Title Page

Protocol Title:		A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Children (6 to < 12 Years) and Adolescents (12 to < 18 Years) With Chronic Migraine (OASIS PEDIATRIC [CM])
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Trade Name:		Not applicable
Sponsor	**Name of Sponsor:**	Amgen Inc.
	Address:	One Amgen Center Drive, Thousand Oaks, CA, 91320, USA
	Telephone Number:	+1 (805) 447-1000
Key Sponsor Contact	**Name:**	[redacted] MD, PhD
	Address:	One Amgen Center Drive, Thousand Oaks, CA, 91320, USA
	Telephone Number:	[redacted]
	Email Address:	[redacted]
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Investigator's Agreement:

I have read the attached protocol entitled A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Children (6 to < 12 Years) and Adolescents (12 to < 18 Years) With Chronic Migraine (OASIS PEDIATRIC [CM]), dated **06 October 2023**, and agree to abide by all provisions set forth therein.

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_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Children (6 to < 12 Years) and Adolescents (12 to < 18 Years) With Chronic Migraine (OASIS PEDIATRIC [CM])

Short Protocol Title: Efficacy and Safety of Erenumab in Pediatric Subjects With Chronic Migraine

Study Phase: 3

Indication: Prevention of Migraine

Rationale

Migraine prevention is an area of large unmet medical need, with existing therapies having modest efficacy and being poorly tolerated. Most treatments currently used are approved only in adults, except topiramate (approved in the United States (US) in adolescents ≥ 12 years of age) and propranolol (approved in Finland in children ≥ 7 years of age). Calcitonin gene-related peptide (CGRP) receptor antagonism is a novel approach to migraine preventive therapy.

Erenumab is a human monoclonal antibody directed against the canonical CGRP receptor and inhibits the action of CGRP. Due to its long half-life, erenumab selectively antagonizes the CGRP receptor for prolonged periods, which makes erenumab suitable for the preventative treatment of migraine. The present study is a pivotal, phase 3 trial intended to assess the efficacy and safety of erenumab for prevention of migraine in pediatric subjects (6 to < 18 years of age) with chronic migraine (CM).

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared with placebo on the change in monthly migraine days (MMD) from baseline to week 9 through week 12 (month 3) of the double-blind treatment phase (DBTP).	• Change from baseline in MMD to week 9 through week 12 (month 3) of the DBTP. The primary estimand consists of: • The target population, which is the adolescent subjects (12 to < 18 years of age) diagnosed with CM. • The primary endpoint, which is the change in MMD from baseline to week 9 through week 12 (month 3) of the DBTP. • The summary measure, which is the difference between the mean of the primary endpoint for the combined erenumab dose group and placebo. • The intercurrent event is treatment discontinuation. The treatment effect will be estimated for all randomized subjects regardless of adherence to treatment.
Secondary	
• To evaluate the effect of erenumab compared with placebo on the change in monthly headache days from baseline to week 9 through week 12 (month 3) of the DBTP.	• Change from baseline in monthly headache days to week 9 through week 12 (month 3) of the DBTP.
• To evaluate the effect of erenumab compared with placebo on the proportion of subjects with at least 50% reduction in MMD from baseline to week 9 through week 12 (month 3) of the DBTP.	• Achievement of at least 50% reduction in MMD from baseline to week 9 through week 12 (month 3) of the DBTP.
• To evaluate the effect of erenumab compared with placebo on the change in MMD from baseline to the average of the first 3 months (week 1 through week 12) of the DBTP.	• Change from baseline in MMD to the average of the first 3 months (week 1 through week 12) of the DBTP.

Objectives	**Endpoints**
• To evaluate the effect of erenumab compared with placebo on the change in monthly average severity of migraine attacks from baseline to week 9 through week 12 (month 3) of the DBTP.	• Change from baseline in monthly average severity of migraine attacks to week 9 through week 12 (month 3) of the DBTP.
• To evaluate the effect of erenumab compared with placebo on the change in migraine-related disability and productivity as measured by the modified Pediatric Migraine Disability Assessment (PedMIDAS) from baseline to **week 9 through week 12 (**month 3**)** of the DBTP.	• Change from baseline in migraine-related disability and productivity as measured by the modified PedMIDAS to **week 9 through week 12 (**month 3**)** of the DBTP.
Safety	
• To evaluate the safety and tolerability of erenumab.	**All Subjects:** • Treatment-emergent adverse events. • Clinical laboratory values, electrocardiograms (ECGs), and vital signs. • Serum bone metabolism markers (C terminal telopeptide of type 1 collagen [CTX] and procollagen Type 1 N-propeptide [P1NP]). • Anti-erenumab antibodies. • Growth and development as assessed by physical measurements based on age-adjusted Z-scores for height and weight. • Treatment-emergent suicidal ideation and behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS). **Group 1 Only (24-week DBTP):** • Injection site pain as assessed by Faces Pain Scale-Revised (FPS-R) at day 1 and week 20. **Group 2 Only (12-week DBTP):** • **Injection site pain as assessed by FPS-R at day 1 and week 8.**

Hypothesis

In pediatric subjects with CM, the combined erenumab dose group has a greater reduction from baseline to week 9 through week 12 (month 3) in MMD when compared with placebo.

Overall Design

This study will evaluate the efficacy and safety of erenumab in migraine prevention in children (6 to < 12 years) and adolescents (12 to < 18 years) with CM.

Subjects consented and enrolled under the original protocol or protocol Amendment 01 will be identified as Group 1 and will follow the assessments outlined in Table 2-1 (Group 1 Schedule of Activities).

Subjects consented and enrolled under protocol Amendment 02, or any future amendments will be identified as Group 2 and will follow the assessments outlined in Table 2-2 (Group 2 Schedule of Activities).

For all subjects, the study consists of a randomized, double-blind, parallel-group, placebo-controlled phase followed by a 40-week optional dose-level-blinded extension phase (DLBEP), during which all subjects receive erenumab at the blinded dose level. The planned length of participation in the study for an individual subject is up to 83 weeks **for Group 1 and up to 71 weeks for Group 2**, which includes the following:

- initial screening phase (up to 3 weeks).
- 4-week prospective baseline phase
- **double-blind treatment period (DBTP):**
  - **Group 1:** 24-week DBTP
  - **Group 2: 12-week DBTP**
- 40-week optional DLBEP
- 12-week safety follow-up (16 weeks after the last dose of investigational product)

Following the 4-week baseline phase, subjects will enter the DBTP and be randomized in a 2:1:1 allocation ratio to **receive** placebo, erenumab dose level 1, or erenumab dose level 2, respectively, with a resulting overall placebo to erenumab allocation ratio of 1:1.

Within each randomized erenumab dose level group, each subject will receive 1 of 2 erenumab doses, determined by the subject's body weight as follows:

	Body Weight	
Erenumab Dose Level	< 40 kg	≥ 40 kg
Dose level 1	35 mg	70 mg
Dose level 2	70 mg	140 mg

At **the end of the DBTP (**week 24 **for subjects in Group 1; week 12 for subjects in Group 2)**, subjects in each treatment group will **have the option to roll** over into the 40-week optional DLBEP.

Subjects who received erenumab treatment during the DBTP will continue to receive the same erenumab dose during the optional DLBEP. Subjects who received placebo during the DBTP will be re-randomized in a 1:1 ratio to receive either erenumab dose level 1 or erenumab dose level 2, also in a double-blinded fashion, at a dose corresponding to their body-weight group at the end of the baseline phase, pre-randomization (during the day 1 visit).

Subjects will have a safety follow-up visit **12 weeks after the last visit or** 16 weeks after the last dose of investigational product, whether the subject discontinues treatment at any point during the study or at the end of the study, after completing the optional DLBEP.

Number of Subjects

Approximately 286 subjects will be enrolled in the study. The cohort of adolescents (from 12 to < 18 years old) will include approximately 256 subjects and the cohort of children (from 6 to < 12 years) will include up to 30 subjects. Based on epidemiological data, CM is much less frequent prior to adolescence; children with CM are allowed into the study for exploratory purposes.

Randomization for the DBTP and optional DLBEP will be performed using an interactive response technology (IRT) system; and subjects will be stratified by age group (children or adolescent), region (North America or Rest of World), and prior preventive treatment failure (yes or no), failure being defined as lack of efficacy or tolerability issues.

Summary of Subject Eligibility Criteria

Children and adolescents should have**:**

- a history of migraine with or without aura for ≥ 12 months

- **a h**istory of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine days per month in each of the 3 months prior to screening

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2

Treatments

Investigational product (ie, erenumab and placebo) will be dosed monthly (QM), subcutaneously (SC).

The 2 dose levels will be designated for each of 2 body-weight groups, based on body-weight assessed at the end of the baseline phase, pre-randomization (during the day 1 visit): a low body-weight group of subjects of < 40 kg and a high body-weight group of subjects of ≥ 40 kg.

- The dose for subjects in the body-weight group < 40 kg is either 35 mg (dose level 1), or 70 mg (dose level 2) SC QM.
- The dose for subjects in the body-weight group ≥ 40 kg is either 70 mg (dose level 1), or 140 mg (dose level 2) SC QM.

Investigational product doses according to the body-weight group will be determined at pre-randomization on day 1 and will not be adjusted for individual subjects during the study. The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen.

Erenumab will be packaged in either (1) 3-mL clear glass vials containing 1 mL of 70 mg/mL erenumab or (2) prefilled syringes (PFSs) containing 1 mL of 70 mg/mL erenumab. Placebo vials and PFS will be packaged to match erenumab but will not contain erenumab.

Group 1 (24-week DBTP):

Double-blind erenumab dose level 1, dose level 2, or placebo will be administered during the 24-week DBTP (ie, at day 1 and weeks 4, 8, 12, 16, and 20). Erenumab dose level 1 or dose level 2 will be administered during the 40-week optional DLBEP (ie, at weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, and 60).

Group 2 (12-week DBTP):

Double-blind erenumab dose level 1, dose level 2, or placebo will be administered during the 12-week DBTP (at day 1 and weeks 4 and 8). Erenumab dose level 1 or dose level 2 will be administered during the 40-week optional DLBEP (at weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48).

Procedures

At the end of the screening phase, only subjects who meet all eligibility criteria will be randomized into the DBTP of the study.

After the parents or legal representatives sign the informed consent and subjects (if developmentally appropriate) sign the assent, subjects will enter the screening phase of up to 7 weeks. The screening phase is composed of an initial screening (up to 3 weeks) followed by a 4-week baseline phase. At the day 1 visit, eligible subjects will be enrolled and randomized into the DBTP and will begin to receive double-blind investigational product QM SC.

Group 1 subjects will use an electronic diary (eDiary) every day throughout the baseline phase, DBTP, and during month 1 of the DLBEP (weeks 25 **to** 28), month 6 of the DLBEP (middle of the DLBEP, weeks 45 **to** 48), and month 10 (last month of the DLBEP, weeks 61 **to** 64).

Group 2 subjects will use an eDiary every day throughout the baseline phase, DBTP, and during month 1 of the DLBEP (weeks 13 to 16), month 6 of the DLBEP (middle of the DLBEP, weeks 33 to 36), and month 10 (last month of the DLBEP, weeks 49 to 52).

The eDiary will report information about **the subject's** migraine and non-migraine headaches and acute headache medication use. Subjects will have scheduled study visits monthly from week -4 through the end of the optional DLBEP. The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing the informed consent/assent and all adverse events and adverse device effects (Amgen PFS device) observed by the investigator or reported by the subject that occur after first dose of investigational product, through the end of the safety follow-up visit are reported using the Event **electronic** case report form (**e**CRF).

All serious adverse events will be collected, recorded and reported to the sponsor or designee **immediately and no later than** 24 hours **after the investigator's awareness of the event.** The investigator will submit any updated serious adverse event data to the sponsor **immediately and no later than** 24 hours of it being available.

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 **(Group 1) and Table 2-2 (Group 2).**

Statistical Considerations

The primary analysis will be performed when the last adolescent subject completes the **last visit of the DBTP (**week 24 **for Group 1; week 12 for Group 2)** assessments or the early termination visit **during the DBTP**. The final analysis for the study will be performed after all subjects (children and adolescents) have completed the study through the safety follow-up visit or discontinued from the study.

The primary estimand consists of:

- The target population, which is the adolescent subjects (12 to < 18 years of age) diagnosed with CM.
- The primary endpoint, which is the change in MMD from baseline to week 9 through week 12 (month 3) of the DBTP.
- The summary measure, which is the difference between the mean of the primary endpoint for combined erenumab dose group and placebo.
- The intercurrent event is treatment discontinuation. The treatment effect will be estimated for all randomized subjects regardless of adherence to treatment.

Formal statistical analyses using statistical models and hypothesis testing will be performed for the adolescent cohort and for the combined erenumab dose against placebo.

The primary comparison of change from baseline in MMD between the combined erenumab group and the placebo group during the DBTP in adolescent subjects will be analyzed using a linear mixed effects repeated measure model including treatment group, baseline value, stratification factors of region and prior preventive treatment failure status, scheduled visit **(as applicable)**, and the interaction of treatment group with scheduled visit, without any imputation for missing data. Subjects will be used as a random effect. The mean change from baseline for each treatment group, and the treatment difference, 95% confidence intervals, and p-value will be reported. Sensitivity analyses for handling missing data **may be performed**.

The continuous secondary endpoints will be analyzed using the same methods as for the primary endpoint, performing the same sensitivity analyses. For the secondary endpoint of achievement of at least 50% reduction from baseline in MMD, a stratified Cochran-Mantel-Haenszel (CMH) test will be used after the missing data are imputed as nonresponse. Sensitivity analyses for **handling** missing data **may be performed**.

If the primary endpoint is statistically significantly different from placebo in the adolescent age group at the 5% significance level based on the primary analysis, the

secondary efficacy endpoints will then be tested to maintain the family-wise type 1 error rate of 5% within this age group: as a gate-keeping process, the following 2 secondary endpoints will first be tested statistically using the Hochberg method at the 5% significance level:

- Change from baseline in monthly headache days to week 9 through week 12 (month 3) of the DBTP.
- Achievement of at least 50% reduction in MMD from baseline to week 9 through week 12 (month 3) of the DBTP.

If these 2 secondary endpoints are statistically significantly different from placebo, the rest of the secondary endpoints based on the primary analysis will be tested using the Hochberg method at the 5% significance level:

- Change from baseline in MMD to the average of the first 3 months (week 1 through week 12) of the DBTP.
- Change from baseline in monthly average severity of migraine attacks to week 9 through week 12 (month 3) of the DBTP.
- Change from baseline in migraine-related disability and productivity as measured by the modified PedMIDAS to **week 9 through the end of the 12 weeks (**month 3**)** of the DBTP.

The treatment effect for each erenumab dose compared to placebo will be evaluated in a descriptive, quantitative manner.

In addition to subgroup analysis by age group (6 to < 12 years and 12 to < 18 years), other prespecified subgroups for the primary and secondary efficacy endpoints will include:

- sex (male; female)
- pubertal status (pre-pubertal; post-pubertal). Subgroups will be defined according to a Pubertal Maturation Self-assessment (Tanner Staging) Scale
- Cognitive Behavioral Therapy (CBT) status (with CBT; without CBT)
- prior preventive treatment failure status (yes; no)

These prespecified analyses will be performed for the primary and secondary endpoints.

All safety analyses will be performed for the DBTP and the optional DLBEP separately. The respective safety analysis set will include all randomized subjects who received at least 1 dose of investigational product within each phase. Subjects will be analyzed according to the randomized treatment unless the incorrect treatment was received during the entire duration of the treatment.

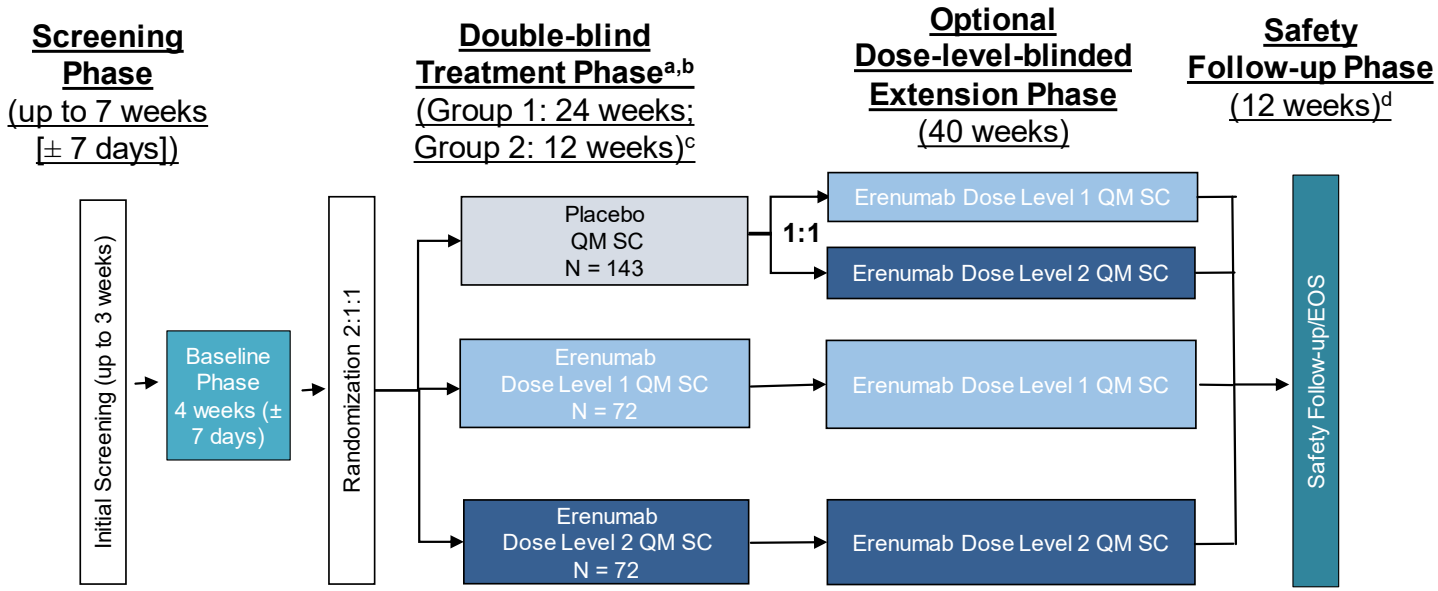
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



DBTP = double-blind treatment phase; QM = monthly; SC = subcutaneous
[a] Blinded sample size re-estimation in adolescents will occur when ≥ 50% of adolescents are enrolled and have completed 12 weeks of the DBTP.
[b] Primary endpoint will be evaluated from week 9 through week 12 (month 3) of the DBTP.

[c] **Group 1 (24-week DBTP): subjects consented and enrolled under the original protocol or protocol Amendment 1; Group 2 (12-week DBTP): subjects consented and enrolled under protocol Amendment 2 or any future amendments.**
[d] The safety follow-up will occur 12 weeks after the last visit or 16 weeks after the last dose of investigational product.

2.2 Schedule of Activities

Table 2-1. Group 1 (24-week DBTP) Schedule of Activities

	Screening Phase		Double-blind Treatment Phase (24 Weeks) (± 5 Days)							Optional Dose-level-blinded Extension Phase (40 Weeks) (± 5 Days)										SFU[b]/ EOS
Procedure	**Initial Screening (up to 3 Weeks)**	**Baseline Wk -4 (±7 days)**	**Day 1[a]**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24/ ET[b,c]**	**Wk 28**	**Wk 32**	**Wk 36**	**Wk 40**	**Wk 44**	**Wk 48**	**Wk 52**	**Wk 56**	**Wk 60**	**Wk 64/ ET[b]**	**16 Weeks After Last Dose of IP**
GENERAL AND SAFETY ASSESSMENTS																				
Informed consent[d]	X								**X**											
Assent form[d]	X								**X**											
Inclusion and exclusion criteria	X		X																	
Demographics	X																			
Physical examination	X		X						X						X				X	X
Physical measurements (weight and height)[e]	X[t]		X						X						X				X	X
Medical history	X																			
Substance use	X								X											
Prior/concomitant medications recording	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
ECG	X		X	X		X			X										X	
Vital signs[f]	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X

Footnotes defined on last page of this table.

Table 2-1. Group 1 (24-week DBTP) Schedule of Activities

Procedure	Screening Phase		Double-blind Treatment Phase (24 Weeks) (± 5 Days)							Optional Dose-level-blinded Extension Phase (40 Weeks) (± 5 Days)										SFU[b]/ EOS
	Initial Screening (up to 3 Weeks)	Baseline Wk -4 (±7 days)	Day 1[a]	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET[b,c]	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64/ ET[b]	16 Weeks After Last Dose of IP
Menses start date (FCBP only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events/Adverse device effect collection/ reporting[g]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse event collection/reporting[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ISR assessment[h]			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		
Injection site pain assessment (FPS-R)[i]			X					X												
LABORATORY ASSESSMENTS																				
Urine drug screen	X		For all subjects: testing as needed throughout study based on investigator's clinical suspicion																	
Serum pregnancy test (FCBP only)[j]	X																			
Urine pregnancy test (FCBP only)[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X		X			X			X							X	X

Footnotes defined on last page of this table.

Table 2-1. Group 1 (24-week DBTP) Schedule of Activities

Procedure	Screening Phase		Double-blind Treatment Phase (24 Weeks) (± 5 Days)							Optional Dose-level-blinded Extension Phase (40 Weeks) (± 5 Days)										SFU[b]/ EOS
	Initial Screening (up to 3 Weeks)	Baseline Wk -4 (±7 days)	Day 1[a]	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET[b,c]	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64/ ET[b]	16 Weeks After Last Dose of IP
Chemistry	X		X	X		X			X			X							X	X
Hepatitis sample collection	X																			
Bone metabolism markers; serum[k]			X						X										X	
Anti-erenumab antibodies; serum[l]			X	X		X			X			X			X				X	X
Biomarker Development; blood			X																	
Pharmacokinetic sampling			X	X		X			X			X			X				X	X
Pharmacogenetic Studies (Optional)			X																	
STUDY TREATMENT																				
Call to IRT system[p]	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Randomization			X[q]							X[r]										
Investigational product administration[s]			X	X	X	X	X	X[u]		X	X	X	X	X	X	X	X	X	X	

Footnotes defined on last page of this table.

