Statistical Analysis Plan

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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Authors:	[redacted]
Sponsor:	Amgen Inc. One Amgen Center Drive, Thousand Oaks, CA, 91320, USA
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	28 June 2017	Original version
Amendment 1 (v2.0)	24 April 2018	• SAP Amendment 1 was done to describe details of the statistical analyses that have been outlined within the protocol for Study 20160354.

		• Section 2.1 (Safety endpoint) updated to clarify calculation one of the safety endpoints which will be calculated based on age-adjusted z-scores for height and weight. [redacted] • Section 2.2 updated to clarify combined erenumab dose group have greater reduction from baseline to week 9 through week 12 (month 3) in MMDs when compared with placebo. • Section 3.1 revised to clarify that the study will evaluate erenumab efficacy and safety for migraine prevention in children (6 to <12 years) and adolescents (12 to <18 years) with Chronic Migraine. The update includes a detailed explanation of the weeks to be considered for both DBTP and DLBEP. Additionally, the randomization allocation ratio has been specified, and the erenumab dose level groupings have been defined based on body weight categories to ensure appropriate dosing for the pediatric population. • Section 3.2 updated to provide clarity on the allocated sample sizes for the study groups. Additionally mentioned stratification groups for the Randomization. • Section 5.1.1 updated to add definitions of newly added efficacy and [redacted] • Section 5.1.2 updated to make precise definitions of safety endpoints. • Section 5.2 updated to add definition of Re-randomization Date in DLBEP. • Section 5.3 updated to add definition of Pre-DLBEP Baseline for Efficacy Endpoints. [redacted] • Section 7.2 revised to provide explicit information regarding the timing of the

		primary analysis and the specific groups to be included in this analysis. • Section 7.3 revised to provide explicit information regarding the timing of the Final analysis and the specific groups to be included in this analysis. • Section 9.1 updated to revised information on the additional analysis models employed for comparing primary and secondary endpoints. • Section 9.2 updated to add Subject accountability tabulations will be presented differently for the primary and final analyses. • Section 9.4 updated to revise summary of demographic and Baseline characteristics tables separately adolescent and children. • Table 9-1 updated to add treatment group information i.e., combined dose of erenumab and placebo group. Additionally updated sensitivity analysis model information to calculate secondary endpoint. • Section 9.5.1 revised to incorporate detailed categorizations for each subgroup. • Section 9.7.1 added [redacted].
Amendment 2 (v3.0)	02 October 2018	• SAP Amendment 2 was triggered due to Protocol Amendment 1 dated 04 September 2018. • List of abbreviations updated to include all abbreviations used in the document. • Section 2.1 (Safety endpoint) updated to add one additional endpoint. [redacted] • Section 5.1.1 updated to add definition of newly added endpoint PGIC. • Section 5.1.2 updated to define definition of Treatment-emergent Adverse Event (TEAE) for DBTP and DLBEP separately.

		• Section 6.0 updated to add additional part in the definition of Analysis set. • Section 6.7 newly added to include the Serum Bone Metabolism Markers Analyses Set(s). • Table 9-1 updated to add Primary Summary and Analysis Method of newly added endpoint (PGIC). • Section 9.5.2 updated to add Logisitic regression model after the missing data are imputed as nonresponse. • Table 9-2 updated to add newly added endpoint related to Serum bone metabolic markers. • Section 9.6.2 updated to add AEs will be summarized by SOC and PT also device related AEs will be calculated for DBTP and DLBEP. • Section 9.6.3 updated to add additional table for suspected Hy's Law cases. • Section 9.6.4 updated to number and percentages of subjects with at least one post-baseline vital sign will be summarized based to mentioned criteria separately for children (6-<12 years) and adolescent (12-<18 years) separately. • Section 9.7.4 added to define Analysis method of [redacted].
Amendment 3 (v4.0)	05 February 2025	• SAP Amendment 3 was triggered due to Protocol Amendment 2 dated 11 September 2023. • List of abbreviations updated to include all abbreviations used in the document. • Section 2.1 (Safety endpoint) specifically Injection site pain assessed by Faces pain Scale-Revised (FPS-R) will be analysed separately on Group 1 only (24-week DBTP) and Group 2 Only (12-week DBTP). • Section 2.1 (Exploratory endpoint) Change from baseline in monthly headache days to the average of the 6-month DBTP (week 1 through week 24) will be analysed for Group 1 only (24-week DBTP), also Change from baseline in MMD to the average of the 6-month DBTP (week 1 through week

		24) will be analysed for Group 1 only (24-week DBTP). • Section 3.1 updated to mention detailed definitions of Group 1 and Group 2. Also update DBTP as Group 1: 24-week DBTP and Group 2: 12-week DBTP. • Section 4.1 and Section 4.2 added clarity on prior preventive treatment failure. • Section 5.1.1 added more details on programming definitions for eDiary endpoints. • Section 5.2 added details for Group 2 • Table 5-1 (a) and Table 5-1 (b) prepared for Group 1 and Group 2 accordingly. • Table 5-2 updated for Group 1 and Group 2 accordingly. • Section 5.2 updated to add the definitions of Last Dose Date in DBTP and Last Dose Date in DLBEP, also updated the section of Primary completion date to add Group1 and Group 2 in week24 and week12 statement. • Section 5.4 Note section updated to remove the additional statement. • Section 5.5 Updated to remove the extra part from the Definition of Completing Study. • Section 5.5 added details for Group 2. • Section 7.1 updated sample size. • Section 7.2 updated for DBTP as (week 24 for Group 1; week 12 for Group 2). • Section 9.1 updated secondary endpoints • Section 9.1 updated to clarify that Primary analysis will be assessed during DBTP. • Table 9-1 updated endpoints summary. • Section 9.5.1 and Section 9.5.2 updated details on analyses of primary and secondary efficacy endpoints. • Table 9-2 added group 1 and group 2. • Section 9.6.2 added events of interest.

		• Section 9.6.2 updated to remove the statement “All treatment-emergent AEs will be listed”. • Section 9.6.7 updated electrocardiogram analyses. • Section 9.1 added group1 and group 2 to other analyses.
Amendment 4 (v5.0)	**05 September 2025**	• **SAP Amendment 4 was triggered due to updates in interval calculation for Dose-level-blinded extension phase (DLBEP).** • **Section 5.4 (Study Time Intervals) updated to reflect the revised interval calculation for the Group 01 and Group 02 of the Dose-level-blinded extension phase (DLBEP).**

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List of Abbreviations

Abbreviation	Explanation
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
CBT	Cognitive Behavioral Therapy
CDC	Center for Disease Control
CM	Chronic Migraine
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-Terminal Telopeptide of Type-1 Collagen
DARS	Data Acquisition Requirements Specification
DBP	Diastolic Blood Pressure
DBTP	Double-Blind Treatment Phase
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)
DMC	Data Monitoring Committee
DMP	Data Management Plan
DILI	Drug-Induced Liver Injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPS-R	Faces Pain Scale-Revised
GSO-DM	Global Study Operations – Data Management

IP	Investigational Product
IPD	Important Protocol Deviation
ISP	Injection Site Pain
ISR	Injection Site Reaction
IVRS	Interactive Voice Response System
LSMs	Least Square Means
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MIN	Minimum
MMDs	Monthly Migraine Days
MNAR	Missing Not At Random
NRI	Non-Responder Imputation
P1NP	Protocollagen Type 1 N-telopeptide
PedMIDAS	Pediatric Migraine Disability Assessment
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PT	Preferred Term
QM	Monthly
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Events
USds	United States
VAS	Visual Analog Scale
WHO Drug	World Health Organization Drug

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the **Protocol Amendment 2** for study 20160354, **AMG 334** dated **11 September 2023**. The scope of this plan includes the interim analysis, the primary analysis and the final analysis that are planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints/Estimands and Hypotheses

2.1 Objectives and Endpoints/Estimands

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared with placebo on the change in monthly migraine days (MMDs) from baseline to week 9 through week 12 (month 3) of the double-blind treatment phase (DBTP).	• Change from baseline in MMDs 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 who were randomized. • The primary endpoint, which is the change in MMDs 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.
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 MMDs from baseline to week 9 through week 12 (month 3) of the DBTP.	• Achievement of at least 50% reduction in MMDs 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 MMDs from baseline to the average of	• Change from baseline in MMDs to the average of the first 3 months (week 1 through week 12) of the DBTP.
• 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	• 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.

baseline 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 protocollagen Type 1 N-telopeptide [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.

Estimand(s) for Primary Objective(s)

- The target population, which is the adolescent subjects (12 to < 18 years of age) diagnosed with CM who were randomized.
- The primary endpoint, which is the change in MMDs 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.

Estimand(s) for Key Secondary Objective(s)

Not applicable for this study.

Estimand(s) for Secondary Objective(s)

Not applicable for this study.

