		X (Daily)								Daily
MPFID		X (Daily)								Daily
HIT-6			X	X	X	X	X	X	X	**Post-randomization on Day 1;** eDiary in clinic
MFIQ			X	X	X	X	X	X	X	**Post-randomization on Day 1;** eDiary in clinic
ASC-12			X			X			X	**Post-randomization on Day 1;** eDiary in clinic

Page 3 of 4

Table 2-1. Schedule of Activities - Study Visits Through Double-blind Treatment

	Screening Period		Treatment Period							
	Initial Screening Period	Baseline Period[a]	Double-blind Treatment Period (24 Weeks)							
PROCEDURE	**(up to 3 weeks before Baseline)**	**(4 weeks before Day 1)**	**Day 1[b]**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24/ ET[c]**	**Notes**
MIDAS			X			X			X	Post-randomization on Day 1; **eDiary** in clinic
BDI-II[h]	X	X[i]				X			X	eDiary; in clinic
GAD-7			X			X			X	Post-randomization on Day 1; **eDiary** in clinic
Sleep Questionnaire			X			X			X	Post-randomization on Day 1; **eDiary** in clinic
PGIC									X	**eDiary i**n clinic
HRU Questionnaire[j]			X						X	Post randomization on Day 1; in clinic

Page 4 of 4

ASC-12 = Allodynia Symptoms Checklist-12; BDI-II = Beck Depression Inventory-II; BP = blood pressure; DBTP = double-blind treatment period; eDiary = electronic diary; ET = early termination; GAD-7 = Generalized Anxiety Disorder 7-item Scale; HIT-6 = Headache Impact Test-6; HIV = human immunodeficiency virus; HR = heart rate; HRU = Health Resource Utilization; **IRT = Interactive Response Technology**; MFIQ = Migraine Functional Impact Questionnaire; MIDAS = Migraine Disability Assessment; MPFID = Migraine Physical Function Impact Diary; OLTP = open-label treatment period; PGIC = Patient Global Impression of Change; RR = respiratory rate

[a] The baseline period ends when either a subject is screen failed or randomized into the study. Randomization occurs at the Day 1 visit which must occur between 29 to 35 days after baseline entry (inclusive of the first day that eDiary device is assigned to subject).

[b] On Day 1, all study assessments should be completed prior to subject's first dose of investigational product.

[c] A subject who discontinues the study during the DBTP will complete the assessments of the week 24/ET visit approximately 28 (+3) days after the last dose of investigational product.

[d] Including pre-filled syringe in DBTP and autoinjector during OLTP.

[e] All clinical laboratory testing at screening (except pregnancy testing) will be performed at a central laboratory.

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

[g] For subjects who provided informed consent for the pharmacogenetic studies, DNA will be obtained from residual cells from the biomarker blood sample. Therefore, additional sampling is not required.

[h] The BDI-II will be collected via paper CRF during screening and eDiary thereafter.

[i] The Baseline Period BDI-II will be completed at the end of the Baseline Period using the eDiary, after at least 28 days of data has been entered in the eDiary.

[j] The baseline HRU questionnaire will have a 24-week recall of prior utilization. The HRU questionnaire assessed at the ET visit before week 24 should only include HRU recalled since the previous assessment to avoid collecting duplicate information. For example, the 24-week HRU questionnaire assessed at week 20 as the ET visit should only include HRU recalled since the previous assessment at day 1 (ie, 20-week recall).

Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period

	Treatment Period								
	Open-label Treatment Period (28 Weeks)								
PROCEDURE	**Wk 24 (OLTP Entry Visit)**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk48**	**Wk 52/ EOS[a]**	**Notes**
GENERAL AND SAFETY ASSESSMENTS									
Clinic Visit	X	X			X			X	
Telephone Contact			X	X		X	X		
IRT call[b]	X	X			X			X	
Physical examination	X				X			X	
Vital signs	X				X			X	BP, HR, RR, and temperature
Adverse events	X	X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	
Adverse device effects[c]	X	X	X	X	X	X	X	X	
Product complaints	X	X	X	X	X	X	X	X	
Concomitant therapies review	X	X	X	X	X	X	X	X	

Page 1 of 3

Footnotes after last page of table.

Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period

	Treatment Period								
	Open-label Treatment Period (28 Weeks)								
PROCEDURE	**Wk 24 (OLTP Entry Visit)**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52/ EOS[a]**	**Notes**
LABORATORY ASSESSMENTS									
Urine pregnancy test (females of childbearing potential only)[d]	X	X			X			X	
Urine drug test	X (to be performed at the discretion of the investigator)								
Chemistry	X (to be performed at the discretion of the investigator)							X	
CLINICAL OUTCOME ASSESSMENTS/PATIENT-REPORTED OUTCOMES									
Site re-assigns eDiary to subject					X				
eDiary					X (Daily)				Daily during assessment **study** months
Subject brings eDiary to center for use during visit or to return								X	Sites should retain eDiary at EOS visit
MPFID					X (Daily)				Daily during assessment **study** months
HIT-6								X	**eDiary** in clinic
MFIQ								X	**eDiary** in clinic
MIDAS								X	**eDiary** in clinic

Footnotes after last page of table.

Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period

	Treatment Period								
	Open-label Treatment Period (28 Weeks)								
PROCEDURE	**Wk 24 (OLTP Entry Visit)**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk48**	**Wk 52/ EOS[a]**	**Notes**
STUDY TREATMENT									
Subject receives training on usage of autoinjector	X								
Self-administration of investigational product at clinic	X	X			X				
Self-administration of investigational product at home			X	X		X	X		
Study staff dispenses and/or reconciles investigational product		X			X			X	
Amgen investigational product[e]	X	X	X	X	X	X	X		Autoinjectors

BP = blood pressure; DBTP = double-blind treatment period; eDiary = electronic diary; EOS = end of study; ET = early termination; HIT-6 = Headache Impact Test-6; HR = heart rate; **IRT =** Interactive Response **Technology**; MFIQ = Migraine Functional Impact Questionnaire; MIDAS = Migraine Disability Assessment; MPFID = Migraine Physical Function Impact Diary; OLTP = open-label treatment period; RR = respiratory rate

[a] A subject who discontinues investigational product during the OLTP or who completes the study will perform the week 52/EOS visit assessments. Subjects who early terminate will complete the assessments approximately 28 (+3) days after the last dose of investigational product.

[b] All subjects will be enrolled via **IRT** in the OLTP to maintain the initial treatment blinding in DBTP. Subjects who received active treatment during the DBTP will remain on the same dose. Subjects who received placebo will receive either 70 mg or 140 mg in a 1:1 ratio.

[c] Including pre-filled syringe in DBTP and autoinjector during OLTP.

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

[e] Study drug supply ceases at week 48.

Table 2-3. Schedule of Activities – Optional Interview-based Substudy (Selected US Sites Only)

			Treatment Period							
	Screening Period	Baseline Period	Double-blind Treatment Period (24 Weeks)							
PROCEDURE	(up to 3 weeks before Baseline)	(4 weeks before Day 1)	Day 1 (post-rand)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET	Notes
INTERVIEW-BASED SUBSTUDY										
Substudy informed consent			X[a]							
Substudy Eligibility Requirements			X							
Interview[b]			X[c]						X[d]	

DBTP = double-blind treatment period; ET = early termination; US = United States.

[a] The Substudy subject informed consent can also be obtained at the same time as the main study informed consent during Screening instead of after randomization.

[b] The first interview (Interview 1) will be conducted within the first week after randomization, the second interview (Interview 2) will be conducted within 1 week after the subject's last visit during the DBTP.

[c] The entry interview will be conducted within 7 days from first investigational product dose.

[d] The exit interview will be conducted in close proximity with the week 24 or early termination visits (within 7 days prior to week 24 visit or within approximately 14 days post early termination visit. If possible within 7 days post early termination will be targeted).

3. Introduction

3.1 Study Rationale

Preclinical models of migraine suggest that prolonged exposure to commonly used migraine-specific (ie, triptans) and nonmigraine specific (ie, opioids, nonsteroidal anti-inflammatory drugs [NSAIDs]) medication may produce long-lasting, pronociceptive neuroplastic changes in the trigeminal system including peripheral nerves, dorsal root ganglion, and nucleus caudalis (Meng et al, 2011). The reduction in pain-eliciting stimuli thresholds induced by acute medication appears to be temporally associated with increased release of calcitonin gene-related peptide (CGRP) on the circulatory system and was successfully abolished by a CGRP receptor antagonist in a triptan-induced medication overuse headache (MOH) rodent model (Meng et al, 2011; De Felice et al, 2010).

In Study 20120295, erenumab 70 mg and 140 mg subcutaneously (SC) every 4 weeks were superior to placebo in reducing monthly migraine days (MMD) from baseline to the last **study** month of the double-blind treatment period (DBTP) in subjects with chronic migraine (CM) with or without medication overuse status at baseline. In a prespecified subgroup analysis including subjects with CM with medication overuse (CM-MO subjects), both doses of erenumab achieved numerical and nominal superiority to placebo in reducing MMD (least-squares mean [LSM]: -3.1 days for both 70 mg and 140 mg versus placebo, $p < 0.001$), achieving $\geq$ 50% reduction in MMD at month 3 (odds ratio: 2.67 and 2.51 for 70 mg and 140 mg, respectively; p = -0.004 and 0.007, respectively) and acute headache medication days (AHMD) (LSM: -3.3 and -2.8 for 70 mg and 140 mg, respectively; $p < 0.001$) (Tepper et al, 2017). A subsequent post hoc subgroup analysis including CM-MO subjects who had failed 1 or more migraine preventive treatment further confirmed this observation with numerically superior reductions for both erenumab doses as compared with placebo in MMD (LSM: 2.54 and 4.44 for 70 mg and 140 mg, respectively), moderate to severe headache days (LSM: 1.81 and 3.82 for 70 mg and 140 mg, respectively) and AHMD (LSM: 2.61 and 4.26 for 70 mg and 140 mg, respectively). In addition, more subjects treated with erenumab (47% and 52% in 70 mg and 140 mg, respectively) met medication overuse-free status at the end of DBTP as compared with placebo (29%).

The safety profile of subjects included in the CM-MO stratum was consistent with that of the 12-week integrated safety analysis set for the erenumab clinical development program. Overall, at least 1 treatment emergent adverse event was reported for 46.2%,

48.7%, and 34.2% of subjects in the erenumab 70 mg, erenumab 140 mg, and placebo groups in the CM-MO stratum, respectively. Majority of treatment-emergent adverse events (TEAEs) were categorized CTCAE grade 1 or 2 with CTCAE grade 3 TEAEs only reported for 6.4%, 1.3%, and 5.3% of subjects in the erenumab 70 mg, erenumab 140 mg, and placebo groups. There were no CTCAE category 4 or deaths reported and serious adverse events (SAEs) were observed in 3.8%, 1.3%, and 1.8% of subjects in the erenumab 70 mg, erenumab 140 mg, and placebo groups, respectively.

Given the unmet medical need that MOH represents, and based on preliminary information obtained from Study 20120295, Study 20170703 is being conducted to confirm the efficacy of erenumab in a dedicated MOH population.

3.2 Background

3.2.1 Disease

In patients with migraine, frequent intake of acute pain medication can yield a paradoxical effect and contribute to increased pain severity and frequency of days with headache (May and Schulte, 2016). This phenomenon is often met with a cyclic pattern of further increase in acute pain medication intake and consequential clinical deterioration which may lead to “chronification” (May and Schulte, 2016) of headache attacks.

Metabolic, functional, and structural brain imaging studies involving subjects without migraine and subjects with CM with or without MOH have provided further evidence that the observed clinical deterioration associated with overuse of acute headache medication is possibly grounded on maladaptive neuroplasticity. Volume-based magnetic resonance imaging (MRI), stimulus-induced functional MRI, resting-state MRI, and positron emission tomography studies have reported changes in volume, connectivity, and metabolism in areas of the lateral pain system (the right supramarginal gyrus, right inferion and superior parietal cortex) and other encephalic areas associated with pain processing (ie, thalamus, insula, ventromedial prefrontal cortex) and the reward system (substantia nigra/ventral tegmentum, striatum, orbitofrontal cortex) (Lai et al, 2016; Riederer et al, 2013; Riederer et al, 2012; Ferraro et al, 2012a; Ferraro et al, 2012b; Grazzi et al, 2010; Chiapparini et al, 2009; Fumal et al, 2006). These functional anatomical changes appeared to be distinctive of MOH irrespective of headache frequency and have been reported to improve upon successful treatment of MOH (Schwedt and Chong, 2017).

Longitudinal epidemiological studies have also strengthened the association between medication overuse and migraine chronification. In the American Migraine Prevalence and Prevention study, high frequency episodic migraine (EM) subjects (ie, 10 to 14 headache days/month) who reported medication overuse had a 12-month conversion to CM risk that was several fold higher than those who reported no medication overuse (Bigal et al, 2008).

In recognition of the potential to accompany and complicate primary headache disorders, the International Classification of Headache Disorders (ICHD) has recognized chronification of a primary headache that is associated with excessive and sustained overuse of acute medication as a secondary headache disorder termed MOH, a term that, in line with preclinical observations, implies a potential causative role for acute medication overuse in peripheral and central pain sensitization.

Medication overuse headache is believed to be a highly pervasive and underrecognized condition. Prevalence estimates in an adult Western population have been reported to range from 1% to 2% with majority of cases (ie, from 80% to 100%) having migraine as an underlying primary headache disorder either isolated or in association with another primary headache (Kristoffersen and Lundqvist, 2014). Known risk factors to date for the development of MOH include a diagnosis of migraine, high frequency of headache attacks, female gender, psychiatric comorbidity, pre-existing pain, and acute pain medication use (migraine-specific [triptans, ergotamines] or nonspecific [eg, NSAIDs, opioids], or combinations thereof), allodynia, lower socioeconomic status, and lifestyle-related factors (Diener et al, 2016).

Clinically, the association of medication overuse headache with CM has been linked to an increased risk of preventive treatment failure, stronger association with psychiatric comorbidities (ie, mood disorders, substance-related disorders), increased migraine-related disability, higher levels of health care utilization, and overall decreased quality of life (Diener et al, 2016; Raggi et al, 2015; Kristoffersen and Lundqvist, 2014). Economically, MOH places a high burden on society with the per-person annual costs being estimated to be approximately 10 times greater than those of tension-type headache and 3 times greater than those of migraine without MOH in Europe (Linde et al, 2012).

Recommended treatment options for MOH include early discontinuation of the overused acute medication, initiation or optimization of a preventive intervention, or a combination of both. Evidence to support efficacy of each 1 of these treatment modalities in isolation

or combined is limited by the lack of large randomized controlled trials in MOH (Chiang et al, 2016). A summary of current standard-of-care options and their evidentiary basis is presented in .

3.2.2 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). Nonclinical studies with erenumab demonstrated that it binds to and antagonizes both human and cynomolgus monkey CGRP receptors with high affinity and potency. Erenumab has been developed for the prevention of migraine in adults based on the observed long serum half-life in humans (28 days), clinical data demonstrating that small molecule CGRP receptor antagonists are effective in acute migraine reversal (Ho et al, 2008a; Ho et al, 2008b), prevention (Ho et al, 2014), and the strong rationale for CGRP's association with migraine pathophysiology (Goadsby et al 2017; Sun et al, 2016; Bellamy et al, 2006; Sarchielli et al, 2006; Juhasz et al, 2005; Petersen et al, 2005; Lassen et al, 2002; Tajti et al, 1999; Gallai et al, 1995; Goadsby et al 1990; Goadsby et al, 1988).

As of the date of approval of this protocol, erenumab 70 mg and 140 mg SC QM have been approved in the United States, European Union (EU), and other regions for the prevention of migraine in adults.

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

3.3 Benefit/Risk Assessment

The identified risks for AMG 334 are documented in Appendix A of the currently approved IB (Edition 11: February 2020). A limited number of adverse drug reactions (injection site reactions, constipation, muscle spasm, and pruritis) have been identified at low frequencies (< 5%) in clinical trials. In post-marketing settings, hypersensitivity reactions (including rash, angioedema and anaphylactoid reactions) and constipation with serious complications have been

reported. Available safety data for the clinical trials with AMG 334 are summarized in Section 6.3 of the AMG 334 Investigator's Brochure, Annex 2.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared with placebo on achieving MOH remission during the double-blind treatment period (DBTP)	• Absence of MOH at month 6 as defined by mean monthly acute headache medication days (AHMD) < 10 days over months 4, 5, and 6 **(week 12 through 24)** OR mean monthly headache days (MHD) < 14 days over months 4, 5, and 6 **(week 12 through 24)** of the DBTP where AHMD include any eDiary day in which an acute headache medication intake is reported
Primary Estimand	
The estimand for the primary efficacy endpoint consists of: • The target population, which includes subjects diagnosed with CM and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month • The endpoint, which is the absence of MOH at month 6 as defined by mean monthly AHMD < 10 days over months 4, 5, and 6 **(week 13 through 24)** OR mean MHD < 14 days over months 4, 5, and 6 **(week 13 through 24)**of the DBTP • The intercurrent event, **which is** adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of investigational product (IP), regardless of adherence to treatment. • The summary measure, which is the odds ratio of absence of MOH between each erenumab dose group (ie, 70 mg or 140 mg) and the placebo group	

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

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

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

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

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

Objectives	Endpoints
	• Occurrence of at least 1 headache-related outpatient clinic visit during the DBTP
• To explore the effect of erenumab compared with placebo on the change from baseline in depression and anxiety symptoms	• Change from baseline in Generalized Anxiety Disorder 7-item scale (GAD-7) score at assessment time points • Change from baseline in Beck Depression Inventory-II (BDI-II) score at assessment time points
• To explore the effect of erenumab compared with placebo on the change from baseline in measures of sleep quality	• Change from baseline in each of the sleep questionnaire domain scores at assessment time points
• To explore the effect of erenumab compared with placebo on the subject's assessment of the change in clinical status since the start of treatment	• Change in clinical status as measured by the Patient's Global Impression of Change (PGIC) as assessed by the subject at month 6 of the DBTP
• To explore the effect of erenumab compared to placebo on the change from baseline in allodynia symptoms	• Change from baseline in Allodynia Symptoms Checklist-12 (ASC-12) score at assessment time points
Exploratory (Open-label treatment period)	
• To explore the rate of MOH relapse in the end of **open-label treatment period (**OLTP**)**	• MOH relapse at year 1, defined as both mean monthly AHMD ≥ 10 days over months 11, 12, and 13 **(week 41 through 52)** AND mean MHD ≥ 14 days over months 11, 12, and 13 **(week 41 through 52)** in subjects who achieved MOH remission at month 6 of the DBTP **Note: This endpoint will be analyzed among subjects who were treated with erenumab throughout the entire study**
• To explore absence of MOH at end of OLTP	• Absence of MOH at end of study as defined by mean monthly AHMD < 10 days over months 11, 12, and 13 **(week 41 through 52)** OR mean MHD < 14 days over months 11, 12, and 13 **(week 41 through 52)**
• To explore sustainability of MOH remission during OLTP	• Sustained absence of MOH over 1 year as defined by absence of MOH over the DBTP (months 1, 2, and 3 **[week 1 through 12]**, OR months 4, 5, and 6 **[week 13 through 24]**) AND OLTP (months 11, 12, and 13 **[week 41 through 52]**).

Objectives	Endpoints
	Note: "Absence of MOH" is achieved when mean monthly AHMD < 10 days OR mean MHD < 14 days over the respective 3-month period **This endpoint will be analyzed among subjects who were treated with erenumab throughout the entire study**
• To explore change in AHMD, MMD, **and** MHD **of at least moderate pain intensity**	• Change from baseline in mean AHMD, MMD and **MHD of at least moderate pain intensity** at assessment time points • Change from week 24 (OLTP baseline) in mean AHMD, MMD, and MHD **of at least moderate pain intensity** at assessment time points during OLTP
• To explore everyday activities as measured by the MPFID	• Change from baseline in monthly average impact on everyday activities score as measured by the MPFID at assessment time points • Change from week 24 (OLTP baseline) in monthly average impact on everyday activities score as measured by the MPFID at assessment time points during OLTP
• To explore physical impairment as measured by the MPFID	• Change from baseline in monthly average physical impairment score as measured by the MPFID at assessment time points • Change from week 24 (OLTP baseline) in monthly average physical impairment score as measured by the MPFID at assessment time points during OLTP
• To explore the daily activity impact of headache as measured by the HIT-6	• Change from baseline in HIT-6 total score at week 52 • Change from week 24 (OLTP baseline) in HIT-6 total score at week 52
• To explore migraine-related disability metrics as measured by MFIQ	• Change from baseline in MFIQ domain scores and overall impact on usual activities global item score at week 52 • Change from week 24 (OLTP baseline) in MFIQ domain scores and overall impact on usual activities global item score at week 52

Objectives	Endpoints
• To explore migraine-related disability and productivity as measured by the MIDAS Questionnaire	• Change from baseline in MIDAS total score, absenteeism score and presenteeism score at week 52 • Change from week 24 (OLTP baseline) in MIDAS total score, absenteeism score, and presenteeism score at week 52
Exploratory (Opioid-treated Cohort Only)[a]	
• To explore the effect of erenumab compared with placebo in reducing consumption of opioids in subjects stratified to the opioid-treated cohort during DBTP	• Change from baseline in monthly opioid/opioid-containing medication days at assessment time points during DBTP • **Change from baseline in mean monthly opioid/opioid-containing medication days over months 4, 5, and 6 (week 13 through 24) of the DBTP**
• To explore the effect of erenumab compared with placebo in reducing consumption of opioids in subjects stratified to the opioid-treated cohort during OLTP	• Change from baseline in monthly opioid/opioid-containing medication days at assessment time points during OLTP

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

4.2 Hypotheses

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

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

For subjects with CM-MOH allocated to the opioid-treated cohort, an additional exploratory clinical hypothesis of Study 20170703 is that preventive treatment with

monthly injections of erenumab could help reduce opioid use as measured by the mean change in monthly opioid medication days from baseline over months 4, 5, and 6 **(week 13 through 24)** of the DBTP. Formal statistical testing does not apply to this exploratory clinical hypothesis.