Table 2-1. Group 1 (24-week DBTP) Schedule of Activities

Procedure	Screening Phase		Double-blind Treatment Phase (24 Weeks) (± 5 Days)							Optional Dose-level-blinded Extension Phase (40 Weeks) (± 5 Days)											SFU[b]/ EOS
	Initial Screening (up to 3 Weeks)	Baseline Wk -4 (±7 days)	Day 1[a]	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ ET[b,c]	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 56	Wk 60	Wk 64/ ET[b]	16 Weeks After Last Dose of IP
SUBJECT COMPLETED ASSESSMENTS																				
Modified PedMIDAS[n]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PGIC						X			X					X					X	
PHQ-A	X	X	X																	
Pubertal maturation self-assessment[o]		X							X										X	
eDiary COA[m]		From baseline through Wk 24								Wk 25 through Wk 28				Wk 45 through Wk 48				Wk 61 through Wk 64		

COA = Clinical Outcome Assessment; C-SSRS = Columbia-Suicide Severity Rating Scale; DBTP = double-blind treatment phase; DLBEP = dose-level-blinded extension phase; ECG = electrocardiogram; eDiary = electronic diary; **EOS = end of study;** ET = early termination; FCBP = females of childbearing potential; FPS-R = Faces Pain Scale-Revised; ICF = informed consent form; IP = investigational product; ISR = injection site reaction; IRT = interactive response technology; PedMIDAS = Pediatric Migraine Disability Assessment; **PFS = prefilled syringe;** PGIC = Patient Global Impression of Change; PHQ-A = patient health questionnaire-9 modified for adolescents; **S**FU = **safety** follow-up; Wk = week (end of week x)

[a] The day 1 visit (enrollment day) has a window of +7 consecutive calendar days. Day 1 visit must occur 28 to 35 days after the week -4 visit date. All study visit target dates are to be calculated from the day 1 visit date. All assessments on day 1 should be done pre-randomization, except for the following: investigational product administration, ISR assessment, injection site pain assessment (FPS-R).

[b] A subject who permanently discontinues the investigational product during the DBTP is to complete all remaining study visits and procedures of the DBTP and the safety follow-up visit 16 weeks after the last dose of investigational product. If a subject is unable to continue in the study, they are to complete the study procedures for the week 24/**ET** visit and the safety follow-up visit (16 weeks after the last dose of investigational product). A subject who permanently discontinues investigational product during the **optional** DLBEP will complete the week 64/ET visit and the safety follow-up visit 12 weeks after the last dose of investigational product.

[c] During the week 24 visit, all assessments for the DBTP should be performed before subjects are to be re-randomized into the **optional** DLBEP. Investigational product administration, followed by ISR assessments, are to be performed last.

[d] All subjects developmentally **able to understand and** personally sign and date the assent and, in all cases, the parent or legal representative must sign and date the ICF before commencement of study-specific activities/procedures.
[e] Height and weight will be measured without footwear (shoes, slippers, sandals, or socks), head gear (hat, cap, hair bows, comb, ribbons), and wearing only light clothes.
[f] Systolic/diastolic blood pressure, heart rate, respiratory rate, and body temperature will be collected. Blood pressure will be obtained after the subject has been in a semi-recumbent position (partial semi-Fowler's position) or supine position in a rested and calm state for at least 5 minutes. At least 2 measurements (separated by at least 5 minutes of rest) should be made and the average recorded. The position selected for a subject should be used for all blood pressure measurements throughout the study.
[g] Serious adverse events will be collected after the signature of the ICF. Adverse events and adverse device effects (Amgen PFS device) will be collected after the first dose of investigational product.
[h] An injection site reaction assessment should be performed approximately 20 to 30 minutes after investigational product administration. If injection site reactions are confirmed by the investigator, they should be appropriately reported as adverse events.
[i] Injection Site Pain should be assessed after the first and last investigational product administration of the DBTP (ie, day 1 and week 20 visits). The FPS-R (Appendix 13) self-assessment should be provided to subjects twice at approximately 1 and 15 minutes after investigational product administration.
[j] Serum and urine pregnancy test will be performed for all FCBP subjects unless surgically sterile. Additional on-treatment urine 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.
[k] C-terminal telopeptide of type 1 collagen (CTX) and procollagen Type 1 N-propeptide (P1NP) will be collected at the beginning (**day 1** pre**-**randomization) and the end of the DBTP as well as at week 64/ET study visit. Due to the circadian rhythm of these markers and the potential confounding effect of fasting, these samples need to be taken in the morning, in fasting conditions.
[l] Subjects who test positive for neutralizing antibodies to the investigational product at the final scheduled study visit must be offered additional follow-up testing. This testing is to occur every 3 months, starting from when the site has been notified of the positive result, until: neutralizing **or binding** antibodies are no longer detectable or the subject has been followed for a period of at least 1 year (± 4 weeks) after the last dose of the investigational product. Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-erenumab antibody response must also be asked to return for additional follow-up testing. **Additional follow-up testing may extend beyond the SFU/EOS visit.**
[m] Subjects (or their caregivers, if developmentally appropriate) should complete the eDiary on a daily basis including the baseline phase, the **24-week** DBTP and 3 specified 1 month periods of the **optional** DLBEP: week 25 to week 28 (first month of the DLBEP), week 45 to week 48 (sixth month of the DLBEP), week 61 to week 64 (**tenth** and last month of the DLBEP).
[n] The modified (monthly) PedMIDAS is to be completed during applicable study visits before investigational product administration.
[o] All subjects (or their caregivers, if developmentally appropriate) will complete a Pubertal Maturation Self-assessment (Tanner Stage) at baseline and at week 64 or the ET visit. The assessment consists of a form with figures for each developmental stage with the safety goal of classifying subjects as pre-puberty (stage 1) or post-puberty (all other stages [ie, stages 2 to 5]) for exploratory analyses. If **ET** occurs at week 24 or prior, then this assessment is required.
[p] Sites will contact IRT system for the following: to enter the subject into the screening phase, DBTP, and the **optional** DLBEP, to obtain the investigational product assignment, register the end of investigational product, and to register **ET** or completion. Subject data will be collected in the IRT System including, but not limited to, reason for screen fail (if applicable).
[q] Randomization for the DBTP (using the IRT System) must occur after the completion of all baseline phase procedures and before the first dose of the double-blind investigational product, the ISR assessment, and the injection site pain assessment (FPS-R).
[r] Treatment assignment in **the optional** DLBEP (using the IRT System) occurs at week 24 after the completion of all week 24 procedures except investigational product administration and the ISR assessment.
[s] Investigational product administration should be completed after all assessments, except for the ISR and injection site pain assessments (FPS-R). After the first investigational product administration of **the** DBTP and DLBEP (day 1 and week 24 visits), subjects will remain on site for at least 2 hours and after each subsequent investigational product administration (week 4 to week 20 and week 28 to week 60), subjects will remain on site at least 30 minutes.

[t] Weight only.
[u] Sites are encouraged to evaluate decision or confirm commitment to participate in DLBEP from week 20 onwards.

Table 2-2. Group 2 (12-week DBTP) Schedule of Activities

Procedure	Screening Phase		Double-blind Treatment Phase (12 Weeks) (± 5 Days)				Optional Dose-level-blinded Extension Phase (40 Weeks) (± 5 Days)										SFU[b]/ EOS
	Initial Screening (up to 3 Weeks)	Baseline Wk -4 (±7 days)	Day 1[a]	Wk 4	Wk 8	Wk 12/ET[b,c]	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ ET[b]	16 Weeks After Last Dose of IP
GENERAL AND SAFETY ASSESSMENTS																	
Informed consent[d]	X					X											
Assent form[d]	X					X											
Inclusion and exclusion criteria	X		X														
Demographics	X																
Physical examination	X		X			X						X				X	X
Physical measurements (weight and height)[e]	X[t]		X			X						X				X	X
Medical history	X																
Substance use	X					X											
Prior/concomitant medications recording	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
ECG	X		X	X		X										X	
Vital signs[f]	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Menses start date (FCBP only)		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	

Footnotes defined on last page of this table.

Table 2-2. Group 2 (12-week DBTP) Schedule of Activities

Procedure	Screening Phase		Double-blind Treatment Phase (12 Weeks) (± 5 Days)					Optional Dose-level-blinded Extension Phase (40 Weeks) (± 5 Days)										SFU[b]/ EOS
	Initial Screening (up to 3 Weeks)	Baseline Wk -4 (±7 days)	Day 1[a]	Wk 4	Wk 8	Wk 12/ET[b,c]		Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ ET[b]	16 Weeks After Last Dose of IP
Adverse events/Adverse device effect collection/ reporting[g]			X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Serious adverse event collection/reporting[g]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	
ISR assessment[h]			X	X	X		X	X	X	X	X	X	X	X	X	X		
Injection site pain assessment (FPS-R)[i]			X		X													
LABORATORY ASSESSMENTS																		
Urine drug screen	X		For all subjects: testing as needed throughout study based on investigator's clinical suspicion															
Serum pregnancy test (FCBP only)[j]	X																	
Urine pregnancy test (FCBP only)[j]		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X		X				X							X	X
Chemistry	X		X	X		X				X							X	X
Hepatitis sample collection	X																	

Footnotes defined on last page of this table.

Table 2-2. Group 2 (12-week DBTP) Schedule of Activities

Procedure	Screening Phase		Double-blind Treatment Phase (12 Weeks) (± 5 Days)				Optional Dose-level-blinded Extension Phase (40 Weeks) (± 5 Days)										SFU[b]/ EOS
	Initial Screening (up to 3 Weeks)	Baseline Wk -4 (±7 days)	Day 1[a]	Wk 4	Wk 8	Wk 12/ET[b,c]	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ ET[b]	16 Weeks After Last Dose of IP
Bone metabolism markers; serum[k]			X			X										X	
Anti-erenumab antibodies; serum[l]			X	X		X			X			X				X	X
Biomarker Development; blood			X														
Pharmacokinetic sampling			X	X		X			X			X				X	X
Pharmacogenetic Studies (Optional)			X														
STUDY TREATMENT																	
Call to IRT system[p]	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X
Randomization			X[q]				X[r]										
Investigational product administration[s]			X	X	X		X	X	X	X	X	X	X	X	X		
SUBJECT COMPLETED ASSESSMENTS																	
Modified PedMIDAS[n]			X	X	X	X		X	X	X	X	X	X	X	X	X	
PGIC						X					X					X	
PHQ-A	X	X	X														

Footnotes defined on last page of this table.

Table 2-2. Group 2 (12-week DBTP) Schedule of Activities

Procedure	Screening Phase		Double-blind Treatment Phase (12 Weeks) (± 5 Days)				Optional Dose-level-blinded Extension Phase (40 Weeks) (± 5 Days)										SFU[b]/ EOS
	Initial Screening (up to 3 Weeks)	Baseline Wk -4 (±7 days)	Day 1[a]	Wk 4	Wk 8	Wk 12/ET[b,c]	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52/ ET[b]	16 Weeks After Last Dose of IP
Pubertal maturation self-assessment[o]		X				X										X	
eDiaryCOA[m]			From baseline through Wk 12				Wk 13 through Wk 16				Wk 33 through Wk 36				Wk 49 through Wk 52		

COA = Clinical Outcome Assessment; C-SSRS = Columbia-Suicide Severity Rating Scale; DBTP = double-blind treatment phase; DLBEP = dose-level-blinded extension phase; ECG = electrocardiogram; eDiary = electronic diary; EOS = end of study; ET = early termination; FCBP = females of childbearing potential; FPS-R = Faces Pain Scale-Revised; ICF = informed consent form; IP = investigational product; ISR = injection site reaction; IRT = interactive response technology; PedMIDAS = Pediatric Migraine Disability Assessment; PFS = prefilled syringe; PGIC = Patient Global Impression of Change; PHQ-A = patient health questionnaire-9 modified for adolescents; SFU = safety follow-up; Wk = week (end of week x)

[a] The day 1 visit (enrollment day) has a window of +7 consecutive calendar days. Day 1 visit must occur 28 to 35 days after the week -4 visit date. All study visit target dates are to be calculated from the day 1 visit date. All assessments on day 1 should be done pre-randomization, except for the following: investigational product administration, ISR assessment, injection site pain assessment (FPS-R).

[b] A subject who permanently discontinues the investigational product during the DBTP is to complete all remaining study visits and procedures of the DBTP and the safety follow-up visit 16 weeks after the last dose of investigational product. If a subject is unable to continue in the study, they are to complete the study procedures for the week 12/ET and the safety follow-up visit (16 weeks after the last dose of investigational product). A subject who permanently discontinues investigational product during the optional DLBEP will complete the week 52/ET visit and the safety follow-up visit 16 weeks after the last dose of investigational product.

[c] During the week 12 visit, all assessments for the DBTP should be performed before subjects are to be re-randomized into the optional DLBEP. Investigational product administration, followed by ISR assessments, are to be performed last.

[d] All subjects developmentally able to understand and personally sign and date the assent and, in all cases, the parent or legal representative must sign and date the ICF before commencement of study-specific activities/procedures.

[e] Height and weight will be measured without footwear (shoes, slippers, sandals, or socks), head gear (hat, cap, hair bows, comb, ribbons), and wearing only light clothes.

[f] Systolic/diastolic blood pressure, heart rate, respiratory rate, and body temperature will be collected. Blood pressure will be obtained after the subject has been in a semi-recumbent position (partial semi-Fowler's position) or supine position in a rested and calm state for at least 5 minutes. At least 2 measurements (separated by at least 5 minutes of rest) should be made and the average recorded. The position selected for a subject should be used for all blood pressure measurements throughout the study.

[g] Serious adverse events will be collected after the signature of the ICF. Adverse events and adverse device effects (Amgen PFS device) will be collected after the first dose of investigational product.

[h] An injection site reaction assessment should be performed approximately 20 to 30 minutes after investigational product administration. If injection site reactions are confirmed by the investigator, they should be appropriately reported as adverse events.

[i] Injection Site Pain should be assessed after the first and last investigational product administration of the DBTP (ie, day 1 and week 8 visits). The FPS-R (Appendix 13) self-assessment should be provided to subjects twice at approximately 1 and 15 minutes after investigational product administration.

[j] Serum and urine pregnancy test will be performed for all FCBP subjects unless surgically sterile. Additional on-treatment urine 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.

[k] C-terminal telopeptide of type 1 collagen (CTX) and procollagen Type 1 N-propeptide (P1NP) will be collected at the beginning (day 1 pre-randomization) and the end of the DBTP as well as at week 52/ET study visit. Due to the circadian rhythm of these markers and the potential confounding effect of fasting, these samples need to be taken in the morning, in fasting conditions.

[l] Subjects who test positive for neutralizing antibodies to the investigational product at the final scheduled study visit must be offered additional follow-up testing. This testing is to occur every 3 months, starting from when the site has been notified of the positive result, until: neutralizing or binding antibodies are no longer detectable or the subject has been followed for a period of at least 1 year (± 4 weeks) after the last dose of the investigational product. Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-erenumab antibody response must also be asked to return for additional follow-up testing. Additional follow-up testing may extend beyond the SFU/EOS visit.

[m] Subjects (or their caregivers, if developmentally appropriate) should complete the eDiary on a daily basis including the baseline phase, the 12-week DBTP and 3 specified 1 month periods of the optional DLBEP: week 13 to week 16 (first month of the DLBEP), week 33 to week 36 (sixth month of the DLBEP), week 49 to week 52 (tenth and last month of the DLBEP).

[n] The modified (monthly) PedMIDAS is to be completed during applicable study visits before investigational product administration.

[o] All subjects (or their caregivers, if developmentally appropriate) will complete a Pubertal Maturation Self-assessment (Tanner Stage) at baseline and at week 52 or the ET visit. The assessment consists of a form with figures for each developmental stage with the safety goal of classifying subjects as pre-puberty (stage 1) or post-puberty (all other stages [ie, stages 2 to 5]) for exploratory analyses. If ET occurs at week 12 or prior, then this assessment is required.

[p] Sites will contact IRT system for the following: to enter the subject into the screening phase, DBTP, and the optional DLBEP, to obtain the investigational product assignment, register the end of investigational product, and to register ET or completion. Subject data will be collected in the IRT System including, but not limited to, reason for screen fail (if applicable).

[q] Randomization for the DBTP (using the IRT System) must occur after the completion of all baseline phase procedures and before the first dose of the double-blind investigational product, the ISR assessment, and the injection site pain assessment (FPS-R).

[r] Treatment assignment in the optional DLBEP treatment phase (using the IRT System) occurs at week 12 after the completion of all week 12 procedures except investigational product administration and the ISR assessment.

[s] Investigational product administration should be completed after all assessments, except for the ISR and injection site pain assessments (FPS-R). After the first investigational product administration of the DBTP and DLBEP (day 1 and week 12 visits), subjects will remain on site for at least 2 hours and after each subsequent investigational product administration (week 4 to week 8 and week 16 to week 48), subjects will remain on site at least 30 minutes.

[t] Weight only.

[u] Sites are encouraged to evaluate decision or confirm commitment to participate in DLBEP from week 8 onwards.

3. Introduction

3.1 Study Rationale

Migraine prevention is an area of large unmet medical need, with existing therapies having modest efficacy and being poorly tolerated. Most treatments currently used are approved only in adults, except topiramate (approved in the United States in adolescents ≥ 12 years of age) and propranolol (approved in Finland in children ≥ 7 years of age). Calcitonin gene-related peptide (CGRP) receptor antagonism is a novel approach to migraine preventive therapy.

Erenumab is a human monoclonal antibody directed against the canonical CGRP receptor and inhibits the action of CGRP. Due to its long half-life, erenumab selectively antagonizes the CGRP receptor for prolonged periods, which makes erenumab suitable for the preventative treatment of migraine. The present study is a pivotal, phase 3 trial intended to assess the efficacy and safety of erenumab for prevention of migraine in pediatric subjects with chronic migraine (CM).

The current study was designed according to the principles outlined in European Medicines Agency (EMA) Guideline on Clinical Investigation of Medicinal Products for the Treatment of Migraine (CPMP/EWP/788 Rev 1; 31 July 2007) and the International Headache Society (IHS) Guidelines for Controlled Trials of Drugs in Migraine (Tfelt-Hansen et al, 2012), and based on feedback obtained from the EMA and US Food and Drug Administration (FDA). This allows for an evaluation of the true effect of the treatment controlling for placebo response, which can be substantial in studies of migraine prevention (Tfelt-Hansen et al, 2012). An active control group was not included as internal validity is supported by a robust development program, including 4 placebo-controlled studies in over 2600 adult subjects. In addition, a key concern regarding the inclusion of an established active comparator is the side effect profiles associated with these treatments and their likelihood to functionally unblind treatment assignments. The lack of established active comparators is further underlined by the results of a recent pediatric study in migraine prevention (CHAMP study) (Powers et al, 2016). These side effects may contribute to higher discontinuation rates in active comparator arms, making interpretation problematic.

Rationale for Endpoints

For migraine prevention studies, both in adults and pediatrics, the current EMA guidelines (CPMP/EWP/788 Rev 1; 31 July 2007) recommend assessing change in the number of monthly migraine attacks as the primary efficacy endpoint. Difficulties with

defining the duration of a migraine attack have led to proposals for number of monthly migraine days (MMD) as an alternative, simpler, and more sensitive efficacy endpoint. Change in the number of MMD or monthly headache days (including both migraine and non-migraine headaches, typically tension-type headache) have both been used as primary or secondary endpoints in the 2 most recent migraine prevention programs approved in adults: topiramate (Silberstein et al, 2004) and onabotulinumtoxinA (Diener et al, 2010). Reduction of monthly headache days has also been used in pediatrics (Powers et al, 2016), and feedback from pediatric headache experts suggests that this endpoint might prove more sensitive in pediatrics since migraine pain features are often bilateral and associated symptoms can be more difficult to assess by young subjects; therefore, making the distinction between migraine and non-migraine headache more difficult and thus less relevant. The IHS guidelines for controlled trials of drugs in migraine (Tfelt-Hansen et al, 2012) recommend, without preference, either migraine attacks or migraine days for the primary endpoint.

For the reasons above, and taking into account feedback from regulatory authorities, the primary endpoint of the study will be the change from baseline in MMD to the 4-week period from week 9 through week 12 (month 3) of the double-blind treatment phase (DBTP) in adolescents (children are allowed into the study on an exploratory basis). The time points/periods of interest for assessing secondary efficacy measures during the DBTP include the following:

1. Month 3 of the DBTP (week 9 through week 12).
2. **Month 1, 2, and** 3 of the DBTP (week 1 through week 12).

The efficacy measures and the assessment time points/periods to be assessed include:

- Monthly migraine days (1 and 2).
- Monthly headache days (1 above).
- Achievement of ≥ 50% reduction from baseline in MMD (1 above).
- Monthly average severity of migraine attacks (1 above).

These different endpoints are in line with feedback received from the Pediatric Committee (PDCO)/EMA and the Pediatric Review Committee (PeRC)/FDA in order to evaluate the efficacy of erenumab after 3 months of treatment. The endpoints on MMD, monthly headache days and achievement of ≥ 50% reduction from baseline in MMD are all considered standard, clinically relevant measures useful for clinicians in the evaluation of efficacy of a migraine prevention treatment.