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 MMDs from baseline to assessment time points.	• Change from baseline in MMDs 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	• Change from baseline in monthly headache days to the average of

headache days from baseline to the average of the first 3 months (week 1 through week 12) of the DBTP.	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 MMDs from baseline to assessment time points.	• Achievement of at least 50% reduction from baseline in MMDs at assessment time points.

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 MMDs 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 MMDs 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 phase.
[redacted]	
• To characterize immunogenicity of erenumab	• Anti-erenumab antibody formation

2.2 Hypotheses and/or Estimations

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

3. Study Overview

3.1 Study 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 of the Protocol Amendment 2 (PA2) (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 of the PA2 (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)

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

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

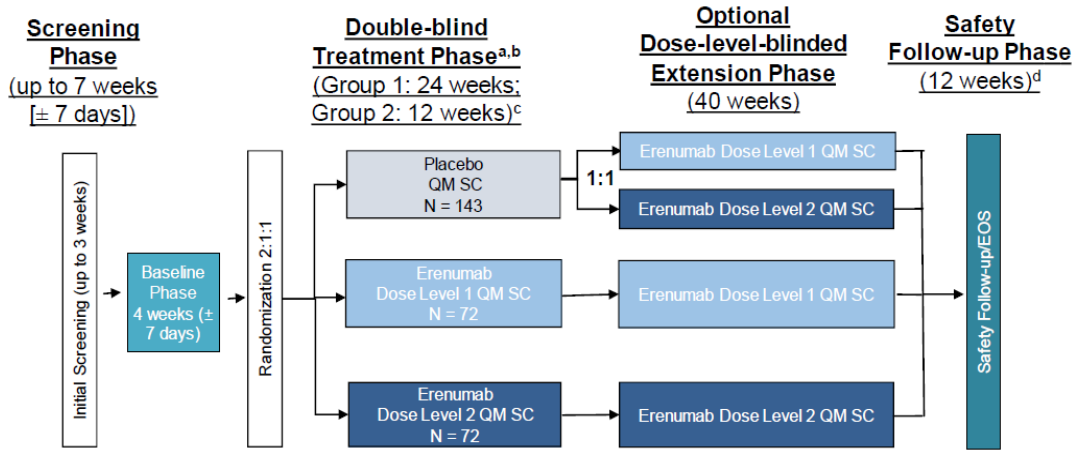
At the end of the DBTP (week 24 for subjects in Group 1; week 12 for subjects in Group 2), subjects in each treatment group will have the option to roll over into the 40-week optional DLBEP.

Subjects who received erenumab treatment during the DBTP will continue to receive the same erenumab dose in a double-blinded fashion during the DLBEP. Subjects who enroll in the DLBEP and 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).

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.

The overall study design is shown in the study schema in Figure 3-1. The endpoints are defined in Section 5.1.

Figure 3-1. Study Schema



DBTP = double-blind treatment phase; EOS = end of study; 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.

3.2 Sample Size

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; [redacted]

The sample size calculation has been performed based on the primary endpoint defined above (change in MMDs from baseline to week 9 through week 12 [month 3] of the DBTP) for the adolescent subgroup (subjects 12 to < 18 years of age). 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 MMDs (erenumab versus placebo) with an SD of 5.70 MMDs 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. [redacted]

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.

3.3 Adaptive Design

The sample size re-estimation is described in Section 7.1

4. Covariates and Subgroups

4.1 Planned Covariates

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

All formal analyses of efficacy endpoints in adolescents will be adjusted for the effect of the stratification factors including region (North America or Rest of World) and prior preventive treatment failure (yes or no [including never used]).

4.2 Subgroups

The primary and secondary efficacy and safety endpoints will be summarized separately for each age group.

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)
- Cognitive Behavior Therapy status (with CBT versus without CBT)
- prior preventive treatment failure status (yes versus no [including never used])
- Region (North America vs. Rest of World)
- Race (White versus non-white)

5. Definitions

5.1 Definition of Terms Included in Study Endpoints

5.1.1 Efficacy Endpoints

eDiary Day

A day in which a subject uses the eDiary.

Qualified Migraine Headache

A qualified migraine headache is defined as a headache lasting for ≥ 30 minutes, and meeting at least one of the following criteria (a and/or b):

a) ≥ 2 of the following pain features:

- Unilateral
- Throbbing
- Moderate to severe
- Exacerbated with exercise/physical activity.

b) ≥ 1 of the following associated symptoms:

- Nausea and/or vomiting.
- Photophobia and phonophobia

OR

A headache resulting in administration of migraine specific medication (triptan or ergotamine derivatives), regardless of duration and pain features/associated symptoms.

Qualified Headache

For each headache event reported (identified by unique headache event ID), identify whether it is a qualifying headache or not using the criteria below:

Qualified migraine headache as defined above

OR

Headache duration >=30 min

OR

Any headache resulting in administration of acute medication, regardless of duration (Acute medication including migraine specific medication and non-migraine specific medication. If “other” medication is selected and is not updated by medication code or name, then it will be treated as acute medication but NOT as migraine specific medication)

Migraine Day

Any calendar day with:

at least one qualified migraine headache as defined above

OR

migraine-specific medication (i.e., triptan or ergotamine derivative) use on that day, based on non-missing medication taken date.

Monthly Migraine Days

Number of migraine days between each monthly IP dose. Monthly migraine days at baseline are the number of migraine days in the baseline phase. Days without eDiary data in each monthly interval are handled by proration according to Section 8.3.

Headache Day

A calendar day with

At least one qualified headache as defined above

OR

Acute medication use for headache on that day, based on non-missing medication taken date (Acute medication including migraine specific medication and non-migraine specific medication. If “other” medication is selected and is not updated by medication code or name, then it will be treated as acute medication but NOT as migraine specific medication).

OR

Migraine specific medication (triptan or ergotamine) use with or without headache on that day, based on non-missing medication taken date.

Monthly Headache Days

Number of headache days between each monthly IP dose. Monthly headache days at baseline are the number of headache days in baseline phase. Days without eDiary data in each monthly interval are handled by proration according to Section 8.3.

Diary Day

A day in which a subject uses the eDiary.

Information Day

Information day includes:

1. Any date a Diary is completed is counted as an information day.

2. Any date that a recall period touches (48 hours back from Diary Day) is counted as an information day.

3. Any date that is a Qualified Headache Day or a Migraine Day is counted as an information day

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 an acute migraine-specific medication (i.e., 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 Episode

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

Monthly Migraine Episode

Number of migraine episodes days between each monthly IP dose. Monthly migraine episodes days at baseline are the number of migraine episode days in the baseline

phase. Days without eDiary data in each monthly interval are handled by proration according to Section 8.3.

Migraine Attack

A migraine attack is an event 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 (i.e., ≤ 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 (i.e., ≤ 48 hours between the start of the migraine attack to the time of the recurrence) will be considered as 1 attack.

Monthly Average Severity of Migraine Episodes

Severity of qualified migraine headache will be measured by using 100 mm Visual Analogue Scale (VAS).

The monthly average severity of migraine episodes is defined as the sum of the severity of each observed migraine episodes between two consecutive monthly IP doses divided by the total number of observed migraine episodes in that monthly interval. If less than 14 Information days in each monthly interval are recorded, the monthly average severity of migraine episodes will be set as missing.

Monthly Average Severity of Migraine Attacks

Severity of qualified migraine attack as defined above will be measured by using 100 mm VAS. The monthly average severity of migraine attack is defined as the sum of the severity of each distinct migraine attack as defined above between two consecutive monthly IP doses divided by the total number of migraine attacks in that monthly interval. If less than 14 Information days in each monthly interval are recorded, the monthly average severity of migraine attacks will be set as missing.

Response

At least a 50% reduction from baseline in monthly migraine days or in monthly headache days.

Modified Pediatric Migraine Disability Assessment (PedMIDAS)

The modified PedMIDAS is a 6-item self-administered questionnaire that measures the 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 monthly on site.

Patient Global Impression of Change (PGIC)

Patient Global Impression of Change (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, and up to 7 = very much worse (Guy, 1976).

5.1.2 Safety Endpoints

Treatment-emergent Adverse Event (TEAE)

DBTP

An Adverse Event (AE) recorded on the Events eCRF page that occurs on or after first dose of IP as determined by the flag indicating the event did not start prior to first dose of IP on the Events eCRF and up to and including the minimum of

- a day prior to first dose of DLBEP (if the subject receive dose in DLBEP),
- 112 days after the last dose of IP (in DBTP),
- end of study day (if the subject did not enter or did not receive any dose in DLBEP).

DLBEP

An Adverse Event (AE) recorded on the Events eCRF page that occurs on or after first dose of IP in DLBEP and up to and including the minimum of

- 112 days after the last dose of IP in DLBEP,
- end of study day.