5. Study Design

5.1 Overall Design

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

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

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

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

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 687 subjects (549 subjects in the nonopioid-treated cohort and up to 138 subjects in the opioid-treated cohort) will be enrolled in the study. Subjects with a

baseline intake of opioid/opioid-containing medication that exceeds 4 days per month during the baseline period will be allocated to the opioid-treated cohort.

The opioid-treated cohort will be capped at no more than 20% of the total randomized population to improve study feasibility.

Subjects in this clinical investigation shall be referred to as "subjects". For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

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

5.2.2 Number of Sites

Approximately 80 investigative sites in 12 countries are expected to participate in Study 20170703. Additional sites and/or countries within North America, Europe, or Asia Pacific may be added as deemed necessary by the study management team.

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

5.3 End of Study

5.3.1 End of Study Definition

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

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

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

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

5.3.2 Study Duration for Subjects

The total study duration for subjects who successfully complete the study will be **approximately** 59 weeks. Total study duration includes:

- An up to 3-week initial screening period
- A 4-week baseline period
- An up to 52-week treatment period comprised of a 24-week DBTP and a 28-week OLTP

5.4 Justification for Investigational Product Dose

Erenumab 70 mg and 140 mg SC every 4 weeks are approved in Europe, US, and other regions for the prevention of migraine in adults. Regulatory approval was based on established superiority against placebo for each dose in 4 independent randomized clinical studies (1 CM and 3 EM). Based on treatment response observed in subjects with medication overuse enrolled in Study 20120295, dose response in this study is expected to be comparable to migraine. In addition, data from the CM study (Study 20120295) indicated that erenumab 140 mg SC every 4 weeks may provide incremental benefit in inducing MOH remission as compared with 70 mg in subjects with CM, medication overuse, and prior treatment failure. Consequently, the adoption of 2 active dose levels in this study is justified to further inform on efficacy and safety of the 2 approved doses in a dedicated MOH population.

5.5 Patient Input on Study Design

Patient input was not collected during study design.

6. 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 the up to 3-week screening period (part 1) and a 4-week baseline period (part 2). At the end of baseline period, subjects who successfully met eligibility criteria will be randomized on study.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 12.3).

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

6.1 Inclusion Criteria Part 1

To be assessed during the 3-week screening period, prior to the baseline period.

Subjects are eligible to be included in the study only if all of the following criteria apply:

101. Subject has provided informed consent prior to initiation of any study-specific activities/procedures
102. Age ≥ 18 years on entry into the study
103. Documented history of migraine without aura and/or migraine with aura according to the ICHD-3 Classification for ≥ 12 months at screening
104. Documented history of CM (refer to Section 12.1 for definition of CM) for a minimal duration of 6 months before screening
105. Current diagnosis of MOH (refer to Section 12.1 for ICHD-3 definition of MOH)
106. History of treatment failure with at least 1 preventive treatment as defined as treatment discontinuation due to lack of efficacy, adverse event or general poor tolerability

6.2 Exclusion Criteria Part 1

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

Disease Related

201. Age > 50 years at migraine onset or > 65 years at CM onset
202. History of hemiplegic migraine, cluster headache or other trigeminal autonomic cephalalgia
203. Current concomitant diagnosis of a secondary type of headache other than MOH
204. History of clinically significant orofacial pain (eg, painful cranial neuropathies, temporomandibular disorder) that in the opinion of the investigator or Amgen's physician, if consulted, could interfere with the study evaluation, procedures or completion
205. Chronic headache with continuous pain, in which the subject does not experience headache-free periods of any duration
206. No therapeutic response in prevention of migraine after an adequate therapeutic trial of > 3 of the following medication categories. These medication categories include:

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

    Note: no therapeutic response is defined as no reduction in headache frequency, duration or severity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) and is based on the investigator's assessment. Subjects do not meet this exclusion criteria if:

    1. The subject discontinued the medication prior to achieving a therapeutic response due to adverse events related to the medication

2. Based on investigator opinion, the subject did not receive an adequate dose of the medication for at least 6 weeks

235. Changes in drug regimen (ie, changes in dose or frequency of use) of an allowed migraine preventive medication within 2 months **prior to start of baseline** (refer to Section 7.1.7 for the list of these medications)

208. Received botulinum toxin in the head and/or neck region within 4 months prior to screening

236. Documented history of treatment with an anti-CGRP **preventive treatment**

210. Anticipated to require any excluded medication/device or procedure during the study (Refer to Section 7.1.7 for the list of excluded medications, devices or procedures)

211. 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 [COAs]) to the best of the subject's and investigator's knowledge.

Other Medical Conditions

212. History or evidence of unstable or clinically significant medical condition that, in the opinion of the investigator or Amgen's physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

237. Excluded medical conditions include:

- Currently diagnosed with fibromyalgia and/or chronic pelvic pain;
- Currently diagnosed with a clinically significant cervical or intracranial disease (eg, chronic cervical radiculopathy, space-occupying lesions, intracranial aneurysms) that, in the opinion of the investigator, might confound or mimic migraine symptomatology;
- History of major psychiatric disorder (such as schizophrenia or other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder), or current evidence of depression based on a BDI-II total score $>$ 24 at screening.
- History of malignancy within the past 5 years, with the following exception[s]:
  - Malignancy treated with curative intent and with no known active disease present for $\geq$ 5 years before **screening** and felt to be at low risk for recurrence by the treating physician
  - Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease
  - Prostatic intraepithelial neoplasia without evidence of prostate cancer
  - Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- Known human immunodeficiency virus (HIV) infection
- Known hepatic disease with potential for hepatic function impairment or evidence of acute or chronic hepatitis B or hepatitis C (hepatitis status will be evaluated by testing for hepatitis B surface antigen [HepBsAg], total hepatitis B core antibody [HepBcAb] and hepatitis C antibody at screening)
- Total bilirubin $\geq$ 2.0x upper limit of normal (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$ 3.0 x ULN, as assessed by the central laboratory at screening

214. Myocardial infarction, stroke, transient ischemic attack, unstable angina, or coronary artery bypass surgery, or other revascularization procedures within 6 months prior to screening

215. Any known history of substance-related disorders (eg, abuse, misuse or addiction) or addictive disorders (eg, pathological gambling)

216. Evidence of "recreational use" of illicit drugs within 12 months prior to screening, based on medical records, self-report, or a positive drug test performed during screening.

   – Note: positivity for some prescribed substances such as opioids may not be exclusionary. (Refer to Section 7.1.7)

Prior/Concomitant Therapy

218. Used an excluded concomitant medication, procedure or device as outlined in Section 7.1.7

238. Exceeded 15 days per month of a short-acting opioid/opioid-containing medication during any of the **2** months prior to screening

239. Had a concomitant use of a short-acting opioid/opioid-containing medication in a frequency that exceeds 4 days per month with any of the following prescribed psychoactive substances:

- Regular use of barbiturates as defined as any use that exceeds 4 days per month during any of the **2** months prior to screening
- Regular use of central nervous system sedative-hypnotic drugs or drugs that may increase opioid risk such as benzodiazepines, z-drugs, gabapentinoids, tricyclic antidepressants, butyrophenones, phenothiazines, anticonvulsants, and muscle relaxants as defined as any use that exceeds 15 days per month during any of the 3 months prior to screening.

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

241. Subject has known **hyper**sensitivity to any of the components to be administered during dosing.

223. Subject is likely to not be able or available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures (eg, COAs) to the best of the subject and investigator's knowledge.

6.3 Inclusion Criteria Part 2

To be assessed at the end of the baseline period and prior to enrolment into DBTP.

Based on information collected through the electronic diary (eDiary) during the baseline period, the following requirements must be met:

107. ≥ 14 headache days during the 28-day baseline period out of which ≥ 8 headache days meet criteria as migraine days (refer to Section 12.1 for a definition of migraine days)
108. Observation of acute migraine medication overuse during the baseline period. Medication overuse at baseline is defined as:
    - ≥ 10 days of combination treatment OR
    - ≥ 10 days of short-acting opioids/opioid-containing medication OR
    - ≥ 10 days of triptans, ergots, OR
    - ≥ 15 days of NSAIDs or simple analgesics intake
109. At least 2 acute headache medication days per week for each week with at least 5 diary days
110. Demonstrated at least 80% compliance with the eDiary (eg, must complete eDiary items on at least 23 out of 28 days during the baseline period)

6.4 Exclusion Criteria Part 2

Study procedures

224. Likely to not be able or available to complete all protocol required study visits or procedures, and/or comply with all required study procedures (eg independent completion of eDiary items) to the best of the subject's and investigator's knowledge

Concomitant treatment at baseline

242. Taken a **short-acting** opioid or opioid-containing analgesic for any indication **for** > 15 days during baseline period

243. **Short-acting o**pioid use during baseline period that in the opinion of the investigator or Amgen's physician, if consulted, constitutes any of the following:

- misuse (use that is contrary to the prescriber's directions, eg, unsolicited dose escalation)
- abuse (use for nonmedical intention, eg, euphoria or altered consciousness)
- dependence (use that is compulsive or potentially harmful)
- diversion (transfer of a legally prescribed controlled substance from the individual for whom it was prescribed to another person for any illicit use)

227. Changed or planning to change the dose of an allowed concomitant medication that may have migraine preventive effect during baseline period or postrandomization

228. Use of any of the excluded concomitant medications, procedures or devices as outlined in Section 7.1.7.

Medical conditions newly diagnosed during baseline

229. Unstable or clinically significant medical condition 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

244. At risk of self-harm or harm to others as evidenced by scoring ≥ 1 point in BDI-II item 9 **(Suicidal Thoughts or Wishes)** and concomitant demonstration of strong suicidal ideation (ie, presence of suicidal planning)

231. Evidence of drug or alcohol abuse or dependence or "recreational use" of illicit drugs as demonstrated by subject self-report, medical records or a positive drug screen test at baseline

232. Newly diagnosed substance-related disorder as assessed by the investigator and/or an addiction specialist

Contraception, pregnancy or breastfeeding

233. Unwillingness to maintain acceptable contraception method, when applicable
234. Evidence of pregnancy or breastfeeding per subject self-report, medical records or positivity on baseline pregnancy screening tests, through end of study

6.5 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 12.3).

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

After signing informed consent, subjects will be evaluated for eligibility criteria during an up to 3-week screening period (part 1), and a 4-week baseline period (part 2). Once the subject is determined by the investigator to meet part 1 eligibility criteria as part of the screening period, the subject will be evaluated for part 2 eligibility under the baseline period.

Upon completion of screening period procedures, the subject is evaluated by the investigator, and if the subject meets all Part 1 and Part 2 eligibility criteria he/she is subsequently randomized to a treatment regimen. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF). The subject is considered enrolled when the subject is randomized.

Subjects who do not meet either Part 1 or Part 2 eligibility criteria will be considered screen failures.

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

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

6.6 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if the condition that led to screen failure is expected to be transient. Refer to Section 9.1.1.

A subject who is determined to be ineligible must be registered as a screen fail in the **IRT**.

7. Treatments

Study treatment is defined as any investigational product(s), noninvestigational 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 noninvestigational product are referred to as investigational medicinal product and noninvestigational 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 7-1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Study Treatments

	Amgen Investigational Product:[a]	
Study Treatment Name	Erenumab	**Placebo**
Dosage Formulation	• DBTP - Erenumab will be packaged in single prefilled syringes containing 1 mL of 70 mg/mL of erenumab. • OLTP - Erenumab will be packaged in an autoinjector containing 1 mL of 70 mg/mL or 140 mg/mL of erenumab.	• Placebo will be presented in identical devices, and stored/packaged the same as erenumab
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	• Erenumab 70 mg and 140 mg will be administered every 4 weeks during DBTP and OLTP. • To preserve blinding integrity during the DBTP, the 70 mg dose level will be composed of one 1 mL injection of erenumab 70 mg and one 1 mL injection of matching placebo, and the 140 mg dose level will be composed of two 1 mL injections of erenumab 70 mg. • During OLTP, subjects will be maintained on their original dose assignment and receive IP as an autoinjector device.	• Placebo will be administered every 4 weeks during the 24-week DBTP (ie, at day 1 and visit weeks 4, 8, 12, 16, and 20). • To preserve blinding integrity during the DBTP, there will be two 1 mL injections of matching placebo for placebo assigned subjects**.** • Upon completion of DBTP, placebo-treated subjects will be allocated to an active dose arm by **IRT** to receive either 70 mg or 140 mg of erenumab every 4 weeks.
Route of Administration	• Subcutaneous administration. • The anatomical sites for administration of investigational product are the upper arm, upper thigh or abdomen, Refer to the IPIM for investigational product details.	
Accountability	• The quantity, start date, start time, injection site, and box number(s) of investigational product are to be recorded on each subject's CRF. During OLTP, start date, start time and injection site are to be recorded by the subject for at-home IP administrations.	
Dosing Instructions	• Treatment doses to be administered at clinic visits by authorized investigational site study staff during the DBTP. During OLTP, subjects will be trained to self-administer with an autoinjector device in the clinic and are expected to self-administer at home or in clinic during OLTP. • Investigational product doses are fixed and cannot be adjusted • Erenumab dose received during DBTP will be maintained the same during OLTP for subjects assigned to active treatment during DBTP. Subjects assigned to placebo during DBTP will be allocated in a 1:1 fashion to either dose of erenumab during OLTP. • The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen. Overdose with this product has not been reported.	

CRF = case report form; DBTP = double-blind treatment period; IPIM = investigational product instruction manual; **IRT = Interactive Response Technology**; OLTP = open-label treatment period

[a] Erenumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Noninvestigational Products

Not applicable.

7.1.3 Medical Devices

The following investigational medical device(s) provided by Amgen for use in this study are the prefilled syringe (PFS) during the DBTP and the autoinjector (AI) during OLTP (Table 7-1).

The erenumab PFS is a single-use, disposable, handheld manual injection device for fixed dose SC injection of 70 mg in a 1 mL deliverable volume.

The erenumab AI is a single-use, disposable, handheld manual injection device for fixed dose SC injection of either 70 mg or 140 mg in a 1 mL deliverable volume.

Additional details are in the IPIM.

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

Noninvestigational 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.

Refer to Section 7.1.7 for a list of prohibited medical devices.

7.1.4 Other Protocol-required Therapies

Not applicable.

7.1.5 Other Treatment Procedures

Not applicable.

7.1.6 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(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

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

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

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

Concomitant treatment with **up to 2** oral migraine preventive medication is allowed under the following conditions:

(1) drug regimen (ie, formulation, frequency of use, dose) is stable ≥ 2 months prior to baseline period start

(2) drug regimen is at generally accepted dose, frequency and route for its use in migraine

(3) drug regimen is not anticipated to change during baseline period or postrandomization (ie, during the subject's study participation).

Examples of such medications include but are not limited to the following:

- Antiepileptics (eg, divalproex sodium, sodium valproate, topiramate, carbamazepine, levetiracetam).
- Angiotensin receptor blockers (eg, candesartan) or ACE inhibitors (eg, lisinopril).
- Beta blockers.
- Calcium channel blockers (verapamil, amlodipine, cinnarizine, lomerizine) or calcium antagonists (eg, flunarizine).
- Tricyclic antidepressants.
- Other antidepressants (eg, serotonin-norepinephrine reuptake inhibitors, selective serotonin-reuptake inhibitors).
- Other drugs used for migraine prevention (eg, **coenzyme Q10,** clonidine, guanfacine, methysergide, cyproheptadine, pizotifen, butterbur, feverfew, magnesium (≥ 500 mg/day), riboflavin (≥ 100 mg/day).

Prohibited Medications	**Time Period for Exclusion**
Concurrent use of non-investigational anti-CGRP mAbs	Prior history of treatment with and throughout the study
Use of the following acute medications for the acute treatment of migraine**:** Barbiturates or butalbital-containing medication for > 4 days/month **Short-acting o**pioids or **short-acting** opioid-containing medication for >15 days/month **Long-acting opioids or long-acting opioid-containing medication** **Cannabidiol (CBD)-containing products anticipated to have a systemic effect (eg, ingested or inhaled products) > 4 days/month**	**2** months before the start of the screening period and throughout the study
Investigational medications	30 days or 5 half-lives before the start of the screening period and throughout the study
Botulinum toxin (in the head and/or neck region)	4 months before the start of the screening period and throughout the study
Prohibited Procedures or Devices	Time Period for Exclusion
For any indication Infusion **rescue** therapy (ie, steroids, valproate sodium, dihydroergotamine) Note: infusion **rescue** therapy may be allowed during DBTP if medically justified	During screening period or baseline period
For any indication Devices (such as stimulation devices), or procedures (such as nerve blocks, or psychotherapy).	3 months before the start of the screening period and throughout the study
Cognitive Behavioral Therapy Subjects on a stable, maintenance phase of a cognitive behavioral therapy (CBT) program for migraine are allowed. CBT is defined as stable, on a maintenance phase if subject has undergone ≥ 6 weekly or biweekly sessions of CBT administered by adequately trained psychologists and who, for at least 3 months before the start of the baseline period, only follow “booster” CBT sessions at a monthly, bimonthly or quarterly frequency.	3 months before the start of the screening period

7.2 Method of Treatment Assignment

Subjects will be randomized in a 1:1:1 allocation ratio, to erenumab 70 mg/mL SC every 4 weeks, erenumab 140 mg/mL SC every 4 weeks, or matching placebo, respectively, in a double-blind manner for nonopioid-treated cohort and opioid-treated cohort separately.

The randomization will be performed by **IRT**, and the randomization number will be assigned by **IRT** and appear on the **IRT** randomization document. The randomization number is different than the subject identification number and will not be utilized by the site as a subject identifier.

The randomization will be stratified by concomitant treatment with an oral preventive (Yes or No) in the nonopioid-treated cohort.

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

7.3 Blinding

This study has a 24-week DBTP and a 28-week OLTP. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below. **During the 24-week DBTP, treatment assignment will be blinded to all subjects, site personnel, and Amgen. Following the DBTP, during the 28-week OLTP, study team members in direct contact with sites, investigators, and subjects will remain blinded to the initial dose level.**

7.3.1 Site Personnel Access to Individual Treatment Assignments

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

7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is completed. Unblinding and potentially unblinding information is not to be distributed to study team members in direct contact with sites, investigators or subjects prior to the final analysis.

7.4 Dose Modification

7.4.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

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

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

7.4.2.1 Amgen Investigational Product: Erenumab or Matching Placebo

Dose adjustments are not permitted.

7.4.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 12.7 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

7.5 Preparation/Handling/Storage/Accountability

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

7.6 Treatment Compliance

Administration of investigational product will be conducted at sites or at home during scheduled time points.

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

7.7 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.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

For prior migraine preventive medications ending 2 months prior to start of baseline, therapy name, indication, dose, unit, frequency, start and stop dates will be collected in the prior migraine preventive medication CRF.

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

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies are to be collected from screening through the end of study.

Concomitant medication that is taken to treat headaches or migraine symptoms acutely and/or may lead or contribute to MOH will be reported in the eDiary.

All other concomitant medications will be reported on the Concomitant Medications electronic case report form (eCRF) including any allowable concomitant migraine preventive medication.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, 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 other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and device-related events, as applicable and must document this decision in the subject's

medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies 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 who permanently discontinue investigational product during the DBTP are to continue eDiary entry and to complete the remaining study visits through the week 24/ ET visit for the assessment of primary and secondary endpoints.

Subjects who permanently discontinue investigational product during the OLTP are to complete the study procedures for the week 52 End of Study visit.

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
- Noncompliance
- Adverse event
- Subject request
- Pregnancy

8.2 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 12.6 for further details). Refer to the Schedule of Activities (Table 2-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study after enrollment/randomization are:

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

8.3 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.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

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.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure. After the subject has signed the informed consent form, the site will register the subject in the **IRT** and screen the subject in order to assess eligibility for participation.