Exploratory endpoints include the change from baseline in all efficacy variables described above, at all assessment time points during the **study** with the addition of monthly acute headache medication days and monthly modified Pediatric Migraine Disability Assessment (PedMIDAS) scores (except that the modified PedMIDAS score at **week 9 through week 12 (**month 3**)** is designated as a secondary endpoint), 2 other common measures of efficacy of migraine prevention and disability, respectively, as well as the Patient Global Impression of Change (PGIC).

Refer to Section 5.6 for the definition of migraine day. The definition of migraine day is consistent with the diagnostic criteria of migraine and probable migraine according to the International Classification of Headache Disorder (ICHD-3) and is consistent with that implemented in the phase 3 episodic migraine (EM) prophylaxis trials for erenumab in adults with the exception that in this study the specific features for pediatric migraine included in the ICHD-3 criteria (ie, reduced duration, possibility of bilateral pain features, and associated symptoms inferred by behavior) are taken into account.

3.2 Background

3.2.1 Disease

3.2.1.1 Migraine Spectrum

Migraine headaches are recurring and commonly incapacitating headaches with specific clinical pain features (ie, unilateral, throbbing, moderate to severe, exacerbated by physical activities) and associated symptoms (nausea, vomiting, photophobia, phonophobia). Migraine is diagnosed if a patient has recurring headache attacks, with or without aura (at least 2 or 5 respectively), and is divided into 2 broad classifications, EM and CM, based on the monthly frequency of headache days. According to the ICHD-3 (IHS, 2013) criteria, EM is characterized by < 15 headache days per month; while CM is characterized by ≥ 15 headache days per month, of which ≥ 8 days must meet criteria for migraine with or without aura, for > 3 consecutive months. Beyond sharing most of the clinical features of the attacks (ie, pain features, accompanying symptoms, triggers), approximately 2.5% of individuals with EM progress to CM over the course of a year (Bigal and Lipton, 2008), and CM often remits to EM (2-year transition rate of 26%) (Manack et al, 2011). Furthermore, migraine commonly appears in childhood, increases in prevalence during adolescence, and reaches a peak prevalence in those 30 to 39 years of age in both women (24.4%) and men (7.4%) (Lipton et al, 2007). The similar clinical features along with other epidemiological and neurological evidence (such as similar altered central neuronal processing and activation

of the trigeminovascular system) support conceptualizing migraine as a continuum or spectrum disorder, in which EM may evolve into CM or vice versa (Katsarava et al, 2012; Aurora, 2009).

3.2.1.2 Incidence and Prevalence

Migraine prevalence increases from childhood and early adult life until 30 to 50 years of age (depending on specific migraine subgroups), after which prevalence starts to decline. The overall adult prevalence is 11.7% in the US, 14.6% in Canada, and 14.7% in Europe (Stovner and Andree, 2010; Lipton et al, 2007), and migraine is 3 times more frequent in women than men.

There is no literature reporting migraine before 2 years of age, which is likely due not only to the rarity of the condition at this early age but also to the atypical presentations migraine can have and the difficulties inherent to diagnosis in infants.

Prevalence figures for specific age subgroups reveal a pattern of slowly increasing overall prevalence from childhood into adolescence (Table 3-1). In the 3- to 5-year age range, migraine has a higher prevalence in boys than in girls, followed by an equal prevalence until 12 to 14 years of age. During and following the transition from adolescence into adulthood, there is a higher migraine prevalence in women than in men (Merikangas, 2011; Abu Arafeh et al, 2010). Six global studies covering groups from 3 to 13 years of age reported a mean overall migraine prevalence (EM and CM) of 3.5% in boys and 4.7% in girls. When data from children 12 to 14 years of age was included, the mean prevalence increased to 4.7% in boys and 7.0% in girls. Data from adolescents and young adults < 20 years of age showed a prevalence of 6.0% in boys and 9.7% in girls (review and meta-analysis of 37 global population-based studies on migraine prevalence in children and adolescents < 20 years of age from 1990 to 2007 [N = 131 228; migraine subjects = 10 093]; Abu Arafeh et al, 2010).

There are limited data reporting on prevalence of migraine in children. Two population based studies in children 5 to 12 years of age reported a CM prevalence of 0.8% and 0.6% and EM prevalence of 2.96% and 9.0%, respectively (Arruda et al, 2010), although, a CM prevalence of 0.8% appears high for children, particularly given that a 0.8% prevalence has been observed in studies of adolescents (Krogh et al, 2015; Lipton et al, 2011) and some adult studies report an even lower prevalence of CM (Buse et al, 2012). Based on these limited epidemiological data, the real-world EM:CM ratio for the children age group appears to likely be in the range of 5:1 to 15:1 (Ozge et al, 2013; Arruda and Bigal, 2012). These figures are consistent with the

concept that CM is uncommon in childhood but tends to increase in prevalence during adolescence or thereafter, reaching a peak prevalence in the 40 to 49 years of age range (1.89% in women and 0.79% in men; Buse et al, 2012).

Table 3-1. Migraine Prevalence in Children and Adolescents

Study Reference	Age Group (Years)	N (n with migraine)	Diagnosis	Prevalence (%)
Arruda et al, 2010[a]	5 to 12	1994 (75)	EM or CM	3.76
	≤ 6			2.58
	7			2.86
	8			3.25
	9			4.92
	≥ 10			5.50
	5 to 12	1994 (16)	CM	0.8
	≤ 6			0.65
	7			1.14
	8			0.50
	9			0.41
	≥ 10			1.72
Abu-Arafeh et al, 2010[b]	< 14	33 900 (1967)	Overall	5.8
			boys	4.7
			girls	7.0
	< 20	131 228 (10093)	Overall	7.7
			boys/men	6.0
			girls/women	9.7
Lipton et al, 2007[c]	12 to 17	13 951	EM	
			boys	4.9
			girls	7.3
Buse et al, 2012[c]	12 to 17	13 951	CM	
			boys	0.24
			girls	0.46

CM = chronic migraine; EM = episodic migraine

[a] Population-based study implemented in primary and secondary schools in Brazil. N = 1995 surveys responded followed by phone interviews.

[b] Review and meta-analysis of 37 global population-based studies on migraine prevalence in children and adolescents aged < 20 years from 1990 to 2007 (N = 13 1228; with migraine = 10 093); global studies included countries in the European Union, North and South America, Middle-East, Asia, Brazil, Australia.

[c] Data corresponding to the 12 to 17 years of age group extracted from American Migraine Prevalence and Prevention Study (AMPP) study: (responded surveys accounted for 162 576 household members 12 years of age or older, out of whom 13 951 were 12 to 17 years of age).

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).

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

A detailed description of the chemistry, pharmacology, efficacy, and safety of erenumab is provided in the Erenumab **i**nvestigator's **b**rochure.

3.3 Benefit/Risk Assessment

3.3.1 Therapeutic Context

Migraine headache is the most common primary headache disorder and can significantly impact functioning. In children and adolescents, migraine impacts particularly school life (in terms of performance and lost days) and social life. Migraine prevalence in the general population increases from childhood (~3%) through adolescence (~6%) and into adulthood (11.7% in the United States, Lipton et al, 2007 and 14.7% in Europe, Stovner and Andree, 2010). After puberty, migraine is more common in women than men (3:1). Migraine can be divided into episodic migraine (< 15 headache days per month) and chronic migraine (≥ 15 headache days per month of which ≥ 8 days must be days with migraine) (IHS, 2013). Chronic migraine typically starts to be diagnosed in adolescence; in adults the EM:CM ratio is approximately 9:1. Episodic migraine and CM can be considered as parts of the same continuum of disease, sharing headache pain features (eg, unilateral, throbbing, moderate to severe, exacerbated by physical activities), and associated symptoms (eg, nausea, vomiting, photophobia, phonophobia) (Katsarava et al, 2012; Aurora, 2009).

Pharmacological treatment of migraine can be divided into acute (abortive) treatment to reduce pain and shorten the attacks, or preventive (prophylactic) treatment to reduce

their frequency and severity. In clinical practice, prophylactic medications are considered when patients have > 3 migraine headaches per month or when migraines are so severe that they interfere with normal activities (Gunner et al, 2008; Damen et al, 2006). While some medications may be used in clinical practice, none is licensed for the treatment of migraine in children, except for propranolol (only approved in children ≥ 7 years of age in Finland) and topiramate (only approved for adolescents in the US). Furthermore, the evidence supporting the use of current migraine preventive medications in the pediatric population is very limited. In fact, the Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine (CHAMP Study), a phase 3, multicenter, double-blind, placebo controlled trial funded by the US National Institutes of Health (NIH), showed that there were no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline or topiramate, as compared to placebo, and the active drugs were associated with higher rates of adverse events (Powers et al, 2016). Therefore, there remains an unmet need for new migraine prophylactic treatments for children and adolescents.

3.3.2 Key Benefits

The clinical benefits of treatment with erenumab are derived from its target, the CGRP receptor. There is substantial evidence that the CGRP pathway is relevant to migraine pathophysiology (Hay and Poyner, 2009; Durham, 2004; Edvinsson and Goadsby, 1994). Erenumab is a fully human monoclonal IgG2 that binds to and blocks the canonical CGRP receptor. Although the biological consequences of blocking the CGRP receptor are not fully understood, possible effects of blocking the CGRP receptor include the inhibition of pain transmission in the trigeminal pathway. Because erenumab has long half-life, high affinity and exquisite selectivity (Erenumab **i**nvestigator's **b**rochure), it is hypothesized that it antagonizes the CGRP receptor for prolonged periods, preventing activation by CGRP and resulting in the prevention of migraine headaches.

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

convenience (Q4W injections with the option of self-administration), and rapid onset of effect.

Similar benefits in efficacy are expected for pediatric patients.

3.3.3 Key Risks and Mitigation

To date, based on comprehensive review of the safety data, including non-clinical and clinical data, erenumab has demonstrated a favorable safety profile, and no key risks that could materially alter the benefit-risk profile of erenumab have been identified. Erenumab has been evaluated in a series of safety pharmacology and toxicology studies in cynomolgus monkeys of up to 6 months of treatment with erenumab. The developmental age of the animals in these toxicology studies ranged from the equivalent of human late childhood/early adolescence through sexual maturity. There were no differences in toxicological profile between younger and older animals in these studies. An enhanced pre/postnatal development (ePPND) study in cynomolgus monkeys also demonstrated that erenumab had no effects on fetal/infant loss, growth or development. While there is no data from juvenile toxicology studies and the clinical experience is limited to adults, erenumab is not anticipated to have a different safety profile in pediatric subjects.

3.3.3.1 Risks

In adults, the safety profile of erenumab has been favorable in clinical trials and in the post-marketing setting. A limited number of adverse drug reactions (injection site reactions, constipation, muscle spasm, and pruritus) have been identified at low frequencies (< 5%) in adults in clinical trials. There is no safety data on these adverse drug reactions or other adverse events from pediatric population in completed clinical trials. In the long-term use of erenumab, the safety profile remained consistent through 5 years of open-label treatment. In post-marketing settings, hypersensitivity reactions (including rash, angioedema and anaphylactoid reactions), and constipation with serious complications have been reported. In addition, oral sores (eg, stomatitis, mouth ulceration, oral mucosal blistering), alopecia and rash (eg, rash papular, exfoliative rash, rash erythematous, urticaria, blister) have been observed in post-marketing surveillance.

Reference should be made to the currently approved **i**nvestigator's **b**rochure and Prescribing Information, where Aimovig® is approved, for further data on erenumab.

3.3.3.2 Mitigations

Non-clinical: A juvenile toxicology study in cynomolgus monkey (11 to 12 months old) to determine potential toxicity and toxicokinetics of erenumab has been completed. In this study, no effects were observed on any parameter tested, including body weight, neurobehavioral observations, learning ability (Wisconsin Learning Test), cardiovascular investigations, bone mineral content, bone mineral density, radiographic analyses of skeletal development, hematology, coagulation, clinical chemistry, urinalysis, macroscopic observations, organ weights, or toxicologically relevant effects on microscopic evaluation. The dose of 50 mg/kg twice weekly was considered a NOAEL with Cmax of 1100 μg/mL and AUC0-7d of 154,000 μg•day/mL at week 52.

Clinical: In this study, **the** enrollment **was** staggered by age with adolescents 12 to < 18 years of age starting enrollment first. Children 6 to < 12 years of age **commenced** enroll**ment after data from the 52-week juvenile toxicology study in cynomolgus monkeys (Study 1770628) and** pharmacokinetic (PK) and preliminary safety data from **the** phase 1 **study (Study 20160172) became** available.

Further, to mitigate risks associated with a potential hypersensitivity reaction, after the first investigational product administration of **the** DBTP and DLBEP (day 1 and week 24 visits **for Group 1; day 1 and week 12 visits for Group 2**) subjects will remain on site for at least 2 hours and after each subsequent investigational product administration (**w**eek 4 to **w**eek 20 and **w**eek 28 to **w**eek 60 **for Group 1; week 4 to week 8 and week 16 to week 48 for Group 2**) subjects will remain on site at least 30 minutes.

The above benefit risk assessment supports the conduct of this clinical trial.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared with placebo on the change in monthly migraine days (MMD) from baseline to week 9 through week 12 (month 3) of the double-blind treatment phase (DBTP).	• Change from baseline in MMD to week 9 through week 12 (month 3) of the DBTP. The primary estimand consists of: • The target population, which is the adolescent subjects (12 to < 18 years of age) diagnosed with CM. • The primary endpoint, which is the change in MMD from baseline to week 9 through week 12 (month 3) of the DBTP. • The summary measure, which is the difference between the mean of the primary endpoint for the combined erenumab dose group and placebo. • The intercurrent event is treatment discontinuation. The treatment effect will be estimated for all randomized subjects regardless of adherence to treatment.
Secondary	
• To evaluate the effect of erenumab compared with placebo on the change in monthly headache days from baseline to week 9 through week 12 (month 3) of the DBTP.	• Change from baseline in monthly headache days to week 9 through week 12 (month 3) of the DBTP.
• To evaluate the effect of erenumab compared with placebo on the proportion of subjects with at least 50% reduction in MMD from baseline to week 9 through week 12 (month 3) of the DBTP.	• Achievement of at least 50% reduction in MMD from baseline to week 9 through week 12 (month 3) of the DBTP.
• To evaluate the effect of erenumab compared with placebo on the change in MMD from baseline to the average of the first 3 months (week 1 through week 12) of the DBTP.	• Change from baseline in MMD to the average of the first 3 months (week 1 through week 12) of the DBTP.

Objectives	Endpoints
• To evaluate the effect of erenumab compared with placebo on the change in monthly average severity of migraine attacks from baseline to week 9 through week 12 (month 3) of the DBTP.	• Change from baseline in monthly average severity of migraine attacks to week 9 through week 12 (month 3) of the DBTP.
• To evaluate the effect of erenumab compared with placebo on the change in migraine-related disability and productivity as measured by the modified Pediatric Migraine Disability Assessment (PedMIDAS) from baseline to **week 9 through week 12 (**month 3**)** of the DBTP.	• Change from baseline in migraine-related disability and productivity as measured by the modified PedMIDAS to **week 9 through week 12 (**month 3**)** of the DBTP
Safety	
• To evaluate the safety and tolerability of erenumab.	**All Subjects:** • Treatment-emergent adverse events. • Clinical laboratory values, electrocardiograms (ECGs), and vital signs. • Serum bone metabolism markers (C terminal telopeptide of type 1 collagen [CTX] and procollagen Type 1 N-propeptide [P1NP]). • Anti-erenumab antibodies. • Growth and development as assessed by physical measurements based on age-adjusted Z-scores for height and weight. • Treatment-emergent suicidal ideation and behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS). **Group 1 Only (24-week DBTP):** • Injection site pain as assessed by Faces Pain Scale-Revised (FPS-R) at day 1 and week 20. **Group 2 Only (12-week DBTP):** • **Injection site pain as assessed by FPS-R at day 1 and week 8.**

Objectives	Endpoints
Exploratory	
• To evaluate the effect of erenumab compared with placebo on change in monthly acute headache medication treatment days from baseline to assessment time points.	• Change from baseline in monthly acute headache medication treatment days at assessment time points.
• To evaluate the effect of erenumab compared with placebo on change in MMD from baseline to assessment time points.	• Change from baseline in MMD at assessment time points.
• To evaluate the effect of erenumab compared with placebo on change in monthly headache days from baseline to assessment time points.	• Change from baseline in monthly headache days at assessment time points.
• To evaluate the effect of erenumab compared with placebo on the change in monthly headache days from baseline to the average of the first 3 months (week 1 through week 12) of the DBTP.	• Change from baseline in monthly headache days to the average of the first 3 months (week 1 through week 12) of the DBTP.
Group 1 Only (24-week DBTP): • To evaluate the effect of erenumab compared with placebo on the change in monthly headache days from baseline to the average of the 6-month DBTP (week 1 through week 24).	**Group 1 Only (24-week DBTP):** • Change from baseline in monthly headache days to the average of the 6-month DBTP (week 1 through week 24).
• To evaluate the effect of erenumab compared with placebo on change in monthly average severity of migraine attacks from baseline to assessment time points.	• Change from baseline in monthly average severity of migraine attacks at assessment time points.
• To evaluate the effect of erenumab compared with placebo on change in monthly average severity of migraine episodes from baseline to assessment time points.	• Change from baseline in monthly average severity of migraine episodes at assessment time points.
• To evaluate the effect of erenumab compared with placebo on change in monthly migraine episodes from baseline to assessment time points.	• Change from baseline in average monthly migraine episodes at assessment time points.
• To evaluate the effect of erenumab compared with placebo on the proportion of subjects with at least 50% reduction in MMD from baseline to assessment time points.	• Achievement of at least 50% reduction from baseline in MMD at assessment time points.

Objectives	Endpoints
Group 1 Only (24-week DBTP): • **To evaluate the effect of erenumab compared with placebo on the change in MMD from baseline to the average of the 6-month DBTP (week 1 through week 24).**	**Group 1 Only (24-week DBTP):** • **Change from baseline in MMD to the average of the 6-month DBTP (week 1 through week 24).**
• To evaluate the effect of erenumab compared with placebo on the proportion of subjects with at least 50% reduction in monthly headache days from baseline to assessment time points.	• Achievement of at least 50% reduction from baseline in monthly headache days at assessment time points.
• To evaluate the effect of erenumab compared with placebo on change in migraine-related disability and productivity as measured by the modified PedMIDAS from baseline to assessment time points.	• Change from baseline in migraine-related disability and productivity as measured by the modified PedMIDAS at assessment time points.
• To evaluate the effect of erenumab compared with placebo on the Patient Global Impression of Change (PGIC) at **week 12 (**month 3**)** of the DBTP.	• PGIC at **week 12 (**month 3**)** of the DBTP.
• To evaluate the effect of erenumab compared with placebo on the change in MMD from baseline to **week 9 through week 12 (**month 3**)** of the DBTP for the entire population (6 to < 18 years).	• Change from baseline in MMD to **week 9 through week 12 (**month 3**)** of the DBTP for the entire population (6 to < 18 years).
• To evaluate long-term efficacy of erenumab.	• Endpoints listed above will be summarized in the dose-level-blinded extension period.
• To characterize erenumab pharmacokinetics (PK) in children and adolescents.	• To characterize erenumab exposure.
• To characterize immunogenicity of erenumab.	• Anti-erenumab antibody formation.

4.2 Hypothesis

In pediatric subjects with CM, the combined erenumab dose group has a greater reduction from baseline to week 9 through week 12 (month 3) in MMD when compared with placebo.

5. Study Design

5.1 Overall Design

This study will evaluate the efficacy and safety of erenumab in migraine prevention in children (6 to < 12 years) and adolescents (12 to < 18 years) with CM.

Subjects consented and enrolled under the original protocol or protocol Amendment 1 will be identified as Group 1 and will follow the assessments outlined in Table 2-1 (Group 1 Schedule of Activities).

Subjects consented and enrolled under protocol Amendment 02, or any future amendments will be identified as Group 2 and will follow the assessments outlined in Table 2-2 **(Group 2 Schedule of Activities).**

For all subjects, the study consists of a randomized, double-blind, parallel-group, placebo-controlled phase followed by a 40-week optional dose-level-blinded extension phase (DLBEP), during which all subjects receive erenumab at the blinded dose level.

In this study the enrollment **was** staggered by age **with** adolescents 12 to < 18 years of age start**ing** enrollment first. Children 6 to < 12 years of age **commenced** enrollment **after the 52-week, juvenile toxicology study in cynomolgus monkeys (Study 1770628) and** PK and safety data from the phase 1 study **(Study 20160172) became** available.

For details on investigational product dosing, refer to Section 5.4.

Following the 4-week baseline phase, subjects will enter the DBTP and be randomized in a 2:1:1 allocation ratio to placebo, erenumab dose level 1, or erenumab dose level 2, respectively, with a resulting overall placebo to erenumab allocation ratio of 1:1. Within each randomized erenumab dose level group, each subject will receive 1 of the 2 erenumab doses, determined by the subject's body weight as follows:

	Body Weight	
Erenumab Dose Level	< 40 kg	≥ 40 kg
Dose level 1	35 mg	70 mg
Dose level 2	70 mg	140 mg

At **the end of the DBTP (**week 24 **for subjects in Group 1; week 12 for subjects in Group 2)**, subjects in each treatment group will have the option to roll over into the 40-week **optional** DLBEP. Subjects who received erenumab treatment during the DBTP will continue to receive the same erenumab dose in a double-blinded fashion during the optional DLBEP. Subjects who received placebo during the DBTP will be

re-randomized in a 1:1 ratio to receive either erenumab dose level 1 or erenumab dose level 2, also in a double-blinded fashion, at a dose corresponding to their body-weight group at the end of the baseline phase, pre-randomization (during day 1 visit).