Serious TEAE

A serious treatment-emergent adverse event is a serious AE (SAE) considered to be treatment-emergent.

The Faces Pain Scale-Revised

The FPS-R is a validated pain self-assessment tool for use in pediatric subjects. This is on the scale of 0, 2, 4, 6, 8, and 10 where 0 is no pain and 10 is very much pain. This pain scale will be used for injection site pain during DBTP but not for severity of episodes or severity of attacks.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician rating of suicidal behavior and ideation. The C-SSRS consists of a maximum of 20 items to evaluate suicidal behavior and suicidal ideation. 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 adult's (used for adolescents') version (for subjects at least 12 years old).

Age-adjusted Z scores for Height and Weight

Height-for-age Z-score is defined as the difference between the subject's height and the median height for the population with the same age and gender, divided by the population standard deviation:

$$\text{Height} - \text{for} - \text{age Z} - \text{score} = \frac{\text{measured value} - \text{median of refernce population}}{\text{standard deviation of the reference population}}$$

Weight-for-age Z-score is defined in the similar manner and similarly calculated (https://www.cdc.gov/growthcharts/cdc_charts.htm).

Note:

1. Use age numbers for the calculation instead of age group.
2. The median/SD of reference population should be calculated by each visit.

5.2 Study Dates

eDiary Device Assignment Date

The date on which an eDiary device is assigned to a subject and parent or legal representative at the week -4 visit (after confirming the subject's eligibility to enter the baseline phase).

Randomization (Enrollment) Date in DBTP

Randomization (Enrollment) date in DBTP is the date on which a subject is assigned a randomization ID through the Interactive Voice Response System (IVRS) in the DBTP.

Re-randomization Date in DLBEP

Re-randomization date in DLBEP is the date on which a subject is re-assigned to one of the erenumab dose levels through the IVRS in DLBEP. Only subjects that were assigned to placebo in DBTP will be re-randomized.

First Dose Date in DBTP

The first dose date is the date on which a subject is administered the first dose of IP following randomization. The date of the first dose of investigational product is defined as Study Day 1.

Last Dose Date in DBTP

The last dose date is the date on which a subject is administered the last dose of IP during DBTP.

First Dose Date in DLBEP

The first DLBEP IP dose date is the date on which a subject is administered the first dose of IP in DLBEP following completion of DBTP.

Last Dose Date in DLBEP

The last DLBEP IP dose date is the date on which a subject is administered the last dose of IP during DLBEP.

End of IP Administration Date

The end of IP admin date for each subject is defined as the date the decision was made to end IP as recorded on the End of IP eCRF page.

Subject-level End of Study (EOS) Date

The end of study (EOS) date for each subject is defined as the last date on which the protocol specified assessments are completed for an individual subject. The date will be recorded on the End of Study eCRF page.

Primary Completion Date

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

The primary completion date is the date when the last adolescent subject has completed the assessments for week 24 (Group 1) or week 12 (Group 2), or when all adolescent subjects have the opportunity to complete the week 24 (Group 1) or week 12 (Group 2) assessments.

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

End of Study Date

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 (i.e., last subject last visit), following any additional parts in the study (e.g., safety follow-up), as applicable.

5.3 Study Points of Reference

Baseline Assessment

Baseline assessment is defined as the last non-missing measurement for the endpoint of interest taken before the first dose of investigational product. In cases where baseline measurements are taken on the same day as IP, it will be assumed that these measurements are taken prior to IP being administered. For subjects who are randomized but not dosed after the randomization, the baseline of the study is defined as the last non-missing measurement prior to or on the date of randomization.

For measurements with multiple individual items such as C-SSRS and ECG, all individual items from the same set of measurement will be used for analysis. If some items from the same set are missing, then the latest complete set of measurement prior to the first dose of IP will be used as baseline. Similar rule holds for post-baseline measurements.

Pre-DLBEP Baseline for Efficacy Endpoints

Pre-DLBEP baseline for efficacy endpoints is defined as the last non-missing monthly measurement before the first dose of DLBEP IP. In cases the measurements are taken on the same day as first dose of DLBEP IP, it will be assumed that these measurements are taken prior to IP being administered.

Pre-DLBEP Baseline for Safety Endpoints

Pre-DLBEP baseline for safety endpoints is defined as the last non-missing measurement for the endpoint of interest taken before the first dose of DLBEP IP. In cases the measurements are taken on the same day as first dose of DLBEP IP, it will be assumed that these measurements are taken prior to IP being administered.

For safety endpoints analyzed by phase, all data occurring before the first dose of DLBEP IP will be used to define pre-DLBEP baseline.

Study Day 1

Study Day 1 is defined as the first IP dose date. For subjects who are randomized but not dosed after randomization, the Study Day 1 is defined as the date of randomization.

Study Day

Study Day is defined as the number of days from Study Day 1.

Before Study Day 1:

Study Day = (date of interest – date of Study Day 1)

On or after Study Day 1:

Study Day = (date of interest – date of Study Day 1) + 1

Therefore, the day prior to Study Day 1 is Day -1.

5.4 Study Time Intervals

Monthly Interval for Efficacy Endpoints

Monthly efficacy measurements will be calculated based on monthly IP dosing schedule defined below using eDiary data collected from beginning of baseline phase (week -4 visit) up to week 64 for group 1 and (week -4 visit) up to week 52 for group 2 (end of eDiary use). Any eDiary data occurring after EOS date or after the end date of the last monthly interval defined below, whichever comes earlier, will not be included in the analysis.

Table 5-1 (a). Monthly Interval for Efficacy Endpoints for Group 1

Study Phase	Assessment Timepoint	Monthly Interval (Group 1)	
		Start Date	**End Date**
Baseline Phase	Baseline	• eDiary device assignment date (week -4 visit)	• The day prior to Study Day 1
Double-blind Treatment Phase Note: Monthly intervals	Week 4	• Study Day 1	• Week 4 dose date – 1 • Study day 28 if Week 4 dose is not received (either missed or IP discontinued prior to Week 4)

during DBTP will be set up to week 24 for each randomized subject regardless of the subject completing DBTP IP or not.			Note: if study day 1 dose is the last IP dose subject received, the rest of monthly rates during DBTP will be calculated based on consecutive 28-day interval beginning on study day 29 (i.e., 29-56 for week 8, 57-84 for week 12, 85-112 for week 16, 113-140 for week 20, and 141-168 for week 24).
	Week 8	• Week 4 dose date • Study day 29 if Week 4 dose is not received (either missed or IP discontinued prior to Week 4)	• Similar rule as above
	Week X (X = 12, 16, 20)	• Similar rule as above	• Similar rule as above
	Week 24	• Week 20 dose date • Study day 141 if Week 20 dose is not received (either missed or IP discontinued prior to Week 20)	• Week 24 dose date – 1 • If week 24 dose is not received (either missed or IP discontinued prior to Week 24): • MIN (Study Day 168, EOS) if Week 20 dose is not received.

			• MIN (Week 20 dose date + 27, EOS) if week 20 dose is received.
Dose level blinded extension phase	Week 28	• Week 24 dose date for subjects who receive DLBEP dose at week 24. • MAX (the end date of week 24 interval + 1, Study Day 169) for subjects who received at least one DLBEP dose but did not receive DLBEP dose at week 24 (e.g., the first DLBEP dose was received at week 28). Note: the start date of week 28 interval will be referred to as DLBEP Day 1 in order to set up following monthly intervals in DLBEP.	• Week 28 dose date – 1 • DLBEP Day 28 if Week 28 dose is missed/skipped. • MIN (Week 24 dose date + 27, EOS) if week 24 dose is the last dose subject received.
	Week 48	• **Week 44 dose date** • DLBEP **Day 141** if **week 44** dose is missed/skipped. • Monthly efficacy data will not be calculated for **Week 28** and beyond if **week 20** is	• Week 48 dose date – 1 • DLBEP Day 168 if Week 48 dose is missed/skipped. • MIN (**Week 44** dose date + 27, EOS) if **week 44** dose is the

		the last IP dose subject received.	last dose subject received.
	Week 64	• **Week 60 dose date** • **DLBEP Day 253 if week 60 dose is missed/skipped.**	• **MIN (DLBEP Day 280, EOS) if Week 60 dose is missed/skipped.** • **MIN (Week 60 dose date + 27, EOS) if week 60 dose is the last dose subject received.**