9.1.1.1 Screening Period

The screening period is up to 7 weeks, which consists of an up to 3-week initial screening period **and a** 4-week baseline period.

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

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

Rescreen subjects must first be registered as screen failures in **IRT** and subsequently registered as rescreens. Once the subject is registered as rescreened, a new **up to 7-week** screening period will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than **60** days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

9.1.1.2 Baseline Period

The 4-week baseline period starts when the subject has met all Part 1 eligibility criteria (refer to Section 6.1 and Section 6.2) and enters the baseline period and ends when the subject **is randomized or** does not complete baseline or does not meet all Part 2 eligibility criteria (refer to Section 6.3 and Section 6.4) **and is screen failed**.

The total duration of the baseline period must be at least 29 days and no more than 35 days. Refer to Sections 9.2.2.1 and 9.2.2.3 for information on the BDI-II and eligibility calculation, which are to be completed at the end of the baseline period using the eDiary.

9.1.1.3 Randomization

Upon completion of the baseline period, subjects found to meet eligibility requirements will undergo randomization in **IRT** and be assigned a study treatment in a blinded manner.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). The date of the first dose of IP is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. On-study visits may be completed ± 3 days of the scheduled visit. Administration of IP is to be administered once every 4 weeks during each visit that it is required.

9.1.3 Early Termination

Upon permanent discontinuation from the study for any reason other than study completion or withdrawal of consent, an ET visit will be performed approximately 28 days after the last dose of investigational product.

Subjects who early terminate the study before week 24 should complete the week 24/ET assessments (Table 2-1).

Subjects who early terminate the study after week 24 and before week 52 should complete the week 52/EOS assessments (Table 2-2).

9.1.4 End of Study

Subjects who reach week 52 will end the study and complete all week 52/EOS assessments, according to Table 2-2.

9.2 Description of General Study Assessments and Procedures

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

9.2.1 General Assessments

9.2.1.1 Informed Consent

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

9.2.1.2 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.

Additionally, demographic data will be used to study the impact on biomarker variability of the investigational product.

9.2.1.3 Medical History

The Investigator or designee will collect a complete medical (including targeted cardiovascular), psychiatric, and surgical history that started within 120 days prior to medical history assessment at screening. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, migraine history must date back to the original diagnosis. The current severity will be collected for each condition that has not resolved.

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

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

9.2.1.5 Physical Measurements

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

9.2.1.6 Performance Status

Not applicable.

9.2.2 Efficacy Assessments

9.2.2.1 Clinical Outcome Assessments and Electronic Diaries (eDiaries)

The COAs will be collected by subjects using a handheld eDiary at various frequencies. The eDiary will collect the following COAs daily at home starting in the baseline period and throughout the DBTP, and then again daily starting from week 40 **visit** through the week 52/EOS visit of the OLTP:

- Date and time of start of headache (ie, migraine or nonmigraine headache)
- Date and time of end of each headache
- Worst pain severity per headache day
- Pain features (eg, 1-sided, throbbing, worsens, with exercise/physical activity)
- Other migraine symptoms (eg, aura, nausea, vomiting, photophobia, phonophobia)

- Use of acute medications **to treat headaches or migraine symptoms** (medication name [from pre-entered list] date and time of dosing, number of times taken of each date, number of units taken)

Study center staff will assign and provide an eDiary to the subject at the week -4 visit (after confirming the subject's part 1 eligibility prior to baseline period entry). The study center staff will train the subject on how to use the eDiary (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day and to bring the eDiary to every study visit. **During the baseline period after at least 28 full calendar days have passed (inclusive of the day the subject was set-up on the eDiary device), the subject will return for their end of baseline period visit/ day 1 visit.** 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. **During this visit, site staff will be able to activate the baseline period BDI-II on the subject's eDiary device, as well as perform the eligibility calculation.**

For randomized subjects, all Day 1 study assessments, including eDiary questionnaires, should be completed prior to subject's first dose of investigational product. For subsequent study visits, the order of completing study assessments will be at the investigator's discretion.

The subject's eDiary will also be used for the completion of the following patient-reported outcome measures:

- MPFID
- HIT-6
- MFIQ
- MIDAS questionnaire
- Sleep questionnaire
- Allodynia symptoms checklist 12 items (ASC-12) questionnaire
- BDI-II
- GAD-7
- PGIC

9.2.2.2 Allodynia Symptoms Checklist 12 items (ASC-12)

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

The subject answers each question using the following categories: “Does not apply to me”, “Never”, “Rarely”, “Less than half of the time”, “Half the time or more”. Responses to each question are assigned a score. A positive response to answer options 1 to 3 is scored as 0, a positive response to answer option 4 is scored as a 1, and a positive response to answer option 5 is scored a 2. The final grading is based on the sum of the 12 items.

Subjects will complete the ASC-12 using the eDiary.

9.2.2.3 Beck Depression Inventory (BDI-II)

The BDI-II is a 21-item questionnaire that assesses the severity of depression. Each item is scored from 0 to 3. The total score is categorized into 4 severity grades: minimal depression (0 to 13), mild depression (14 to 19), moderate depression (20 to 28), and severe depression (29 to 63). The BDI-II will be collected at the initial screening, baseline and DBTP periods. At initial screening, BDI-II will be collected in the electronic case report form (eCRF) for eligibility purposes only. The baseline period and DBTP BDI-II will be collected by eDiary.

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

9.2.2.4 General Anxiety Disorder 7-item questionnaire (GAD-7)

The GAD-7 is a self-administered 7-item instrument that uses some of the DSM-V criteria for general anxiety disorder (GAD) to identify probable cases of GAD along with measuring anxiety symptom severity. Responders are asked to rate the frequency of anxiety symptoms in the last 2 weeks on a Likert scale ranging from 0 (‘not at all’) to

3 ('nearly every day'). Items are summed to provide a total score. Score interpretation is as follows: 1 to 4 minimal symptoms, 5 to 9 mild symptoms, 10 to 14 moderate symptoms, and 15 to 21 severe symptoms. Changes of 5 points or more are clinically meaningful.

9.2.2.5 Headache Impact Test-6 (HIT-6)

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

For each HIT-6 item, 6, 8, 10, 11, or 13 points, respectively, are assigned to the response provided. These points are summed to produce a total HIT-6 score that ranges from 36 to 78. The HIT-6 scores are categorized into 4 grades, representing little or no impact (49 or less), some impact (50 to 55), substantial impact (56 to 59), and severe impact (60 to 78) due to headache. No recall period is specified for the first 3 items. The recall period is the past 4 weeks for the last 3 items.

Subjects will complete the HIT-6 using the eDiary.

9.2.2.6 Migraine Disability Assessment Questionnaire (MIDAS)

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

The score is categorized into 4 severity grades: grade I = 0 to 5 (defined as minimal or infrequent disability), grade II = 6 to 10 (mild or infrequent disability), grade III = 11 to 20 (moderate disability), and grade IV = 21 and over (severe disability). Two other

questions (A and B) are not scored, but were designed to provide the physician with clinically relevant information on headache frequency and pain severity.

Subjects will complete the modified MIDAS using the eDiary.

9.2.2.7 Migraine Functional Impact Questionnaire (MFIQ)

The MFIQ is a self-administered 26-item instrument measuring the impact of migraine on broader functioning (ie, Physical, Social, and Emotional Functioning). It has 4 domains, Impact on Physical Functioning (5 items), Impact on Usual Activities (10 items), Impact on Social Functioning (5 items), and Impact on Emotional Functioning (5 items). In addition, there is 1 stand-alone global item assessing the overall impact on usual activities. Subjects respond to items using a 5-point scale assigned scores from 1 to 5, with 5 representing the greatest burden. The scores 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 will complete the MFIQ using the eDiary.

9.2.2.8 Migraine Physical Function Impact Diary (MPFID)

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

Subjects respond to items using a 5-point scale, with difficulty items ranging from "Without any difficulty" to "Unable to do" and frequency items ranging from "None of the time" to "All of the time". These are assigned scores from 1 to 5, with 5 representing the greatest burden. For each domain, the scores will be calculated as the sum of the item responses and the sum will be rescaled to a 0 to 100 scale, with higher scores representing greater impact of migraine (ie, higher burden). There will be a score for each of the 2 domains and a third score for the stand-alone item. The recall period is the past 24 hours. Subjects will complete the MPFID daily using the eDiary.

9.2.2.9 Patient Global Impression of Change (PGIC)

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

9.2.2.10 Sleep Questionnaire (ARMR sleep questionnaire)

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

Subjects will complete the ARMR sleep questionnaire using the eDiary.

9.2.2.11 Health Resource Utilization Resource Questionnaire (HRU)

The questionnaire is designed to collect data on HRU. Specifically, the HRU questionnaire aims to capture frequency of **headache**-related inpatient hospitalizations and outpatient emergency department visits, urgent care visits, and other clinical visits. The recall period for the HRU questionnaire is 24 weeks. The questionnaire with the 24-week recall will be administered at day 1 and week 24 of the DBTP.

The HRU questionnaire assessed at the ET visit before week 24 should only include HRU recalled since the previous assessment to avoid collecting duplicate information. For example, the 24-week HRU questionnaire assessed at week 20 as the ET visit should only include HRU recalled since the previous assessment at day 1 (ie, 20-week recall).

HRU questionnaire is a clinician-reported outcome (CRO) to be collected at clinic visits through subject interview. The HRU data is to be inputted in the eCRF.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 2-1).

9.2.3.1 Adverse Events

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

9.2.3.1.1.1 Adverse Events

Adverse events related to any study procedures/study-activity are reported **after the first dose of investigational product**. All other adverse events are reported after the first dose of investigational product.

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

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Section 12.4.

9.2.3.1.1.2 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 the end of study are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.4. 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.

9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. 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, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 12.4.

9.2.3.1.2 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 nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 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 8.3). Further information on follow-up procedures is given in Section 12.4.

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

9.2.3.1.4 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.

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

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects **who become pregnant,** will be collected after the start of study treatment **through 16 weeks after the last dose of study drug**.

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 12.5. 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 12.5.

9.2.3.1.6 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.

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

Product complaints are described in Section 7.1.6.

Further details regarding adverse device effects can be found in Section 12.4.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: heart rate, QRS, QT, QTc, and PR intervals. The PI or (eg, designated site physician) will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Findings should be recorded on the ECG electronic case report form (eCRF).

9.2.3.4 Vital Status

Not applicable.

9.2.3.5 Other Safety

Not applicable.

9.2.4 Clinical Laboratory Assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 2-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

Urine drug tests (UDTs) performed at screening that return positive likely due to the use of an allowable over-the-counter (OTC) medication may be retested prior to eligibility determination.

All protocol-required laboratory assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 2-1).

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

9.2.4.1 Pregnancy Testing

A high sensitive urine pregnancy test should be completed at screening and at day 1 pre-randomization 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 12-2). Refer to Section 12.5 for contraceptive requirements.

Post day 1 pregnancy testing should be completed as per the Schedule of Activities (Table 2-1, Table 2-2). Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.4.2 Prespecified Biomarker Assessments

Not applicable.

9.2.5 Pharmacokinetic Assessments

Not applicable.

9.2.6 Pharmacodynamic Assessments

Not applicable.

9.2.7 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of migraine and other neurological diseases, and/or to identify subjects who may have positive or negative response to erenumab. For subjects who consent to this analysis, DNA may be extracted.

The final disposition of samples will be described in Section 12.6.

9.2.8 Antibody Testing Procedures

Not applicable.

9.2.9 Biomarker Development

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

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

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to erenumab to investigate and further understand CM.

Blood samples are to be collected for biomarker development at the time points specified in the Schedule of Activities (Table 2-1).

9.2.10 Clinical Outcome Assessments

Refer to Section 9.2.2 for COA details.

9.2.11 Health Economics OR Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- Duration of hospitalization (total days or length of stay, including duration by wards eg, intensive care unit)
- Number and type of diagnostic and therapeutic tests and procedures
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

9.2.12 Optional Substudies

Up to 30 subjects will be asked to participate in an optional interview-based substudy. The substudy will be conducted at selected US sites and will consist of 2 qualitative interviews to be conducted during the first week after randomization (ie, substudy interview 1) and no later than a week after the subject's last visit in the DBTP (ie, substudy interview 2).

The objective of the substudy is to evaluate individual subjects' experiences related to migraine, especially as it relates to the impact on functioning during and between migraine attacks and the perceived effect of study treatment. The relationship between headache and migraine attack and the subject-level perception of treatment effect will also be explored and will help illustrate the subject perspective of treatment response.

Participation in the substudy is optional and a separate consent form will be requested for substudy inclusion. Substudy participants who discontinue study treatment early are encouraged to complete substudy interview 2.

Refer to Appendix 8 for more information on the substudy.

9.2.13 Other Assessments

Not applicable.

10. Statistical Considerations

10.1 Sample Size Determination

The sample size calculation has been performed based on the primary endpoint (absence of MOH at month 6 **[week 24]**) for the nonopioid-treated cohort.

Based on a subgroup analysis of subjects who failed preventive migraine medication**,** overused acute headache medication, and had at least 14 MHD at baseline in the erenumab CM pivotal Study 20120295, 33.1%, 50.5%, and 64.1% of subjects in placebo, erenumab 70 mg and erenumab 140 mg treatment group, respectively, achieved absence of MOH at month 3 **(week 12)**. Assuming similar response rates over month 4, 5 and 6 **(week 13 through 24)** and a conservative scenario that includes a dropout rate of 20% during the 6-month DBTP, the planned sample size of 183 subjects per group will provide 85% power for 70 mg versus placebo and > 99% power for 140 mg versus placebo using a 2-sample chi-squared test with a 2-sided significance level of 0.05.

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

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

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

10.2.1.1 Full Analysis Set

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

10.2.1.2 Efficacy Analysis Set

The efficacy analysis set (EAS) for the binary efficacy endpoint during DBTP is a subset of FAS consisting of subjects who receive at least 1 dose of investigational product during DBTP. The EAS for the continuous secondary endpoint expressed as change from baseline is a subset of FAS consisting of subjects who receive at least 1 dose of investigational product and have at least 1 change from baseline value during the DBTP. The respective EAS will be used to perform the analyses for the efficacy endpoints of interest during DBTP. Other efficacy endpoints will use this set or appropriate subsets of

this set depending on the endpoint. Subjects will be analyzed according to their randomized treatment in DBTP, regardless of the treatment received.

10.2.1.3 Safety Analysis Set

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

10.2.1.4 Open-label Treatment Period Analysis Set

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

10.2.2 Covariates

All formal analyses of efficacy endpoints in nonopioid-treated cohort will be adjusted for the following covariates:

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

10.2.3 Subgroups

The primary and key secondary endpoints for the nonopioid cohort will be analyzed in the subgroups defined by concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No), key demographics (eg, geographic region), prior history of treatment with onabotulinumtoxinA (Yes or No), total number or prior treatment failures (1, 2**,** or 3 or more treatment failures), and acute headache medication overuse category (triptan medication overuse, simple analgesics and/or NSAIDs medication overuse, **combination analgesics overuse,** or combination **therapies** overuse).

10.2.4 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of reasons. In general, data could be missing due to a subject's early withdrawal from the study, a missed visit, or inability to evaluate an endpoint at a particular point in time. For this study, efficacy endpoints 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 **in efficacy** will be handled.

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

Missing items in each COA questionnaire will be handled based on the scoring algorithm for each COA.

Continuous monthly measurements derived based on above approach will be analyzed using generalized linear mixed model without imputation for missing data. For dichotomous endpoints, non-response imputation (NRI) will be used to impute missing monthly measurements.

Missing data in safety data will not be imputed except for partial AE start dates.

10.2.4.1 Missing and Incomplete Dates

Missing or incomplete dates will be listed as reported, except for incomplete start date of an AE or concomitant medication, which will be imputed as follows:

Missing	Imputation	Exception
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	—

10.3 Adaptive Design

Not applicable.

10.4 Statistical Analyses

Below is a summary of the timing and methods for the planned statistical analyses.

10.4.1 Planned Analyses

10.4.1.1 Primary Analysis

The primary hypothesis will be tested once the last subject in the nonopioid-treated cohort has completed the week 24**/ET** assessments **during the DBTP**, and all data for the primary endpoint has been collected. At this time, the DBTP treatment assignment for this cohort will be unblinded to the sponsor. If data collection for all subjects in the opioid-treated cohort for the DBTP is also complete, the DBTP treatment assignment for this cohort will also be unblinded. **Otherwise, the unblinding of treatment assignment for this cohort and the analysis of the DBTP data for opioid-treated cohort will be done in the final analysis.** Study subjects and investigators will remain blinded to original DBTP treatment assignment until study completion. All efficacy analyses and safety analyses will be conducted for the DBTP. However, safety data collected during OLTP before the data cutoff date for the primary analysis will also be summarized.

10.4.1.2 Final Analysis

The final analysis will be performed after all subjects (nonopioid-treated and opioid-treated) have completed the study through the **week 52/EOS** visit.

10.4.2 Methods of Analyses

10.4.2.1 General Considerations

Formal statistical analyses using statistical models and hypothesis testing will be performed for the nonopioid-treated cohort only.

Summary statistics will be computed by treatment group and visit. For continuous endpoints, the following descriptive statistics will be computed: number of observations, means, medians, standard deviations, standard errors, first and third quartiles, minimums and maximums, and 2-sided 95% CIs of the means (CIs will be provided for efficacy endpoints only). For categorical endpoints, the summaries will contain the number and percentage of subjects in each category.

The dichotomous efficacy endpoints will be analyzed using the stratified Cochran-Mantel-Haenszel (CMH) test after the missing data is imputed as nonresponse. Continuous secondary endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data at the monthly level.

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

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

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

Primary and secondary endpoints in erenumab 70 mg versus placebo**:**

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

Patient reported outcome-related secondary endpoints for the non-EU region

7. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)
8. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)
9. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)
10. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)

OR

Patient reported outcome-related secondary endpoints for the EU region

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

10.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary comparison of absence of MOH at month 6 **(week 24)** between each erenumab dosing group and placebo will be analyzed using a stratified CMH test after the missing data are imputed as nonresponse. The proportion of subjects with absence of MOH will be reported for each treatment group. The odds ratio between each erenumab group and placebo, the corresponding 95% CI and p-value will be reported.
Secondary	The continuous secondary endpoints will be analyzed using a linear mixed effects repeated measure model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The LSM change from baseline with the 95% CI for each treatment group, the treatment difference (each erenumab group – placebo) with the 95% CI, and p-value will be reported. The dichotomized secondary endpoint will be analyzed using the same methodology as for the primary endpoint.
Exploratory	The continuous exploratory efficacy endpoints at each assessment time will be analyzed using the repeated measures linear mixed effects model that includes treatment group, baseline values, stratification factor, scheduled visit, and the interaction of treatment and scheduled visit without any imputation for missing data. Dichotomized endpoints will be analyzed using a stratified CMH test with missing data imputed as nonresponse. The difference in LSM (or odds ratios) of treatment groups and placebo with associated 95% CIs and p-values will be reported.

10.4.2.3 Safety Analyses

10.4.2.3.1 Analyses of Primary Safety Endpoint(s)

All safety analyses will be performed for the DBTP and the OLTP separately. For safety endpoints in the DBTP, all randomized subjects who received at least 1 dose of investigational product (ie, SAS) will be analyzed according to the randomized treatment unless a subject has received the incorrect dose during the entire DBTP.

10.4.2.3.2 Adverse Events

Subject incidence or exposure-adjusted subject incidence rates 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 device effects, adverse events leading to withdrawal from investigational product, treatment-related adverse events and significant treatment emergent adverse events will also be provided.

10.4.2.3.3 Laboratory Test Results

Not applicable, laboratory measurements are only to be performed at screening.

10.4.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics over time by treatment group.

10.4.2.3.5 Physical Measurements

Not applicable, physical measurements are only to be performed at baseline and day 1.

10.4.2.3.6 Electrocardiogram

Not applicable; ECG is only to be measured at baseline.

10.4.2.3.7 Antibody Formation

Not applicable.

10.4.2.3.8 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP by treatment group and treatment period.

10.4.2.3.9 Exposure to Other Protocol-required Therapy

Not applicable.

10.4.2.3.10 Exposure to Concomitant Medication

Number and proportion of subjects receiving headache-related medication will be summarized by acute medication category for each treatment group.

10.4.2.4 Other Analyses

Not applicable.

11. References

Bellamy JL, Cady RK, Durham PL. Salivary levels of CGRP and VIP in rhinosinusitis and migraine patients. *Headache*. 2006;46:24-33.

Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population based study. *Headache*. 2008;48:1157-1168.

Chiang CC, Schwedt TJ, Wang SJ, Dodick DW. Treatment of medication-overuse headache: A systematic review. *Cephalalgia*. 2016;36(4):371-86.