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 286 subjects will be enrolled in the study. The cohort of adolescents (from 12 to < 18 years old) will include approximately 256 subjects and the cohort of children (from 6 to < 12 years) will include up to 30 subjects.

On day 1, subjects will be randomized in a 2:1:1 allocation ratio to placebo, erenumab dose level 1, or erenumab dose level 2, respectively, with a resulting overall placebo to erenumab allocation ratio of 1:1. During the optional DLBEP, subjects who received erenumab treatment during the DBTP will continue to receive the same erenumab dose. Subjects who received placebo during the DBTP will be re-randomized (at the week 24 visit **for Group 1; at the week 12 visit for Group 2**) in a 1:1 ratio to receive either erenumab dose level 1 or erenumab dose level 2. All subjects, site staff, and Sponsor will remain blinded to the dose level during the optional DLBEP.

Randomization for the DBTP will be stratified by age group (adolescents or children), by region (North America or Rest of World), and by prior preventive treatment failure (yes or no), failure being defined as lack of efficacy or tolerability issues.

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 77 investigative sites globally will be included in the study. Sites that do not enroll subjects within 4 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

An individual subject is considered to have completed the study if he/she has completed the last scheduled procedure shown in the Schedule of Activities. 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 planned length of participation in the study for an individual subject is up to 83 weeks **for Group 1 and up to 71 weeks for Group 2**, which includes the following:

- initial screening phase (up to 3 weeks)
- 4-week prospective baseline phase
- **double-blind treatment period (DBTP):**
  - **Group 1:** 24-week DBTP
  - **Group 2: 12-week DBTP**
- 40-week optional DLBEP
- 12-week safety follow-up (16 weeks after the last dose of investigational product)

5.4 Justification for Investigational Product Dose

The selected doses for each body-weight group **were** chosen based on the results of the pivotal CM (Study 20120295) and EM (Study 20120296) studies in adults that evaluated the 70 and 140 mg doses. In each study, both doses were efficacious when compared to placebo, although erenumab 140 mg showed numerically greater efficacy compared with erenumab 70 mg at most time points tested on most of the efficacy endpoints.

Body weight was the only significant covariate influencing the PK of erenumab in adults. Therefore**,** dosing in pediatric patients is planned according to 2 body-weight groups: < 40 kg (the expected weight of most children 6 to < 12 years of age) and ≥ 40 kg (the expected weight of most adolescents 12 to < 18 years of age) (McDowell et al, 2008). Subjects weighing < 40 kg will receive either 35 mg or 70 mg erenumab subcutaneously (SC). These 2 doses are expected to provide low-body weight subjects (most of them children) similar exposures as that from the 70 mg and 140 mg doses in the adults. Subjects weighing ≥ 40 kg will receive either 70 mg or 140 mg SC erenumab. These 2 doses are expected to provide high-body weight subjects (most of them adolescents) similar exposures as that for the 70 mg and 140 mg doses in adults, given the significant overlap in body weights that is anticipated between subjects in this body-weight group and adults (eg, the lower body weight quartile in Study 20120296 [EM pivotal study] included subjects from 43 to 63 kg). Treatments will be allocated to qualifying subjects within either group in a randomized fashion using IRT system.

The QM dosing interval is supported by PK data in adults, in addition to clinical efficacy and safety data in adult studies. The effective half-life is approximately 28 days at

therapeutic doses/concentrations. Following SC administrations once **Q4W**, erenumab was able to achieve drug exposures throughout the dosing interval that resulted in clinically meaningful efficacy. Alternative regimens using other dosing intervals were not formally tested.

The PK profile of erenumab data is being studied in the phase 1 Study 20160172 in children and adolescents with migraine 6 to < 18 years of age with migraine to confirm that safety and exposure of erenumab in pediatric subjects are similar to that in adults. **The final analysis of this study showed that mean exposures were similar between subjects weighing < 40 kg who received 35 mg Q4W and subjects weighing ≥ 40 kg who received 70 mg Q4W. Mean exposures were also similar between subjects weighing < 40 kg who received 70 mg Q4W and subjects weighing ≥ 40 kg who received 140 mg Q4W. The extent and variability of erenumab exposures in children and adolescents appears to be similar to adults from previous studies. The adverse event profiles for subjects weighing < 40 kg and those weighing ≥ 40 kg were generally consistent across cohorts and dosing groups. The safety profile of erenumab in children (aged 6 to < 12 years) and adolescents (aged 12 to < 18 years) appears to be consistent with the known safety profile of erenumab in adults, and no new or unexpected safety signals were identified. Therefore, these results support the proposed dosing regimen for the phase 3 studies (this study [Study 20160354] and [Study 20150125]).**

5.5 Age Groups, Sex Subgroups, and Prior Preventive Treatment Failure Subgroup

The **cohort** of adolescents will include up to approximately 256 subjects.

Due to the epidemiology of migraine in adolescents with a female to male ratio of 2 to 3:1, it is expected that more adolescent females than males will ultimately be enrolled. The group of adolescents will include at least **20**% males and at least 30% subjects with inadequate response (ie, failure, this being defined as lack of efficacy and/or tolerability issues) to 1 or more prior preventive treatment(s). Enrollment of female adolescents will stop once its target sample size has been reached.

Chronic migraine is relatively infrequent in children and it only becomes more frequent during adolescence (prevalence ranging from 0.8% to 1.7%; Buse et al, 2012). It is expected that only up to 30 children with CM will be enrolled for exploratory purposes. In children, it is expected that the sex ratio will be approximately 1:1, in line to epidemiological data; therefore, no sex ratio is considered required for this subgroup.

It is expected that a significant portion of the pediatric population using erenumab, once available, will be comprised of patients who have failed ≥ 1 migraine preventive treatment due to either lack of efficacy or poor tolerability. Given increasing migraine prevalence during adolescence and the limited use of migraine prevention in children, it is anticipated that most pediatric patients having failed ≥ 1 migraine preventive treatments will be adolescents. In order to evaluate the safety and efficacy of erenumab in this specific subgroup, ≥ 30% of adolescents will have failed ≥ 1 migraine preventive treatment (see list of migraine prevention treatments [1 to 3] in Table 7-2).

Prior migraine preventive failure will be assessed by the investigator and will be based on **inadequate response (defined as** lack of efficacy and/or tolerability issues**)**. There is no limit to the number of prior migraine preventive treatment failures due to tolerability issues. However, the number of failures due to no therapeutic response are limited according to exclusion criterion 203 (see Section 6.2).

No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally accepted therapeutic dose(s) based on the investigator's assessment. Lack of sustained response, partial, suboptimal response to a medication, or failure to tolerate a therapeutic dose do not constitute cases of no therapeutic response.

5.6 Definitions of Terms Used in Endpoints

Migraine Day: Any calendar day in which the subject develops 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 ≥ 30 minutes, and meeting at least 1 of the following criteria (1 and/or 2):

1. ≥ 2 of the following pain features:
   - Unilateral or bilateral.
   - Throbbing.
   - Moderate to severe.
   - Exacerbated with exercise/physical activity.
2. ≥ 1 of the following associated symptoms:
   - Nausea and/or vomiting.
   - Photophobia and phonophobia (these could be reported by the subject or inferred from the behavior in children).

If the subject took a migraine-specific medication (ie, triptan or ergotamine derivative) or to treat an aura and/or headache on a calendar day, then it will be counted as a qualified migraine headache regardless of the duration and pain features/associated symptoms.

Headache Day: Any calendar day in which the subject develops a qualified headache (onset, continuation, or recurrence of the headache). A qualified headache is defined when at least 1 of the following criteria is met:

- A qualified migraine headache (including, for example, an aura-only event that is treated with acute migraine-specific medication).
- A qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache.
- A headache of any duration for which acute headache treatment is administered.

Acute Headache Medication Treatment Day: Any calendar day during which the subject took an acute headache medication (migraine specific or non-migraine specific).

Acute Migraine-specific Medication Treatment Day: Any calendar day during which the subject took a migraine-specific medication (ie, triptan or ergotamine derivative).

Monthly eDiary Data: Data collected by the electronic diary (eDiary) based on the subject's monthly investigational product dosing schedule when at least 14 days of eDiary data are collected within that interval. Monthly frequency measurements will be prorated to 28-day equivalents.

Migraine Attack: An episode of any qualified migraine headache. The following rules will be used to distinguish an attack of long duration from 2 attacks, or to distinguish between attacks and relapses:

- A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (ie, ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as 1 attack instead of 2 attacks.
- An attack treated successfully with medication but with relapse within 48 hours (ie, ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as 1 attack.

Migraine Episode: An episode of any qualified migraine headache with a unique start time/end time and collected directly from the eDiary.

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). This log may be completed and updated via an IRT **system**.

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent/assent must be obtained (see Appendix 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

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

101 Children (6 to < 12 years of age) or adolescent (12 to < 18 years of age) at the time of signing, if developmentally appropriate, the formal assent to participate to the study.

102 Subject's parent or legal representative has provided written informed consent before initiation of any study-specific activities/procedures.

103 History of migraine (with or without aura) for ≥ 12 months before screening according to the IHS Classification ICHD-3 (Headache Classification Committee of the International Headache Society, 2013) based on medical records and/or subject self-report or parents' or legal representative's report.

The following ICHD-3 specifications for pediatric migraine (subjects aged < 18 years), should be considered for the diagnosis of migraine:

- Attacks may last 2 to 72 hours.
- Migraine headache is more often bilateral than in adults; unilateral pain usually emerges in late adolescence or early adult life.
- Migraine headache is usually frontotemporal. Occipital headache in children is rare and calls for diagnostic caution.
- A subset of otherwise typical subjects have facial location of pain, which is called 'facial migraine' in the literature; there is no evidence that these subjects form a separate subgroup of migraine subjects.
- In young children, photophobia and phonophobia may be inferred from their behavior.

104 History of ≥ 15 headache days per month of which ≥ 8 headache days were assessed by the subject as migraine days per month in each of the 3 months prior to screening (refer to Section 5.6 for definition of headache day).

Criteria to be assessed prospectively during the 4-week baseline phase and confirmed before randomizing the subject into the DBTP:

105 Migraine frequency: ≥ 8 migraine days based on the eDiary data during the last 28 days of the baseline phase if > 28 days in duration.

106 Headache frequency of ≥ 15 headache days based on the eDiary data during the last 28 days of the baseline phase if > 28 days in duration.

107 Demonstrated at least 80% compliance with the eDiary based on the last 28 days of the baseline period, if > 28 days in duration (eg, completing eDiary items for at least 23 out of the last 28 days of the baseline phase).

6.2 Exclusion Criteria

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

Disease Related

201 History of cluster headache or hemiplegic migraine headache.

202 Chronic migraine with continuous pain, in which the subject does not have any pain free periods (of any duration) during the 1 month prior to screening.

203 No therapeutic response with > 3 of the following 10 medication categories for prophylactic treatment of migraine after an adequate therapeutic trial. These medication categories are:

- Category 1: beta blockers (eg, propranolol, atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, timolol)
- Category 2: tricyclic antidepressants (eg, amitriptyline, nortriptyline, protriptyline)
- Category 3: topiramate
- Category 4: divalproex sodium, sodium valproate
- Category 5: serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine, desvenlafaxine, duloxetine, milnacipran)
- Category 6: cyproheptadine
- Category 7: flunarizine, cinnarizine
- Category 8: botulinum toxin
- Category 9: lisinopril/candesartan
- Category 10: medications targeting the CGRP pathway

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

The following scenarios do not constitute lack of therapeutic response:

- Lack of sustained response to a medication.
- **P**artial, suboptimal response to a medication**.**
- Failure to tolerate a therapeutic dose.

Other Medical Conditions

204 Malignancy within 5 years before screening.

205 History of suicidal behavior or the subject is at risk of self-harm or harm to others as evidenced by endorsement of items 4 or 5 on the C-SSRS assessed at screening.

206 Evidence of drug or alcohol abuse or dependence within 12 months before screening, based on medical records, subject self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids or barbiturates).

207 Human immunodeficiency virus (HIV) infection by history.

208 History of seizure disorder or other significant neurological disorder other than migraine. Note: a single childhood febrile seizure is not exclusionary.

209 History of major psychiatric disorder (such as schizophrenia, schizoaffective disorder, bipolar disorder, obsessive-compulsive disorder, or pervasive developmental disorder), or current evidence of major depressive disorder based on a patient health questionnaire-9 modified for adolescents (PHQ-A) score **(**≥ 10 at screening **for adolescents or based on medical judgement of the investigator for children)**. Subjects with anxiety disorder and/or mild major depressive disorder (with PHQ-A score ≤ 9 **for adolescents or based on medical judgement of the investigator for children**) are permitted in the study if they are considered by the investigator to be stable and are taking no more than 1 medication for each disorder. Subjects must have been on a stable dose within the 3 months before the start of the baseline phase.

Prior/Concomitant Therapy

210 Use of a prohibited medication within **15 days** before the start of the baseline phase and/or during the baseline phase (refer to Table 7-2 for the lists of these medications and specific exclusion periods).

211 Use of prohibited devices (such as stimulation devices) or procedures (such as acupuncture, biofeedback, relaxation techniques, or psychotherapy) with the goal of preventing migraines, within 3 months before the start of the baseline phase and/or during the baseline phase (refer to Table 7-2 for the lists of these devices and procedures, and specific exclusion periods).

Subjects receiving Cognitive Behavioral Therapy (CBT) are excluded unless they are on a stable, maintenance phase of a CBT program for migraine for at least 3 months before the start of the baseline phase. Subjects undergoing CBT are considered on a stable, maintenance phase if they have 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 phase, only follow "booster" CBT sessions at a monthly, bimonthly or quarterly frequency.
Note: Subjects who have discontinued CBT within 3 months prior to the start of the baseline phase are eligible for the study provided that there is evidence of CBT failure/lack of efficacy prior to initial screening (per medical records or investigator's assessment).

212 Received botulinum toxin in the head and/or neck region within 4 months before the start of the baseline phase or during the baseline phase.

213 Received medication targeting the CGRP pathway within 4 months before the start of the baseline phase or during the baseline phase.

214 Taken the following for any indication in any month during the 2 months before the start of the baseline phase, or during the baseline phase:

- Opioid or butalbital-containing analgesics on ≥ 4 days per month.

Prior/Concurrent Clinical Study Experience

215 Currently receiving treatment in another investigational device or drug study, or less than 90 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Diagnostic Assessments

216 Subject has clinically significant vital signs, laboratory results, or ECG abnormality during screening that, in the opinion of the investigator, could pose a risk to subject safety or interfere with the study evaluation.

217 Hepatic disease by history or total bilirubin (TBL) ≥ 2.0 x upper limit of normal (ULN) or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3.0 x ULN, as assessed by the central laboratory at initial screening.

Other Exclusions

218 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during the study and for an additional 16 weeks after the last dose of investigational product. (Females of childbearing potential should only be included in the study after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test.)

219 Female subjects of childbearing potential unwilling to use an acceptable method of effective contraception during treatment and for an additional 16 weeks after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information.

220 Subject has known sensitivity to any of the products or components to be administered during dosing (refer to the Investigational Product Instruction Manual [IPIM] for details).

221 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 legal representative and investigator's **awareness**.

Note: completion of the eDiary can be done or assisted by the parent, caregiver, or legal representative, provided it is always the same person throughout the study.

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

6.3 Lifestyle Restrictions

6.3.1 Caffeine, Alcohol, and Tobacco

Subjects should not consume caffeine-containing beverages or tobacco within 30 minutes before each study visit, throughout the screening phase on study days where vital signs will be taken. Subjects should not participate in this study if there is evidence of drug or alcohol abuse within 12 months before screening.

6.3.2 Activity

Subjects will abstain from strenuous exercise 24 hours before each study visit.

6.4 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), assent form (as applicable), and all other subject information and/or recruitment material, if applicable (see Appendix 3).

The subject (if developmentally appropriate) or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent and assent before commencement of study-specific procedures.

The screening phase is composed of an initial screening phase (up to 3 weeks) followed by a 4-week baseline phase. At the end of the screening phase, only subjects who meet all eligibility criteria will be randomized into the DBTP of the study.

After the parents or legal representatives sign the informed consent and subjects (if developmentally appropriate) sign the assent, subjects will enter the screening phase of up to 7 weeks.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria for the study. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment **e**CRF.

If the subject, generally a child aged 6 to < 12 years, is assessed not developmentally mature to understand, date and sign the formal assents, this should be documented in the corresponding assent forms and signed by the investigator.

Before any study-related activities/procedures are performed, each subject who enters into the screening phase for the study (defined as when both the assent [if developmentally appropriate] and/or the ICF are signed and dated by the subject and the parent or legal representative, respectively) receives a unique subject identification

number. The subject identification number will be assigned by IRT System. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

The subject identification number will not necessarily be the same as the randomization number assigned for the study.

Staggered Enrollment

In this study, enrollment **was** staggered by age **with** adolescents 12 to < 18 years of age start**ing** enrolment first. Children 6 to < 12 years of age) **commenced enrollment after the 52-week juvenile toxicology study in cynomolgus monkeys (Study 1770628) and** PK and safety data from the phase 1 study **(Study 20160172)** became available.

6.5 Screen Failures

Screen failures are defined as subjects who consent/assent to participate in the clinical study but are not subsequently enrolled in the study.

A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Investigators may rescreen a subject if the investigator is reasonably certain that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Reasons to rescreen may include but are not limited to the following:

- Laboratory value(s) being out of range due to sampling error or there is a medical reason to expect that the laboratory value(s) will be within range after rescreening. Note: before screen failing and then rescreening the subject, efforts should be made to repeat the laboratory assessment(s) during the original initial screening phase.
- The subject has a medical condition that can be stabilized or resolved before the repeat screening attempt OR
- Additional time is required following the subject's last dose of an excluded medication.

Investigators are encouraged to consult with Amgen before rescreening subjects for other reasons.

Assent from the subject (when developmentally appropriate) and/or informed consent from the parent or legal representative must be obtained before the initiation of any rescreening procedures only if 30 or more days have elapsed since the date of the initial informed consent/assent by the subject's parent or legal representative. The subject is

entered into rescreening in the IRT System, and all screening procedures must be repeated except as noted in the inclusion/exclusion criteria. A subject may be screened up to 2 times (ie, no more than 1 rescreen).

Near the end of study enrollment, sites may be notified when no additional subjects will be screened or rescreened.

7. Treatments

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

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

The 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

Study Treatment Name	**Amgen Investigational Product:**[a] **Erenumab**	**Placebo**
Dosage formulation	Erenumab will be packaged in either (1) 3-mL clear glass vials containing 1 mL of 70 mg/mL erenumab or (2) prefilled syringes (PFS) containing 1 mL of 70 mg/mL erenumab.	Placebo will be packaged to match the active drug product in either (1) 3-mL clear glass vials containing 1 mL of placebo or (2) PFS containing 1 m**L** of placebo.
Unit dose strength(s)/ Dosage level(s) and dosage frequency	All subjects will be dosed QM according to the randomized dose level and body-weight group. Subjects in the low body-weight group of < 40 kg will be administered two 0.5 m**L** SC injections from glass vials as described below: • Dose level 1 (35 mg erenumab): – 1 injection of 0.5 mL of 70 mg/mL erenumab (from one vial) – 1 injection of 0.5 mL of placebo (from another vial) • Dose level 2 (70 mg erenumab): – 1 injection of 0.5 mL of 70 mg/mL erenumab (from one vial) – 1 injection of 0.5 mL of 70 mg/mL erenumab (from another vial).	All subjects will be dosed QM according to the randomized dose level and body-weight group. Subjects in the low body-weight group of < 40 kg will be administered two 0.5 m**L** SC injections of matching placebo in glass vials of 0.5 mL each.
Unit dose strength(s)/ Dosage level(s) and dosage frequency	Subjects in the high body-weight group of ≥ 40 kg will be administered two 1 m**L** SC injections in PFS as described below: • Dose level 1 **(**70 mg erenumab**):** – 1 injection of 1.0 mL of 70 mg/mL erenumab – 1 injection of 1.0 mL of placebo • Dose level 2 **(**140 mg erenumab**):** – 1 injection of 1.0 mL of 70 mg/mL erenumab	Subjects in the high body-weight group of ≥ 40 kg will be administered **two** 1 mL SC injections of matching placebo in PFS of 1.0 mL each.

Study Treatment Name	Amgen Investigational Product:[a] Erenumab	Placebo
	– 1 injection of 1.0 m**L** of 70 mg/m**L** erenumab	
Route of administration	SC	SC
Accountability	The quantity, start date/time, and box number of investigational product are to be recorded on each subject's **e**CRF.	The quantity, start date/time, and box number of investigational product are to be recorded on each subject's **e**CRF.