Table 5-1 (b). Monthly Interval for Efficacy Endpoints for Group 2

Study Phase	Assessment Timepoint	Monthly Interval (Group 2)	
		Start Date	**End Date**
Baseline Phase	Baseline	• eDiary device assignment date (week -4 visit)	• The day prior Study Day – 1
Double-blind Treatment Phase Note: Monthly intervals during DBTP will be set up to week 12 for each randomized subject regardless of the subject completing DBTP IP or not.	Week 4	• Study Day 1	• Week 4 dose date – 1 • Study day 28 if Week 4 dose is not received (either missed or IP discontinued prior to Week 4). Note: if study day 1 dose is the last IP dose subject received, the rest of monthly rates during DBTP will be calculated based on consecutive 28-day interval beginning on study day 29 (i.e., 29-56 for week 8, 57-84 for week 12).
	Week 8	• Week 4 dose date • Study day 29 if Week 4 dose is not received (either missed or IP discontinued prior to Week 4).	• Similar rule as above.
	Week 12	• Week 8 dose date • Study day 57 if Week 8 dose is not received (either	• Week 12 dose date – 1. • If week 12 dose is not received (either

		missed or IP discontinued prior to Week 8).	missed or IP discontinued prior to Week 12): • MIN (Study Day 84, EOS) if Week 8 dose is not received. • MIN (Week 8 dose date + 27, EOS) if week 8 dose is received.
Dose level blinded extension phase	Week 16	• Week 12 dose date for subjects who receive DLBEP dose at week 12. • MAX (the end date of week 12 interval + 1, Study Day 85) for subjects who received at least one DLBEP dose but did not receive DLBEP dose at week 12 (e.g., the first DLBEP dose was received at week 16) Note: the start date of week 16 interval will be referred to as DLBEP Day 1 in order to set up following monthly intervals in DLBEP.	• Week 16 dose date -1 • DLBEP Day 28 if Week 16 dose is missed/skipped. • MIN (Week 12 dose date + 27, EOS) if week 12 dose is the last dose subject received.
	Week 36	• **Week 32 dose date**	• Week 36 dose date -1

		• DLBEP **Day 141** if **week 32** dose is missed/skipped. • Monthly efficacy data will not be calculated for **Week 16** and beyond if **week 8** is the last IP dose subject received.	• DLBEP Day 168 if Week 36 dose is missed/skipped. • MIN (**Week 32** dose date + 27, EOS) if **week 32** dose is the last dose subject received.
	Week 52	• **Week 48 dose date** • **DLBEP Day 253 if week 48 dose is missed/skipped.**	• **MIN (DLBEP Day 280, EOS) if Week 48 dose is missed/skipped.** • **MIN (Week 48 dose date + 27, EOS) if week 48 dose is the last dose subject received.**

Study Visit

Since the actual visit for a subject may not exactly coincide with their targeted visit date, the actual visit date is mapped to the study visit as following. The study day window will be utilized to define study visit for lab, vital signs, and physical measurements collected during office visit before dose is administered**.** Any data occurring after EOS date will not be included in analysis with the exception of antibody data. Data included in the primary analysis is up to the primary completion date. This will include complete data from the DBTP.

Table 5-2. Study Visits

Study Visit	Target Day	Study Day (Group 01)	Study Day (Group 02)
Baseline	Please refer Section 5.3 Baseline Assessment of the Study		
Day 1	1	1	1
Week 4	29	16-43	16-43

Week 8	57	44-71	44-71
Week 12	85	72-99	• 72 to (week 12 DLBEP dose date) for subjects who receive DLBEP dose at week 12. • 72-99 for subjects who did not receive DLBEP dose at week 12
Week 16	113	100-127	• Week 12 DLBEP dose date + 1 to 127 for subjects who receive DLBEP dose at week 12. • 100-127 for subjects who received at least one DLBEP dose and did not receive DLBEP dose at week 12 (e.g., first DLBEP dose was postponed)
Week 20	141	128-155	128-155
Week 24	169	• 156 to (week 24 DLBEP dose date) for subjects who receive DLBEP dose at week 24. • 156-183 for subjects who did not receive DLBEP dose at week 24	156-183
Week 28	197	• Week 24 DLBEP dose date + 1 to 211 for subjects who receive DLBEP dose at week 24. • 184-211 for subjects who received at least one DLBEP dose and did not receive DLBEP dose at week 24	184-211

		(e.g., first DLBEP dose was postponed)	
Week 32	225	212-239	212-239
Week 36 to Week 64		• Following similar monthly windowing as Week 32	
Week 36 to Week 52			Following similar monthly windowing as Week 32
Safety follow-up	Based on visit name from RAVE or other source data; safety follow-up visit only applies to safety data and should be excluded from above analysis visit window in this table.		

Note:

If more than one visit (including the unscheduled visits) falls within the same defined window with non-missing measurements, scheduled visit will be used regardless of the distance from the target day. Unscheduled visit will only be used when there is no measurement from scheduled visit in the defined window. The closest visit to the target day among the same type of visit (i.e., scheduled vs. unscheduled) will be considered for analysis. If two assessment dates are equidistant from the target date, the latter visit will be considered for analysis.

For safety analyses which are summarized by study phase (AEs, anti-erenumab antibodies, standard laboratory assessments, ECGs, injection site reactions (ISR), injection site pain (ISP), vital signs, C-SSRS scores, anti-erenumab antibodies), analysis windows will be set up as below. Any data occurring after EOS date will not be included in analysis with the exception of the anti-erenumab antibodies data. 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: (1) neutralizing 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.

Table 5-3. Study Phases

Study Phase	Start Time Point	End Time Point
Double-blind Treatment Phase	For TEAE: • Study Day 1 For anti-erenumab antibodies, laboratory assessments, ECG, ISR, ISP, vital signs, C-SSRS scores: • Study Day 2	For TEAE: • Min (First DLBEP Dose Date - 1, last IP dose (in DBTP) date + 112 days, data cut-off date) for subjects who received DLBEP IP dose. • Min (EOS Date, data cut-off date, last IP dose (in DBTP) date + 112 days) for subjects who did not receive any DLBEP IP dose. For anti-erenumab antibodies, laboratory assessment, vital signs, C-SSRS: • Min (First DLBEP Dose Date, data cut-off date) for subjects who received DLBEP IP dose. • Min (EOS Date, data cut-off date) for subjects who did not receive any DLBEP IP dose.
Dose level blinded extension phase	For TEAE: • 1st DLBEP IP Dose Date For anti-erenumab antibodies, laboratory	For TEAE: • Min (EOS Date, last DLBEP IP dose date + 112 days)

	assessments, ECG, ISR, vital signs, C-SSRS scores: • 1st DLBEP IP Dose Date + 1	For laboratory assessments, ECG, ISR, vital signs, C-SSRS scores: • All data up to EOS Date For anti-erenumab antibodies: • All data will be included in the analyses even if it occurred post EOS

5.5 Subject Disposition

Randomized

Individuals are considered randomized if they have been assigned a randomization number. Randomized individuals are referred to as “subjects”.

Completing the DBTP

Subjects are defined as completing the DBTP if they complete week 24 or week 12 assessment or miss the week 24 or week 12 assessment but continue to enter the DLBEP. It will be determined from the End of Double-blind Treatment Phase eCRF page with “Completed” as the reason for ending study phase.

Completing the DLBEP

Subjects are defined as completing the DLBEP phase if they complete the week 64 and week 52 assessments for Group 01 and Group 02, respectively**.** It will be determined from the End of DLBEP eCRF page with “Completed” as the reason for ending study phase.

Completing Study

Subjects are defined as completing study if they complete the last scheduled procedure defined in protocol. It will be determined from the End of Study eCRF page with “Completed” as the primary reason for ending study.

Exposed to IP

Subjects are defined as exposed if they receive at least one dose of IP.

Completing the Double-blind IP

Subjects are defined as completing double-blind IP if they complete week 20 IP for group 1 or week 8 IP dose for group 2 or temporally withhold IP at week 24 or week 12

and continue to receive IP during DLBEP. It will be derived from the End of IP DBTP eCRF page with “Completed” as the reason for ending IP.

Completing the DLBEP IP

Subjects are defined as completing DLBEP IP if they complete the week 60 IP dose for group 1 or week 48 for group 2. It will be derived from the End of IP DLBEP eCRF page with “Completed” as the reason for ending IP.

On-study

Subjects are considered on-study if they have been randomized and have not yet had their end of study visit.

5.6 Arithmetic Calculations

Duration of Migraine

The number of years from the diagnosis date of migraine (migraine with or without aura, whichever is earlier) to the date informed consent is signed.

If month or day of the diagnosis date is missing, follow the formula below to calculate the duration:

Table 5-4. Duration Calculation

Observed portion	Missing portion	Formula to Calculate Duration
Year, Month, Day		(Informed Consent Day – diagnosis date)/365.25
Year, Month	Day	[Year (Informed Consent Day)-Year (Diagnosis Date)] + [Month (Informed Consent Day)-Month (Diagnosis Date)]/12 *If it equals 0, add 1 month or 1/12 years (this is to avoid a disease duration of 0)
Year	Month, Day	[Year (Informed Consent Day)-Year (Diagnosis Date)] *If it equals 0, add 1 month or 1/12 years (this is to avoid a disease duration of 0)

Exposure

For all calculations of exposure, dose date refers to receiving dose > 0 but can include partial dose.