Chiapparini L, Grazzi L, Ferraro S, et al. Functional-MRI evaluation of pain processing in chronic migraine with medication overuse. *Neurol Sci*. 2009;30(Suppl 1):S71-4.

De Felice M, Ossipov MH, Wang R, et al Triptan-induced latent sensitization: a possible basis for medication overuse headache. *Ann Neurol*. 2010;67(3):325-337.

Diener HC, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. N*at Rev Neurol*. 2016;12(10):575-583.

Ferraro S, Grazzi L, Mandelli ML, et al. Pain processing in medication overuse headache: a functional magnetic resonance imaging (fMRI) study. *Pain Med*. 2012a;13(2):255-262.

Ferraro S, Grazzi L, Muffatti R, et al. In medication-overuse headache, fMRI shows long-lasting dysfunction in midbrain areas. *Headache*. 2012b;52(10):1520-1534.

Fumal A, Magis D, Schoenen J. [Medication overuse headache]. *Rev Med Liege*. 2006;61(4):217-222.

Gallai V, Sarchielli P, Floridi A, et al. Vasoactive peptide levels in the plasma of young migraine patients with and without aura assessed both interictally and ictally. *Cephalalgia*. 1995;15:384-390.

Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol*. 1990;28:183-187.

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, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. *Ann Neurol*. 1988;23:193-196.

Goadsby PG, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. *N Engl J Med*. 2002;364(4):257-270.

Grazzi L, Chiapparini L, Ferraro S, et al. Chronic migraine with medication overuse pre-post withdrawal of symptomatic medication: clinical results and FMRI correlations. *Headache*. 2010;50(6):998-1004.

Ho TW, Ferrari MD, Dodick DW, et al. Efficacy and tolerability of MK 0974 (telcagepant), a new oral antagonist of calcitonin gene related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo controlled, parallel treatment trial. *Lancet*. 2008a;372:2115-2123.

Ho TW, Mannix LK, Fan X, et al; MK 0974 Protocol 004 study group. Randomized controlled trial of an oral CGRP receptor antagonist, MK 0974, in acute treatment of migraine. *Neurology*. 2008b;70:1304-1312.

Ho TW, Connor KM, Zhang Y, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology*. 2014;83:958-966.

Juhasz G, Zsombok T, Jakab B, Nemeth J, Szolcsanyi J, Bagdy G. Sumatriptan causes parallel decrease in plasma calcitonin gene-related peptide (CGRP) concentration and migraine headache during nitroglycerin induced migraine attack. *Cephalalgia*. 2005;25(3):179-183.

Kristoffersen ES, Lundqvist C. Medication overuse headache: a review *J Pain Research* 2014;7:367-378.

Lai TH, Chou KH, Fuh JL, et al. Gray matter changes related to medication overuse in patients with chronic migraine. *Cephalalgia*. 2016;36(14):1324-1333.

Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. *Cephalalgia*. 2002;22:54-61.

Linde M, Gustavsson A, Stovner LJ, et al. The cost of headache disorders in Europe: the Eurolight project. *Eur J Neurol*. 2012;19(5):703-711.

May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. *Nat Rev Neurol*. 2016;12(8):455-464.

Meng ID, Dodick D, Ossipov MH, Porreca F. Pathophysiology of Medication Overuse headache: insights and hypotheses from preclinical studies. *Cephalalgia*. 2011;31(7):851-860.

Petersen KA, Lassen LH, Birk S, Lesko L, Olesen J. BIBN4096BS antagonizes human alpha-calcitonin gene related peptide-induced headache and extracerebral artery dilatation. *Clin Pharmacol Ther*. 2005;77:202-213.

Raggi A, Schiavolin S, Leonardi M, et al. Chronic migraine with medication overuse: Association between disability and quality of life measures, and impact of disease on patients' lives. *J of Neuro Sci*. 2015;348(1-2):60-66.

Riederer F, Gantenbein AR, Marti M, Luechinger R, Kollias S, Sándor PS. Decrease of Gray Matter Volume in the Midbrain is Associated with Treatment Response in Medication-Overuse Headache: Possible Influence of Orbitofrontal Cortex *J of Neuro Sci*. 2013;33(39):15343-15349.

Riederer F, Marti M, Luechinger R, et al. Grey matter changes associated with medication-overuse headache: correlations with disease related disability and anxiety. *World J Biol Psychiatry*. 2012;13(7):517-525.

Sarchielli P, Pini LA, Zanchin G, et al. Clinical-biochemical correlates of migraine attacks in rizatriptan responders and non-responders. *Cephalalgia*. 2006;3:257-265.

Schwedt TJ, Chong CD. Medication overuse headache: pathophysiological insights from structural and functional brain MRI research. *Headache*. 2017;57(7):1173-1178.

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 SJ, Diener HC, Ashima M, et al. Efficacy of erenumab for the treatment of patients with chronic migraine in presence of medication overuse. Poster 18th International Headache Society Meeting – Vancouver, 7-10 September 2017

12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
AAN	American Academy of Neurology
ACE	angiotensin-converting enzyme
Acute headache medication	**Acute headache medications include:** • **Triptan-based migraine medications** • **Ergotamine-based migraine medications** • **Non-opioid acute headache medications** • **Non-opioid butalbital containing medications** • **Opioid-containing acute headache medications** • **Opioid-containing butalbital containing medications**
Acute **headache** medication day	Any **calendar** day in which an acute headache medication intake is reported.
Acute migraine-specific medication	Acute medication that is considered specific for the treatment of migraine (ie, ergotamine derivatives or triptans)
AHMD	Acute headache medication day
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASC	Allodynia symptom checklist
AST	Aspartate aminotransferase
BDI-II	Beck Depression Inventory - II
BIL	Bilirubin
CBD	**Cannabidiol**
CBT	Cognitive behavioral therapy
CFR	US Code of Federal Regulations
CGRP	Calcitonin gene-related peptide

Abbreviation or Term	Definition/Explanation
CM	Chronic migraine
(per ICHD-3)	**defined as headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache.** **A. Headache (migraine-like or tension-type-like) on ≥ 15 days/month for >3 months, and fulfilling criteria B and C** **B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for Migraine without aura and/or criteria B and C for Migraine with aura** **C. On ≥ 8 days/month for >3 months, fulfilling any of the following:** **1.criteria C and D for Migraine without aura** **2.criteria B and C for Migraine with aura** **3.believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative** **D. Not better accounted for by another ICHD-3 diagnosis**
CM-MOH	Chronic migraine subjects who met thresholds for medication overuse **headache**
CMH	Cochran-Mantel-Haenszel
COA	Clinical outcomes assessment
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DBTP	Double-blind treatment period
DILI	drug induced liver injury
EAS	Efficacy analysis set
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDiary	Electronic diary
EM	Episodic Migraine (ie, < 15 headache days/month)
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
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 (EOT)	defined as the last assessment for the protocol-specified treatment period of the study for an individual subject

Abbreviation or Term	Definition/Explanation
Enrollment	When the investigator decides that the subject has met Part 1 and Part 2 eligibility criteria and follow procedures for subject randomization
ET	Early termination
EU	European Union
FAS	Full analysis set
FSH	follicle stimulating hormone
GAD-7	Generalized Anxiety Disorder 7-item scale
GCP	Good Clinical Practice
Headache day	A headache day is defined as any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as: • A qualified migraine headache or • A qualified nonmigraine headache, which is a headache that lasts ≥ 4 hours and is not a qualified migraine headache or • A headache of any duration for which acute headache treatment is administered
Headache day (moderate to severe)	A qualified headache day that subjects indicate its peak severity as being **of at least** moderate sever**ity**
Headache episode	A headache event that is defined by the date and hour of reported headache onset and headache cessation. A headache day may contain multiple short headache episodes and a single headache episode may last more than a day
HepBcAb	Hepatitis B core antibody
HepBsAg	Hepatitis B surface antigen
HIT-6	Headache Impact Test-6
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
HRU	Health resource utilization
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd Edition
IgG	Immunoglobulin G
IHS	International headache society
INR	International normalized ratio
IPIM	Investigational product instruction manual
IRB/IEC	Institutional Review Board/Independent ethics committee
IRT	**interactive response technology that is linked to a central computer in real time as an interface to collect and process information**
IUD	intrauterine device

Abbreviation or Term	Definition/Explanation
IUS	Intrauterine hormonal-releasing system
LSM	Least squares mean
Medication overuse (per ICHD-3)	> 3 consecutive months of regular medication overuse above the following thresholds: • Triptans, ergotamine, opioids/opioid-containing medication, combination therapies: ≥ 10 days per month • Simple analgesics and NSAIDS only: ≥ 15 days per month of simple analgesics and NSAIDs
Medication overuse (per protocol)	Mean monthly acute **headache** medication days above the following thresholds • Triptans, ergotamine, opioids/opioid-containing medication, combination therapies: ≥ 10 days per study month • Simple analgesics and NSAIDS only: ≥ 15 days per study month of simple analgesics and NSAIDs
MFIQ	Migraine Functional Impact Questionnaire
MHD	Monthly headache days
MIDAS	Migraine Disability Assessment
Migraine day	A migraine day is defined as any calendar day in which the subject experiences a qualified migraine headache (onset, continuation or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura lasting for ≥ 4 hours, and meeting at least 1 of the following criteria (a and/or b): a. ≥ 2 of the following pain features: • Unilateral • Throbbing • Moderate to severe • Exacerbated with exercise/physical activity b. ≥ 1 of the following associated symptoms: • Nausea • vomiting • Phonophobia and photophobia If the subject took a migraine-specific medication (ie, triptan, or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.
Migraine-free day	A migraine-free day is defined as any calendar day in which the subject does not experience any headache pain or any symptoms including aura, nausea, vomiting, phonophobia, and photophobia, and does not take any acute headache medication.
MMD	Monthly migraine days
MO	Medication overuse
MOH	Medication overuse headache

Abbreviation or Term	Definition/Explanation
MOH (ICHD-3 definition)	Headache occurring on 15 or more days per month in a subject with a pre-existing primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medication) for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped. Diagnostic criteria (per ICHD-3): a. Headache occurring on ≥ 15 days per month in a subject with a pre-existing headache disorder b. Regular overuse for > 3 months of 1 or more drugs that can be taken for acute and/or symptomatic treatment of headache c. Not better accounted for by another ICHD-3 diagnosis
MOH (protocol defined)	Mean monthly acute **headache** medication days over 3 consecutive study months at or above ICHD-3 defined thresholds AND mean monthly qualified headache days of any severity ≥ 14 days over the same consecutive study months
MPFID	Migraine Physical Function Impact Diary
MRI	Magnetic resonance imaging
NCT	National Clinical Trials
NSAID	Nonsteroidal anti-inflammatory drug
OLTP	Open-label treatment period
Opioid medication day	Any day in which an opioid/opioid containing medication was administered
PFS	Prefilled syringe
PGIC	Patient's Global Impression of Change
QM	every 4 weeks (ie, 28 days ±4)
Randomization	A subject is randomized to a treatment assignment
SAS	Safety analysis set
SC	Subcutaneous
Source Data	Information from an original record or certified copy of the original record containing subject 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
Study month	**generally 4 weeks**
TBL	total bilirubin
ULN	upper limit of normal

Abbreviation or Term	Definition/Explanation
US	United States

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory, except urine pregnancy testing. **During the Baseline period and through the DBTP, hematology and chemistry testing will be at the discretion of the investigator, as well as** chemistry testing during the OLTP.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the **case report form (**CRF**)**.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.4 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 12-1. Analyte Listing

Central Laboratory: Chemistry[a]	Central Laboratory: Hematology[b]	Other Labs[c]
Sodium Potassium Chloride Bicarbonate Total protein Calcium Adjusted calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Uric acid LDH Cholesterol[d] HDL[d] LDL[d] Triglycerides Total bilirubin	RBC Hemoglobin Hematocrit MCV MCH MCHC RDW Reticulocytes Platelets WBC Differential • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Central Laboratory: Urine drug screening Pharmacogenetic studies (optional) Biomarker development Hep B surface antigen **Total Hep B core antibody** Hep C antibody HIV Local Laboratory: Pregnancy testing-urine

Central Laboratory: Chemistry[a]	Central Laboratory: Hematology[b]	Other Labs[c]
Direct bilirubin		
ALP		
AST (SGOT)		
ALT (SGPT)		
Albumin		

Footnotes defined on next page
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count
[a] During the **Baseline Period, DBTP, and** OLTP, chemistry testing will be at the discretion of the investigator and performed at central laboratories.
[b] **During the Baseline Period and DBTP**, hematology testing will be at the discretion of the investigator and performed at central laboratories
[c] Performed at either central or local laboratories, as noted.
[d] To be tested at screening only.

12.3 Appendix 3. Study Governance Considerations

Independent Review Committee

Not applicable.

Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral patients through existing professional networks or other community sources such as patient advocacy groups. All patient facing materials must be reviewed/approved by the sponsor (Amgen Inc.) and the local IRB/IEC.

Informed Consent Process

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

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

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

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

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

The acquisition of informed consent is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

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

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

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within **60** days from the previous informed consent form signature date.

The informed consent form 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.

Data Protection/Subject Confidentiality

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

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

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

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

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

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

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

Publication Policy

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

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

ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

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

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

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

Data Quality Assurance

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

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

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

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

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

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

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

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

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

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

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

Source Documents

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

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

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

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

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

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

Study and Site Closure

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

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

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

Compensation

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

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

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

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

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

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen medical devices provided for use in the study (see Section 7.1.3 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.

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 case report form (CRF). • 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); • Severity (or toxicity defined below); • Assessment of relatedness to investigational product (erenumab or placebo) or Amgen medical devices (prefilled syringes); and • Action taken. • If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The **Common Terminology Criteria for Adverse Events**, version 4.0**3** 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 and device and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

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

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • 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 12-1) 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 12-1).

Adverse Device Effects: Recording, Evaluating and Reporting

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

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Report 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. Protocol specified hospitalizations are exempt.

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

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

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

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 # 20170703 AIMOVIG (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?				**Outcome of Event** Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
						Erenumab (AMG 334)		Prefilled Syringe			
						No✓	Yes✓	No✓	Yes✓		
				☐ Yes ☐ No							
				☐ Yes ☐ No							
				☐ Yes ☐ No							

Serious Criteria:			
	01 Fatal	**03** Required/prolonged hospitalization	**05** Congenital anomaly / birth defect
	02 Immediately life-threatening	**04** Persistent or significant disability /incapacity	**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 Syringe (PFS)	☒ open label							Lot # _____ ☐ Unknown Serial # _____

AMGEN Study # 20170703 AIMOVIG (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 # 20170703 AIMOVIG (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 –	Title	Date
_____ *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.*		

12.5 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 6.2.

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

Definition of Females of Childbearing Potential

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

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

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

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Female Subjects

Acceptable Methods of Effective Contraception

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device (IUD)

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

Unacceptable Methods of Birth Control for Female Subjects

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

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

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks after the last dose of study drug.
  - Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). 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 poststudy 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 12.4. 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 8.1 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 **the last dose of study drug**, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) 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.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 16 weeks after the last dose of study drug.
- Information will be recorded on the Lactation Notification 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 235.
- 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 the last dose of study drug after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20170703

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 DOB:** mm / dd / yyyy_____

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 LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

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:** _____

Effective Date: March 27, 2011

Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20170703

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 Date of Birth:** mm_____ / dd_____/ yyyy_____

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:** _____

****

Effective Date: 03 April 2012, version 2.

Page 1 of 1

12.6 Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand migraine, the dose response and/or prediction of response to erenumab, characterize antibody response, 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 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 12.3 for subject confidentiality.

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit BIL glucuronidation (eg, indinavir, atazanavir)
- Alpha-1 antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Nonhepatic causes (eg, rhabdomyolysis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> **2**x ULN at any time	> **3**x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate Case Report Form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 12.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, BIL (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL.

The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin G (IgG), anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels
- A more detailed history of:
- Prior and/or concurrent diseases or illness
- Exposure to environmental and/or industrial chemical agents
- Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
- Prior and/or concurrent use of alcohol, recreational drugs and special diets
- Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

12.8 Appendix 8. Substudy: Qualitative Interview Substudy to 'A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache.'

Substudy Background and Rationale

Qualitative interviews enable access to qualitative aspects of experiences of clinical trial participants to supplement the quantitative data collected as part of the study. These interviews enable the capture of data from study subjects to complement the finding from clinical trials. For example, treatment satisfaction can be assessed to understand which aspects of the treatment are valued by patients such as symptom benefit, delivery method, adverse event (AE) tolerability and used to help generate value messages for the product. Interviewing clinical trial participants at the start and end of the double-blind treatment period can also help identify benefits most relevant and meaningful to patients. This can also complement and help interpret the quantitative data collected using clinical outcome assessment (COA) instruments in the clinical trial.

Regulatory agencies are showing increasing interest in understanding patients' experiences of the risk-benefit related to new interventions being tested in clinical trials (FDA, 2017). Qualitative interviews at the start and end of clinical trials help to understand the patient experience of the treatment in the trial setting: their events, viability of proposed dosing regimen, and informal cost/benefit trade-offs.

Research Question and Objective(s) of the Qualitative Interview Substudy

The objective of this substudy is to assess the experience of treatment benefit experienced by subjects in Study 20170703, especially in terms of change in functioning during and in between migraine attacks, resulting from a preventive treatment for migraine.

Substudy Design

Qualitative interviews will be conducted with subjects who opt in to this optional substudy. Interviews will be conducted via entry interviews, conducted within **7** days of the first IP dose, and exit interviews, conducted within **7** days of the week 24 visit or within approximately **14** days of the early termination (ET) visit. **If possible, within 7 days from early termination notification will be targeted.**

Substudy Study Population or Data Resource

The population for this substudy will be comprised of adult subjects with migraine participating in the Amgen clinical trial of erenumab (Study Number 20170703) who opt

in to this optional substudy at selected sites. Subjects will be recruited throughout the study accrual period at approximately five (5) US-based sites participating in the main or parent clinical trial. An additional site participating in the parent clinical trial may be added to the substudy in order to ensure recruitment feasibility. Data sources will include the transcripts of audio-recordings of the telephone interviews. Clinical trial data and data to characterize the sample collected in the clinical trial (Study Number 20170703) will be accessed for the subjects interviewed as part of the current substudy, to characterize the sample.

Summary of Substudy Subject Eligibility Criteria

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

1) Be randomized in Study 20170703 and have successfully received a first dose of investigational product (IP);
2) Have provided supplementary informed consent to participate in the substudy;
3) Be willing and able to participate in two (2) telephone interviews lasting approximately one hour in duration each;
4) Able to read, understand, and speak English sufficiently to participate in the interviews;
5) Be willing and able to be audio-recorded during the interview sessions.

Meeting any of the following criterion will exclude a subject from enrollment into the substudy:

1) Unable to complete entry interview within **seven (7)** days from first IP dose;
2) Unable to complete exit interview within **seven (7)** days prior to week 24 visit or within approximately **14** days post early termination visit;
3) Has any clinically relevant medical or psychiatric condition that, in the opinion of the investigator and/or study coordinator, would interfere with the completion of the substudy activities. This includes but is not limited to language, speech, hearing or cognitive disorders that could impact a subject's ability participate in an interview-based discussion.

Substudy Duration and Substudy Procedures

Subjects are required to participate in two telephone interviews, lasting approximately one-hour each. Entry interviews will be conducted within **seven** (**7**) days from first IP dose; exit interviews will be conducted in close proximity with the week 24 or early termination visits (within **7** days prior to week 24 visit or within approximately **14** days post early termination visit**. If possible, within 7 days from early termination notification will be targeted**).

Subjects enrolled in the clinical trial 20170703 will be approached by clinic staff for recruitment and possible enrollment into this substudy.

At participating sites, **subjects** will be provided an option to opt in to the qualitative interview substudy and be provided with additional information about the substudy **either at time of screening for the main study or after randomization and successful dosing with IP, depending on site preference**. Clinical site staff will explain the substudy objectives and procedures to the subject and obtain a supplementary written informed consent. The subject will sign two copies of the consent form. Sites will send a wet-ink version of the informed consent to Evidera and will retain a copy of the signed informed consent for their study records. Clinic site staff will provide Evidera contact information for each participant enrolled in the substudy and Evidera will subsequently contact each participant to schedule interviews.

The subject must personally sign and date the IRB/IEC approved substudy informed consent before commencement of substudy specific procedures. A subject is considered enrolled in the substudy when the investigator decides that the subject has met the substudy eligibility criteria and subject has signed and dated the substudy informed consent.

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

Patients will take part in a telephone-based entry interview at the start of treatment (no later than **7** days from first IP dose), lasting approximately one-hour. Subjects will be

specifically asked about their experiences with functioning during and in between migraine attacks before receiving the initial study dose.