Dosing instructions	• Only authorized healthcare professionals are to administer Amgen investigational product.
	• Double-blind erenumab 35 mg or 70 mg (for subjects in the weight group of < 40 kg), or erenumab 70 or 140 mg (for subjects in the weight group of ≥ 40 kg), will be administered during the double-blind treatment phase:
	  • **Group 1:** at day 1 and visit weeks 4, 8, 12, 16, and 20.
	  • **Group 2: at day 1 and visit weeks 4 and 8.**
	• The dose received during the 40-week optional DLBEP is the same as that for the DBTP for subjects in the active treatment arms of the DBTP. Subjects in the placebo arm of the DBTP will be re-randomized at week 24 **(Group 1) or week 12 (Group 2)** to receive either erenumab dose level 1 or erenumab dose level 2; the actual dose will be based on body weight assessed at day 1.
	  • **Group 1: DLBEP visits** at weeks 24, 28, 32, 36, 40, 44, 48, 52, 56, and 60.
	  • **Group 2: DLBEP visits at weeks 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.**
	• Investigational product doses are fixed and will not be adjusted for individual subjects during the study.
	• The anatomical sites for administration of investigational product are the upper arm, upper thigh, or abdomen.
		• Only authorized healthcare professionals are to administer placebo.
		• Placebo will be administered during the double-blind treatment phase**:**
		  • **Group 1:** at day 1 and visit weeks 4, 8, 12, 16, and 20.
		  • **Group 2: at day 1 and visit weeks 4 and 8.**
		• Placebo doses are fixed and will not be adjusted for individual subjects during the double-blind treatment phase of the study.
		• The anatomical sites for administration of placebo are the upper arm, upper thigh, or abdomen.
		• Use of preventive measures for injection site pain prior to **investigational product** administration, such as icing or local anesthetics (eg, EMLA cream), is prohibited on**:**
		  • **Group 1:** day 1 and **visit** week 20.
		  • **Group 2: day 1 and visit week 8.**

Study Treatment Name	Amgen Investigational Product:[a] Erenumab	Placebo

	• Use of preventive measures for injection site pain prior to **investigational product** administration, such as icing or local anesthetics (eg, EMLA cream), is prohibited on:
	  • **Group 1:** day 1 and **visit** week 20.
	  • **Group 2: day 1 and visit week 8.**
	• Overdose with this product has not been reported. In the case of overdose, the subject should be treated symptomatically and supportive measures implemented as necessary.	

Observation Period post investigational product administration	**Group 1** After investigational product administration at the day 1 and week 24 visits, subjects will remain on site for at least 2 hours, and after each subsequent investigational product administration (week 4 to week 20 and week 28 to week 60), subjects will remain on site at least 30 minutes. **Group 2** **After investigational product administration at the day 1 and week 12 visits, subjects will remain on site for at least 2 hours, and after each subsequent investigational product administration (week 4 to week 8 and week 16 to week 48), subjects will remain on site at least 30 minutes.**	**Group 1** After investigational product administration (day 1) **and week 24 visits**, subjects will remain on site for at least 2 hours, and after each subsequent investigational product administration (week 4 to week 20 **and week 28 to week 60**), subjects will remain on site at least 30 minutes. **Group 2** **After investigational product administration (day 1) and week 12 visits, subjects will remain on site for at least 2 hours, and after each subsequent investigational product administration (week 4 to week 8 and week 16 to week 48), subjects will remain on site at least 30 minutes.**

eCRF = **electronic** case report form; DLBEP = dose-level-blinded extension phase; PFS = prefilled syringe; QM = monthly; SC = subcutaneous
[a] Erenumab will be manufactured and packaged by Amgen and distributed using Amgen clinical investigational product distribution procedures.

7.1.2 Non-investigational Products

Not applicable for this study.

7.1.3 Medical Devices

The investigational medical device provided by Amgen for use in this study is the Amgen prefilled syringe (PFS).

The erenumab and placebo PFS is a single-use, disposable, handheld manual injection device for fixed dose SC injection of erenumab 70 mg deliverable volume. Please refer to Table 7-1 for the number of PFS that will be used in each investigational product administration.

Additional details are provided in the Investigational Product Instruction Manual (IPIM).

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

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

7.1.4 Non-investigational Product(s)/Auxiliary Medicinal Product(s)

Not applicable for this study.

7.1.5 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(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 drug(s), device(s) or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

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

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

Table 7-2. Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Prohibited Therapeutic	Time Period for Exclusion
For any indication: • Antiepileptics (for example: divalproex sodium, sodium valproate, topiramate, carbamazepine, gabapentin). • Beta blockers (for example: atenolol, bisoprolol, metoprolol, nadolol, nebivolol, pindolol, propranolol, timolol). • Tricyclic antidepressants (for example: amitriptyline, nortriptyline, protriptyline). • Venlafaxine, desvenlafaxine, duloxetine, milnacipran. • Flunarizine, cinnarizine, verapamil, lomerizine. • Lisinopril, candesartan. • Clonidine, guanfacine. • Cyproheptadine. • Methysergide. • Pizotifen. • Butterbur, feverfew, magnesium (**elemental magnesium** ≥ 500 mg/day), riboflavin (≥ 100 mg/day).	**15 days** prior the start of the baseline phase and throughout the study.
For migraine prevention • Triptans • Ergotamine-derivatives • Steroids NOTE: Use of triptans or ergotamine derivatives is allowed for acute treatment of migraine	2 months before the start of the baseline phase and throughout the study
For any indications: Opioid or butalbital-containing analgesics on ≥ 4 days per month	2 months before the start of the baseline phase and throughout the study
For migraine prevention Devices (such as stimulation devices), or procedures (such as acupuncture, biofeedback, relaxation techniques, or psychotherapy).	3 months before the start of the baseline phase and throughout the study

Cognitive Behavioral Therapy Subjects on a stable, maintenance phase of a 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 phase, only follow "booster" CBT sessions at a monthly, bimonthly**,** or quarterly frequency. Note: Subjects who have discontinued CBT within 3 months prior to the start of the baseline phase are eligible for the study provided that there is evidence of CBT failure/lack of efficacy prior to initial screening (per medical records or investigator's assessment).	3 months before the start of the baseline phase and throughout the study unless on a stable, maintenance phase as defined here
Investigational medications and devices	4 months before the start of the baseline phase and throughout the study
Botulinum toxin (in the head and/or neck region)	4 months before the start of the baseline phase and throughout the study
Medications targeting the CGRP pathway	4 months before the start of the baseline phase and throughout the study

CBT = **C**ognitive **B**ehavioral **T**herapy; CGRP = calcitonin gene-related peptide

7.2 Method of Treatment Assignment

Randomization for DBTP must occur on day 1 of the DBTP, after the completion of procedures associated with the screening and end of the baseline phase.

After the baseline phase, approximately 30 children and 256 adolescents will be randomized in a 2:1:1 allocation ratio to placebo, erenumab dose level 1, or erenumab dose level 2, respectively, with a resulting overall placebo to erenumab allocation ratio of 1:1. The dose of erenumab received throughout the DBTP will be determined by randomization to treatment arm and the subject's body-weight at the end of the baseline phase, pre-randomization (during the day 1 visit). The dose of erenumab will not change even in the case that the subject changes weight above or below 40 kg, respectively.

At **the end of the DBTP (**week 24 **for Group 1; week 12 for Group 2),** subjects in each treatment group will be rolled over into the **40-week** optional DLBEP. Subjects who received erenumab treatment during the DBTP will continue to receive the same erenumab dose in a double-blinded fashion during the optional DLBEP. Subjects who received placebo during the DBTP will be randomized **(at the week 24 visit for Group 1; at the week 12 visit for Group 2)** in 1:1 allocation ratio to receive either

erenumab dose level 1 or erenumab dose level 2, also in a double-blinded fashion; the actual erenumab dose for each dose level will be based on their body-weight at the end of the baseline phase, pre-randomization (during the day 1 visit).

The randomization will be stratified by age group (adolescents or children), by region (North America or Rest of World), and by prior preventive treatment failure (yes or no). Randomization will be based on a schedule generated by Amgen before the start of the study and will be centrally executed using the IRT system. The subject, site randomization treatment group assignment. The randomization dates are to be documented in the subject's medical record and on the enrollment **electronic case report form (e**CRF**)**.

7.3 Blinding

This study has a DBTP **(Group 1:** 24-week **duration; Group 2: 12-week duration)** and 40-week optional DLBEP. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below.

During the DBTP, treatment assignment will be blinded to all subjects, site personnel, and Amgen. Following the DBTP, select team members from Amgen will be unblinded in order to conduct the primary analysis. During the 40-week optional DLBEP, all subjects, site personnel, and Amgen will be blinded to the dose level. More details are provided in Section 7.3.1 and 7.3.2 .

7.3.1 Site Personnel Access to Individual Treatment Assignments

During the DBTP and optional DLBEP, a subject's treatment assignment is to only be unblinded when knowledge of the treatment is essential for further clinical management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation. The Amgen Trial Manager must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the subject's condition. In this case, 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 **e**CRF, as applicable.

7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Pre-identified members of the Amgen study team will be partially unblinded to whether the subject received erenumab or placebo for conducting the primary analysis, but will

not be unblinded to the dose of erenumab received by the subject until the final analysis. Other members of the Amgen study team will not have access to unblinding information for the DBTP and DLBEP until the completion of the final analysis.

7.4 Dose Modification

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

7.4.1.1 Amgen Investigational Product: Erenumab

The dosage of investigational product is fixed for all subjects and cannot be adjusted.

Missed or delayed doses should be noted on the investigational product administration **e**CRF, but no attempt should be made to administer any missed doses at the subject's next visit.

Refer to Section 8.1 for subjects who permanently discontinue investigational product during the DBTP or DLBEP.

7.4.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Appendix 7 for details regarding drug-induced liver injury (DILI) 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 and other **non-investigational product(s)/auxiliary medicinal product(s)** during the study are provided in the IPIM.

7.6 Treatment Compliance

Administration of SC medicinal products will occur at the study site.

Non-compliance is to be documented in the medical file and will be reflected in the **e**CRF. Non-compliant subjects are to be re-educated on the importance of adhering to the investigational product administration schedule and reminded that repeated cycles of non-compliance 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

Prior therapies that were being taken/used from 90 days before the start of the baseline phase and through the baseline will be collected. In addition to this, the complete history of the subject's migraine preventive medication and acute migraine-specific medications (triptans and ergotamine-derivatives, alone or in combination) will be collected along with the determination of adequate therapeutic trial (for definition, see Section 6.2, Exclusion Criterion 203) and the reason for discontinuation.

The therapy name, indication, dose, unit, frequency, route, start date, and stop date are to be recorded on each subject's **e**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 Table 7-2.

Concomitant therapies are to be collected from informed consent/assent through the end of study/safety follow-up visit. The therapy name, indication, dose, unit, frequency, route, start date, and stop date are to be recorded on each subject's **e**CRF or eDiary.

During the initial screening phase, the subject and investigator are to agree on the acute headache medications and the appropriate dose(s) that the subject may take on an as-needed basis throughout the study. To avoid confounding the study results, efforts should be made throughout the study to not introduce new acute medications (ie, triptans or ergotamines).

Acute medications taken during aura or to treat a headache will be collected in the eDiary, and data will include the medication name, date of administration, time of administration, dose, and route of administration. In the eCRF, only record information about types of acute headache medication that have been prescribed to the subject to be used on an 'as needed' basis. Other concomitant therapies will be collected in the **e**CRF, and data will include the generic drug name/treatment, indication, dose, and start and stop dates of administration.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product**(s) and/or non-investigational product(s)/auxiliary medicinal product(s)**, 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**(s), non-investigational product(s)/auxiliary medicinal product(s)**, **device, and/or 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 (or a legally acceptable representative) can decline to continue receiving investigational product and/or **non-investigational product(s)/auxiliary medicinal product(s)** 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 **non-investigational product(s)/auxiliary medicinal product(s)** and must discuss with the subject the possibilities for continuation of the Schedule of Activities in Table 2-1 **(Group 1) and Table 2-2 (Group 2),** 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 and adverse events, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or **non-investigational product(s)/auxiliary medicinal product(s) and/or** other procedures should continue in the study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other **non-investigational product(s)/auxiliary medicinal product(s)** by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Appendix 3.

Reasons for removal from investigational product(s) **and/**or **procedures** include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation

- Non-compliance
- Adverse event
- Subject request
- Requirement for alternative therapy not allowed by protocol
- Pregnancy

Subjects who permanently discontinue investigational product during the DBTP are to complete all remaining study visits and procedures until the end of the DBTP and the safety follow-up visit 16 weeks after the last dose of investigational product. If **the** subject is unable to continue in the study, they are to complete the study procedures for the week 24/early termination visit **(Group 1) or the week 12/early termination visit (Group 2)** and the safety follow-up visit (16 weeks after the last dose of investigational product).

Subjects who permanently discontinue investigational product during the optional DLBEP are to complete the study procedures for the week 64/early termination visit **(Group 1) or the week 52/early termination visit (Group 2)** and the safety follow-up visit 12 weeks after the last DLBEP visit (16 weeks after the last dose of investigational product).

8.2 Discontinuation From the Study

Withdrawal of consent/assent for a study means that the subject does not wish to, or is unable to continue further study participation. Subject data up to withdrawal of consent/assent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent/assent. 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 Appendix 6 for further details). Refer to the Schedule of Activities **in Table 2-1 (Group 1) and Table 2-2 (Group 2)** 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 Invasive Procedures

Not applicable for this study.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent/assent 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.

9. Study Assessments and Procedures

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

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

Subjects will undergo a screening to determine eligibility. Informed consent and assent for the study must be obtained before any study evaluations may be performed. The screening phase consists of an initial screening (up to 3 weeks) and a baseline phase

(4 weeks). The screening phase starts when both the assent (if developmentally appropriate) and the ICF are signed and dated by the subject and the parent or legal representative, respectively. The screening phase ends when the subject completes the baseline phase and is randomized or screen failed. The initial screening phase must not exceed 3 weeks, except after consultation with and approval by Amgen, in a case by case basis. Amgen may grant such approval in cases for which additional time is required to confirm eligibility.

The initial screening phase is followed by a 4-week baseline phase. Certain initial screening phase procedures may be repeated during the original initial screening phase (note: repeating procedures during the original initial screening phase is a part of screening and is not considered "rescreening"). These procedures include, for example, laboratory assessments due to value(s) being out of range due to sampling error or there is a medical reason to expect that the laboratory value(s) will be in range after repeating. The baseline phase must not exceed 35 days, but it may be restarted after consultation with and approval by Amgen, on a case by case basis. Amgen may grant such approval in cases where the eligibility criteria cannot be met in 35 days due to extraordinary circumstances such as technical reasons. If the baseline restart occurs less than 30 days since the first week -4 visit, week -4 procedures do not need to be repeated. If more than 30 days have passed, week -4 assessments should be repeated. Additional safety assessments from initial screening may be repeated following discussion between the investigator and medical monitor.

Randomization for DBTP must occur on day 1 of the DBTP, after the completion of procedures associated with the screening and end of the baseline phase. The DBTP will last 24 weeks **for** subjects **in Group 1 and 12 weeks for subjects in Group 2. S**ubjects will receive erenumab or placebo **Q4W**.

At the **end of the DBTP**, subjects in each treatment group will have the option to roll over into a DLBEP and all subjects to receive erenumab **Q4W** for 40 weeks.

Allowable windows for visits are the following:

- The day 1 visit (enrollment day) has a window of + 7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 visit date, unless baseline is repeated.
- Each study visit during the DBTP, optional DLBEP, and safety follow-up has a window of ± 5 consecutive calendar days.
- All study visit target dates are to be calculated from the day 1 visit date.

- All study procedures for a given study visit are to be completed on the same day.

Study visits should be conducted without additional non-protocol therapies and subjects should be reminded about the investigational nature of the investigational product.

9.1.1 Screening, Enrollment and/or Randomization

Informed consent and assent (if developmentally appropriate) must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After informed consent and assent is obtained, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window for the initial screening phase is up to 3 weeks.

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 at the end of the screening phase, the subject will be registered as a screen fail. Screen fail subjects may be eligible to repeat the screening process 1 time.

Rescreen subjects must first be registered as screen failures in IRT System and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 3-week initial screening window will begin. Subjects will retain the same subject identification number that is assigned at the original screening. If the rescreening phase begins more than 30 days after the original signing of the ICF/assent, all screening procedures, including informed consent/assent, must be repeated.

9.1.2 Treatment Phase

Visits will occur per the Schedule of Activities **in Table 2-1 (Group 1) and Table 2-2 (Group 2)**. The date of the first dose of investigational product is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Except day 1 visit, all study visits during the DBTP and optional DLBEP may be completed within ± 5 days of the scheduled day of the visit.

9.1.3 Safety Follow-up

Subjects who complete the DBTP, optional DLBEP or who discontinue investigational product for any reason during the DBTP or DLBEP will have a safety follow-up visit 16 weeks after the last dose of investigational product.

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 developmentally adequate subjects must personally sign and date the assents and all subjects' parents or legal representative must personally sign and date the Amgen/IEC approved ICFs and before any study-specific procedures are performed.

The subject must personally sign and date the Amgen/IEC approved ICF for adults if age of majority is reached during study participation.

9.2.1.2 Calls to Interactive Response Technology (IRT) System

Sites are to use the IRT System for the following: to enter the subject into the initial screening phase, to randomize an eligible subject into the DBTP, to enroll a subject into the optional DLBEP, to obtain the investigational product assignment, to register the end of investigational product, and to register study early termination or completion. Subject data will be collected in the IRT System including, but not limited to, reason for screen fail (if applicable).

9.2.1.3 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 during initial screening.

9.2.1.4 Medical History

The Investigator or designee will collect a complete medical and psychiatric history up to the signing of the informed consent/assent. Medical history will also include information on the subject's concurrent medical conditions. Record all findings on the medical history **e**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.

9.2.1.5 Physical Examination

Physical examination will be performed as per standard of care (including neurological exam) at the time points specified in the Schedule of Activities **in** Table 2-1 **(Group 1) and Table 2-2 (Group 2)**. Physical examination findings should be recorded on the appropriate **e**CRF (eg, medical history, event).

9.2.1.6 Physical Measurements

All measurements are to be recorded on the Physical Measurements **e**CRF.

9.2.1.6.1 Height

Height in centimeters will be measured without footwear (ie, shoes, slippers, sandals, or socks) or head gear (ie, hat, cap, hair bows, comb, or ribbons). The procedure will follow international standardize procedures (World Health Organization [WHO], 2005).

9.2.1.6.2 Weight

Weight in kilograms will be measured with the subject wearing light clothing without footwear (ie, shoes, slippers, sandals**,** or socks) or head gear (ie, hat, cap, hair bows, comb, or ribbons). The procedure will follow international standardized procedures (WHO, 2005). Weight will be collected at initial screening and day 1. The weight at initial screening will be used for **investigational product** planning purposes only as subjects < 40 kg require a different presentation of the **investigational product**.

9.2.1.6.3 Blood Samples

For subjects in Group 1, the protocol includes the collection of blood samples at 7 visits during screening, rescreening (if applicable), and the DBTP (up to approximately 78 mL in total) and 3 additional visits during the optional DLBEP (approximately 18.9 mL in total).

For subjects in Group 2, the protocol includes the collection of blood samples at 6 visits during screening, rescreening (if applicable), and the DBTP (up to approximately 72 mL in total) and 3 additional visits during the optional DLBEP (approximately 18.9 mL in total).

These blood samples will be collected for screening purposes (at screening visit) and for PK and safety analyses in line with regulatory requirements. Details on blood sample analytes, timing, and volumes are provided in either the Schedule of Activities (Table 2-1 [Group 1] and Table 2-2 [Group 2]) and/or the ICF.

9.2.1.7 Hepatitis Testing

If a hepatic event is suspected during the study, hepatitis testing will be performed on a blood sample collected and stored during screening and a blood sample collected around the time of the event. Hepatitis testing will be performed by the central laboratory.

The following laboratory tests will be performed to determine hepatitis B and C status:

- Hepatitis B surface antigen (HepBsAg) and total hepatitis B core antibody (HepBcAb).
  - If results are HepBcAb positive and HepBsAg positive, no additional testing is necessary.
  - If results are HepBcAb positive and HepBsAg negative, additional testing for hepatitis B virus DNA by polymerase chain reaction is necessary.
- Hepatitis C virus antibody.
  - If results are hepatitis C virus antibody positive, additional testing for hepatitis C virus RNA by polymerase chain reaction is necessary.

9.2.1.8 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of tobacco, caffeine, and illicit drugs during initial screening and week 24**/early termination visit (Group 1) or the week 12/early termination visit (Group 2)**.

9.2.1.9 Urine Drug Screening

Subjects will be tested for substances of abuse at initial screening to confirm subject eligibility. During the study, urine drug tests can also be performed at the investigator's discretion based on clinical suspicion. Urine samples will be analyzed by the central laboratory. For a subject with a positive urine drug screen during the study (except for certain prescribed medications), the investigator should consider discontinuing the subject from investigational product.

9.2.1.10 Pubertal Maturation Self-assessment (Tanner Staging)

All **Group 1** subjects will perform a Pubertal Maturation self-assessment (Tanner Staging; Appendix 11) during the baseline visit on site and at the early termination or week 64 visit. If early termination occurs at week 24 or prior, then this assessment is required**.**

All Group 2 subjects will perform a Pubertal Maturation self-assessment during the baseline visit on-site and at the early termination or week 52 visit. If early termination occurs at week 12 or prior, then this assessment is required.

The self-assessment form contains illustrations of the 5 different stages of pubertal maturation based on breast development and pubic hair (for females) and genitals and pubic hair (for males). No physical exam by a healthcare provider will be performed to assess puberty maturation. The goal of this is to classify subjects as pre-pubertal (stage 1) or post-pubertal (all other stages [ie, 2 to 5]) for exploratory analyses.

9.2.1.11 Menses Start Dates

For female subjects who present menstrual cycles, start date of menses each month should be collected according to the Schedule of Activities **in Table 2-1 (Group 1) and Table 2-2 (Group 2)**.

9.2.2 Efficacy Assessments

9.2.2.1 Modified Pediatric Migraine Disability Assessment Questionnaire (PedMIDAS)

The modified PedMIDAS (Appendix 8) is a 6-item self-administered questionnaire that measures disability in 2 settings: at school and at home. The modified PedMIDAS also assesses disability in family, social, and leisure activities. The modified PedMIDAS score is the sum of missed school days, days when activities at school or home were reduced by at least half due to headaches, and days when other family, social, leisure activities, were reduced by at least half due to headaches. The recall period is the past 1 month.

Subjects will complete the modified PedMIDAS during the study visits as specified in the Schedule of Activities **in Table 2-1 (Group 1) and Table 2-2 (Group 2)**.