Duration of DBTP IP Exposure

If subject enter into DLBEP,

Duration = Minimum (Last DBTP Dose Date + 27, First DLBEP Dose Date - 1, EOS Date) – First DBTP Dose Date + 1

Otherwise,

Minimum (Last DBTP Dose Date + 27, EOS Date) – First DBTP Dose Date + 1

Duration of DLBEP IP Exposure

For primary analysis:

Minimum (Last DLBEP Dose Date + 27, EOS Date, data cut-off date) – First DLBEP Dose Date + 1

For final analysis:

Minimum (Last DLBEP Dose Date + 27, EOS Date) – First DLBEP Dose Date + 1

Change From Baseline in Monthly Efficacy Measurements

The change from baseline in monthly efficacy measurements is the monthly efficacy measurement in the monthly interval prior to the given time point minus the baseline monthly efficacy measurement. Please refer to the Monthly Interval for Efficacy Endpoints defined in Section 5.4. For example, change from baseline in monthly migraine days at week 24 will be calculated based on the following:

(Monthly migraine days during the week 24 interval) – (monthly migraine days during the baseline phase)

If the baseline or post-baseline value is missing, then the change from baseline is set to missing.

Following Efficacy endpoints will be calculated as above:

- Change from baseline in monthly migraine days.
- Change from baseline in monthly headache days.
- Change from baseline in monthly acute headache medication treatment days.
- Change from baseline in monthly average severity of migraine attacks.
- Change from baseline in migraine-related disability and productivity as measured by the modified PedMIDAS
- Change from baseline in monthly average severity of migraine episodes.

- Change from baseline in monthly migraine episodes.

Change From Baseline in Mean Monthly Efficacy Measurement over Multiple Months

The Change from Baseline in Mean Monthly Efficacy Measurement is the Arithmetic mean of monthly values for the months considered - baseline monthly value.

Percent Change from Baseline

The change from baseline divided by baseline and multiplied by 100:

(Post-baseline – Baseline) * 100 / Baseline

If the baseline value is 0, then the percent change from baseline is set to be missing.

Percent change from baseline calculation will be used to determine 50% responder in monthly migraine days and monthly headache days.

Subject Incidence

The subject incidence for a given event in a given phase is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects who entered that phase. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

Exposure-adjusted Subject Incidence Rate

The exposure-adjusted subject incidence rate for a given event in a given phase is defined as the number of subjects with at least one reported occurrence of the event in a given time phase divided by total subject-years at risk in that phase, presented per 100 subject-years. For subjects with multiple occurrences of the same event, the event will be only counted once per subject. The time at risk for each subject will differ for each adverse event. For subjects with the event, only the time from the first dose of IP until the first event contributes to the total subject-years at risk. For subjects without the event, the time from the first dose of IP until the end of the phase contributes to the total subject-years at risk. The time phase at risk will be calculated based on the time phases defined in Table 5-3 of Section 5.4.

5.7 Disease Characteristics

[redacted]

6. Analysis Sets

The following subsections define the analysis sets for this study. Each analysis set will be defined separately for children (6 to < 12 years) and adolescents (12 to < 18 years).

6.1 Full Analysis Set

The full analysis set (FAS) for the DBTP includes all subjects who were randomized in the study.

FAS for DLBEP includes all subjects who chose to roll over into the DLBEP.

6.1.1 Primary Analysis Set

Not applicable for this study.

6.2 Safety Analysis Set

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

6.3 Per Protocol Analysis Set(s)

Not applicable for this study.

6.4 Health-related Quality-of-Life or Health Economics Analyses Set(s)

Not applicable for this study.

[redacted]

6.6 Interim Analyses Set(s)

The Interim Analysis Set is a subset of the FAS and includes ≥ 50% of the planned total sample of adolescents that have been enrolled in the study in the DBTP. This analysis set will be used to re-estimate variance and the sample size in a blinded manner.

6.7 Serum Bone Metabolism Markers Analyses Set(s)

For each serum bone metabolism markers (CTX and P1NP), the analysis set includes all subjects in the safety analysis set who have baseline and ≥ 1 post-baseline assessments for the endpoint of interest.

7. Planned Analyses

The following subsections defines the planned analyses for this study.

7.1 Interim Analysis and Early Stopping Guidelines

Data Monitoring Committee

An independent data monitoring committee (DMC) will review and make recommendations regarding the safety of the study subjects 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. Data from the open-label phase 1, PK and safety study (Study 20160172) which will start enrollment before Study 20160354 commenced, 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.

Interim Analysis

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 Type I error and integrity of the study. The blinded sample size re-estimation will be performed when ≥ 50% of the planned 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.

7.2 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 doses of erenumab compared with placebo during the DBTP.

7.3 Final Analysis

The final analysis for the study will be performed on a locked database after all subjects (adolescents and children) 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.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will receive and store all data to be used in the planned analyses. This study will use the RAVE database and eDiary data, [redacted], antibody, [redacted], central lab and ECG data (outside of RAVE database). The database will be subjected to edit check outlined in the Data Management Plan (DMP). Additional details will be provided in the DMP and Data Acquisition Requirements Specification (DARS).

8.3 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of causes. In general, data could be missing due to a subject's early withdrawal from study, a missed visit, or inability to evaluate an endpoint at a particular point in time. Each subject will be given an eDiary throughout the baseline phase, DBTP, and during of the DLBEP, to report information about their migraine and non-migraine headaches and acute headache medication use.

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 as the primary analysis method. Sensitivity analyses for the primary endpoint will include, but are not limited to, the following imputation methods for handling the missing data:

(1) multiple imputation (MI) with assumptions of missing at random (MAR), (2) MI with assumptions of missing not at random (MNAR), and (3) baseline observation carried forward (BOCF).

Secondary Endpoints: The same sensitivity analyses used for the primary endpoint will be performed for continuous secondary endpoints. For the achievement of at least 50% reduction from baseline secondary endpoint, a stratified Cochran-Mantel-Haenszel (CMH) test will be used after the missing data are imputed as nonresponse as the primary analysis method. Sensitivity analyses for the binary endpoint include: (1) generalized linear mixed model without imputation of missing data, and (2) logistic regression model after the missing data are imputed as nonresponse.

Missing eDiary data in the calculation of monthly measurements about subjects' migraine and non-migraine headache will be handled using the following method.

Table 8-1. Handling of Missing and Incomplete eDiary Data

Monthly Endpoint	**Condition**	**Proration Method (Without Rounding)**
Monthly frequency measurements (including migraine days, headache days, acute headache medication treatment days, migraine episode)	If information days in each baseline or post-baseline interval ≥ 14, then do proration for that monthly interval. Else monthly frequency measurement is set to missing	Number of observed event days * 28/ Number of information days in the monthly interval Note: event above refers to migraine days, headache days, acute headache medication treatment days, and migraine episode
Monthly average severity of migraine episodes and monthly average severity of migraine attacks	If information days in entire baseline or interval post baseline > = 14 (including retrospective eDiary days), then calculate the average. Else missing	Arithmetic mean of the observed pain scores of qualified migraine headaches over the monthly interval

Missing data for safety endpoints will not be imputed.

Missing and incomplete dates for AEs and concomitant medications will be handled using methods describe in Section 8.3.1. Missing antibody data will not be imputed.

8.3.1 Missing and Incomplete Dates

Imputation Rules for Partial or Missing Start Dates

Missing or incomplete dates will be listed as it is in any listings.

Incomplete start date of an adverse event or concomitant medication taken will be handled by following rule:

	Missing	Imputation	Exception
Start date. (AE, concomitant medication)	Day	01	Default to Study Day 1 if an event starts the same year and month as Study Day 1 and the flag indicates that the event started on or after the first dose on the Events eCRF
	Day/Month	01JAN	Default to Study Day 1 if an event started the same year as Study Day 1 and the flag indicates that the event started on or after the first dose on the Events eCRF
	Day/Month/Year	No imputation	

Imputation Rules for Partial or Missing Stop Dates

If the month and year are present, impute the last day of the month. If only the year is present, impute December 31 of that year. If the stop date is entirely missing, assume the event or medication is ongoing. If a partial or complete stop date is present and the 'ongoing' or 'continuing' box is checked, then it will be assumed that the AE or Concomitant Medication stopped and the stop date will be imputed, if partial. Ensure the imputed stop date is on or after the complete or imputed start date.

8.3.1 Missing Baseline Evaluation

Baseline values are defined in Section 5.3 “Baseline Assessment of the Study”. Missing baseline evaluations will not be imputed.

All subjects included in the efficacy analysis set will have baseline monthly rate or monthly average of migraine and non-migraine headaches related measurements after applying proration rule defined in Section 8.3 since only subject with ≥ 80% compliance of eDiary use during baseline phase will be eligible for randomization.