During the exit interview portion of the substudy, the subjects will take part in a final telephone interview, approximately one-hour in duration (within **7** days prior to week 24 visit or within approximately **14** days post early termination visit**. If possible, within 7 days from early termination notification will be targeted**). Subjects will be specifically asked to compare their experience from the end of the DBTP or early termination visit around changes in functioning during and in between migraine attacks after receiving the preventive treatment for migraine. After open ended questions, if subjects do not mention the impacts they noted at entry interview, the interviewer will probe on those impacts. The interviews will also explore what aspects of improvement or worsening of their migraine (eg, frequency, severity, duration) drove the changes, as well as the 'meaningfulness' of change/no change reported by the patient.

All interviews, both entry and exit, will be conducted using a standardized interview guide to drive the conversation and elicit concepts of interest important to the current study, such as migraine impact, effectiveness of treatment, and day-to-day functioning of the subject.

Variables

Substudy Outcome Variable(s)

Subjects' prospective and qualitative data of changes resulting from treatment received in the double-blind period will be collected via telephone interview. Concepts that emerge from the qualitative interviews in relation to migraine impact, treatment efficacy, and migraine experience will be the outcome. Data will be analyzed by subjects' perception of change, subjects' perception of treatment benefit, and subjects' description of migraine experience using qualitative data analysis software (ie, Atlas.ti). Upon unblinding as outlined in the parent protocol, the clinical trial data may be further used to explore response perceptions.

Exposure Variable(s)

Subjects will be randomized to placebo, erenumab 70 mg subcutaneously (SC) injections every 4 weeks, or erenumab 140 mg SC injections every 4 weeks in the DBTP of study protocol 20170703. Interviewers and subjects will be blinded to the treatment that subjects are/were administered during the DBTP of the parent clinical trial.

Substudy Sample Size

The substudy is based on a convenience sample, aiming to enroll clinical trial subjects willing to opt in to this optional study at study sites where the substudy will be conducted. The substudy sample size was selected to allow a probability of conducting interviews with subjects enrolled on all three treatment arms.

The substudy sample will be a subset of up to 30 subjects who will be recruited from Amgen-identified clinical sites participating in the clinical trial 20170703 across the United States. Best efforts will be made to ensure that the sample includes subjects with diverse demographic characteristics from the pool of trial subjects.

The substudy sample is limited by the clinical trial sample during the timeline for this study.

Substudy Data Analysis

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

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

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

text data to be coded with key concepts codes. The coding dictionary will be iteratively updated with emerging themes and concepts from discussions.

Evidera proposes to conduct longitudinal qualitative research (LQR) analyses (Calman et al, 2013; Saldana, 2003), which is distinguished from a traditional qualitative approach by the fact that the key focus of analysis is on how and why patient experiences/perceptions change over time. This innovative approach will be used to characterize changes in patients' perceptions and experiences over time, particularly in concepts the patients perceive as most important.

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

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

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

Collection of Safety Information and Product Complaints

There will be no substudy specific safety database for collection, recording, and reporting of adverse events reported during the conduct of the substudy. All safety data collection, recording, and reporting will be performed through the parent study and will follow the detailed procedures outlined in study protocol 20170703. Adverse events, serious adverse events or product complaints reported during the conduct of an interview will be reported to Amgen and to investigational sites within 1 business day of awareness.

Definition of Safety Events

Refer to **S**ection 9.2.3.1 of the parent protocol for definition of safety events.

Safety Reporting Requirements

The clinic site Investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) are reported in accordance to Amgen's clinical trial 20170703 protocol. Evidera will report any AEs to the clinic site and Amgen within 1 business day of awareness.

Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) which will be the responsibility of the subject's clinic site in accordance with clinical trial 20170703 protocol.

References

Calman L, Brunton L, Molassiotis A. Developing longitudinal qualitative designs: lessons learned and recommendations for health services research. BMC Med Res Methodol. 2013;13:14.

Food and Drug Administration (FDA). Plan for Issuance of Patient-Focused Drug Development Guidance. 2017. Available at: https://www.fda.gov/downloads/forindustry/userfees/.../ucm563618.pdf.

Friese S, Ringmayr T. ATLAS.ti 7 User Guide and Reference. Berlin: ATLAS.ti Scientific Software Development GmBH; 2013.

Saldana J. Longitudinal Qualitative Research: Analyzing Change Through Time. AltaMira Press, US; 2003.

Amendment 2

Protocol Title: A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache

Amgen Protocol Number (Erenumab) 20170703

EudraCT number 2018-003342-16

NCT number NCT03971071

Amendment Date: 27 May 2020

Rationale:

This protocol is being amended to:

- Update duration of study to approximately 59 weeks
- Schedule of Activities
    - Clarify the baseline period as 4 weeks before day 1
    - Clarify the information collected and process will be done by interactive response technology (IRT)
    - Clarify the clinical outcome assessment or patient reported outcomes for HIT-6, MFIQ, and ASC 12 will be done post-randomization on day 1 in the clinic
    - Clarify the substudy informed consent can also be obtained at the same time as the main study informed consent during screening instead of after randomization
    - Clarify the entry interview will be conducted within 7 days from first dose of investigational product and the exit interview will be conducted within 7 days prior to week 24 visit or within approximately 14 days post early termination visit
- Clarify key exclusion criteria
    - Update changes in drug regimen (ie, changes in dose or frequency of use) of an allowed migraine preventive medication within 2 months from screening

  - Removed criterion for subjects with body mass index > 40 kg/m^2 assessed at screening
  - Clarify if subject has known hypersensitivity to any of the components to be administered during dosing will be excluded from the study
  - Update the subjects taking short-acting opioid or opioid-containing analgesic for any indication as exclusion criteria

- Clarify that the blinding will be continued in both double-blind and open-label treatment period
- Update the exploratory objectives and endpoints of both double-blind and open-label treatment periods

Other Changes:

- Updated primary completion and end of study definitions
- Updated the lifestyle restrictions to be followed to participate in the study
- Medical history and the prior therapies were deleted from the list of minimal set of screen failure information collected
- Updated Excluded Treatments, Medical Devices, and/or Procedures During Study Period
- Updated method of collection of information for prior treatment and concomitant treatment
- Updated time period and frequency for collecting and reporting safety event information
- Updated reasons for removal from study
- Updated list of abbreviations and definitions of terms
- Included cardiac risk factor case report form (CRF) to collect the medical history information
- Updated time points to activate the baseline period BDI-II on the eDiary
- Updated time points of additional pregnancy testing and collection of information regarding pregnancies and lactation during the study

Description of Changes

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Global

Change: Updated protocol date from 19 April 2019 to **27 May 2020**.

Section: Global

Change: Revised "months" to "study months" when referring to the timing of the study.

Section: Title page

Replace:

NCT Number:	Unavailable for first version

With:

NCT Number:	**NCT03971071**

Section: Title page

Add:

Protocol Date:	Document Version	Date
	Original	20 September 2018
	Amendment 1 (v2.0)	19 April 2019
	Amendment 2 (v3.0)	**27 May 2020**

Section: 1, Protocol Synopsis, Objective(s)/Endpoint(s), Primary

Replace:

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared with placebo on achieving MOH remission during the double-blind treatment period (DBTP)	• Absence of MOH at month 6 as defined by mean monthly treatment acute headache medication days (AHMD) < 10 days over months 4, 5, and 6 OR mean

Objectives	Endpoints
	monthly headache days (MHD) < 14 days over months 4, 5, and 6 of the DBTP where AHMD include any eDiary day in which an acute headache medication intake is reported

With:

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared with placebo on achieving MOH remission during the double-blind treatment period (DBTP)	• Absence of MOH at month 6 as defined by mean monthly acute headache medication days (AHMD) < 10 days over months 4, 5, and 6 **(week 13 through 24)** OR mean monthly headache days (MHD) < 14 days over months 4, 5, and 6 **(week 13 through 24)** of the DBTP where AHMD include any eDiary day in which an acute headache medication intake is reported

Section: 1, Protocol Synopsis, Objective(s)/Endpoint(s), Primary Estimand and Secondary

Add:

Objectives	Endpoints
Primary Estimand	
The estimand for the primary efficacy endpoint consists of: • The target population, which includes subjects diagnosed with CM and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month • The endpoint, which is the absence of MOH at month 6 as defined by mean monthly AHMD < 10 days over months 4, 5, and 6 **(week 13 through 24)** OR mean MHD < 14 days over months 4, 5, and 6 **(week 13 through 24)** of the DBTP • The intercurrent event, **which is** adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of investigational product (IP), regardless of adherence to treatment. • The summary measure, which is the odds ratio of absence of MOH between each erenumab dose group (ie, 70 mg or 140 mg) and the placebo group	
Secondary	
• To evaluate the effect of erenumab compared with placebo in reducing acute headache	• Change from baseline in mean monthly AHMD over months 4, 5, and 6 **(week 13 through 24)** of the DBTP

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

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

Section: 1, Protocol Synopsis, Objective(s)/Endpoint(s), Safety

Replace:

Objectives	Endpoints
Safety	
• To evaluate the safety and tolerability of erenumab in subjects with CM-MOH	• Adverse events • Clinical laboratory values and vital signs

With:

Objectives	Endpoints
Safety	
• To evaluate the safety and tolerability of erenumab in subjects with CM-MOH	• Adverse events • **V**ital signs

Section: 1, Protocol Synopsis, Hypothesis

Add:

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

Section: 1, Protocol Synopsis, Procedures, paragraph 1

Delete:

After signing informed consent, subjects will enter an up to 7-week screening period**,** which is composed of an initial screening period up to 3 weeks ~~(21 days)~~ followed by a 4-week ~~(28-day)~~ baseline period. Subjects will be randomized/enrolled into the 24-week DBTP and will begin to receive double-blind investigational product SC every 4 weeks. Subjects who successfully complete the DBTP will have the opportunity to enter a 28-week OLTP. Subjects will use an electronic diary (eDiary) everyday throughout the baseline period, DBTP, and during the last quarter of the OLTP (defined as starting at the week 40 visit through week 52/End of Study [EOS]) to report information about their migraine and nonmigraine headaches, other migraine-related symptoms, and acute headache medication use. Subjects will have scheduled in-clinic study visits throughout the study.

Section: 1, Protocol Synopsis, Statistical Considerations, paragraph 5,6, 7,8

Replace:

The primary analysis will be performed when the last subject in the nonopioid-treated cohort completes the week 24 assessments or discontinues the DBTP. The final analysis for the study will be performed after all subjects (nonopioid-treated and opioid-treated cohorts) complete the study through the OLTP last visit or discontinue from the study.

Formal statistical analyses using statistical models and hypothesis testing will be performed for the nonopioid-treated cohort only.

For the primary and other dichotomous efficacy endpoints, a stratified Cochran-Mantel-Haenszel test will be used after the missing data is imputed as nonresponse. Continuous secondary endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The mean change from baseline for each treatment group, the treatment difference, 95% CI, and p-value will be reported.

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

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

6. Absence of MOH at month 6 of the DBTP (140 mg)
7. Change from baseline in mean monthly AHMD over months 4, 5, and 6 of the DBTP (140 mg)
8. Sustained MOH remission during DBTP (140 mg)

Primary and secondary endpoints in erenumab 70 mg versus placebo**:**

9. Absence of MOH at month 6 of the DBTP (70 mg)
10. Change from baseline in mean monthly AHMD over months 4, 5, and 6 of the DBTP (70 mg)

Sustained MOH remission during DBTP (70 mg)Patient-reported outcome-related secondary endpoints for the non-European Union (EU) region:

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

OR

Patient-reported outcome-related secondary endpoints for the EU region**:**

7. Change from baseline in mean HIT-6 score over months 4, 5, and 6 of the DBTP (140 mg)
8. Change from baseline in mean HIT-6 score over months 4, 5, and 6 of the DBTP (70 mg)

For a full description of statistical analysis methods, please refer to Section 10.

With:

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

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

Primary and secondary endpoints in erenumab 70 mg versus placebo**:**

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

Patient-reported outcome-related secondary endpoints for the non-European Union (EU) region:

21. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)
22. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)
23. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)
24. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)

OR

Patient-reported outcome-related secondary endpoints for the EU region**:**

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

For a full description of statistical analysis methods, please refer to Section 10.

Section: 2.2, Schedule of Activities, Table 2-1. Schedule of Activities - Study Visits Through Double-blind Treatment Period, header rows

Delete:

	Screening Period		Treatment Period							
	Initial Screening Period	Baseline Period	Double-blind Treatment Period (24 Weeks)							
PROCEDURE	(up to 3 weeks before Baseline)	(~~up to~~ 4 weeks before Day 1)	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET[a]	Notes

Section: 2.2, Schedule of Activities, Table 2-1. Schedule of Activities - Study Visits Through Double-blind Treatment Period, table rows

Replace:

IVRS/IWRS call	X		X	X	X	X	X	X	X	
CLINICAL OUTCOME ASSESSMENTS/PATIENT-REPORTED OUTCOMES										
HIT-6			X	X	X	X	X	X	X	eDiary in clinic
MFIQ			X	X	X	X	X	X	X	eDiary in clinic
ASC-12			X			X			X	eDiary in clinic

With:

IRT call	X		X	X	X	X	X	X	X	
CLINICAL OUTCOME ASSESSMENTS/PATIENT-REPORTED OUTCOMES										
HIT-6			X	X	X	X	X	X	X	**Post-randomization on Day 1;** eDiary in clinic
MFIQ			X	X	X	X	X	X	X	**Post-randomization on Day 1;** eDiary in clinic
ASC-12			X			X			X	**Post-randomization on Day 1;** eDiary in clinic

Section: 2.2, Schedule of Activities, Table 2-1. Schedule of Activities - Study Visits Through Double-blind Treatment Period, table rows

Replace:

	Screening Period		Treatment Period							
	Initial Screening Period	Baseline Period	Double-blind Treatment Period (24 Weeks)							
PROCEDURE	(up to 3 weeks before Baseline)	(up to 4 weeks before Day 1)	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET[a]	Notes
MIDAS			X			X			X	Post-randomization on Day 1; in clinic
BDI-II[f]	X	X				X			X	eDiary; in clinic
GAD-7			X			X			X	Post-randomization on Day 1; in clinic
Sleep Questionnaire			X			X			X	Post-randomization on Day 1; in clinic
PGIC									X	In clinic

With:

	Screening Period		Treatment Period							
	Initial Screening Period	Baseline Period[a]	Double-blind Treatment Period (24 Weeks)							
PROCEDURE	(up to 3 weeks before Baseline)	(4 weeks before Day 1)	Day 1[b]	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET[c]	Notes
MIDAS			X			X			X	Post-randomization on Day 1; **eDiary** in clinic
BDI-II[h]	X	X[i]				X			X	eDiary; in clinic
GAD-7			X			X			X	Post-randomization on Day 1; **eDiary** in clinic
Sleep Questionnaire			X			X			X	Post-randomization on Day 1; **eDiary** in clinic
PGIC									X	**eDiary i**n clinic

Section: 2.2, Schedule of Activities, Table 2-1. Schedule of Activities - Study Visits Through Double-blind Treatment Period, Table abbreviations footnote "c"

Replace:

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ASC-12 = Allodynia Symptoms Checklist-12; BDI-II = Beck Depression Inventory-II; BP = blood pressure; DBTP = double-blind treatment period; eDiary = electronic diary; ET = early termination; GAD-7 = Generalized Anxiety Disorder 7-item Scale; HIT-6 = Headache Impact Test-6; HIV = human immunodeficiency virus; HR = heart rate; HRU = Health Resource Utilization; IVRS/IWRS = Interactive Voice Response System/Interactive Web Response System; MFIQ = Migraine Functional Impact Questionnaire; MIDAS = Migraine Disability Assessment; MPFID = Migraine Physical Function Impact Diary; OLTP = open-label treatment period; PGIC = Patient Global Impression of Change; RR = respiratory rate

[a] A subject who discontinues the study during the DBTP will complete the assessments of the week 24/ ET visit approximately 28 (+3) days after the last dose of investigational product.
[b] Including pre-filled syringe in DBTP and autoinjector during OLTP.
[c] All clinical laboratory testing at screening (except pregnancy testing) will be performed at a central laboratory. Thereafter, only ALP, AST, and ALT will be performed routinely at a central laboratory.
[d] Additional on-treatment local laboratory pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
[e] For subjects who provided informed consent for the pharmacogenetic studies, DNA will be obtained from residual cells from the biomarker blood sample. Therefore, additional sampling is not required.
[f] The BDI-II will be collected via paper CRF during screening and eDiary thereafter.
[g] The baseline HRU questionnaire will have a 24-week recall of prior utilization. The HRU questionnaire assessed at the ET visit before week 24 should only include HRU recalled since the previous assessment to avoid collecting duplicate information. For example, the 24-week HRU questionnaire assessed at week 20 as the ET visit should only include HRU recalled since the previous assessment at day 1 (ie, 20-week recall).

With:

ASC-12 = Allodynia Symptoms Checklist-12; BDI-II = Beck Depression Inventory-II; BP = blood pressure; DBTP = double-blind treatment period; eDiary = electronic diary; ET = early termination; GAD-7 = Generalized Anxiety Disorder 7-item Scale; HIT-6 = Headache Impact Test-6; HIV = human immunodeficiency virus; HR = heart rate; HRU = Health Resource Utilization; **IRT = Interactive Response Technology**; MFIQ = Migraine Functional Impact Questionnaire; MIDAS = Migraine Disability Assessment; MPFID = Migraine Physical Function Impact Diary; OLTP = open-label treatment period; PGIC = Patient Global Impression of Change; RR = respiratory rate

[a] The baseline period ends when either a subject is screen failed or randomized into the study. Randomization occurs at the Day 1 visit which must occur between 29 to 35 days after baseline entry (inclusive of the first day that eDiary device is assigned to subject).
[b] On Day 1, all study assessments should be completed prior to subject's first dose of investigational product.
[c] A subject who discontinues the study during the DBTP will complete the assessments of the week 24/ ET visit approximately 28 (+3) days after the last dose of investigational product.
[d] Including pre-filled syringe in DBTP and autoinjector during OLTP.
[e] All clinical laboratory testing at screening (except pregnancy testing) will be performed at a central laboratory.
[f] Additional on-treatment local laboratory pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
[g] For subjects who provided informed consent for the pharmacogenetic studies, DNA will be obtained from residual cells from the biomarker blood sample. Therefore, additional sampling is not required.
[h] The BDI-II will be collected via paper CRF during screening and eDiary thereafter.
[i] The Baseline Period BDI-II will be completed at the end of the Baseline Period using the eDiary, after at least 28 days of data has been entered in the eDiary.
[j] The baseline HRU questionnaire will have a 24-week recall of prior utilization. The HRU questionnaire assessed at the ET visit before week 24 should only include HRU recalled since the previous assessment to avoid collecting duplicate information. For example, the 24-week HRU questionnaire assessed at week 20 as the ET visit should only include HRU recalled since the previous assessment at day 1 (ie, 20-week recall).

Section: 2.2, Schedule of Activities, Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period, General and Safety Assessments, table rows

Replace:

IVRS/IWRS call[b]	X	X			X			X	

With:

IRT call[b]	X	X			X			X	

Section: 2.2, Schedule of Activities, Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period

Replace:

	Treatment Period								
	Open-label Treatment Period (28 Weeks)								
PROCEDURE	Wk 24 (OLTP Entry Visit)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ EOS[a]	Notes
LABORATORY ASSESSMENTS									
Urine pregnancy test (females of childbearing potential only)[d]	X	X	X	X	X	X	X	X	
Urine drug test	X (to be performed at the discretion of the investigator)								

With:

	Treatment Period								
	Open-label Treatment Period (28 Weeks)								
PROCEDURE	Wk 24 (OLTP Entry Visit)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ EOS[a]	Notes
LABORATORY ASSESSMENTS									
Urine pregnancy test (females of childbearing potential only)[d]	X	X			X			X	
Urine drug test	X (to be performed at the discretion of the investigator)								

Section: 2.2, Schedule of Activities, Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period,rows

Replace:

CLINICAL OUTCOME ASSESSMENTS/PATIENT-REPORTED OUTCOMES									
Site re-assigns eDiary to subject					X				
eDiary					X (Daily)				Daily during assessment months
Subject brings eDiary to center for use during visit or to return								X	Sites should retain eDiary at EOS visit
MPFID					X (Daily)				Daily during assessment months

With:

CLINICAL OUTCOME ASSESSMENTS/PATIENT-REPORTED OUTCOMES									
Site re-assigns eDiary to subject					X				
eDiary					X (Daily)				Daily during assessment **study** months
Subject brings eDiary to center for use during visit or to return								X	Sites should retain eDiary at EOS visit
MPFID					X (Daily)				Daily during assessment **study** months

Section: 2.2, Schedule of Activities, Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period

Replace:

	Treatment Period							
	Open-label Treatment Period (28 Weeks)							
PROCEDURE	Wk 24 (OLTP Entry Visit)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ EOS[a]	Notes
HIT-6								X	In clinic
MFIQ								X	In clinic
MIDAS								X	In clinic

With:

	Treatment Period							
	Open-label Treatment Period (28 Weeks)							
PROCEDURE	Wk 24 (OLTP Entry Visit)	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ EOS[a]	Notes
HIT-6								X	**eDiary** in clinic
MFIQ								X	**eDiary** in clinic
MIDAS								X	**eDiary** in clinic

Section: 2.2, Schedule of Activities, Table 2-2. Schedule of Activities - Study Visits Through Open-label Treatment Period

Replace:

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; DBTP = double-blind treatment period; eDiary = electronic diary; EOS = end of study; ET = early termination; HIT-6 = Headache Impact Test-6; HR = heart rate; IVRS/IWRS = Interactive Voice Response System/Interactive Web Response System; MFIQ = Migraine Functional Impact Questionnaire; MIDAS = Migraine Disability Assessment; MPFID = Migraine Physical Function Impact Diary; OLTP = open-label treatment period; RR = respiratory rate

[a] A subject who discontinues investigational product during the OLTP or who completes the study will perform the week 52/EOS visit assessments. Subjects who early terminate will complete the assessments approximately 28 (+3) days after the last dose of investigational product.