9.2.2.2 Patient Global Impression of Change (PGIC)

The PGIC is a subject reported outcome developed in 1976 by the National Institute of Mental Health (US). It consists of one item (taken from the Clinical Global Impression and adapted to the subject). The subject should assess how much change has occurred since the initiation of the therapy with a scale spanning from 1 = very much improved, through 4 = no change, up to 7 = very much worse (Guy, 1976).

9.2.3 Safety Assessments

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

9.2.3.1 Adverse Events and Serious Adverse Events

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 Appendix 4.

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

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Appendix 4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of the safety follow-up visit (the DBTP or DBLEP) are reported using the Events **e**CRF.

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/assent through the end of the safety follow-up visit (the DBTP or DLBEP) for a particular subject are reported using the Events **e**CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee **immediately and no later than** 24 hours **of the investigator's awareness of the event**, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor **immediately and no later than** 24 hours of it being available.

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

9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to **actively** monitor study subjects for serious adverse events following the protocol-required reporting period (as defined in Section 9.2.3.1.1.2) or after end of study. However, **if the investigator becomes aware of** serious adverse events **suspected to be related to investigational product, then** these serious adverse events **will** be reported to Amgen **immediately and no later than 24 hours following the investigator's awareness of the event.**

Serious adverse events reported **after the end** of the **study** will be captured within the safety database as clinical **study** cases and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

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 non-leading 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 Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen **immediately and no later than** 24 hours **after investigator's awareness** of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events **e**CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from **investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s)** 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 **external review body** 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 **i**nvestigator's **b**rochure and will notify the **external review body**, if appropriate according to local requirements.

For studies in which the treatment assignment is blinded, 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.

Amgen will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report in the European Union) for the Amgen Investigational Product. To ensure that consolidated safety information for the trial is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical study, if applicable.

9.2.3.1.5 Safety Monitoring Plan

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

9.2.3.1.6 Pregnancy and Lactation

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

If a pregnancy is reported, the investigator is to inform Amgen **immediately and no later than** 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 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 Appendix 5.

Pregnancy Testing

A high**ly** sensitive (urine or serum) pregnancy test should be completed at screening and within 7 days prior to initiation of investigational product for females of childbearing potential.

Note: **Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements**. If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification **Form**, see Figure 12-2. Refer to Appendix 5 for contraceptive requirements.

Additional pregnancy testing should be performed at monthly intervals **during** treatment **with investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s)** and at 16 weeks after the last dose of investigational product.

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

9.2.3.1.7 Adverse Device Effects

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

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

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

The investigator is responsible for ensuring that all adverse device effects observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of the safety follow-up visit are reported using the Events eCRF.

Product complaints are described in Section 7.1.5.

Further details regarding adverse device effects can be found in Appendix 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 and heart rate 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 **e**CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs **e**CRF. Record all measurements on the vital signs **e**CRF.

Blood pressure should be measured in the following manner:

- Subjects should be lying in a semi-recumbent position (partial semi-Fowler's position) or supine position quietly and comfortably for at least 5 minutes. The upper arm should be bare without constrictive clothing and supported at heart level.
- Caffeine, exercise, and smoking should be avoided for at least 30 minutes before measurement.
- An appropriately-sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least 2 measurements (separated by at least 5 minutes) should be made and the average recorded. If there is a high value, it is acceptable to wait approximately 30 minutes before the next 2 blood pressure measurements are taken for the purpose of averaging and recording in the **e**CRF.
- Blood pressure will initially be recorded in both of the subject's arms unless a concomitant condition favors the use of a particular arm. The arm with the higher systolic reading at initial screening should then be used for blood pressure determinations throughout the study.
- Neither the subject nor the observer (measurer) should talk during measurement.

If abnormalities in vital signs are found and they are considered to be adverse events, record on the adverse event summary **e**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 investigator and central reader 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.

It is the responsibility of the investigator to determine if the ECG tracings are consistent with a subject's safe participation in the study.

Any ECG abnormality noted by the central reader must be evaluated by the investigator and discussed with the Amgen medical monitor as deemed necessary to determine if the

ECG finding is representative of an unstable or clinically significant medical condition. Please refer to the central ECG reader manual for details.

9.2.3.4 Other Safety

9.2.3.4.1 Columbia-suicide Severity Rating Scale (C-SSRS)

The C-SSRS (Appendix 10) is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items (typically 3 for a subject with no risk and no prior history of suicidal behavior). Two versions of the C-SSRS will be used during the study: the C-SSRS children's version (for children 6 to 11 years old) and the C-SSRS adolescents' version (for subjects at least 12 years old). Each of these versions has a screening form, to be administered at the screening visit, and a "since last visit" form which will be administered at each subsequent in clinic study visit to assess possible suicidal ideation and behavior. If reports of suicidal ideation with intent to act (endorse item 4 or 5), reports of actual, aborted, or interrupted suicide attempts, or reports of behavior preparatory for an attempt are identified, the investigator is to appropriately manage the subject in accordance with standard of care.

9.2.3.4.2 Injection Site Reactions

Injection site reactions (ISR) should be evaluated at every visit, approximately 20 to 30 minutes after administration of investigational product. Confirmed injection site reactions should be appropriately reported as adverse events.

9.2.3.4.3 Injection Site Pain

Injection site pain will be assessed after the first and last administration of investigational product of the DBTP (ie, at day 1 and week 20 visits **for Group 1; at day 1 and week 8 visits for Group 2**) using the Faces Pain Scale-Revised (FPS-R; Hicks et al, 2001; Appendix 13). The FPS-R is a validated pain self-assessment tool for use in pediatric patients. The FPS-R should be given to subjects at approximately 1 and 15 minutes after administration of investigational product.

9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities 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 Events **e**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.

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

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.

9.2.5 Pharmacokinetic Assessments

Blood samples will be collected **for measurement of** erenumab serum concentration **as specified in the Schedule of Activities in Table 2-1 (Group 1) and Table 2-2 (Group 2). Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.**
Approximately 5 mL of whole blood will be collected at each time point. Please refer to the central laboratory for instructions on sample collection, processing, and shipping of PK samples.

During the study visits at which investigational product is administered, the investigator will administer the investigational product to the subject after the PK sample has been collected.

The PK samples will be analyzed only for those subjects assigned to an erenumab treatment group. **Drug concentration values will unblind the individual treatment assignment and will not be reported to investigative sites or accessible by blinded study team personnel until the completion of the final.**

9.2.6 Pharmacogenetic Assessments

If the subject consents/assents 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/or to identify subjects who may have positive or negative response to investigational product. A single sample is collected for this part of the study (day 1 visit pre-randomization). For

subjects who consent to this/these analysis/analyses, DNA may be extracted. The final disposition of samples will be described in Appendix 6.

9.2.7 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities **in Table 2-1 (Group 1) and Table 2-2 (Group 2)** for the measurement of anti-erenumab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity**,** and presence of immune complexes. Additional blood samples may be obtained to rule out anti-erenumab antibodies during the study.

Subjects who test positive for Neutralizing antibodies (NAb) to the investigational product at the final scheduled study visit must be offered additional follow-up testing. This testing is to occur every 3 months, starting from when the site has been notified of the positive result, until: (1) neutralizing **or binding** antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) after the last dose of the investigational product.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-erenumab antibody response must also be asked to return for additional follow-up testing. **Additional follow up testing may extend beyond the safety follow up/end of study visit.** Refer to the Schedule of Activities **in Table 2-1 (Group 1) and Table 2-2 (Group 2)**, as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions. **More frequent antibody testing or testing for a longer period of time may be requested in the event of safety-related concerns.**

9.2.8 Biomarkers

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

9.2.8.1 Biomarker Development

Samples will also be collected to develop or address biomarker hypotheses related to erenumab activity, eg, to evaluate potential biomarkers that may correlate with treatment response.

A single blood sample is to be collected for biomarker development at day 1 pre-randomization (see the Schedule of Activities **in Table 2-1 [Group 1] and Table 2-2 [Group 2]**).

9.2.8.2 Biomarker Future Research

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

If consent is provided by subjects, any remaining samples collected at the time points specified in the Schedule of Activities, including samples collected for biomarker assessments may be used for future research as described in Appendix 6. No additional samples will be collected for future research.

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 migraine.

9.2.9 Clinical Outcome Assessments

Clinical outcome assessments will be collected using a handheld device or "eDiary". The content and presentation of the eDiary will be adapted in language and presentation to a pediatric population (< 18 years of age). The person using the eDiary (caregivers, children, or adolescents) must remain the same throughout the duration of the study.

The eDiary should be used at various frequencies.

The eDiary will collect the following COAs on a daily basis, preferably at home, before going to bed:

- Date and time of start of headache (ie, migraine or non-migraine headache).
- Date and time of end of headache.
- Visual analog scale for severity of headache.
- Pain features (eg, unilateral or bilateral, throbbing, worsens with exercise/physical activity).
- Accompanying symptoms (eg, aura, nausea, vomiting, photophobia, phonophobia). If the caregiver is completing the eDiary, photophobia and phonophobia can be inferred from the behavior of the child.
- Use of acute headache medications (medication name [from pre-entered list], date of dosing, number of times taken of each date, number of units taken).

Site study staff will assign and provide an eDiary to the subject and parent or legal representative at the week -4 visit (after confirming the subject's eligibility to enter the baseline phase). The site study staff will train the subject and parent or legal

representative 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. At the day 1 study visit the investigator will use the subject's eDiary to confirm the relevant inclusion and exclusion criteria before randomizing the subject.

Subjects (or their caregivers, if developmentally appropriate) should complete the eDiary on a daily basis as defined in the Schedule of Activities (Table 2-1 **[Group 1] and Table 2-2 [Group 2]**), including the baseline phase, DBTP and 3 specified 1-month periods of the optional DLBEP:

- **Group 1:** week 25 to week 28 (first month of the DLBEP), week 45 to week 48 (sixth month of the DLBEP), and week 61 to week 64 (**tenth** and last month of the DLBEP).
- **Group 2: week 13 to week 16 (first month of the DLBEP), week 33 to week 36 (sixth month of the DLBEP), and week 49 to week 52 (tenth** and last month of the DLBEP).

Please refer to the eDiary manual for additional details.

10. Statistical Considerations

10.1 Sample Size Determination

The sample size calculation has been performed based on the primary endpoint defined above (change in MMD from baseline to week 9 through week 12 [month 3] of the DBTP) for the adolescent subgroup. At this time, no efficacy information is available on erenumab in pediatric subjects.

Using a 2-sided significance level of 5%, 256 CM adolescents (128 on placebo, 64 on erenumab dose level 1, and 64 on erenumab dose level 2) will provide 90% power to detect a difference of −2.45 MMD (erenumab versus placebo) with an SD of 5.70 MMD from baseline to week 9 through week 12 of the DBTP in adolescents. This sample size calculation is based on the assumption that both dose levels are efficacious (as has been previously shown in adults), with an overall treatment difference of -2.45 MMD at 3 months for both doses (based on the results observed in the pivotal Study 20120295 in CM. This calculation allows for a 10% dropout rate at 12 weeks.

Enrollment will be open to children 6 to < 12 years of age. However given the natural history of the disease and epidemiology (CM status is reached after several years of illness, generally during late adolescence or adulthood) and due to expected challenges in the enrollment of this very young population in clinical trials), it is expected that this subgroup of subjects will be small, up to approximately 30 subjects, who will also be

randomized into a 2:1:1 allocation ratio to placebo: dose level 1: dose level 2. Analyses in this subgroup will be exploratory.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

Full Analysis Set: The full analysis set includes all subjects who were randomized in the study.

Safety Analysis Set: The safety analysis set for the DBTP includes all randomized subjects who received at least 1 dose of investigational product (ie, erenumab or placebo) during the DBTP and will be analyzed according to the randomized treatment unless a subject has received the incorrect treatment during the entire DBTP. The safety analysis set for the optional DLBEP includes all subjects who received at least 1 dose of investigational product (ie, erenumab) during the optional DLBEP.

10.2.2 Covariates

All analyses will be performed separately by age group (children or adolescents).

All formal analyses of efficacy endpoints in adolescents will be adjusted for the effect of the stratification factors region (North America or Rest of World) and prior preventive treatment failure (yes or no).

10.2.3 Subgroups

In addition to subgroup analysis by age group (children versus adolescents), other prespecified subgroups for the primary and secondary efficacy endpoints will include

- sex (male versus female)
- pubertal status (pre-pubertal versus post-pubertal defined according to a Pubertal Maturation Self-assessment [Tanner Staging] Scale)
- CBT status (with CBT versus without CBT)
- prior preventive treatment failure status (yes versus no).

These prespecified analyses will be performed for the primary and secondary endpoints.

10.2.4 Handling of Missing and Incomplete Data

The method of handling missing data for efficacy endpoints will be described for each set of endpoints. Missing data will not be imputed for safety endpoints.

Primary Endpoint: The primary endpoint will be analyzed without any imputation for missing data. Sensitivity analyses for the primary endpoint will include, but are not limited to the following imputation methods for handling missing data **may be performed**.

Secondary Endpoints: The same sensitivity analyses used for the primary endpoint will be performed for continuous secondary endpoints. For the achievement of 50% reduction from baseline secondary endpoint, a stratified Cochran-Mantel-Haenszel (CMH) test will be used after the missing data are imputed as nonresponse. Sensitivity analyses for **handling of** missing data, **may be performed**.

10.3 Statistical Analyses

Below is a summary of the timing and methods for the planned statistical analyses. The final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.3.1 Planned Analyses

10.3.1.1 Interim Analyses and Early Stopping Guidelines

In order to ensure the study is not underpowered, the uncertainty of the SD used in the sample size derivation will be tested by performing a blinded interim sample size re-estimation on the data collected in adolescents. Performing the sample size re-estimation in a blinded manner will not adversely impact the overall **t**ype 1 error and integrity of the study. The blinded sample size re-estimation will be performed when ≥50% of the total sample of adolescents has been enrolled in the study and completed 12 weeks of the DBTP. Following this blinded analysis, the sample size may either remain the same or increase to a total of up to **436** adolescent **subjects**, based on enrollment feasibility.

10.3.1.2 Primary Analysis

The primary analysis will be performed when the last adolescent subject completes the **last visit of the DBTP (**week 24 **for Group 1; week 12 for Group 2)** or the early termination visit during the DBTP**, and the data has been entered, cleaned, and locked**. The primary analysis will assess the combined dose of erenumab compared with placebo **during the DBTP**.

10.3.1.3 Final Analysis

The final analysis for the study will be performed after all subjects (children and adolescents) have completed the study through the safety follow-up or discontinued from the study. For the final analysis, each erenumab dose compared to placebo will be evaluated, as appropriate.

10.3.2 Methods of Analyses

10.3.2.1 General Considerations

The primary estimand consists of:

- The target population, which is the adolescent subjects (12 to < 18 years of age) diagnosed with CM.
- The primary endpoint, which is the change in MMD from baseline to week 9 through week 12 (month 3) of the DBTP.
- The summary measure, which is the difference between the mean of the primary endpoint for combined erenumab dose group and placebo.
- The intercurrent event is treatment discontinuation. The treatment effect will be estimated for all randomized subjects regardless of adherence to treatment.

The full analysis set will be used to tabulate demographic data, baseline disease characteristics, and subject disposition. The full analysis set will also be used to analyze efficacy endpoints in the DBTP. The respective safety analysis set will be used to analyze safety endpoints in each treatment phase.

Descriptive statistics by age group (adolescent and children) and treatment group will be tabulated at each visit. For continuous endpoints, the descriptive statistics include, but are not limited to: number of subjects, mean, median, SD, minimum, and maximum. For categorical endpoints, frequency, and percentage will be reported. Formal statistical analyses using statistical models and hypothesis testing will be performed for the adolescent age group only.

10.3.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary analysis of change from baseline in MMD to week 9 through week 12 (month 3) of the DBTP will be performed on the full analysis set. The primary comparison of change from baseline in MMD between the combined erenumab groups and the placebo group during the DBTP in adolescent subjects will be analyzed using a linear mixed effects repeated measure model including treatment group, baseline value as covariate, stratification factors of region and prior preventive treatment failure status, scheduled visit **(as applicable)**, and the interaction of treatment group with scheduled visit, without any imputation for missing data. Subjects will be used as a random effect. The mean change from baseline for each treatment group, and the treatment difference, 95% confidence intervals, and p-value will be reported. Sensitivity analyses for handling missing data **may be performed**. If the difference between the combined erenumab group and the placebo group is found to be statistically significant, the efficacy of each erenumab dose compared to placebo will be evaluated in a descriptive, quantitative manner at the final analysis when full unblinding is available.
Secondary	The continuous secondary endpoints will be analyzed using the same methods as for the primary endpoint, performing the same sensitivity analyses. For the achievement of at least 50% reduction from baseline secondary endpoint, a stratified CMH test will be used after the missing data are imputed as nonresponse. Sensitivity analyses for **handling** missing data **may be performed.** If the primary endpoint is statistically significantly different from placebo in the adolescent age group at the 5% significance level based on the primary analysis, the secondary efficacy endpoints will then be tested (combined erenumab group compared with placebo group) to maintain the family-wise type 1 error rate of 5%: as a gate-keeping process, the following 2 secondary endpoints will first be tested statistically using the Hochberg method at the 5% significance level: • Change from baseline in monthly headache days to week 9 through week 12 (month 3) of the DBTP. • Achievement of at least 50% reduction in MMD from baseline to week 9 through week 12 (month 3) of the DBTP. If these 2 secondary endpoints are statistically significantly different from placebo, the rest of the secondary endpoints based on the primary analysis will be tested (combined erenumab group compared with placebo group) using the Hochberg method at the 5% significance level: • Change from baseline in MMD to the average of the first 3 months (week 1 through week 12) of the DBTP.

Endpoint	Statistical Analysis Methods
Secondary (Continued)	• Change from baseline in monthly average severity of migraine attacks to week 9 through week 12 (month 3) of the DBTP. • Change from baseline in migraine-related disability and productivity as measured by the modified PedMIDAS to **week 9 through week 12 (**month 3**)** of the DBTP. If the difference between the combined erenumab group and the placebo group is found to be statistically significant, the efficacy of each erenumab dose compared to placebo will be evaluated in a descriptive, quantitative manner at the final analysis when full unblinding is available.

10.3.2.3 Safety Analyses

10.3.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	Statistical Analysis Methods
Primary safety endpoints	All safety analyses will be performed for the DBTP and DLBEP separately. The respective safety analysis set will include all randomized subjects who received at least 1 dose of investigational product within each phase. Subjects will be analyzed according to the randomized treatment unless the incorrect treatment was received during the entire duration of the treatment phase. The Medical Dictionary for Regulatory Activities will be used to code all adverse events. Subject incidence (DBTP) and exposure-adjusted subject incidence (DLBTP) of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product**(s) or non-investigational product(s)/auxiliary medicinal product(s)**, and significant treatment-emergent adverse events will also be provided. The analyses of safety laboratory endpoints will include summary statistics over time. Shift tables of the worst on-study safety laboratory toxicity based on grade relative to baseline will be tabulated. The analyses of vital signs will include summary statistics over time. The incidence and percentage of subjects who develop anti-AMG 334 antibodies (binding and if positive, neutralizing) at any time will be tabulated.

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
adolescent	12 to < 18 years of age
ADR	adverse drug reaction
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIL	total bilirubin
BLA	biologics license application
BOCF	baseline observation carried forward
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
children	6 to < 12 years of age
CM	chronic migraine
CMH	Cochran-Mantel-Haenszel
COA	Clinical Outcome Assessment
CRF	case report form
C-SSRS	Columbia-suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C terminal telopeptide of type 1 collagen
DBTP	double-blind treatment period
DLBEP	dose-level-blinded extension phase (all subjects will be receiving erenumab at either dose level 1 or dose level 2, and the dose level will be double-blinded)
DILI	drug-induced liver injury
DMC	data monitoring committee
DSUR	**Development Safety Update Report**
ECG	electrocardiogram
eCRF	**electronic case report form**
EDC	electronic data capture
eDiary	electronic diary
EM	episodic migraine
EMA	European Medicines Agency
End of Follow-up	defined as when the last subject completes the last protocol-specified assessment in the study

Abbreviation or Term	Definition/Explanation
End of Study (end of trial)	defined as the date when the last subject 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 Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
FCBP	Females of child-bearing potential
FDA	Food and Drug Administration
FPS-R	Faces Pain Scale-Revised
GCP	Good Clinical Practice
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorder
IEC	independent ethics committee
IgG	immunoglobulin
IgG2	immunoglobulin G2
IHS	International Headache Society
INR	international normalized ratio
Interactive Response Technology (IRT) system	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information
IPIM	Investigational Product Instruction Manual
IRB	institutional review board
ISR	injection site reaction
MAR	missing at random
MI	multiple imputation
MMD	monthly migraine day
MNAR	missing not at random
NSAIDs	nonsteroidal anti-inflammatory drugs
P1NP	procollagen Type 1 N-propeptide
PDCO	Pediatric Committee

Abbreviation or Term	Definition/Explanation
PedMIDAS	Pediatric Migraine Disability Assessment
PeRC	Pediatric Review Committee
PFS	prefilled syringe
PGIC	Patient Global Impression of Change
PHQ-A	patient health questionnaire-9 modified for adolescents
PK	pharmacokinetic
Q4W	**4 times weekly**
QM	monthly
SC	subcutaneous
SMQ	Standard MedDRA Query
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/**non-investigational product(s)/auxiliary medicinal product(s)** is/are administered to the subject
TBL	total bilirubin
ULN	upper limit of normal
US	United States
WHO	World Health Organization

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the central laboratory (unless otherwise noted as “Amgen/designee” or “local” laboratory).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 6.1 to Section 6.2 of the protocol.