8.3.2 Missing Post-baseline Evaluation in the DBTP

Primary analysis method of continuous efficacy endpoints during the randomized DBTP will be conducted using the linear mixed effects model or fixed effect ANCOVA model, as appropriate, on observed data without imputation.

For the descriptive summary of mean monthly value calculated using the monthly value from each of the first 3 months of the DBTP, if a subject has at least one month’s value, then the subject contributes to the summary statistics. For the descriptive summary of mean monthly value calculated using the monthly value from all 6 months of the DBTP, if a subject has at least one month’s value, then the subject contributes to the summary statistics.

If significant amount of mis-stratification are observed, sensitivity analyses may be performed where appropriate to evaluate the impact. In the sensitivity analysis on primary and secondary efficacy endpoints during the DBTP, missing continuous monthly efficacy endpoints will be handled using MI under the assumption of MAR, MI under the assumption of MNAR, and BOCF.

In BOCF, post-baseline missing monthly continuous efficacy endpoints during the DBTP will be imputed using the baseline observed value. For example, if the last month value is missing, the missing value will be BOCF even if the previous post-baseline values are non-missing, then all of the post-baseline values will be imputed using the observed baseline value.

In non-responder imputation (NRI) method, post-baseline missing dichotomous efficacy endpoints (responder [Yes/No]) based on ≥50% reduction from baseline in monthly migraine days or monthly headache days during the DBTP will be imputed as non-responder at each corresponding time point. The dichotomous endpoints derived based on the mean change from baseline over the first 3 months or all 6 months of the DBTP will be imputed as non-responder if the mean change from baseline over the first

3 months or all 6 months of the DBTP are missing (i.e., all applicable change from baseline values are missing).

If the proportion of missing data in primary endpoint is high (e.g., > 20%), further analyses will be performed to

- examine the frequency and reason of missing data
- determine if there are any patterns in the missing data
- distinguish true missing values from other unknown values (e.g., due to measurement or sample processing error)

8.4 Detection of Bias

This study has been designed to minimize potential bias by allocating treatment groups randomly, assessing endpoints and handling withdrawals without knowledge of the treatment. Other factors that may bias the results of the study include:

- important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints.
- inadvertent breaking of the blind before formal unblinding
- investigational product dosing non-compliance
- the timing of and reasons for early withdrawal from treatment and from study

The incidence of these factors may be assessed. Important protocol deviations will be listed and/or tabulated in the clinical study report (CSR). If necessary, the incidence of other factors will be tabulated.

Any breaking of the blind for individual subjects prior to formal unblinding of the study will be documented in the CSR.

The timing of and reasons for early withdrawal from treatment and from study will be tabulated and/or listed.

8.5 Outliers

Histograms will be examined to identify outliers in any of the continuous variables used in the analyses. Unexpected and/or unexplained values in categorical data will be identified by utilizing frequency tables.

Outliers due to data entry errors will be corrected by the study team before final database lock. The validity of any questionable values or outliers will be confirmed.

Outliers or any questionable values with confirmed validity will be included in the analyses presented in this statistical analysis plan unless there is sufficient justification to exclude them. However, ad-hoc sensitivity analyses may be conducted to evaluate the influence of extreme values in the data.

8.6 Distributional Characteristics

Continuous endpoints of change from baseline value will be analyzed under normality assumption. If they deviate appreciably from normality, appropriate transformations or the non-parametric alternatives, such as Quade test (Quade D, 1966) may additionally be considered.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

The primary objective of this study is to evaluate the effect of erenumab compared with placebo on the change from baseline in MMDs to week 9 through week 12 (month 3) of the DBTP, in adolescents' subjects with CM.

The primary estimand consists of:

- The target population, which is the adolescent subjects (12 to < 18 years of age) diagnosed with CM who were randomized.
- The primary endpoint, which is the change in MMDs 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 intervention effect, which describes the summary measure for the primary endpoint that would have been observed for all randomized subjects regardless of adherence to treatment.

Subjects will remain in the DBTP even if they discontinue IP and therefore the analyses will include all randomized subjects who remained in the study for the intended duration regardless of adherence to treatment.

The primary analysis will be performed on a locked database when the last adolescent subject completes the DBTP assessments, or the early termination visit during DBTP. The primary analysis will assess the combined erenumab dose group compared with placebo during DBTP. This will include all analyses evaluating the difference between the combined erenumab dose group and placebo group for all data collected during DBTP: demographic, efficacy, and safety. The assessment of DBTP in the primary analysis will not be repeated at the time of the final analysis.

The final analysis for the study will be performed on a locked database after all subjects (adolescents and children) 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.

Subjects will be analyzed based on their randomized treatment group assignment.

The FAS will be used to tabulate demographic data, baseline disease characteristics, and subject disposition. The FAS will also be used to analyze efficacy endpoints. The safety analysis set will be used to analyze safety endpoints.

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

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 as covariate, stratification factors of region and prior preventive treatment failure status, scheduled visit, 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.

In general, the continuous secondary endpoints will be analyzed using the same methods as for the primary endpoint. The same sensitivity analyses used for primary endpoint will be performed. For the secondary endpoint of achievement of at least 50% reduction from baseline in MMD, a stratified CMH test will be used after the missing data are imputed as nonresponse.

Sensitivity analyses for the binary endpoint include: (1) generalized linear mixed model without imputation of missing data, and (2) logistic regression model after the missing data are imputed as nonresponse.

If the primary endpoint is statistically significantly different from placebo in the adolescent age cohort 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 levels:

- 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 MMDs 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 5% significance level:

- Change from baseline in MMDs 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 week 12 **(**month 3**)** of the DBTP.

For the final analysis, 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.

Safety analyses will be performed for the DBTP and DLBEP separately based on the respective safety analysis set. For the primary analysis at the end of the DBTP, the difference between the combined erenumab group and the placebo group will be evaluated during DBTP. For the final analysis at the end of the study, the safety of each erenumab dose compared to placebo will be evaluated as applicable.

9.2 Subject Accountability

The disposition of all randomized (enrolled) subjects will be tabulated by randomized treatment group and study phase. The summary for the DBTP will include the number of subjects who are randomized, the number and percent of subjects who receive/never receive the double-blind IP, who complete double-blind IP, discontinue double-blind IP and reasons for discontinuing, who complete the DBTP, and who withdraw prematurely from the study before completion of the double-blind treatment phase and their reasons for withdrawal.

The summary for the DLBEP will include the number and percent of subjects who receive the DLBEP IP, who complete or are continuing DLBEP IP, discontinue DLBEP IP and reasons for discontinuing, who complete the DLBEP and who withdraw prematurely from the study before completion of the DLBEP and their reasons for withdrawal.

In addition, the number of subjects who complete the study or are continuing in the study and who withdraw prematurely from the study and their reasons for withdrawal will be summarized.

A footnote on the subject disposition tables will include the number of subjects screened.

A summary of the study reporting phase including a description of key dates will also be provided, including dates of the first and last subject enrolled, the primary completion date (for the primary analysis) and the last subject's end of study date (for the final analysis).

For the primary analysis at the end of the DBTP, tabulations will include the combined erenumab group and the placebo group. For the final analysis at the end of the study, tabulations will include each erenumab dose and placebo.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

The final IPD list will be used to produce the Summary of IPDs table and the list of subjects with IPDs.

9.4 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics by randomized treatment group and separately for adolescents and children using FAS. If multiple races have been reported for a subject, the subject will be categorized as multiple races.

The following demographic and baseline characteristics will be summarized:

- Age
- Sex
- Ethnicity
- Race
- Region (North America vs. Rest of World)
- Age-adjusted Z-score Height
- Age-adjusted Z-score Weight
- Body Mass Index (BMI, kg/m^2)
- Disease duration of migraine
- Age at onset of migraine
- Monthly migraine days during baseline phase

- Monthly migraine attacks during baseline phase
- Monthly headache days during baseline phase
- Monthly average severity of migraine episodes during baseline phase
- Monthly average severity of migraine attacks during baseline phase
- Monthly acute headache-specific medication treatment days during baseline phase
    a. Migraine-specific
    b. Non-migraine-specific
- Summary of prior preventive treatment and reasons for discontinuation

For the primary analysis at the end of the DBTP, tabulations will include the combined erenumab group and the placebo group. For the final analysis at the end of the study, tabulations will include each erenumab dose and placebo.

9.5 Efficacy Analyses

The primary analysis of efficacy endpoints will utilize the FAS. Subjects will be analyzed according to their randomized treatment group regardless of the actual treatment received during the study.

Detailed primary analysis methods, sensitivity analyses, and covariates included in the models are summarized in the table below.