[b] All subjects will be enrolled via IVRS/IWRS in the OLTP to maintain the initial treatment blinding in DBTP. Subjects who received active treatment during the DBTP will remain on the same dose. Subjects who received placebo will receive either 70 mg or 140 mg in a 1:1 ratio.

[c] Including pre-filled syringe in DBTP and autoinjector during OLTP.

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

[e] Study drug supply ceases at week 48.

With:

BP = blood pressure; DBTP = double-blind treatment period; eDiary = electronic diary; EOS = end of study; ET = early termination; HIT-6 = Headache Impact Test-6; HR = heart rate; **IRT =** Interactive Response **Technology**; MFIQ = Migraine Functional Impact Questionnaire; MIDAS = Migraine Disability Assessment; MPFID = Migraine Physical Function Impact Diary; OLTP = open-label treatment period; RR = respiratory rate

[a] A subject who discontinues investigational product during the OLTP or who completes the study will perform the week 52/EOS visit assessments. Subjects who early terminate will complete the assessments approximately 28 (+3) days after the last dose of investigational product.

[b] All subjects will be enrolled via **IRT** in the OLTP to maintain the initial treatment blinding in DBTP. Subjects who received active treatment during the DBTP will remain on the same dose. Subjects who received placebo will receive either 70 mg or 140 mg in a 1:1 ratio.

[c] Including pre-filled syringe in DBTP and autoinjector during OLTP.

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

[e] Study drug supply ceases at week 48.

Section: 2.2, Schedule of Activities, Table 2-3. Schedule of Activities – Optional Interview-based Substudy (Selected US Sites Only), header rows

Delete:

			Treatment Period							
	Screening Period	Baseline Period	Double-blind Treatment Period (24 Weeks)							
PROCEDURE	(up to 3 weeks before Baseline)	(~~up to~~ 4 weeks before Day 1) ~~Day 1 (pre rand)~~	Day 1 (post-rand)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET	Notes

Section: 2.2, Schedule of Activities, Table 2-3. Schedule of Activities – Optional Interview-based Substudy (Selected US Sites Only)

Replace:

INTERVIEW-BASED SUBSTUDY										
Interview[a]			X[c]						X[d]	

With:

INTERVIEW-BASED SUBSTUDY										
Interview[b]			X[c]						X[d]	

Section: 2.2, Schedule of Activities, Table 2-3. Schedule of Activities – Optional Interview-based Substudy (Selected US Sites Only), footnotes

Replace:

[a] The first interview (Interview 1) will be conducted within the first week after randomization, the second interview (Interview 2) will be conducted within 1 week after the subject's last visit during the DBTP.

With:

[a] **The Substudy subject informed consent can also be obtained at the same time as the main study informed consent during Screening instead of after randomization.**
[b] The first interview (Interview 1) will be conducted within the first week after randomization, the second interview (Interview 2) will be conducted within 1 week after the subject's last visit during the DBTP.
[c] **The entry interview will be conducted within 7 days from first investigational product dose.**
[d] **The exit interview will be conducted in close proximity with the week 24 or early termination visits (within 7 days prior to week 24 visit or within approximately 14 days post early termination visit. If possible within 7 days post early termination will be targeted).**

Section: 3.1 Study Rationale, Paragraph 2

Add:

In Study 20120295, erenumab 70 mg and 140 mg subcutaneously (SC) every 4 weeks were superior to placebo in reducing monthly migraine days (MMD) from baseline to the last **study** month of the double-blind treatment period (DBTP) in subjects with chronic migraine (CM) with or without medication overuse status at baseline. In a prespecified subgroup analysis including subjects with CM with medication overuse (CM-MO subjects), both doses of erenumab achieved numerical and nominal superiority to placebo in reducing MMD (least-squares mean [LSM]: -3.1 days for both 70 mg and 140 mg versus placebo, $p < 0.001$), achieving $\geq 50\%$ reduction in MMD at month 3 (odds ratio: 2.67 and 2.51 for 70 mg and 140 mg, respectively; p = -0.004 and 0.007, respectively) and acute headache medication days (AHMD) (LSM: -3.3 and -2.8 for 70 mg and 140 mg, respectively; $p < 0.001$) (Tepper et al, 2017). A subsequent post hoc subgroup analysis including CM-MO subjects who had failed 1 or more migraine preventive treatment further confirmed this observation with numerically superior reductions for both erenumab doses as compared with placebo in MMD (LSM: 2.54 and 4.44 for 70 mg and 140 mg, respectively), moderate to severe headache days (LSM: 1.81 and 3.82 for 70 mg and 140 mg, respectively) and AHMD (LSM: 2.61 and 4.26 for 70 mg and 140 mg, respectively). In addition, more subjects treated with erenumab (47% and 52% in 70 mg and 140 mg, respectively) met medication overuse-free status at the end of DBTP as compared with placebo (29%).

Section: 3.3, Benefit/Risk Assessment

Replace:

The overall benefit-risk evaluation for erenumab is favorable for the treatment of patients with CM-MOH.

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

3.3.1 Therapeutic Context

Based on the American Academy of Neurology (AAN) "Classification of Evidence Matrix for Therapeutic Questions", none of the existing therapeutic options is currently classified as a class I intervention (ie, "highly likely to be effective") for reducing monthly headache days (MHD), moderate to severe headache days, MMD, or migraine-related disability in patients with MOH.

A summary of current standard of care options and their evidentiary basis is presented in Table 3-1 (Chiang et al, 2016).

Table 3-1. Conclusions and Recommendations for the Treatment of Medication Overuse Headache

Therapeutic Option	Recommendation	AAN Classification of Evidence Matrix for Therapeutic Questions
Early discontinuation (ie, washout) without preventive medication	Possibly effective in reducing headache frequency and acute medication consumption	Class III studies
	Possibly effective in reducing headache frequency and acute medication consumption, improving MIDAS score, quality of life, anxiety and depression up to at least 1 year after discontinuation	Class III studies
Preventive medication without mandatory early discontinuation	Likely that onabotulinumtoxinA is effective in reducing headache days, migraine days, moderate/severe headache days, cumulative hours on headache days, headache episodes, migraine episodes, migraine-related disability (HIT-6), and triptan intake in subjects with CM-MOH	Class II studies
	Likely that topiramate is effective in reducing mean number of monthly migraine days and possible that topiramate is effective in reducing acute medication consumption in CM-MOH	Class II and III studies, respectively
	Likely that nabilone is effective in reducing acute medication consumption, headache severity and improving quality of life	Single Class II study
	Possible that acupuncture is effective in reducing acute medication consumption and headache-related disability	Single Class II study

	Insufficient evidence to support or refute effectiveness of valproic acid, pregabalin, occipital nerve stimulation, occipital nerve block in any measurement of efficacy in MOH	Class III, IV studies

AAN = American Academy of Neurology; CM = chronic migraine; HIT-6 = Headache Impact Test-6; MIDAS = migraine disability assessment; MOH = medication overuse headache.

3.3.2 Key Benefits

Erenumab 70 mg and 140 mg SC QM are approved in Europe, US, and other regions worldwide for the prevention of migraine in adults.

Based on subgroup analyses performed in subjects with CM-MO who participated in Study 20120295, erenumab 70 mg and 140 mg were numerically and nominally superior to placebo in reducing MMD, moderate to severe headache days, AHMD, and reverting medication overuse status at week 12.

3.3.3 Key Risks

The most common adverse reactions in the migraine studies were injection site reactions and constipation. Table 3-2 summarizes all adverse reactions that occurred in Aimovig-treated subjects during the 12-week placebo-controlled period of the pooled trials. Most adverse reactions were mild or moderate in severity.

Table 3-2. Adverse Reactions With Aimovig

System Organ Class	Adverse Reaction Preferred Term	Frequency Category	Overall subject incidence at 70 mg (N = 893) n (%)	Overall subject incidence at 140 mg (N = 507) n (%)	Nature/ Severity/ Seriousness
General disorders and administration site conditions	Injection site reactions[a]	Common	50 (5.6) [a]	23 (4.5)[a]	
Gastrointestinal disorders	Constipation	Common	12 (1.3)	16 (3.2)	
Musculoskeletal and connective tissue disorders	Muscle spasm	Common	1 (0.1)	10 (2.0)	One grade 3 (0.2%) event was reported; all others were grade 1 or 2[b]

Skin and subcutaneous tissue disorders	Pruritus[c]	Common	6 (0.7) [c]	9 (1.8)[c]	

Note: Frequency is provided by the Council for International Organizations of Medical Sciences category (eg, Very Common [≥ 10%], Common [≥ 1% and < 10%], uncommon [≥ 0.1% and < 1%], rare [≥ 0.01% and < 0.1%], very rare [< 0.01%]).
[a] Injection Site Reactions includes multiple preferred terms, such as injection site pain and injection site erythema.
[b] Severity grades are based on the Common Terminology Criteria for Adverse Events (CTCAE): grade 1, mild; grade 2, moderate; grade 3, severe or medically significant; grade 4, life-threatening consequences; grade 5, death.
[c] Pruritus includes preferred terms of generalized pruritus, pruritus, and pruritic rash.

In placebo-controlled clinical studies, 1.3% of subjects treated with erenumab discontinued double-blind treatment because of adverse events. The most frequent injection site reactions were injection site pain, injection site erythema, and injection site pruritus.

Key risks of treatment in MOH are expected to be similar to those of treatment in migraine.

3.3.3.1 Risks Not Established in Special Populations

The safety of erenumab has not been established in migraine subjects with major cardiovascular disease (myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months prior to screening), in the long-term use of erenumab, in elderly subjects > 65 years of age, in a pediatric population < 18 years of age, or during pregnancy and breastfeeding.

With:

The identified risks for AMG 334 are documented in Appendix A of the currently approved IB (Edition 11: February 2020). A limited number of adverse drug reactions (injection site reactions, constipation, muscle spasm, and pruritis) have been identified at low frequencies (< 5%) in clinical trials. In post-marketing settings, hypersensitivity reactions (including rash, angioedema and anaphylactoid reactions) and constipation with serious complications have been reported. Available safety data for the clinical trials with AMG 334 are summarized in Section 6.3 of the AMG 334 Investigator's Brochure, Annex 2.

Section: 4.1, Objectives and Endpoint

Delete:

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared with placebo on achieving	• Absence of MOH at month 6 as defined by mean monthly ~~treatment~~ acute headache medication days

Objectives	Endpoints
MOH remission during the double-blind treatment period (DBTP)	(AHMD) < 10 days over months 4, 5, and 6 OR mean monthly headache days (MHD) < 14 days over months 4, 5, and 6 of the DBTP where AHMD include any eDiary day in which an acute headache medication intake is reported

Section: 4.1, Objectives and Endpoint, Primary Estimand and Secondary

Add:

Objectives	**Endpoints**
Primary	
• To evaluate the effect of erenumab compared with placebo on achieving MOH remission during the double-blind treatment period (DBTP)	• Absence of MOH at month 6 as defined by mean monthly acute headache medication days (AHMD) < 10 days over months 4, 5, and 6 **(week 12 through 24)** OR mean monthly headache days (MHD) < 14 days over months 4, 5, and 6 **(week 12 through 24)** of the DBTP where AHMD include any eDiary day in which an acute headache medication intake is reported
Primary Estimand	
The estimand for the primary efficacy endpoint consists of: • The target population, which includes subjects diagnosed with CM and MOH who have a history of at least 1 preventive treatment failure and do not use opioid medication for more than 4 days per month • The endpoint, which is the absence of MOH at month 6 as defined by mean monthly AHMD < 10 days over months 4, 5, and 6 **(week 13 through 24)** OR mean MHD < 14 days over months 4, 5, and 6 **(week 13 through 24)**of the DBTP • The intercurrent event, **which is** adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects in the target population who receive at least 1 dose of investigational product (IP), regardless of adherence to treatment. • The summary measure, which is the odds ratio of absence of MOH between each erenumab dose group (ie, 70 mg or 140 mg) and the placebo group	

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

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

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

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

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

Objectives	Endpoints
	• Occurrence of at least 1 headache-related outpatient urgent care visit during the DBTP • Occurrence of at least 1 headache-related outpatient clinic visit during the DBTP
• To explore the effect of erenumab compared with placebo on the change from baseline in depression and anxiety symptoms	• Change from baseline in Generalized Anxiety Disorder 7-item scale (GAD-7) score at assessment time points • Change from baseline in Beck Depression Inventory-II (BDI-II) score at assessment time points
• To explore the effect of erenumab compared with placebo on the change from baseline in measures of sleep quality	• Change from baseline in each of the sleep questionnaire domain scores at assessment time points
• To explore the effect of erenumab compared with placebo on the subject's assessment of the change in clinical status since the start of treatment	• Change in clinical status as measured by the Patient's Global Impression of Change (PGIC) as assessed by the subject at month 6 of the DBTP
• To explore the effect of erenumab compared to placebo on the change from baseline in allodynia symptoms	• Change from baseline in Allodynia Symptoms Checklist-12 (ASC-12) score at assessment time points
Exploratory (Open-label treatment period)	
• To explore the rate of MOH relapse in the end of **open-label treatment period (**OLTP**)**	• MOH relapse at year 1, defined as both mean monthly AHMD ≥ 10 days over months 11, 12, and 13 **(week 41 through 52)** AND mean MHD ≥ 14 days over months 11, 12, and 13 **(week 41 through 52)** in subjects who achieved MOH remission at month 6 of the DBTP **Note: This endpoint will be analyzed among subjects who were treated with erenumab throughout the entire study**
• To explore absence of MOH at end of OLTP	• Absence of MOH at end of study as defined by mean monthly AHMD < 10 days over months 11, 12, and 13 **(week 41 through 52)** OR mean MHD < 14 days over months 11, 12, and 13 **(week 41 through 52)**
• To explore sustainability of MOH remission during OLTP	• Sustained absence of MOH over 1 year as defined by absence of MOH over the DBTP (months 1,

Objectives	Endpoints
	2, and 3 **[week 1 through 12]**, OR months 4, 5, and 6 **[week 13 through 24]**) AND OLTP (months 11, 12, and 13 **[week 41 through 52]**). **Note:** "Absence of MOH" is achieved when mean monthly AHMD < 10 days OR mean MHD < 14 days over the respective 3-month period **This endpoint will be analyzed among subjects who were treated with erenumab throughout the entire study**
• To explore change in AHMD, MMD, **and** MHD **of at least moderate pain intensity**	• Change from baseline in mean AHMD, MMD and **MHD of at least moderate pain intensity** at assessment time points • Change from week 24 (OLTP baseline) in mean AHMD, MMD, and MHD **of at least moderate pain intensity** at assessment time points during OLTP
• To explore everyday activities as measured by the MPFID	• Change from baseline in monthly average impact on everyday activities score as measured by the MPFID at assessment time points • Change from week 24 (OLTP baseline) in monthly average impact on everyday activities score as measured by the MPFID at assessment time points during OLTP
• To explore physical impairment as measured by the MPFID	• Change from baseline in monthly average physical impairment score as measured by the MPFID at assessment time points • Change from week 24 (OLTP baseline) in monthly average physical impairment score as measured by the MPFID at assessment time points during OLTP
• To explore the daily activity impact of headache as measured by the HIT-6	• Change from baseline in HIT-6 total score at week 52 • Change from week 24 (OLTP baseline) in HIT-6 total score at week 52

Objectives	Endpoints
• To explore migraine-related disability metrics as measured by MFIQ	• Change from baseline in MFIQ domain scores and overall impact on usual activities global item score at week 52 • Change from week 24 (OLTP baseline) in MFIQ domain scores and overall impact on usual activities global item score at week 52
• To explore migraine-related disability and productivity as measured by the MIDAS Questionnaire	• Change from baseline in MIDAS total score, absenteeism score and presenteeism score at week 52 • Change from week 24 (OLTP baseline) in MIDAS total score, absenteeism score, and presenteeism score at week 52
Exploratory (Opioid-treated Cohort Only)[a]	
• To explore the effect of erenumab compared with placebo in reducing consumption of opioids in subjects stratified to the opioid-treated cohort during DBTP	• Change from baseline in monthly opioid/opioid-containing medication days at assessment time points during DBTP • **Change from baseline in mean monthly opioid/opioid-containing medication days over months 4, 5, and 6 (week 13 through 24) of the DBTP**
• To explore the effect of erenumab compared with placebo in reducing consumption of opioids in subjects stratified to the opioid-treated cohort during OLTP	• Change from baseline in monthly opioid/opioid-containing medication days at assessment time points during OLTP

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

Section: 4.2 Hypotheses

Add:

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

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

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

Section: 5.2.2,Number of Sites

Add:

Approximately 80 investigative sites in 12 countries are expected to participate in Study 20170703. Additional sites and/or countries within North America, Europe, or Asia Pacific may be added as deemed necessary by the study management team.

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

Section: 5.3.1, End of Study Definition, Primary Completion, paragraph 2 (new)

Add:

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

Section: 5.3.2, Study Duration for Subjects, paragraph 1

Replace:

The total study duration for subjects who successfully complete the study will be up to 59 weeks. Total study duration includes:

With:

The total study duration for subjects who successfully complete the study will be **approximately** 59 weeks. Total study duration includes:

Section: 6.2, Exclusion Criteria Part 1

Replace:

207. Changes in drug regimen (ie, changes in dose or frequency of use) of an allowed migraine preventive medication within 2 months from screening OR change in drug regimen of a medication with potential for migraine prevention within 2 months from screening (refer to Section 7.1.7 for the list of these medications)

209 Documented history of treatment with an anti-CGRP product

213 Excluded medical conditions include:

- Currently diagnosed with fibromyalgia and/or chronic pelvic pain;
- Currently diagnosed with a clinically significant cervical or intracranial disease (eg, chronic cervical radiculopathy, space-occupying lesions, intracranial aneurysms) that, in the opinion of the investigator, might confound or mimic migraine symptomatology;
- History of major psychiatric disorder (such as schizophrenia or other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder), or current evidence of depression based on a BDI-II total score $>$ 24 at screening.
- History of malignancy within the past 5 years, with the following exception[s]:
  - Malignancy treated with curative intent and with no known active disease present for $\geq$ 5 years before enrollment and felt to be at low risk for recurrence by the treating physician
  - Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease
  - Prostatic intraepithelial neoplasia without evidence of prostate cancer
  - Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- Known human immunodeficiency virus (HIV) infection
- Known hepatic disease with potential for hepatic function impairment or evidence of acute or chronic hepatitis B or hepatitis C (hepatitis status will be evaluated by testing for hepatitis B surface antigen [HepBsAg], total hepatitis B core antibody [HepBcAb] and hepatitis C antibody at screening)
- Total bilirubin $\geq$ 2.0x upper limit of normal (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq$ 3.0 x ULN, as assessed by the central laboratory at screening

219 Exceeded 15 days per month of a short-acting opioid/opioid-containing medication during any of the 3 months prior to screening

220 Had a concomitant use of a short-acting opioid/opioid-containing medication in a frequency that exceeds 4 days per month with any of the following prescribed psychoactive substances:

- Regular use of barbiturates as defined as any use that exceeds 4 days per month during any of the 3 months prior to screening
- Regular use of central nervous system sedative-hypnotic drugs or drugs that may increase opioid risk such as benzodiazepines, z-drugs, gabapentinoids, tricyclic antidepressants, butyrophenones, phenothiazines, anticonvulsants, and muscle relaxants as defined as any use that exceeds 15 days per month during any of the 3 months prior to screening.

221 Currently receiving treatment in another investigational device or drug study, or < 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.