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

Table 12-1. Analyte Listing

Chemistry	Hematology	Other Labs
Sodium	RBC	Pregnancy testing-serum
Potassium	Hemoglobin	Pregnancy testing-urine (local)
Chloride	Hematocrit	Hepatitis B surface antigen (HepBsAg)
Bicarbonate	MCV	Hepatitis B core antibody (HepBcAb)
Total protein	MCH	Hepatitis C virus antibody
Albumin	MCHC	Polymerase chain reaction for hepatitis B and hepatitis C
Calcium	RDW	Urine drug screening
Corrected calcium (adjusted by albumin)	Reticulocytes	Serum bone metabolism markers (P1NP and CTX) (Amgen/designee)
Magnesium	Platelets	Anti-erenumab antibodies (Amgen/designee)
Phosphorus	WBC	Biomarker development (Amgen/designee)
Glucose	WBC Differential	Pharmacogenetic studies (optional) (Amgen/designee)
BUN or Urea	• Neutrophils	Pharmacokinetic studies
Creatinine	• Eosinophils	
Uric acid	• Basophils	
Total bilirubin	• Lymphocytes	
Direct bilirubin	• Monocytes	
ALP		
AST (SGOT)		
ALT (SGPT)		
CPK		

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; CTX = C terminal telopeptide of type 1 collagen; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; P1NP = procollagen Type 1 N-propeptide; RBC = red blood cell; RDW = red blood cell distribution width; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell count

12.3 Appendix 3. Study Governance Considerations

Data Monitoring Committee

An independent data monitoring committee (DMC) will review and make recommendations regarding the safety of the study participants throughout the study. The DMC will be composed of external advisors, including at least 2 clinicians (at least 1 being a pediatrician and at least 1 being a neurologist) and a biostatistician. Summaries of data at the treatment group level will be prepared and presented by an independent biostatistician at the DMC meeting. **D**ata from the open-label phase 1, pharmacokinetic (PK) and safety study (Study 20160172)**,** which start**ed** enrollment before Study 20160354 commence**d, was shared with the DMC**.

Records of all meetings will be maintained by the DMC for the duration of the study. Records of all meetings will be transferred and stored in the trial master folder at the conclusion of the study. Further details are provided in the DMC charter.

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 laws and regulations

The protocol, protocol amendments, informed consent form (ICF), **i**nvestigator's **b**rochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an institutional review board/independent ethics committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol **i**nvestigator's **s**ignature 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

Informed Consent Process

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

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

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative (defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study) will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

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

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The

investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally acceptable representative 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 ICF(s) during their participation in the study.

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

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 ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood. (Refer to Section 4.8.9 of ICH GCP guideline).

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

The ICFs will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory 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 exploratory 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 **electronic** case report form (**e**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 ICFs) are to be kept in confidence by the investigator, except as described below.

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

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

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

event of a security breach, the sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Serious Breach

Suspected Serious Breaches must be reported to the study team or the Clinical Out-of-Hours Support Program: https://wwwext.amgen.com/science/clinical-trials/clinical-out-of-hours-support-program immediately and no later than 1 calendar day from the time of awareness.

A Serious Breach is a breach of any of the following:

- **Good Clinical Practice (GCP)**
- **the clinical trial protocol**
- **an applicable regulation**

That is likely to impact to a significant degree either of the following:

- **the safety, physical, or mental integrity and the rights of the subject**
- **the reliability and robustness of the data and the scientific value of the trial**

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 **e**CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the **e**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 **e**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 **e**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, **e**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 Quality, Compliance, and Audit function (or designees). Inspection of site facilities (eg, pharmacy, **investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s)** 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 repot 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 **e**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 **e**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 interactive response technology (IRT) system (if used, such as subject ID and randomization number) and **e**CRF entries if the **e**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 [COA]).

Data reported on the CRF or entered in the **e**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 **e**CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, **i**nvestigator's **b**rochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including [Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

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

Study and Site Closure

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

Both Amgen and the 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. • **Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).**
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry**, or urinalysis**) or other safety assessments (eg, ECG, 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**, but are not limited to,** adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device. **A combination product is a product composed of any combination of a drug, a device, and a biological product. Each drug, device, and biological product included in a combination product is referred to as a "constituent part" of the combination product.**

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Event **electronic** case report form (**e**CRF). • The investigator must assign the following **mandatory** adverse event attributes: o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms) o Dates of onset and resolution (if resolved) o Did the event start **before** first dose of investigational product o Assessment of seriousness o Severity (or toxicity defined below) o Assessment of relatedness to **investigational product(s), non-investigational product(s)/auxiliary medicinal product(s),** and/or **devices** o Assessment of relatedness to any study-mandated activity/procedure o Action taken o Outcome of event • If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event**s e**CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen in lieu of completion of the Event**s e**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, except **for** 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 **assess** 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 (CTCAE), version 4.0 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**(s), non-investigational product(s)/auxiliary medicinal product(s)**, device(s), study-mandated procedure and each occurrence of each adverse event. • **The investigator is obligated to assess the relationship between investigational product(s), non-investigational product(s)/auxiliary medicinal product(s), device(s),** study-mandated procedure**,** and each occurrence of each 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 **i**nvestigator's **b**rochure and/or **p**roduct **i**nformation, for marketed products, in his/her assessment. • For each adverse event/adverse device effect/serious adverse event, the investigator must document in the medical notes that **they have** reviewed the adverse event/adverse device effect/serious adverse event and has provided an assessment of causality. **For sites reporting serious adverse events via electronic data capture (EDC), the investigator or sub investigator must confirm causality in EDC within 72 hours of the serious adverse event being entered on the Events eCRF.** • 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 **assess** causality for every event before the initial transmission of the serious adverse event data. • The investigator may change **their** opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. **In this case, for sites reporting serious adverse events via EDC, the investigator or sub-investigator must reconfirm causality in the EDC system within 72 hours of the serious adverse event being entered on the Events eCRF.** • 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 healthcare professionals. • If a subject is permanently withdrawn from **investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s)** because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event**s** **e**CRF. • The investigator will submit any updated serious adverse event data to Amgen **immediately and no later than** 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 EDC system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using a **paper-based Serious Adverse Event Contingency Form, also referred to as the** Electronic Serious Adverse Event Contingency Report Form (paper form; see Figure 12-1)**, immediately and no later than** 24 hours of the investigator's **awareness** of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC **system** has been taken off-line, then the site can report this information on an Electronic Serious Adverse Event Contingency Report Form (paper form; see Figure 12-1). • **Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen immediately and no later than 24 hours of the investigator's awareness of the event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.**

Adverse Device Effects: Recording, Evaluating and Reporting

- Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event**s** **e**CRF page.

- It is very important that the investigator provides **their** 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

AMGEN
Study # 20160354
Erenumab (AMG 334)

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Erenumab (AMG 334): No✓ Yes✓ Prefilled Syringe: No✓ Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP/Amgen Device:		Prior to, or at time of Event: Date of Initial Dose Day Month Year	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 # _____ ☐ Unavailable / Unknown

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AMGEN
Study # 20160354
Erenumab (AMG 334)

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Site Number	Subject ID Number

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

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect		Continuing		Dose	Route	Freq.	Treatment Med	
			No✓	Yes✓	No✓	Yes✓				No✓	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 # 20160354 Erenumab (AMG 334)	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

	Site Number	Subject ID Number	

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

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

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12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female **subjects** who have reached puberty are outlined in Section 6.2.

Male and female subjects who have reached puberty must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for an additional 16 weeks after the last dose of **investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s**).

Definition of Females of Childbearing Potential

A female is considered fertile **after** menarche **and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be** considered **not** of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- **A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause**

OR

- **A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.**

Contraception Methods for Female Subjects

Acceptable Methods of Effective Contraception

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

- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (**if** 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 **study** and the preferred and usual lifestyle of the subject)
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

Unacceptable Methods of Birth Control for Female Subjects

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

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

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking **investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s)** through 16 weeks after the last dose of investigational product**(s) and/or non-investigational product(s)/auxiliary medicinal product(s**).
- Information will be recorded on the Pregnancy Notification **Form** (see Figure 12-2). The **Form** must be submitted to Amgen Global Patient Safety **immediately and no later** 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification **Form** that violates the country or regions local privacy laws.)

- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking **investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s)** through 16 weeks after the last dose of investigational product. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 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 or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 16 weeks after the last dose of investigational product, the information will be recorded on the Pregnancy Notification **Form**. The **form** (see Figure 12-2) must be submitted to Amgen Global Patient Safety **immediately and no later than** 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification **Form** that violates the country or regions local privacy laws.)
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking **investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s)** through an additional 16 weeks after the last dose of investigational product.
- Information will be recorded on the Lactation Notification **Form** (see below) and submitted to Amgen Global Patient Safety **immediately and no later than** 24 hours of the investigator's **awareness** of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 218.
- 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 **investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s)** through an additional 16 weeks after discontinuing **investigational product(s) and/or non-investigational product(s)/auxiliary medicinal product(s)**.

Figure 12-2. Pregnancy and Lactation Notification Form

Amgen Proprietary - Confidential

Pregnancy Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20160354

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

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

1. Case Administrative Information

Protocol/Study Number: 20160354

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

12.6 Appendix 6. Sample Storage and Destruction

Any blood (eg, biomarker, anti-erenumab antibody) sample collected according to the Schedule of Activities **in Table 2-1 (Group 1) and Table 2-2 (Group 2)** 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 **before** 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 the migraine, the dose response and/or prediction of response to erenumab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. **After** the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining sample types (eg, blood, tumor) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples **before** 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 Appendix 3 for subject confidentiality.

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments

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 **investigational product(s) and/or noninvestigation product(s)/auxiliary medicinal product(s)**, 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/or Non-investigational Product(s)/Auxiliary Medicinal Product(s) 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 bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, 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(s) and Non-investigational Product(s)/Auxiliary Medicinal Product(s) Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 x ULN at any time	> 2 x ULN
		OR
INR	--	> 1.5 x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8 x ULN at any time > 5 x ULN but < 8 x ULN for ≥ 2 weeks > 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule > 3 x 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 > 3 x ULN (when baseline was < ULN)
	OR	
ALP	> 8 x ULN at any time	--

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

Criteria for Rechallenge of Amgen Investigational Product(s) and Non-investigational Product(s)/Auxiliary Medicinal Product(s) 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 erenumab 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 **immediately and no later than** 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate **e**CRF (eg, Events eCRF) 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 Appendix 4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) **and/**or **non-investigational product(s)/auxiliary medicinal product(s)** 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, bilirubin (BIL) (total and direct), and INR within 24 hours
- In cases of TBL > 2 x 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) **and/**or **non-investigational product(s)/auxiliary medicinal product(s)** 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 (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 non-prescription 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, and 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**/or non-investigational product(s)/auxiliary medicinal product(s)**.

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

12.8 Appendix 8. Modified Pediatric Migraine Disability Assessment Questionnaire (Modified PedMIDAS)

The following questions try to assess how much the headaches are affecting day-to-day activity over the past month. Your answers should be based on the last month. There are no “right” or “wrong” answers so please put down your best guess.

1. How many full school days of school were missed in the last month due to headaches?
2. How many partial days of school were missed in the last month due to headaches (do not include full days counted in the first question)?
3. How many days in the last month did you function at less than half your ability in school because of a headache (do not include days counted in the first two questions)?
4. How many days were you not able to do things at home (ie, chores, homework, etc) due to a headache?
5. How many days did you not participate in other activities due to headaches (ie, play, go out, sports, etc)?
6. How many days did you participate in these activities, but functioned at less than half your ability (do not include days counted in the 5th question)?

Total modified PedMIDAS Score _____

Headache Frequency _____

Headache Severity _____

12.9 Appendix 9. Patient Global Impression of Change (PGIC)

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PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the study, my overall status is:

✓*one box only:*

[1] ☐ Very Much Improved
[2] ☐ Much Improved
[3] ☐ Minimally Improved
[4] ☐ No Change
[5] ☐ Minimally Worse
[6] ☐ Much Worse
[7] ☐ Very Much Worse

(US/English)

USA/English – Version of 05 April 2005
PGI-C_TB1.0_ID2036-2387_eng-USorl.doc

12.10 Appendix 10. Columbia-suicide Severity Rating Scale

C-SSRS Children's Baseline/Screening Scale (Sample):

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., ***"I've thought about killing myself"***) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, ***"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*** ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)?*** ***What did you think about?*** If yes, describe:	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to ***"I have the thoughts but I definitely will not do anything about them."*** ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself? Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes No** ☐ ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response***_____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, o get something else to happen)? (***Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** **Has subject engaged in Self-Injurious Behavior, intent unknown?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐

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Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; ***medical*** hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; ***medical*** hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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C-SSRS Children's Since Last Visit Scale (Sample):

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you wish you weren't alive anymore?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)? What did you think about?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you decided how or when you would make yourself not alive anymore/kill yourself? Have you planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out these details), was any part of you thinking about actually doing it?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response*** _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you do anything to try to kill yourself or make yourself not alive anymore? What did you do?*** ***Did you hurt yourself on purpose? Why did you do that?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, not at all to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** **Has subject engaged in Self-Injurious Behavior, intent unknown?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything? What did you do?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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C-SSRS Adult's (Used for Adolescents') Baseline/Screening Scale: (Sample)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No** ☐ ☐

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INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* _____ *Type # (1-5)* _____ *Description of Ideation* Past X Months - *Most Severe Ideation:* _____ *Type # (1-5)* _____ *Description of Ideation*	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes No ☐ ☐ Total # of # Attempts _____ Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐

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Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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C-SSRS Adult's (Used for Adolescents') Since Last Visit Scale (Sample):

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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12.11 Appendix 11. Pubertal Maturation Self-assessment (Tanner Staging) Scale

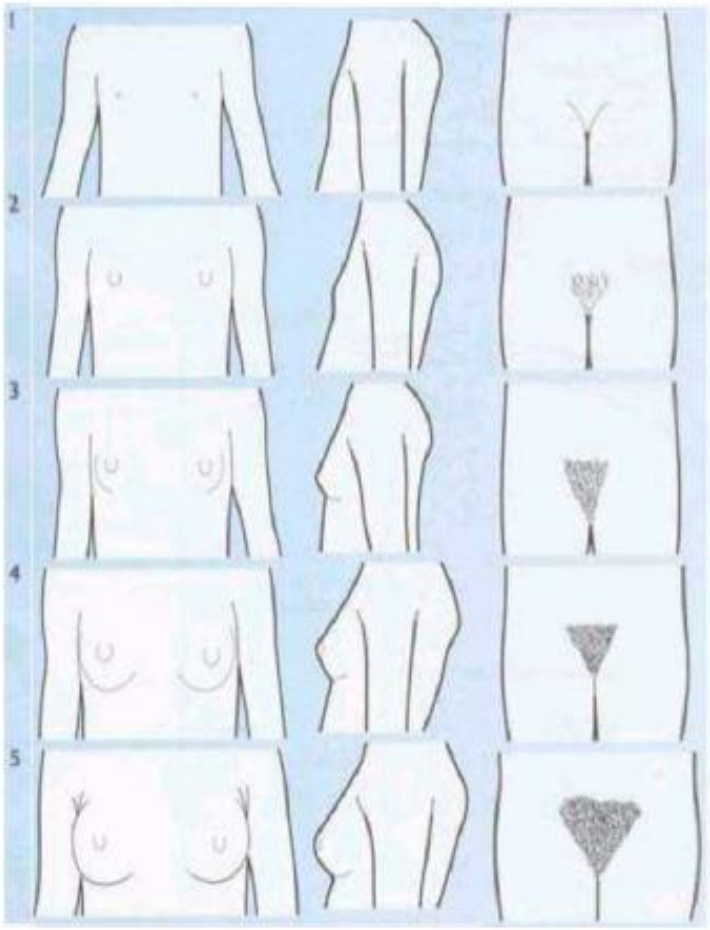
Female Tanner Staging (Sample)

Pubertal Maturation Self-assessment (Tanner Staging) Scale

Female version

Dear subject

Please look at the pictures below and circle one number (either 1, 2, 3, 4 or 5) next to the set of pictures that looks most like you



Pubertal Maturation Self-assessment (Tanner Staging) Scale – Female Version

1 November 2019_Generic English

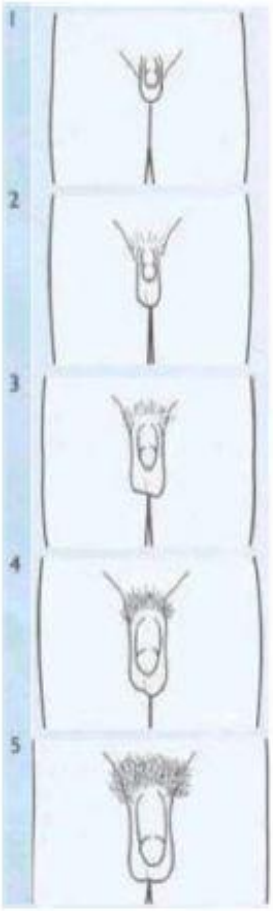
Male Tanner Staging (Sample)

Pubertal Maturation Self-assessment (Tanner Staging) Scale

Male Version

Dear subject

Please look at the pictures below and circle one number (either 1, 2, 3, 4 or 5) next to the picture that looks most like you.



Pubertal Maturation Self-assessment (Tanner Staging) Scale – Male Version

1 November 2019_Generic English

12.12 Appendix 12. Patient Health Questionnaire-9 Modified for Adolescents

Patient Health Questionnaire: modified

Name: _____ **Clinician:** _____ **Date:** _____

Instructions: How often have you been bothered by each of the following symptoms during the past **two weeks**? For each symptom put an **"X"** in the box beneath the answer that best describes how you have been feeling.

	(0) Not At All	(1) Several Days	(2) More Than Half the Days	(3) Nearly Every Day
1. Feeling down, depressed, irritable, or hopeless?				
2. Little interest or pleasure in doing things?				
3. Trouble falling asleep, staying asleep, or sleeping too much?				
4. Poor appetite, weight loss, or overeating?				
5. Feeling tired, or having little energy?				
6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down?				
7. Trouble concentrating on things like school work, reading, or watching TV?				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?				
9. Thoughts that you would be better off dead, or of hurting yourself in some way?				

In the **past year** have you felt depressed or sad most days, even if you felt okay sometimes?
[ ] Yes [ ] No

If you are experiencing any of the problems on this form, how **difficult** have these problems made it for you to do your work, take care of things at home or get along with other people?

[ ] Not difficult at all [ ] Somewhat difficult [ ] Very difficult [ ] Extremely difficult

Has there been a time in the **past month** when you have had serious thoughts about ending your life?
[ ] Yes [ ] No

Have you **EVER**, in your WHOLE LIFE, tried to kill yourself or made a suicide attempt?
[ ] Yes [ ] No

***If you have had thoughts that you would be better off dead or of hurting yourself in some way, please discuss this with your Health Care Clinician, go to a hospital emergency room or call 911.*

Office use only Severity score:

Modified from the PHQ-9 [Modified from PRIME-MD PHQ-9 ®. Copyright© 1999 Pfizer Inc. (Spitzer et al, JAMA, 1999)], Revised PHQ-A (Johnson, 2002), and the Columbia DDS (DISC Development Group, 2000)

12.13 Appendix 13. Faces Pain Scale-revised

FPS-R - Australia/English - Version of 30 Jan 14 - Mapi.
ID7288 / FPS-R_AU2D_eng-AU.doc

Faces Pain Scale – Revised (FPS-R)

In the following instructions, say "hurt" or "pain", whichever seems right for a particular child.

"**These faces show how much something can hurt. This face** *[point to face on far left]* **shows no pain. The faces show more and more pain** *[point to each from left to right]* **up to this one** *[point to face on far right]* **- it shows very much pain. Point to the face that shows how much you hurt** [right now]."

Score the chosen face ***0****,* ***2****,* ***4****,* ***6****,* ***8****, or* ***10****, counting left to right, so "0" = "no pain" and "10" = "very much pain". Do not use words like "happy" or "sad". This scale is intended to measure how children feel inside, not how their face looks.*

Permission for Use. Copyright of the FPS-R is held by the International Association for the Study of Pain (IASP) © 2001. This material may be photocopied for non-commercial clinical, educational and research use. For reproduction of the FPS-R in a journal, book or web page, or for any commercial use of the scale, request permission from IASP online at www.iasp-pain.org/FPS-R.

Sources. Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The Faces Pain Scale – Revised: Toward a common metric in pediatric pain measurement. Pain 2001;93:173-183. Bieri D, Reeve R, Champion GD, Addicoat L, Ziegler J. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: Development, initial validation and preliminary investigation for ratio scale properties. Pain 1990;41:139-150.

(fold along dotted line)

10 **8** **6** **4** **2** **0**



12.14 Appendix 14. Country-specific Requirements

This appendix provides language for country-specific regulatory requirements and other procedures to follow in the execution of the global study in these countries.

The summary of changes outlined below specify requirements for sites and subjects participating in the European Union. The country-specific requirements for Japan will be outlined in a separate country-specific supplement.