9.5.1 Analyses of Primary Efficacy Endpoint(s)/Estimand(s)

The primary endpoint, the change from baseline in MMDs, over week 9 through week 12 (month 3), will be tested in adolescent subjects using a linear mixed effects repeated measure model based on observed monthly data from the DBTP between the combined erenumab group and the placebo group.

The model will include treatment group, baseline value as covariate, stratification factors of region and prior preventive treatment failure status, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. Subject will be fitted as a random effect. Least squares mean (LSMs), standard errors, and associated 95% confidence intervals for each treatment group, difference of LSMs compared to placebo group, associated 95% confidence intervals and nominal two-sided p-values will be reported.

The following sensitivity analyses will be performed:

1. Analysis of imputed data using MI under the assumption of MAR (a fixed effects ANCOVA model will be applied to imputed data at month 3, including treatment group, baseline value as covariate, and stratification factors).
2. Analysis of imputed data using MI under the assumption of MNAR (a fixed effects ANCOVA model will be applied to imputed data at month 3, including treatment group, baseline value as covariate, and stratification factors).
3. Analysis of imputed data using BOCF (a fixed effects ANCOVA model will be applied to imputed data at month 3, including treatment group, baseline value as covariate, and stratification factors).

Summary statistics (data from adolescents and children separately) and formal analyses and statistical modelling (data from adolescents only for the combined erenumab dose

groups and placebo group) may be performed for the following subgroups as appropriate:

- Region (North America versus Rest of World)
- Prior preventive treatment failure (Yes versus No)
- Sex (male versus female)
- Pubertal status (pre-pubertal versus post-pubertal defined according to a Pubertal Maturation Self-assessment [Tanner Staging] Scale)
- Race (White versus non-white)
- CBT (with CBT versus without CBT)

The purpose of the subgroup analyses is to explore if the treatment effect varies across subgroups of interest. Subgroup analyses will be performed using the same method as primary analysis method but within level of each subgroup of interest. The treatment difference with associated 95% confidence intervals and p-values will be reported within each subgroup for adolescents. The heterogeneity of the treatment effect across the subgroups for adolescents will be evaluated by examining the treatment by subgroup interaction in the primary analysis model and a p-value will be presented.

Formal subgroup analyses and statistical modelling for adolescents will only be performed if the sample sizes of the respective subgroups allow for meaningful interpretation of the data.

Table 9-1. Primary Efficacy Endpoint Summary Table

Endpoint/Estimand	Primary Summary and Analysis Method	Sensitivity Analysis
Change from baseline in monthly headache days to week 9 through week 12 (month 3) of the DBTP.	1. Summary statistics using observed data. 2. The mean change from baseline for each treatment group (combined dose of erenumab group and placebo group), the treatment difference (combined dose of erenumab group minus placebo group), 95% confidence intervals for	The mean change from baseline for each treatment group (combined dose of erenumab group and placebo group), the treatment difference (combined dose of erenumab group minus placebo group), 95% confidence intervals for the treatment difference, and

Endpoint/Estimand	Primary Summary and Analysis Method	Sensitivity Analysis
	the treatment difference, and p-value, from 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, and interaction of treatment with scheduled visit. Subjects will be used as a random effect.	p-value, from a fixed effects ANCOVA model applied to imputed data at month 3, including treatment group, baseline value as covariate, and stratification factors of region and prior preventive treatment failure status. Data will be imputed using the following methods: 1. MI under the assumption of MAR 2. MI under the assumption of MNAR 3. BOCF

9.5.2 Analyses of Secondary Efficacy Endpoint(s)/Estimand(s)

In general, continuous secondary endpoints based on observed monthly data from DBTP will be analyzed using the same methods as described the for the primary efficacy endpoint. However, for continuous secondary endpoints with one value per subject (e.g., the change from baseline in MMDs to the average of the first 3 months [week 1 through week 12] of the DBTP), a fixed effects ANCOVA model will be used to analyze the data, including terms for treatment group (combined dose of erenumab group and placebo group), baseline value as covariate, and stratification factors of region and prior preventive treatment failure status. LSMs for each treatment group, standard errors, associated 95% confidence intervals, difference of LSMs compared to placebo group, associated 95% confidence intervals and nominal two-sided p-values will be tabulated by treatment group.

For all continuous secondary efficacy endpoints, summary statistics (data from adolescents and children separately) and formal analyses and statistical modelling (data from adolescents only), and the same sensitivity analyses will be performed as those performed for the primary efficacy endpoint, and also the same subgroup analyses, as described in Section 9.5.1.

For dichotomous secondary efficacy endpoints, the achievement of at least 50% reduction from baseline, common odds ratios compared to placebo group, associated 95% confidence intervals and nominal two-sided p-values will be provided based on stratified CMH test after the missing data are imputed as non-response and tabulated by treatment group. Here, the Breslow-Day test will be conducted to test the homogeneity of the odds ratios across the strata and a p-value will be presented.

The following sensitivity analyses for handling missing data may be performed for the dichotomous secondary endpoints:

- Odds ratio estimated from a generalized linear mixed effects repeated measure model, including treatment group (combined erenumab group or placebo group), baseline value as covariate, stratification factors of region and prior preventive treatment failure status, scheduled visit, and interaction of treatment with scheduled visit. Subjects will be used as a random effect.
- Logistic regression model after the missing data is imputed as nonresponse.

For all dichotomous secondary efficacy endpoints, summary statistics (data from adolescents and children separately) and formal analyses and statistical modelling (data from adolescents only), and the same subgroup analyses will be performed as those performed for the primary efficacy endpoint, as described in Section 9.5.1.

The odds ratio with associated 95% confidence intervals and p-values will be reported within each subgroup for adolescents.

For endpoints based on proportions, a logistic regression model that includes treatment group, stratification factors, baseline value, subgroup, and treatment group by subgroup interaction, will be used to evaluate the heterogeneity of the treatment effect across the subgroups for adolescents and a p-value for the interaction term will be presented. If there is separation of data points due to insufficient sample size, then firth logistic regression will be used.

Formal subgroup analyses and statistical modelling for adolescents will only be performed if the sample sizes of the respective subgroups allow for meaningful interpretation of the data.

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint/Estimand	Primary Summary and Analysis Method	Sensitivity Analysis
Change from baseline in monthly headache days to week 9 through week 12 (month 3) of the DBTP.	Same as primary endpoint.	Same as primary endpoint.
Achievement of at least 50% reduction in MMDs from baseline to week 9 through week 12 (month 3) of the DBTP	1. Summary statistics using observed data. 2. A stratified Cochran-Mantel-Haenszel (CMH) test will be used after the missing data are imputed as non-response. Breslow-Day test will be conducted to test the homogeneity of the odds ratios across the strata and a p-value will be presented.	Odds ratio estimated from a generalized linear mixed effects repeated measure model, including treatment group (combined dose of erenumab group or placebo group), baseline value as covariate, stratification factors of region and prior preventive treatment failure status, scheduled visit (as applicable), and interaction of treatment with scheduled visit. Subjects will be used as a random effect.
Change from baseline in MMDs to the average of the first 3 months (week 1 through week 12) of the DBTP	1. Summary statistics using observed data. 2. The mean change from baseline for each treatment group (combined dose of erenumab group and placebo group), the treatment difference (combined dose of erenumab group minus placebo group), 95% confidence intervals for the treatment difference, and p-value, from a fixed effects ANCOVA model	Same as primary endpoint.

Endpoint/Estimand	Primary Summary and Analysis Method	Sensitivity Analysis
Change from baseline in monthly average severity of migraine attacks to week 9 through week 12 (month 3) of the DBTP.	Same as primary endpoint.	Same as primary endpoint.
Change from baseline in migraine-related disability and productivity as measured by the modified PedMIDAS to week 9 through 12 **(**month 3**)** of the DBTP.	Same as primary endpoint.	Same as primary endpoint.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

Analysis of exploratory efficacy endpoints will be conducted in a similar manner as the primary analyses performed for the primary and secondary efficacy endpoints.

Summary statistics will be presented by age cohort, separately for children and adolescents; formal analyses and statistical modelling will also be presented for data from the adolescent cohort.

The continuous exploratory efficacy endpoints at each assessment time will be analyzed using the linear mixed effects repeated measure model or fixed effects ANCOVA model, as appropriate, without any imputation for missing data. The dichotomous exploratory efficacy endpoints will be analyzed using stratified CMH test with missing data imputed as non-response. No sensitivity analyses will be performed for the exploratory endpoints.