222 Subject has known sensitivity to any of the components to be administered during dosing.

With:

235 Changes in drug regimen (ie, changes in dose or frequency of use) of an allowed migraine preventive medication within 2 months **prior to start of baseline** (refer to Section 7.1.7 for the list of these medications)

236 Documented history of treatment with an anti-CGRP **preventive treatment**

237 Excluded medical conditions include:

- Currently diagnosed with fibromyalgia and/or chronic pelvic pain;
- Currently diagnosed with a clinically significant cervical or intracranial disease (eg, chronic cervical radiculopathy, space-occupying lesions, intracranial aneurysms) that, in the opinion of the investigator, might confound or mimic migraine symptomatology;
- History of major psychiatric disorder (such as schizophrenia or other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder), or current evidence of depression based on a BDI-II total score > 24 at screening.
- History of malignancy within the past 5 years, with the following exception[s]:
  - Malignancy treated with curative intent and with no known active disease present for ≥ 5 years before **screening** and felt to be at low risk for recurrence by the treating physician
  - Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease
  - Prostatic intraepithelial neoplasia without evidence of prostate cancer
  - Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- Known human immunodeficiency virus (HIV) infection
- Known hepatic disease with potential for hepatic function impairment or evidence of acute or chronic hepatitis B or hepatitis C (hepatitis status will be evaluated by

testing for hepatitis B surface antigen [HepBsAg], total hepatitis B core antibody [HepBcAb] and hepatitis C antibody at screening)

- Total bilirubin ≥ 2.0x upper limit of normal (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3.0 x ULN, as assessed by the central laboratory at screening

238 Exceeded 15 days per month of a short-acting opioid/opioid-containing medication during any of the **2** months prior to screening

239 Had a concomitant use of a short-acting opioid/opioid-containing medication in a frequency that exceeds 4 days per month with any of the following prescribed psychoactive substances:

- Regular use of barbiturates as defined as any use that exceeds 4 days per month during any of the **2** months prior to screening
- Regular use of central nervous system sedative-hypnotic drugs or drugs that may increase opioid risk such as benzodiazepines, z-drugs, gabapentinoids, tricyclic antidepressants, butyrophenones, phenothiazines, anticonvulsants, and muscle relaxants as defined as any use that exceeds 15 days per month during any of the 3 months prior to screening.

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

241 Subject has known **hyper**sensitivity to any of the components to be administered during dosing.

Section: 6.2, Exclusion Criteria Part 1

Delete:

~~217 Body mass index (BMI) > 40 kg/m2 as assessed at screening~~

Section: 6.4, Exclusion Criteria Part 2

Replace:

225. Taken an opioid or opioid-containing analgesic for any indication on > 15 days during baseline period

226. Opioid use during baseline period that in the opinion of the investigator or Amgen's physician, if consulted, constitutes any of the following:

- misuse (use that is contrary to the prescriber's directions, eg, unsolicited dose escalation)
- abuse (use for nonmedical intention, eg, euphoria or altered consciousness)
- dependence (use that is compulsive or potentially harmful)
- diversion (transfer of a legally prescribed controlled substance from the individual for whom it was prescribed to another person for any illicit use)

230 At risk of self-harm or harm to others as evidenced by scoring ≥ 1 point in BDI-II item 9 and concomitant demonstration of strong suicidal ideation (ie, presence of suicidal planning)

With:

242 Taken a **short-acting** opioid or opioid-containing analgesic **for** any indication on > 15 days during baseline period

243 **Short-acting o**pioid use during baseline period that in the opinion of the investigator or Amgen's physician, if consulted, constitutes any of the following:

- misuse (use that is contrary to the prescriber's directions, eg, unsolicited dose escalation)
- abuse (use for nonmedical intention, eg, euphoria or altered consciousness)
- dependence (use that is compulsive or potentially harmful)
- diversion (transfer of a legally prescribed controlled substance from the individual for whom it was prescribed to another person for any illicit use)

244 At risk of self-harm or harm to others as evidenced by scoring ≥ 1 point in BDI-II item 9 **(Suicidal Thoughts or Wishes)** and concomitant demonstration of strong suicidal ideation (ie, presence of suicidal planning)

Section: 6.5. Lifestyle Restrictions

Delete:

~~6.5 Lifestyle Restrictions~~

~~6.5.1 Caffeine, Alcohol, and Tobacco~~

~~Subjects should not consume caffeine-containing beverages or tobacco within 30 minutes before each study visit where vital signs will be taken. Subjects should not participate in this study if there is evidence of a consistent pattern of alcohol abuse that may indicate an alcohol use disorder (see exclusion criterion 231).~~

~~6.5.2 Activity~~

~~Subjects should abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.~~

Section: 6.5, Subject Enrollment

Replace:

The subject identification number will be assigned via IVRS/IWRS.

With:

The subject identification number will be assigned via **interactive response technology (IRT)**.

Section: 6.6, Screen Failures, paragraph 1

Delete:

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if the condition that led to screen failure is expected to be transient. Refer to Section 9.1.1.

Section: 6.6, Screen Failures, paragraph 3

Replace:

A subject who is determined to be ineligible must be registered as a screen fail in the IVRS/IWRS.

With:

A subject who is determined to be ineligible must be registered as a screen fail in the **IRT**.

Section: 7.1.1, Table 7-1. Study Treatments

Replace:

Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	• Erenumab 70 mg and 140 mg will be administered every 4 weeks during DBTP and OLTP. • To preserve blinding integrity during the DBTP, the 70 mg dose level will be composed of one 1 mL injection of erenumab 70 mg and one 1 mL injection of matching placebo, and the 140 mg dose level will be composed of two 1 mL injections of erenumab 70 mg. • During OLTP, subjects will be maintained on their original dose assignment and receive IP as an autoinjector device.	• Placebo will be administered every 4 weeks during the 24-week DBTP (ie, at day 1 and visit weeks 4, 8, 12, 16, and 20). • To preserve blinding integrity during the DBTP, there will be two 1 mL injections of matching placebo for placebo assigned subjects • Upon completion of DBTP, placebo-treated subjects will be allocated to an active dose arm by IVRS/IWRS to receive either 70 mg or 140 mg of erenumab every 4 weeks.

With:

Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	• Erenumab 70 mg and 140 mg will be administered every 4 weeks during DBTP and OLTP. • To preserve blinding integrity during the DBTP, the 70 mg dose level will be composed of one 1 mL injection of erenumab 70 mg and one 1 mL injection of matching placebo, and the 140 mg dose level will be composed of two 1 mL injections of erenumab 70 mg. • During OLTP, subjects will be maintained on their original dose assignment and receive IP as an autoinjector device.	• Placebo will be administered every 4 weeks during the 24-week DBTP (ie, at day 1 and visit weeks 4, 8, 12, 16, and 20). • To preserve blinding integrity during the DBTP, there will be two 1 mL injections of matching placebo for placebo assigned subjects**.** • Upon completion of DBTP, placebo-treated subjects will be allocated to an active dose arm by **IRT** to receive either 70 mg or 140 mg of erenumab every 4 weeks.

Section: 7.1.1, Table 7-1. Study Treatments, table abbreviations

Replace:

CRF = case report form; DBTP = double-blind treatment period; IPIM = investigational product instruction manual; IVRS/IWRS = Interactive Voice Response System/Interactive Web Response System; OLTP = open-label treatment period

With:

CRF = case report form; DBTP = double-blind treatment period; IPIM = investigational product instruction manual; **IRT = Interactive Response Technology**; OLTP = open-label treatment period

Section: 7.1.7, Excluded Treatments, Medical Devices, and/or Procedures During Study Period, paragraph 1

Replace:

Concomitant treatment with 1 oral migraine preventive medication is allowed under the following conditions:

With:

Concomitant treatment with **up to 2** oral migraine preventive medication is allowed under the following conditions:

Section: 7.1.7, Excluded Treatments, Medical Devices, and/or Procedures During Study Period, bullet 7

Add:

- Other drugs used for migraine prevention (eg, **coenzyme Q10,** clonidine, guanfacine, methysergide, cyproheptadine, pizotifen, butterbur, feverfew, magnesium (≥ 500 mg/day), riboflavin (≥ 100 mg/day).

Section: 7.1.7, Excluded Treatments, Medical Devices, and/or Procedures During Study Period, Prohibited Medications

Replace:

Prohibited Medications	Time Period for Exclusion
Concurrent use of non-investigational anti-CGRP mAbs	Prior history of treatment with and throughout the study
Cannabinoids	Within 2 months prior to screening and throughout the study

Prohibited Medications	Time Period for Exclusion
Use of the following acute medications for the acute treatment of migraine Barbiturates or butalbital-containing medication for > 4 days/month Opioids or opioid-containing medication for >15 days/month	3 months before the start of the screening period and throughout the study
Investigational medications	30 days or 5 half-lives before the start of the screening period and throughout the study
Botulinum toxin (in the head and/or neck region)	4 months before the start of the screening period and throughout the study
Prohibited Procedures or Devices	Time Period for Exclusion
For any indication Infusion therapy (ie, steroids, valproate sodium, dihydroergotamine) Note: infusion therapy may be allowed during DBTP if medically justified	During screening period or baseline period
For any indication Devices (such as stimulation devices), or procedures (such as nerve blocks, acupuncture, biofeedback, relaxation techniques, or psychotherapy).	3 months before the start of the screening period and throughout the study
Cognitive Behavioral Therapy Subjects on a stable, maintenance phase of a cognitive behavioral therapy (CBT) program for migraine are allowed. CBT is defined as stable, on a maintenance phase if subject has undergone ≥ 6 weekly or biweekly sessions of CBT administered by adequately trained psychologists and who, for at least 3 months before the start of the baseline period, only follow "booster" CBT sessions at a monthly, bimonthly or quarterly frequency.	3 months before the start of the screening period

With:

Prohibited Medications	Time Period for Exclusion
Concurrent use of non-investigational anti-CGRP mAbs	Prior history of treatment with and throughout the study
Use of the following acute medications for the acute treatment of migraine**:** Barbiturates or butalbital-containing medication for > 4 days/month **Short-acting o**pioids or **short-acting** opioid-containing medication for >15 days/month **Long-acting opioids or long-acting opioid-containing medication**	**2** months before the start of the screening period and throughout the study

Prohibited Medications	Time Period for Exclusion
Cannabidiol (CBD)-containing products anticipated to have a systemic effect (eg, ingested or inhaled products) > 4 days/month	
Investigational medications	30 days or 5 half-lives before the start of the screening period and throughout the study
Botulinum toxin (in the head and/or neck region)	4 months before the start of the screening period and throughout the study
Prohibited Procedures or Devices	Time Period for Exclusion
For any indication Infusion **rescue** therapy (ie, steroids, valproate sodium, dihydroergotamine) Note: infusion **rescue** therapy may be allowed during DBTP if medically justified	During screening period or baseline period
For any indication Devices (such as stimulation devices), or procedures (such as nerve blocks, or psychotherapy).	3 months before the start of the screening period and throughout the study
Cognitive Behavioral Therapy Subjects on a stable, maintenance phase of a cognitive behavioral therapy (CBT) program for migraine are allowed. CBT is defined as stable, on a maintenance phase if subject has undergone ≥ 6 weekly or biweekly sessions of CBT administered by adequately trained psychologists and who, for at least 3 months before the start of the baseline period, only follow "booster" CBT sessions at a monthly, bimonthly or quarterly frequency.	3 months before the start of the screening period

Section: 7.2, Method of Treatment Assignment, paragraph 2

Replace:

The randomization will be performed by IVRS/IWRS, and the randomization number will be assigned by IVRS/IWRS and appear on the IVRS/IWRS randomization document. The randomization number is different than the subject identification number and will not be utilized by the site as a subject identifier.

With:

The randomization will be performed by **IRT**, and the randomization number will be assigned by **IRT** and appear on the **IRT** randomization document. The randomization number is

different than the subject identification number and will not be utilized by the site as a subject identifier.

Section: 7.3, Blinding

Replace:

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

With:

This study has a 24-week DBTP and a 28-week OLTP. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below. **During the 24-week DBTP, treatment assignment will be blinded to all subjects, site personnel, and Amgen. Following the DBTP, during the 28-week OLTP, study team members in direct contact with sites, investigators and subjects will remain blinded to the initial dose level.**

Section: 7.8.1, Prior Treatment

Replace:

Prior therapies that were being taken/used from 120 days before screening through the signing of the informed consent will be collected.

With:

For prior migraine preventive medications, which are required to have ended 2 months prior to baseline, therapy name, indication, dose, unit, frequency, start and stop dates will be collected in the prior migraine preventive medication CRF.

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

Section: 7.8.2, Concomitant Treatment, paragraph 3 and 4 (new)

Add:

Concomitant medication that is taken to treat headaches or migraine symptoms acutely and/or may lead or contribute to MOH will be reported in the eDiary.

All other concomitant medications will be reported on the Concomitant Medications electronic case report form (eCRF) including any allowable concomitant migraine preventive medication.

Section: 8.2.2, Reasons for Removal From Study, bullet 5 and 6

Delete:

- ~~Protocol-specified criteria (after subject is enrolled/randomized on study)~~
- ~~New pregnancy, decision to breastfeed, or decision of unwillingness to maintain an acceptable contraception method during the baseline period~~

Section: 9.1.1, Screening, Enrollment and/or Randomization

Replace:

Informed consent must be obtained before completing any screening procedure. After the subject has signed the informed consent form, the site will register the subject in the IVRS/IWRS and screen the subject in order to assess eligibility for participation.

With:

Informed consent must be obtained before completing any screening procedure. After the subject has signed the informed consent form, the site will register the subject in the **IRT** and screen the subject in order to assess eligibility for participation.

Section: 9.1.1.1, Screening Period

Replace:

The up to 3-week initial screening period starts when the subject signs and dates the informed consent form and ends when the subject is deemed eligible to enter the 4-week baseline period or discontinues before baseline entry and/or does not meet all Part 1 eligibility criteria (refer to Sections 6.1 and 6.2).

With:

The screening period is up to 7 weeks, which consists of an up to 3-week initial screening period **and a** 4-week baseline period.

Section: 9.1.1.2, Baseline Period

Replace:

The 4-week baseline period starts when the subject has met all Part 1 eligibility criteria (refer to Section 6.1 and Section 6.2) and enters the baseline period and ends when the subject does not complete baseline or does not meet all Part 2 eligibility criteria (refer to Section 6.3 and Section 6.4), or is enrolled/randomized.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all Part 2 eligibility criteria prior to enrollment/ randomization. If a subject has not met all Part 2 eligibility criteria during the baseline period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for rescreening 1 time. Refer to Section 9.1.1.1 for additional details regarding screen failures and rescreening.

With:

The 4-week baseline period starts when the subject has met all Part 1 eligibility criteria (refer to Section 6.1 and Section 6.2) and enters the baseline period and ends when the subject **is randomized or** does not complete baseline or does not meet all Part 2 eligibility criteria (refer to Section 6.3 and Section 6.4) **and is screen failed**.

The total duration of the baseline period must be at least 29 days and no more than 35 days. Refer to Sections 9.2.2.1 and 9.2.2.3 for information on the BDI-II and eligibility calculation, which are to be completed at the end of the baseline period using the eDiary.

Section: 9.1.1.3, Randomization

Replace:

Upon completion of the baseline period, subjects found to meet eligibility requirements will undergo randomization in IVRS/IWRS and be assigned a study treatment in a blinded manner.

The subject is considered enrolled when the investigator decides that the subject has met Part 1 and Part 2 eligibility criteria and follow procedures for subject randomization.

With:

Upon completion of the baseline period, subjects found to meet eligibility requirements will undergo randomization in **IRT** and be assigned a study treatment in a blinded manner.

Section: 9.1.2.1, Double-blind Treatment Period

Delete:

~~9.1.2.1 Double-blind Treatment Period~~

~~During the DBTP, 2 SC injections will be administered per day at day 1, weeks 4, 8, 12, 16, and 20 (12 injections in total). Both SC injections are to be administered within 30 minutes during each visit that it is required. Subjects randomized to:~~

~~Erenumab 70 mg every 4 weeks will receive a total of 12 injections (1 injection of erenumab 70 mg/mL PFS and 1 injection of matching placebo) at day 1, weeks 4, 8, 12, 16, and 20.~~

~~Erenumab 140 mg every 4 weeks will receive a total of 12 injections (2 injections of erenumab 70 mg/mL PFS) at day 1, weeks 4, 8, 12, 16, and 20.~~

~~Placebo will receive a total of 12 injections (2 injections of placebo) at day 1, weeks 4, 8, 12, 16, and 20.~~

Section: 9.1.2.2, Open-label Treatment Period

Delete:

~~9.1.2.2 Open-label Treatment Period~~

~~Subjects who successfully complete the DBTP of the study will be given the option to continue in an OLTP of 28 weeks. Entry in OLTP must occur no earlier than week 24 OLTP visit and no later than week 28 visit. All subjects originally assigned to placebo will be allocated in a 1:1 ratio to erenumab 70 mg or erenumab 140 mg in order to protect original treatment blinding. Subjects who received active treatment during the DBTP will remain on the same dose. After receiving training at the week 24 visit, subjects will self-administer erenumab at home or during clinic visits using an auto injector. All subjects will be encouraged to do self-administration, but those who either refuse or who are determined by the staff to not be proficient will be required to return to the clinic every 4 weeks for injections with the auto-injector performed by a qualified staff member.~~

Section: 9.2.1.3, Medical History

Add:

The Investigator or designee will collect a complete medical (including targeted cardiovascular), psychiatric, and surgical history that started within 120 days prior to medical history assessment at screening. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition

to the medical history above, migraine history must date back to the original diagnosis. The current severity will be collected for each condition that has not resolved.

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

Section: 9.2.1.5, Physical Measurements

Delete:

~~Body Mass Index should be calculated using the following formula: BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2~~

Section: 9.2.2.1, Clinical Outcome Assessments and Electronic Diaries (eDiaries), paragraph 1

Add:

The COAs will be collected by subjects using a handheld eDiary at various frequencies. The eDiary will collect the following COAs daily at home starting in the baseline period and throughout the DBTP, and then again daily starting from week 40 **visit** through the week 52/EOS visit of the OLTP:

Section: 9.2.2.1, Clinical Outcome Assessments and Electronic Diaries (eDiaries), bullet 6

Add:

- Use of acute medications **to treat headaches or migraine symptoms** (medication name [from pre-entered list] date and time of dosing, number of times taken of each date, number of units taken)

Section: 9.2.2.1, Clinical Outcome Assessments and Electronic Diaries (eDiaries), paragraph 2

Add:

Study center staff will assign and provide an eDiary to the subject at the week -4 visit (after confirming the subject's part 1 eligibility prior to baseline period entry). The study center staff will train the subject on how to use the eDiary (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day and to bring the eDiary to every study visit. **During the baseline period after at least 28 full**

calendar days have passed (inclusive of the day the patient was set-up on the eDiary device), the subject will return for their end of baseline period visit/ day 1 visit. 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. **During this visit, site staff will be able to activate the baseline period BDI-II on the subject's eDiary device, as well as perform the eligibility calculation.**

Section: 9.2.2.1, Clinical Outcome Assessments and Electronic Diaries (eDiaries), paragraph 3 (new)

Add:

For randomized subjects, all Day 1 study assessments, including eDiary questionnaires, should be completed prior to subject's first dose of investigational product. For subsequent study visits, the order of completing study assessments will be at the investigator's discretion.

Section: 9.2.2.3, Beck Depression Inventory (BDI-II), paragraph 2 (new)

Add:

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

Section: 9.2.2.11, Health Resource Utilization Resource Questionnaire (HRU), header

Add:

9.2.2.11 Health **Resource** Utilization Resource Questionnaire (HRU)

Section: 9.2.2.11, Health Resource Utilization Resource Questionnaire (HRU), paragraph 1

Replace:

The questionnaire is designed to collect data on HRU. Specifically, the HRU questionnaire aims to capture frequency of migraine-related inpatient hospitalizations and outpatient emergency department visits, urgent care visits, and other clinical visits. The recall period for the HRU questionnaire is 24 weeks. The questionnaire with the 24-week recall will be administered at day 1 and week 24 of the DBTP.

With:

The questionnaire is designed to collect data on HRU. Specifically, the HRU questionnaire aims to capture frequency of **headache**-related inpatient hospitalizations and outpatient emergency department visits, urgent care visits, and other clinical visits. The recall period for the HRU questionnaire is 24 weeks. The questionnaire with the 24-week recall will be administered at day 1 and week 24 of the DBTP.

Section: 9.2.3.1.1.1, Adverse Events, paragraph 1

Replace:

Adverse events related to any study procedures/study-activity are reported from signing of the informed consent form. All other adverse events are reported after the first dose of investigational product. The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Section 12.4.

With:

Adverse events related to any study procedures/study-activity are reported **after the first dose of investigational product**. All other adverse events are reported after the first dose of investigational product.

Section: 9.2.3.1.1.2, Serious Adverse Events, paragraph 1

Replace:

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

With:

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 the end of study are reported using the Event CRF.

Section: 9.2.3.1.5, Pregnancy and Lactation, paragraph 1

Replace:

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

With:

Details of all pregnancies and/or lactation in female subjects and, if indicated, female partners of male subjects **who become pregnant,** will be collected after the start of study treatment **through 16 weeks after the last dose of study drug**.