Table 12-3. Belgium Summary of Changes

Protocol Section	Text in Protocol	Text for Belgium
3.3.3.2, Mitigations	Clinical: In this study, the enrollment was staggered by age with adolescents 12 to < 18 years of age starting enrollment first. Children 6 to < 12 years of age commenced enrollment after data from the 52-week juvenile toxicology study in cynomolgus monkeys (Study 1770628) and pharmacokinetic (PK) and preliminary safety data from the phase 1 study (Study 20160172) became available. Further, to mitigate risks associated with a potential hypersensitivity reaction, after the first investigational product administration of the DBTP and DLBEP (day 1 and week 24 visits for Group 1; day 1 and week 12 visits for Group 2) subjects will remain on site for at least 2 hours and after each subsequent investigational product administration (week 4 to week 20 and week 28 to week 60 for Group 1; week 4 to week 8 and week 16 to week 48 for Group 2) subjects will remain on site at least 30 minutes.	Clinical: In this study, enrollment will be staggered by age with adolescents 12 to < 18 years of age starting enrollment first. Children 6 to < 12 years of age will be enrolled, **once data from the 52-week, juvenile toxicology study in cynomolgus monkeys (Study 1770628) as well as** pharmacokinetic (PK) and preliminary safety data from **the** phase 1 Study **20160172** becomes available. Further, in order to mitigate risks associated with a potential hypersensitivity reaction, after the first investigational product administration of DBTP and DLBEP (day 1 and week 24 visits) subjects will remain on site for at least 2 hours and after each subsequent investigational product administration (week 4 to week 20 and week 28 to week 60) subjects will remain on site at least 30 minutes. **Subjects should be warned about the risk of constipation, recommended to maintain adequate fluid intake to prevent hardening of stool, asked about new-onset constipation at study visits, and advise to seek medical attention in case constipation does not resolve or worsens. Subjects should seek medical attention immediately if they develop severe constipation. Constipation**

Protocol Section	Text in Protocol	Text for Belgium
		should be managed promptly as clinically appropriate. For severe constipation, discontinuation of treatment should be considered.
5.1, Overall Design	In this study the enrollment was staggered by age with adolescents 12 to < 18 years of age starting enrollment first. Children 6 to < 12 years of age commenced enrollment after the 52-week, juvenile toxicology study in cynomolgus monkeys (Study 1770628) and pharmacokinetic (PK) and safety data from the phase 1 study (Study 20160172) became available.	Enrollment will be staggered by age; adolescents (12 to < 18 years of age) will start enrollment first. Some countries might require PK and preliminary**, interim analysis** safety data from a phase 1 study **in children and adolescents with migraine (Study 20160172)** before they start enrolling adolescents. Children (6 to < 12 years of age) will be enrolled once **data from the 52-week, juvenile toxicology study in cynomolgus monkeys (Study 1770628) as well as p**harmacokinetics (PK) and preliminary safety data from the phase 1 Study **20160172** becomes available.
6.2, Exclusion Criteria, 219	Female subjects of childbearing potential unwilling to use an acceptable method of effective contraception during treatment and for an additional 16 weeks after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information.	Female subjects of childbearing potential unwilling to use a **highly effective** method of contraception during treatment and for an additional 16 weeks after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information.
6.4, Subject Enrollment, Staggered Enrollment	In this study, enrollment was staggered by age with adolescents 12 to < 18 years of age starting enrolment first. Children 6 to < 12 years of age) commenced enrollment after the 52-week juvenile toxicology study in cynomolgus monkeys (Study 1770628) and PK and safety data from the phase 1 study (Study 20160172) became available.	Enrollment will be staggered by age: adolescents (12 to < 18 years of age) will start enrollment first, once pharmacokinetics (PK) and preliminary safety data from a phase 1 study become available. Children (6 to < 12 years of age) will start enrollment later, once **data from the 52-week, juvenile toxicology study in cynomolgus monkeys (Study 1770628) as well as** pharmacokinetics (PK) and preliminary safety data from the phase 1 Study **20160172** becomes available.
9.2.1.6.3, Blood Samples	For subjects in Group 1, the protocol includes the collection of blood samples at 7 visits during screening, rescreening (if applicable), and the	**The protocol includes the collection of blood samples at 5 visits during screening and the DBTP (approximately 83 mL**

Protocol Section	Text in Protocol	Text for Belgium
	DBTP (up to approximately 78 mL in total) and 3 additional visits during the optional DLBEP (approximately 18.9 mL in total). For subjects in Group 2, the protocol includes the collection of blood samples at 6 visits during screening, rescreening (if applicable), and the DBTP (up to approximately 72 mL in total) and 3 additional visits during the optional DLBEP (approximately 18.9 mL in total). These blood samples will be collected for screening purposes (at screening visit) and for PK and safety analyses in line with regulatory requirements. Details on blood sample analytes, timing, and volumes are provided in either the Schedule of Activities (Table 2-1 and Table 2-2) and/or the ICF.	**in total) and 4 visits during the DLBEP (approximately 19 mL in total). These blood samples will be collected for screening purposes (at screening visit) and for PK and safety analyses in line with regulatory requirements. Details on blood sample analytes, timing, and volumes are provided in either the Schedule of Activities (Table 2-1) and/or the ICF.**
12.5, Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information, Contraception Methods for Female Subjects	Acceptable Methods of Effective Contraception • Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route • Intrauterine device • Intrauterine hormonal-releasing system • Bilateral tubal ligation/occlusion • Vasectomized partner (if 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 study	**Highly Effective Contraception Methods** **Note: Failure rate of < 1% per year when used consistently and correctly.** • Combined (estrogen and progestogen containing) hormonal **contraception associated with inhibition of ovulation (**oral, intravaginal, **or** transdermal**)** • **Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)** • Intrauterine device • Intrauterine hormonal-releasing system • Bilateral tubal ligation/occlusion • Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing

Protocol Section	Text in Protocol	Text for Belgium
	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)	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)

DBTP = double-blind treatment period; DLBEP = dose-level-blinded extension phase (all subjects will be receiving erenumab at either dose level 1 or dose level 2, and the dose level will be double-blinded; ICF = informed consent form

Table 12-4. Italy Summary of Changes

Protocol Section	Text in Protocol	Text for Italy
2.2, Schedule of Activities, Physical Examination, Table 2-1. Group 1 (24-week DBTP) Schedule of Activities	For Group 1 physical examinations are to be performed at the following visits: • Initial Screening • Day 1 • Week 24/ET • Week 48 • Week 64/ET • Safety Follow-up	For Group 1 physical examinations are to be performed at the following visits: • Initial Screening • Day 1 • **Week 4** • **Week 8** • **Week 12** • Week 24/ET • Week 48 • Week 64/ET • Safety Follow-up
2.2, Schedule of Activities, Physical Examination, Table 2-2. Group 2 (12-week DBTP) Schedule of Activities	For Group 2 physical examinations are to be performed at the following visits: • Initial Screening • Day 1 • Week 12/ET • Week 36 • Week 52/ET • Safety Follow-up	For Group 2 physical examinations are to be performed at the following visits: • Initial Screening • Day 1 • **Week 4** • **Week 8** • Week 12/ET • Week 36 • Week 52/ET • Safety Follow-up
2.2, Schedule of Activities, Group 1 (24-week DBTP) Footnote	Not applicable	**[v] Physical examination at week 4, 8, and 12 is an Italy requirement only. Physical examination will not be performed at week 4, 8, and 12 according to the global protocol**.
2.2, Schedule of Activities, Group 2 (12-week DBTP) Footnote	Not applicable	**[v] Physical examination at week 4, 8, and 12 is an Italy requirement only. Physical examination will not be performed at week 4, and 8 according to the global protocol**.

Protocol Section	Text in Protocol	Text for Italy
6.2, Exclusion Criteria, 219	219. Female subjects of childbearing potential unwilling to use an acceptable method of effective contraception during treatment and for an additional 16 weeks after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information.	219. Female subjects of childbearing potential unwilling to use a **highly effective** method of contraception during treatment and for an additional 16 weeks after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information.

Protocol Section	Text in Protocol	Text for Italy
12.5, Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information, Contraception Methods for Female Subjects	Acceptable Methods of Effective Contraception • Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route • Intrauterine device • Intrauterine hormonal-releasing system • Bilateral tubal ligation/occlusion • Vasectomized partner (if 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 study 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)	**Highly Effective Contraception Methods** Note: Failure rate of < 1% per year when used consistently and correctly. • Combined (estrogen and progestogen containing) hormonal **contraception associated with inhibition of ovulation (**oral, intravaginal, **or** transdermal**)** • **Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)** • Intrauterine device • Intrauterine hormonal-releasing system • Bilateral tubal ligation/occlusion • Vasectomized partner (if 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 study and the preferred and usual lifestyle of the subject)

ET = early termination.

Superseding Amendment 2

Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Children (6 to < 12 Years) and Adolescents (12 to < 18 Years) With Chronic Migraine (OASIS PEDIATRIC [CM])

Amgen Protocol Number: AMG 334 (Erenumab) 20160354

EU-CT Number: 2023-504928-26

NCT Number: NCT03832998

Amendment Date:	11 September 2023
Superseding Amendment Date	06 October 2023

Rationale:

This protocol is mainly being amended to update the study design to reduce the double-blinding treatment phase (DBTP) from 24 to 12 weeks. Group 1 subjects consented under the original protocol or protocol Amendment 1 will continue a 24-week DBTP (Group 1), while Group 2 subjects consented and enrolled under protocol Amendment 2, or any future amendments will continue a 12-week DBTP. Additional language was included to update/clarify other items in the protocol:

- Updated secondary objectives and endpoints language (Section 1 and 4.1) to:
    - clarify language that Pediatric Migraine Disability Assessment (PedMIDAS) is from baseline to week 9 through week 12 (month 3) of the DBTP.
    - modify language for the change in monthly migraine days (MMD) from baseline to week 24 to instead evaluate the average of the 6-month DBTP (week-1 though week-24)
    - differentiate the timing of the Group 1 and Group 2 safety endpoints to evaluate injection site pain using the Faces Pain Scale-Revised
- Updated exploratory objectives and endpoints language (Section 4.1) to:
    - to clarify that only Group 1 is being evaluated for the effects of erenumab compared with placebo on the change in monthly headache days and MMD from baseline to the average of the 6 month DBTP

- Updated overall design language (Sections 1 and 5.1) to:
    - clarify that consenting Group 1 subjects will consist of subjects that enrolled under the original protocol or protocol Amendment 1 and that they need to follow the Assessments outlined in Table 2-1 of Schedule of Activities (SoA). Conversely, consenting subjects enrolled under protocol Amendment 2, or any future amendments (Group 2), will follow the assessments outlined in Table 2-2 of SoA).
    - clarify that the end of the DBTP is week-24 for Group 1 subjects and week-12 for Group 2 subjects.
    - differentiate the DBTP and dose-level-blinded extension phase (DLBEP) dosing schedules between Groups 1 and 2.
- Updated eDiary language for Groups 1 and 2 in procedure section of protocol synopsis (Section 1).
- Updated Schema (Section 2.1) to distinguish Group 1 and Group 2 DBTP:
    - added ± 7 days to Screening Phase and to Baseline Phase.
- Updated the SoA (Section 2.2) to differentiate Group 1 (24-week DBTP) and Group 2 (12-week DBTP) SoA tables.
- Updated overall design (Section 5.1), mitigation (Section 3.3.3.2), and subject enrollment (Section 6.4) clinical language to clarify that enrollment of children into the study commenced after data from the 52-week juvenile toxicology study in cynomolgus monkeys and pharmacokinetic (PK) and preliminary safety data from the phase 1 study became available.
- Updated the study duration for subjects (Section 5.3.2) to include Group 1 and Group 2 DBTPs.
- Updated justification for investigation product dose language (Section 5.4) to incorporate additional safety information on exposure of erenumab in pediatric subjects.
- Updated exclusion criteria 209 and 210 (Section 6.2).
- Updated the dosing instruction and observation period post investigational product administration information in Table 7-1 of the investigational products section (Section 7.1.1).
- Deleted the other treatment procedure section (previously known as Section 7.1.5)

- Updated Table 7-2 for excluded treatments, medical devices, and/or procedures to:
    - clarify that elemental magnesium is a prohibited therapeutic for this study.
    - change the time period for exclusion from 1 month to 15 days.
- Removed language from Discontinuation From the Study (Section 8.2, in accordance with new protocol template.
- Updated safety follow-up visit language (Section 9.1.3) to clarify time of safety follow-up visit.
- Added blood samples section (Section 9.2.1.6.3) to include blood sample collection instructions for subjects in Group 1 and Group 2.
- Updated the substance abuse history section (Section 9.2.1.8) to clarify that detailed history of prior and/or concurrent use of tobacco, caffeine, and illicit drugs need to be collected during at week-24/early termination visit (Group 1) or the week-12/early termination visit (Group 2), this in addition to the initial screening.
- Updated the pubertal maturation self-assessment (tanner staging) (Section 9.2.1.10) instructions for Group 1 and Group 2.
- Updated safety language (Section 9.2.3.1 and Appendix 4) to align with updated Amgen protocol template language without changing safety data collection requirements.
- Updated contraception guidance language (Appendix 5) to align with new protocol template language.
- Updated PK assessment language (Section 9.2.5) to align with new protocol template language.
- Updated antibody testing procedures language (Section 9.2.7) to clarify more frequent antibody testing or testing for a longer period of time may be requested in the event of safety-related concerns.
- Updated biomarker development language (Section 9.2.8.1) to align with new protocol template language.
- Updated biomarker future research language (Section 9.2.8.2) to align with new protocol template language.
- Updated clinical outcome assessment language (Section 9.2.9) to distinguish Group 1 and Group 2 DLBEPs.

- Updated interim analyses and early stopping guidelines (Section 10.3.1.1) language to clarify that second interim analysis may be performed at the time when all adolescent subjects and at least 40 children have completed the study through the safety follow-up or discontinued from study. This update was also provided to conform with EU regulatory requirements.
- Updated the primary analysis (Section 10.3.1.2) and Efficacy Analysis (Section 10.3.2.2) language to clarify that primary analysis will be performed when the last adolescent subject completes the last visit of the DBTP (week-24 for Group 1; week-12 for Group 2) or the early termination visit during the DBTP.
- Added language to informed consent process in Appendix 3 to comply with study governance considerations.
- Added new Appendix 14 (country-specific requirements) to incorporate Belgium and Italy country-specific supplement (CSS) language; to outline the country-specific requirements for sites and subjects participating in Belgium and Italy.
- Update language from protocol required therapies to non-investigational product(s)/auxiliary medicinal product(s) to align with new protocol template language.
- Administration, typographical, abbreviations, and formatting changes were made throughout the protocol.

After finalization of protocol amendment 2, protocol was superseded on 06 October 2023 to include reference to Belgium country-specific supplement version 3, dated 30 June 2021.

Amendment 2

Protocol Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Erenumab in Children (6 to < 12 Years) and Adolescents (12 to < 18 Years) With Chronic Migraine (OASIS PEDIATRIC [CM])

Amgen Protocol Number: AMG 334 (Erenumab) 20160354

EU-CT Number: 2023-504928-26

NCT Number: NCT03832998

Amendment Date: 11 September 2023

Rationale:

This protocol is mainly being amended to update the study design to reduce the double-blinding treatment phase (DBTP) from 24 to 12 weeks. Group 1 subjects consented under the original protocol or protocol Amendment 1 will continue a 24-week DBTP (Group 1), while Group 2 subjects consented and enrolled under protocol Amendment 2, or any future amendments will continue a 12-week DBTP. Additional language was included to update/clarify other items in the protocol:

- Updated secondary objectives and endpoints language (Section 1 and 4.1) to:
    - clarify language that Pediatric Migraine Disability Assessment (PedMIDAS) is from baseline to week 9 through week 12 (month 3) of the DBTP.
    - modify language for the change in monthly migraine days (MMD) from baseline to week 24 to instead evaluate the average of the 6-month DBTP (week-1 though week-24)
    - differentiate the timing of the Group 1 and Group 2 safety endpoints to evaluate injection site pain using the Faces Pain Scale-Revised
- Updated exploratory objectives and endpoints language (Section 4.1) to:
    - to clarify that only Group 1 is being evaluated for the effects of erenumab compared with placebo on the change in monthly headache days and MMD from baseline to the average of the 6 month DBTP
- Updated overall design language (Sections 1 and 5.1) to:

Amendment 1

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Erenumab in Children (6 to < 12 Years) and Adolescents (12 to < 18 Years) with Chronic Migraine (OASIS PEDIATRIC [CM])

Amgen Protocol Number (AMG 334/Erenumab) 20160354

Amendment Date: 17 December 2020

Rationale:

The following changes were made to the protocol, dated December 17th, 2020, to add clarity to several protocol sections, improve study experiences for sites and subjects, and to clarify/correct other items in the protocol.

Clarifications to entry criteria requirements include:

- Updated inclusion criterion #105, 106 and 107 to clarify the source for data and length of the baseline period requirement.
- Updated exclusion criterion # 210 to clarify eligibility for subjects who discontinued cognitive behavioral therapy within 3 months prior to start of the baseline phase.

Updates to prohibited treatments include:

- Updated exclusion criterion #213 to clarify prohibited treatments prior to or during the baseline phase.
- Updated excluded treatments in Table 7-2 to clarify excluded treatments for any indications 1 and 2 months prior to the start of baseline phase and throughout the study.

Updates to IP injection and post IP injection requirements include:

- Updated justification of investigational product dose with current information.
- Updated dosing instructions to clarify preventive measures for injection site pain prior to IP administration.

- Updated study treatment to include guidance on the observation period post IP administration.

Provisions for home healthcare to improve flexibility and patient experience include:

- Updated dosing instructions to include healthcare professionals to administer IP.
- Added other treatment procedures to include the provision of home healthcare services.

Addition of option for restarting the baseline period to alleviate issues with technical failures with the eDiary device include:

- Updated section 9.1 general study periods to include option for restarting the baseline period due to extraordinary circumstances such as technical reasons.

Other changes include:

- Updated key sponsor contact.
- Updated NCT number.
- Updated primary endpoint of intervention effect to treatment effect.
- Updated schedule of activities to clarify study procedures for subjects unable to continue in study.
- Updated schedule of activities with changes made in other sections.
- Updated investigational product background with current information.
- Updated investigational product risk assessment with current information.
- Updated end of study definition to clarify the end of study for a subject.
- Updated screen failures to clarify information collected.
- Updated blinding to clarify that only select team members from Amgen will be unblinded for the primary analysis.
- Updated discontinuation of study treatment to clarify study procedures to be completed if a subject is unable to continue in the study.
- Updated informed consent to clarify signature requirements once age of majority is reached.
- Updated weight to clarify the weight used for IP planning.

- Updated vital signs to clarify heart rate assessment.
- Updated statistical analysis methods to clarify final analysis when full unblinding is available.
- Updated with current safety template language
- Administration, typographical and formatting changes were made throughout the protocol.

  - clarify that consenting Group 1 subjects will consist of subjects that enrolled under the original protocol or protocol Amendment 1 and that they need to follow the Assessments outlined in Table 2-1 of Schedule of Activities (SoA). Conversely, consenting subjects enrolled under protocol Amendment 2, or any future amendments (Group 2), will follow the assessments outlined in Table 2-2 of SoA).
  - clarify that the end of the DBTP is week-24 for Group 1 subjects and week-12 for Group 2 subjects.
  - differentiate the DBTP and dose-level-blinded extension phase (DLBEP) dosing schedules between Groups 1 and 2.

- Updated eDiary language for Groups 1 and 2 in procedure section of protocol synopsis (Section 1).
- Updated Schema (Section 2.1) to distinguish Group 1 and Group 2 DBTP:
  - added ± 7 days to Screening Phase and to Baseline Phase.
- Updated the SoA (Section 2.2) to differentiate Group 1 (24-week DBTP) and Group 2 (12-week DBTP) SoA tables.
- Updated overall design (Section 5.1), mitigation (Section 3.3.3.2), and subject enrollment (Section 6.4) clinical language to clarify that enrollment of children into the study commenced after data from the 52-week juvenile toxicology study in cynomolgus monkeys and pharmacokinetic (PK) and preliminary safety data from the phase 1 study became available.
- Updated the study duration for subjects (Section 5.3.2) to include Group 1 and Group 2 DBTPs.
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- Updated exclusion criteria 209 and 210 (Section 6.2).
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- Updated the pubertal maturation self-assessment (tanner staging) (Section 9.2.1.10) instructions for Group 1 and Group 2.
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- Updated contraception guidance language (Appendix 5) to align with new protocol template language.
- Updated PK assessment language (Section 9.2.5) to align with new protocol template language.
- Updated antibody testing procedures language (Section 9.2.7) to clarify more frequent antibody testing or testing for a longer period of time may be requested in the event of safety-related concerns.
- Updated biomarker development language (Section 9.2.8.1) to align with new protocol template language.
- Updated biomarker future research language (Section 9.2.8.2) to align with new protocol template language.
- Updated clinical outcome assessment language (Section 9.2.9) to distinguish Group 1 and Group 2 DLBEPs.

- Updated interim analyses and early stopping guidelines (Section 10.3.1.1) language to clarify that second interim analysis may be performed at the time when all adolescent subjects and at least 40 children have completed the study through the safety follow-up or discontinued from study. This update was also provided to conform with EU regulatory requirements.
- Updated the primary analysis (Section 10.3.1.2) and Efficacy Analysis (Section 10.3.2.2) language to clarify that primary analysis will be performed when the last adolescent subject completes the last visit of the DBTP (week-24 for Group 1; week-12 for Group 2) or the early termination visit during the DBTP.
- Added language to informed consent process in Appendix 3 to comply with study governance considerations.
- Added new Appendix 14 (country-specific requirements) to incorporate Belgium and Italy country-specific supplement (CSS) language; to outline the country-specific requirements for sites and subjects participating in Belgium and Italy.
- Update language from protocol required therapies to non-investigational product(s)/auxiliary medicinal product(s) to align with new protocol template language.
- Administration, typographical, abbreviations, and formatting changes were made throughout the protocol.

Approval Signatures

Document Name: Protocol Superseding erenumab 20160354 2

Document Description: Superseding Protocol Amendment 2

Document Number: CLIN-000038726

Approval Date: 06 Oct 2023

Type of Study Protocol: Superseding

Protocol Amendment No.: 2

Document Approvals	
Reason for Signing: Management	Name: [redacted] Date of Signature: 06-Oct-2023 23:40:41 GMT+0000