Section: 9.2.4, Clinical Laboratory Assessments, paragraph 3 (new)

Add:

Urine drug tests (UDTs) performed at screening that return positive likely due to the use of an allowable over-the-counter (OTC) medication may be retested prior to eligibility determination.

Section: 9.2.4.1, Pregnancy Testing, paragraph 3

Replace:

Additional pregnancy testing should be performed at monthly intervals during treatment with protocol-required therapies and up to week 52/EOS visit.

With:

Post day 1 pregnancy testing should be completed as per the Schedule of Activities (Table 2-1, Table 2-2).

Section: 10.1 Sample Size Determination

Add:

The sample size calculation has been performed based on the primary endpoint (absence of MOH at month 6 **[week 24]**) for the nonopioid-treated cohort.

Based on a subgroup analysis of subjects who failed preventive migraine medication**,** overused acute headache medication, and had at least 14 MHD at baseline in the erenumab CM pivotal Study 20120295, 33.1%, 50.5%, and 64.1% of subjects in placebo, erenumab 70 mg and erenumab 140 mg treatment group, respectively, achieved absence of MOH at month 3 **(week 12)**. Assuming similar response rates over month 4, 5 and 6 **(week 13 through 24)** and a conservative scenario that includes a dropout rate of 20% during the 6-month DBTP, the planned sample size of 183 subjects per group will provide 85% power for 70 mg versus placebo and > 99% power for 140 mg versus placebo using a 2-sample chi-squared test with a 2-sided significance level of 0.05.

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

Section: 10.2.3, Subgroups

Replace:

The primary and key secondary endpoints for the nonopioid cohort will be analyzed in the subgroups defined by concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No), key demographics (eg, geographic region), prior history of treatment with onabotulinumtoxinA (Yes or No), total number or prior treatment failures (1, 2. or 3 or more treatment failures), and acute headache medication overuse category (triptan or ergotamine derivative medication overuse, simple analgesics and/or NSAIDs medication overuse, or combination medication overuse).

With:

The primary and key secondary endpoints for the nonopioid cohort will be analyzed in the subgroups defined by concomitant oral migraine preventive treatment initiated before screening and taken during baseline (Yes or No), key demographics (eg, geographic region), prior history of treatment with onabotulinumtoxinA (Yes or No), total number or prior treatment failures (1, 2**,** or 3 or more treatment failures), and acute headache medication overuse category (triptan or ergotamine derivative medication overuse, simple analgesics and/or NSAIDs medication overuse, **combination analgesics overuse,** or combination medication **therapies** overuse).

Section: 10.2.4, Handling of Missing and Incomplete Data, paragraph 1

Add:

Subjects may miss specific data points for a variety of reasons. In general, data could be missing due to a subject's early withdrawal from the study, a missed visit, or inability to evaluate an endpoint at a particular point in time. For this study, efficacy endpoints 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 **in efficacy** will be handled.

Section: 10.2.4, Handling of Missing and Incomplete Data, paragraph 2

Replace:

For the eDiary, if at least 14 days of eDiary are collected in the monthly interval, then the monthly frequency measurements (eg, migraine days, headache days) will be prorated based on the number of days with available information using the following formula:

With:

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

Section: 10.2.4, Handling of Missing and Incomplete Data, paragraph 2

Delete:

~~Number of observed migraine days *28/Number of information days in interval, where an information day is a diary day or headache day.~~

Section: 10.2.4, Handling of Missing and Incomplete Data, paragraph 3 (new)

Add:

Missing items in each COA questionnaire will be handled based on the scoring algorithm for each COA.

Section: 10.2.4, Handling of Missing and Incomplete Data, paragraph 5 (new)

Add:

Missing data in safety data will not be imputed except for partial AE start dates.

Section: 10.4.1.1, Primary Analysis

Replace:

The primary hypothesis will be tested once the last subject in the nonopioid-treated cohort has completed the week 24 assessments or the ET visit, and all data for the primary endpoint has been collected. At this time, the DBTP treatment assignment for this cohort will be unblinded to the sponsor. If data collection for all subjects in the opioid-treated cohort for the DBTP is also complete, the DBTP treatment assignment for this cohort will also be unblinded. Study subjects and investigators will remain blinded to original DBTP treatment assignment until study completion. All efficacy analyses and safety analyses will be

conducted for the DBTP. However, safety data collected during OLTP before the data cutoff date for the primary analysis will also be summarized.

With:

The primary hypothesis will be tested once the last subject in the nonopioid-treated cohort has completed the week 24**/ET** assessments **during the DBTP**, and all data for the primary endpoint has been collected. At this time, the DBTP treatment assignment for this cohort will be unblinded to the sponsor. If data collection for all subjects in the opioid-treated cohort for the DBTP is also complete, the DBTP treatment assignment for this cohort will also be unblinded. **Otherwise, the unblinding of treatment assignment for this cohort and the analysis of the DBTP data for opioid-treated cohort will be done in the final analysis.** Study subjects and investigators will remain blinded to original DBTP treatment assignment until study completion. All efficacy analyses and safety analyses will be conducted for the DBTP. However, safety data collected during OLTP before the data cutoff date for the primary analysis will also be summarized.

Section: 10.4.1.2, Final Analysis

Replace:

The final analysis will be performed after all subjects (nonopioid-treated and opioid-treated) have completed the study through the OLTP last visit or were discontinued from the study.

With:

The final analysis will be performed after all subjects (nonopioid-treated and opioid-treated) have completed the study through the **week 52/EOS** visit.

Section: 10.4.2.1,General Considerations**,** Paragraph 5,6,7,8

Add:

Formal statistical analyses using statistical models and hypothesis testing will be performed for the nonopioid-treated cohort only.

Summary statistics will be computed by treatment group and visit. For continuous endpoints, the following descriptive statistics will be computed: number of observations, means, medians, standard deviations, standard errors, first and third quartiles, minimums and maximums, and 2-sided 95% CIs of the means (CIs will be provided for efficacy

endpoints only). For categorical endpoints, the summaries will contain the number and percentage of subjects in each category.

The dichotomous efficacy endpoints will be analyzed using the stratified Cochran-Mantel-Haenszel (CMH) test after the missing data is imputed as nonresponse. Continuous secondary endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data at the monthly level.

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

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

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

Primary and secondary endpoints in erenumab 70 mg versus placebo**:**

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

Patient reported outcome-related secondary endpoints for the non-EU region

7. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)
8. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (140 mg)
9. Change from the baseline in mean monthly average physical impairment domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)

10. Change from the baseline in mean monthly average impact on everyday activities domain scores as measured by the MPFID over months 4, 5, and 6 **(week 13 through 24)** of the DBTP (70 mg)

OR

Patient reported outcome-related secondary endpoints for the EU region

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

Section: 10.4.2.2,Efficacy Analyses

Add:

Endpoint	Statistical Analysis Methods
Primary	The primary comparison of absence of MOH at month 6 **(week 24)** between each erenumab dosing group and placebo will be analyzed using a stratified CMH test after the missing data are imputed as nonresponse. The proportion of subjects with absence of MOH will be reported for each treatment group. The odds ratio between each erenumab group and placebo, the corresponding 95% CI and p-value will be reported.

Section: 12.1, Appendix 1. List of Abbreviations and Definitions of Terms

Add:

Acute headache medication	**Acute headache medications include:** • **Triptan-based migraine medications** • **Ergotamine-based migraine medications** • **Non-opioid acute headache medications** • **Non-opioid butalbital containing medications** • **Opioid-containing acute headache medications** • **Opioid-containing butalbital containing medications**
CBD	**Cannabidiol**
CM-MOH	Chronic migraine subjects who met thresholds for medication overuse **headache**
IRT	**interactive response technology that is linked to a central computer in real time as an interface to collect and process information**

Medication overuse (per protocol)	Mean monthly acute **headache** medication days above the following thresholds • Triptans, ergotamine, opioids/opioid-containing medication, combination therapies: ≥ 10 days per study month • Simple analgesics and NSAIDS only: ≥ 15 days per study month of simple analgesics and NSAIDs
MOH (protocol defined)	Mean monthly acute **headache** medication days over 3 consecutive study months at or above ICHD-3 defined thresholds AND mean monthly qualified headache days of any severity ≥ 14 days over the same consecutive study months
Study month	**generally 4 weeks**

Section: 12.1, Appendix 1. List of Abbreviations and Definitions of Terms

Delete:

~~Acute migraine-specific medication day~~	~~Any day in which a migraine-specific medication was administered in association to a headache day~~
~~BMI~~	~~Body mass index~~
~~Headache day (acute headache medication day)~~	~~A qualified headache day for which any acute headache medication has been administered in association with a headache episode~~
~~Interactive Voice Response System (IVRS)~~	~~telecommunication technology that is linked to a central computer in real time as an interface to collect and process information~~
~~Interactive Web Response System (IWRS)~~	~~web based technology that is linked to a central computer in real time as an interface to collect and process information~~
~~MAR~~	~~Missing at random~~
~~MI~~	~~Multiple imputation~~
~~MNAR~~	~~Missing not at random~~
Opioid medication day	Any day in which an opioid/opioid containing medication was administered ~~in association to a headache day~~

Section: 12.1, Appendix 1. List of Abbreviations and Definitions of Terms

Replace:

Acute medication day	Any eDiary day in which an acute headache medication intake is reported. Acute medication day is inclusive but not limited to acute headache medication days
CM	Chronic migraine
Headache day (moderate to severe)	A qualified headache day that subjects indicate its peak severity as being moderate or severe

With:

Acute **headache** medication day	Any **calendar** day in which an acute headache medication intake is reported.
CM **(per ICHD-3)**	Chronic migraine **defined as headache occurring on 15 or more days/month for more than 3 months, which, on at least 8 days/month, has the features of migraine headache.** **A. Headache (migraine-like or tension-type-like) on ≥15 days/month for >3 months, and fulfilling criteria B and C** **B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for Migraine without aura and/or criteria B and C for Migraine with aura** **C. On ≥8 days/month for >3 months, fulfilling any of the following:** **1.criteria C and D for Migraine without aura** **2.criteria B and C for Migraine with aura** **3.believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative** **D. Not better accounted for by another ICHD-3 diagnosis**
Headache day (moderate to severe)	A qualified headache day that subjects indicate its peak severity as being **of at least** moderate sever**ity**

Section: 12.2, Appendix 2. Clinical Laboratory Tests, paragraph 1

Replace:

The tests detailed in Table 12-1 will be performed by the central laboratory, except urine pregnancy testing. Hematology testing after screening and chemistry testing during the OLTP will be at the discretion of the investigator.

With:

The tests detailed in Table 12-1 will be performed by the central laboratory, except urine pregnancy testing. **During the Baseline period and through the DBTP, hematology and chemistry testing will be at the discretion of the investigator, as well as** chemistry testing during the OLTP.

Section: 12.2, Appendix 2. Clinical Laboratory Tests, Table 12-1. Analyte Listing, deleted footnote d for HIV of other labs, and replaced footnote of cholesterol, HDL, and LDL of Central Laboratory Chemistry from e to d

Replace:

Central Laboratory: Chemistry[a]	Central Laboratory: Hematology[b]	Other Labs[c]
Sodium	RBC	Central Laboratory:
Potassium	Hemoglobin	Urine drug screening
Chloride	Hematocrit	Pharmacogenetic studies (optional)
Bicarbonate	MCV	Biomarker development
Total protein	MCH	Hep B surface antigen
Calcium	MCHC	Hep C antibody
Adjusted calcium	RDW	HIV[d]
Magnesium	Reticulocytes	
Phosphorus	Platelets	Local Laboratory:
Glucose	WBC	Pregnancy testing-urine
BUN or Urea	Differential	
Creatinine	• Neutrophils	
Uric acid	• Eosinophils	
LDH	• Basophils	
Cholesterol[e]	• Lymphocytes	
HDL[e]	• Monocytes	
LDL[e]		
Triglycerides		
Total bilirubin		
Direct bilirubin		
ALP		
AST (SGOT)		
ALT (SGPT)		
Albumin		

Footnotes defined on next page

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count

[a] During the OLTP, chemistry testing will be at the discretion of the investigator and performed at central laboratories.

[b] After screening, hematology testing will be at the discretion of the investigator and performed at central laboratories

[c] Performed at either central or local laboratories, as noted.

[d] HIV assessment is recommended.

[e] To be tested at screening only.

With:

Central Laboratory: Chemistry[a]	Central Laboratory: Hematology[b]	Other Labs[c]
Sodium	RBC	Central Laboratory:
Potassium	Hemoglobin	Urine drug screening
Chloride	Hematocrit	Pharmacogenetic studies (optional)
Bicarbonate	MCV	Biomarker development
Total protein	MCH	Hep B surface antigen
Calcium	MCHC	**Total Hep B core antibody**
Adjusted calcium	RDW	Hep C antibody
Magnesium	Reticulocytes	HIV
Phosphorus	Platelets	
Glucose	WBC	Local Laboratory:
BUN or Urea	Differential	Pregnancy testing-urine
Creatinine	• Neutrophils	
Uric acid	• Eosinophils	
LDH	• Basophils	
Cholesterol[d]	• Lymphocytes	
HDL[d]	• Monocytes	
LDL[d]		
Triglycerides		
Total bilirubin		
Direct bilirubin		
ALP		
AST (SGOT)		
ALT (SGPT)		
Albumin		

Footnotes defined on next page
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell count; RDW = Red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count
[a] During the **Baseline Period, DBTP, and** OLTP, chemistry testing will be at the discretion of the investigator and performed at central laboratories.
[b] **During the Baseline Period and DBTP**, hematology testing will be at the discretion of the investigator and performed at central laboratories
[c] Performed at either central or local laboratories, as noted.
[d] To be tested at screening only.

Section: 12.3, Appendix 3. Study Governance Considerations, Informed Consent Process

Replace:

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

With:

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within **60** days from the previous informed consent form signature date.

Section: 12.3, Appendix 3. Study Governance Considerations, Data Quality Assurance

Delete:

~~Amgen (or designee) will perform Self-Evident Corrections to obvious data errors in the clinical trial database. Self-Evident Corrections will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the electronic data capture (EDC) system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, (eg, week 4 and early termination) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).~~

Section: 12.3, Appendix 3. Study Governance Considerations, Source Documents

Replace:

Source documents may also include data captured in the Interactive Voice Response System (IVRS) / Interactive Web Response System (IWRS) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

With:

Source documents may also include data captured in the **IRT** system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Section: 12.4, Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Add:

The Common Terminology Criteria for Adverse Events, version 4.0**3** which is available at the following location:

Section: 12.5, Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information, Male Subjects With Partners Who Become Pregnant, bullet 1

Replace:

- In the event a male subject fathers a child during treatment, and for an additional 12 weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) 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).

With:

- In the event a male subject fathers a child during treatment, and for an additional **16** weeks after **the last dose of study drug**, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) 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).

Section: 12.8, Appendix 8. Substudy: Qualitative Interview Substudy to 'A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache, Substudy Design, paragraph 1

Replace:

Qualitative interviews will be conducted with subjects who opt in to this optional substudy. Interviews will be conducted via entry interviews, conducted within 5 days of the first IP dose, and exit interviews, conducted within 5 days of the week 24 visit or within approximately 5 days of the early termination (ET) visit.

With:

Qualitative interviews will be conducted with subjects who opt in to this optional substudy. Interviews will be conducted via entry interviews, conducted within **7** days of the first IP dose, and exit interviews, conducted within **7** days of the week 24 visit or within approximately **14** days of the early termination (ET) visit. **If possible, within 7 days from early termination notification will be targeted.**

Section: 12.8, Appendix 8. Substudy: Qualitative Interview Substudy to 'A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache, Summary of Substudy Subject Eligibility Criteriia

Replace:

1) Unable to complete entry interview within five (5) days from first IP dose;
2) Unable to complete exit interview within five (5) days prior to week 24 visit or within approximately five (5) days post early termination visit;

With:

1) Unable to complete entry interview within **seven (7)** days from first IP dose;
2) Unable to complete exit interview within **seven (7)** days prior to week 24 visit or within approximately **14** days post early termination visit;

Section: 12.8, Appendix 8. Substudy: Qualitative Interview Substudy to 'A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache, Substudy Duration and Substudy Procedures, paragraph 1

Replace:

Subjects are required to participate in two telephone interviews, lasting approximately one-hour each. Entry interviews will be conducted within five (5) days from first IP dose; exit interviews will be conducted in close proximity with the week 24 or early termination visits (within 5 days prior to week 24 visit or within approximately 5 days post early termination visit).

With:

Subjects are required to participate in two telephone interviews, lasting approximately one-hour each. Entry interviews will be conducted within **seven** (**7**) days from first IP dose; exit interviews will be conducted in close proximity with the week 24 or early termination visits (within **7** days prior to week 24 visit or within approximately **14** days post early termination visit**. If possible, within 7 days from early termination notification will be targeted**).

Section: 12.8, Appendix 8. Substudy: Qualitative Interview Substudy to 'A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache, Substudy Duration and Substudy Procedures, paragraph 3

Replace:

At participating sites, randomized subjects that successfully dosed with IP will be provided an option to opt in to the qualitative interview substudy and be provided with additional information about the substudy. Clinical site staff will explain the substudy objectives and procedures to the subject and obtain a supplementary written informed consent. The subject will sign two copies of the consent form. Sites will send a wet-ink version of the informed consent to Evidera and will retain a copy of the signed informed consent for their study records. Clinic site staff will provide Evidera contact information for each participant enrolled in the substudy and Evidera will subsequently contact each participant to schedule interviews.

With:

At participating sites, **subjects** will be provided an option to opt in to the qualitative interview substudy and be provided with additional information about the substudy **either at time of screening for the main study or after randomization and successful dosing with IP, depending on site preference**. Clinical site staff will explain the substudy objectives and procedures to the subject and obtain a supplementary written informed consent. The subject will sign two copies of the consent form. Sites will send a wet-ink version of the informed consent to Evidera and will retain a copy of the signed informed consent for their study records. Clinic site staff will provide Evidera contact information for each participant enrolled in the substudy and Evidera will subsequently contact each participant to schedule interviews.

Section: 12.8, Appendix 8. Substudy: Qualitative Interview Substudy to 'A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache, Substudy Duration and Substudy Procedures, paragraph 6-7

Replace:

Patients will take part in a telephone-based entry interview at the start of treatment (no later than 5 days from first IP dose), lasting approximately one-hour. Subjects will be specifically

asked about their experiences with functioning during and in between migraine attacks before receiving the initial study dose.

During the exit interview portion of the substudy, the subjects will take part in a final telephone interview, approximately one-hour in duration (within 5 days prior to week 24 visit or within approximately 5 days post early termination visit). Subjects will be specifically asked to compare their experience from the end of the DBTP or early termination visit around changes in functioning during and in between migraine attacks after receiving the preventive treatment for migraine. After open ended questions, if subjects do not mention the impacts they noted at entry interview, the interviewer will probe on those impacts. The interviews will also explore what aspects of improvement or worsening of their migraine (eg, frequency, severity, duration) drove the changes, as well as the 'meaningfulness' of change/no change reported by the patient.

With:

Patients will take part in a telephone-based entry interview at the start of treatment (no later than **7** days from first IP dose), lasting approximately one-hour. Subjects will be specifically asked about their experiences with functioning during and in between migraine attacks before receiving the initial study dose.

During the exit interview portion of the substudy, the subjects will take part in a final telephone interview, approximately one-hour in duration (within **7** days prior to week 24 visit or within approximately **14** days post early termination visit**. If possible, within 7 days from early termination notification will be targeted**). Subjects will be specifically asked to compare their experience from the end of the DBTP or early termination visit around changes in functioning during and in between migraine attacks after receiving the preventive treatment for migraine. After open ended questions, if subjects do not mention the impacts they noted at entry interview, the interviewer will probe on those impacts. The interviews will also explore what aspects of improvement or worsening of their migraine (eg, frequency, severity, duration) drove the changes, as well as the 'meaningfulness' of change/no change reported by the patient.

Section: 12.8, Appendix 8. Substudy: Qualitative Interview Substudy to 'A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel group Study to Evaluate the Efficacy

and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache, Substudy Sample Size, paragraph 2

Delete:

The substudy sample will be a subset of up to 30 subjects who will be recruited from ~~up to six (6)~~ Amgen-identified clinical sites participating in the clinical trial 20170703 across the United States.

Amendment 1

Protocol Title: A Phase 4, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Adults With Chronic Migraine and Medication Overuse Headache

Amgen Protocol Number Erenumab 20170703

EudraCT Number 2018-003342-16

Amendment Date: 19 April 2019

Rationale:

This protocol is being amended to:

- Modify primary, secondary, and exploratory endpoints
- Simplify study procedures to reduce patient burden and emulate per label monitoring requirements
- Simplify eligibility requirements
- Make editorial and administrative edits