Table 9-3. Exploratory Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Change from baseline in monthly acute headache medication treatment days at assessment time points.	Same as primary endpoint but based on the assessment time points	
Change from baseline in MMDs at assessment time points	Same as primary endpoint but based on the assessment time points	
Change from baseline in monthly headache days at assessment time points.	Same as primary endpoint but based on the assessment time points	
Change from baseline in monthly headache days to the average of the first 3 months (week 1 through week 12) of the DBTP.	Same as secondary endpoint, change from baseline in MMD to the average of the first 3 months (week 1 through week 12) of the DBTP	
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).	Group 1 only (24-week DBTP): Same as secondary endpoint, change from baseline in monthly headache days 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 at assessment time points.	Same as primary endpoint but based on the assessment time points	

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Change from baseline in monthly average severity of migraine episodes at assessment time points.	Same as primary endpoint	
Change from baseline in monthly migraine episodes at assessment time points.	Same as primary endpoint but based on the assessment time points	
Achievement of at least 50% reduction from baseline in MMDs at assessment time points.	Same as secondary endpoint, achievement of at least 50% reduction in MMDs from baseline to week 9 through week 12 (month 3) of the DBTP but based on the assessment time points.	
Group 1 only (24-week DBTP): Change from baseline in MMDs to the average of the 6-month DBTP (week 1 through week 24).	Group 1 only (24-week DBTP): Same as secondary endpoint, change from baseline in MMDs to the average of the first 3 months (week 1 through week 12) of the DBTP.	
Achievement of at least 50% reduction from baseline in monthly headache days at assessment time points.	Same as secondary endpoint, achievement of at least 50% reduction in monthly headache days from baseline to week 9 through week 12 (month 3) of the DBTP, but based on the assessment time points	

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
Change from baseline in migraine-related disability and productivity as measured by the modified PedMIDAS at assessment time points.	Same as primary endpoint but based on the assessment time points	
PGIC at week 12 **(**month 3**)** of the DBTP	Same as primary endpoint Summary statistics using observed data.	
Change from baseline in MMDs to month 3 of the DBTP for the entire population (6 to < 18 years)	Same as primary endpoint but for entire population. Summary statistics using observed data.	

As part of the final analysis, all endpoints will be summarized for the DLBEP in a descriptive manner to evaluate the long-term efficacy of erenumab.

9.6 Safety Analyses

9.6.1 Analyses of Primary Safety Endpoint(s)

All safety analyses will be performed for the DBTP and DLBEP separately. Safety data will be presented separately for adolescents and children. The 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 (MedDRA) will be used to code all adverse events.

No formal hypothesis testing will be performed.

Table 9-4. Safety Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method	Sensitivity Analysis
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 protocollagen Type 1 N-telopeptide [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.	Summary statistics will be provided for each treatment group and by study phase.	

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 or later will be used to code all adverse events (AE) to a system organ class (SOC) and a preferred term (PT). All AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. All AE tables will be summarized by treatment group.

Overall subject incidence of AEs will be summarized by SOC and PT for all treatment-emergent AEs, serious AEs, AEs or serious AEs leading to withdrawal of Investigational product(s) or non-investigational product(s)/auxiliary medicinal product(s), fatal AEs and device related AEs for the DBTP and DLBEP. The following events of interest will be summarized in both DBTP and DLBEP:

- Injection Site Reactions AMQ (Narrow)
- Hypersensitivity SMQ (Narrow)
- Constipation AMQ (Narrow and Broad)
- Ischaemic Central Nervous System Vascular Conditions SMQ (Narrow)
- Ischaemic Heart Disease SMQ (Narrow and Broad)
- Peripheral Arterial Disease AMQ (Narrow)
- Hypertension SMQ (Narrow and Broad)
- Alopecias AMQ (Narrow and Broad)
- COVID 19 SMQ (Narrow)

Overall subject incidence rates and exposure-adjusted subject incidence rates for the above events will be produced for the DBTP and the DLBEP separately.

In addition, subject incidence and exposure-adjusted subject incidence of all treatment-emergent AEs and serious AEs will be tabulated by SOC, PT and CTCAE grade for the DBTP and DLBEP.

Subject incidence and exposure-adjusted subject incidence of all treatment-emergent AEs and serious AEs will be tabulated by PT in descending order of frequency for both the DBTP and the DLBEP.

AE tables by SOC and PT (and grade), will be sorted alphabetically by SOC and then alphabetically by PT within each SOC. AE tables by preferred term only will be sorted in descending order of frequency based on erenumab first, then placebo, and then alphabetically. Note, for exposure-adjusted AEs the sorting will be based on the exposure-adjusted subject incidence rate.

9.6.3 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to IP by treatment group and by study phase (DBTP and DLBEP).

The number and percentage of subjects with dose change, reason for dose change and duration of exposure to IP in days will be summarized by treatment group and phase.

9.6.4 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics over time by treatment group for all analytes with continuous results. As shift grades may not be available for all lab parameters, shifts in grades of selected safety laboratory values between the baseline and the worst on-study value will be tabulated by treatment group.

Subject incidence of liver function test results (including AST, ALT, Total Bilirubin (TBL), Alkaline Phosphatase (ALP) and suspected Hy's Law cases) will also be summarized by treatment group and study phase.

Listing for Grade 3 or higher lab abnormalities will be provided for both phases (DBTP and DLBEP).

9.6.5 Vital Signs

The analyses of vital signs (systolic/diastolic blood pressure, heart rate and temperature) will include summary statistics of change from baseline (pre- DLBEP baseline for DLBEP) over time by treatment group and age cohort for each study phase.

The number and percentage of subjects with at least one post-baseline vital sign measurement meeting any of these criteria will be summarized:

For Children (6 - < 12 years)

SBP: < 97 mmHg, > 120 mmHg

DBP: < 57 mmHg, > 80 mmHg

Pulse Rate: < 75 bpm, > 118 bpm

Temperature: > 37.5 °C, < 35.5 °C

For adolescents (12 - < 18 years)

SBP: < 110 mmHg, > 131 mmHg

DBP: < 64 mmHg, > 83 mmHg

Pulse Rate: < 60 bpm, > 100 bpm

Temperature: > 37.5 °C, < 35.5 °C

9.6.6 Physical Measurements

Growth and development will be assessed by the physical measurements' height and weight. Percentile and Z-scores will be presented for physical measurements (height and weight).

The analyses of growth and development will include summary statistics of change from baseline (pre- DLBEP baseline for DLBEP) over time by treatment group for each study phase for adolescents and children separately.

To programmatically calculate the Z-scores, the National Center for Health Statistics percentiles growth charts, based on the 2000 Center for Disease Control and Prevention (CDC) (http://www.cdc.gov/growthcharts/cdc_charts.htm), and the CDC Anthropometric Software Package 3.0 Z scores will be used.

9.6.7 Electrocardiogram

The analyses of ECG data will include summary statistics over time by treatment group, and summary of maximum post-baseline and maximum increase from baseline for corrected QT interval (Fridericia).

9.6.8 Antibody Formation

The number and percentage of subjects who develop anti-erenumab antibodies (binding and if positive, neutralizing) at any time will be tabulated for subjects randomized to erenumab dose group during the DBTP in primary analysis.

In addition, the number and percentage of subjects who develop anti-erenumab antibodies after first dose of erenumab will be tabulated by treatment group for entire study in final analysis.

9.6.9 Exposure to Non-investigational Product(s)/Auxiliary Medicinal Product(s)

Not applicable for this study.

9.6.10 Exposure to Concomitant Medication

The number and proportion of Subjects receiving therapies of interest will be categorized and summarized as coded by the World Health Organization Drug (WHO DRUG) dictionary. See Appendix B. Concomitant MedicationsAppendix B. Concomitant MedicationsAppendix B. Concomitant MedicationsAppendix B. Concomitant Medications for a list of selected medications and their groupings.

9.7 Other Analyses

Injection site pain as assessed by Faces Pain Scale-Revised (FPS-R)

The number and percentage of subjects in each category of facial pain (on the scale 0, 2, 4, 6, 8 or 10) will be summarized descriptively by treatment group and at each time point (at day 1 and week 20 approximately 1 and 15 minutes after IP administration for group 01 and at day 1 and week 8 approximately 1 and 15 minutes after IP administration for group 02).

Columbia Suicide Severity Rating Scale (C-SSRS)

No statistical testing will be performed on data from the pediatric C-SSRS. The number and percentage of subjects reporting any suicidal ideation and any suicidal behavior will be summarized descriptively by treatment group and age group separately for DBTP and DLBEP. Shift table of C-SSRS maximum severity of suicidal ideation/behavior compared to baseline (pre-DLBEP baseline for DLBEP) will be provided by treatment group separately for DBTP and DLBEP.

[redacted]

9.7.2 Analyses of Clinical Outcome Assessments

Not applicable for this study.

9.7.3 Analyses of Health Economic Endpoints

Not applicable for this study.

[redacted]

10. Changes From Protocol-specified Analyses

Analysis for serum bone metabolism markers (CTX and P1NP) are included in SAP (Section 6.7 and Section 9.7.4).

11. Literature Citations / References

Quade, D. (1966), Rank analysis of covariance, University of North Carolina, Institute of Statistics Mimeo Series. No. 483.

Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts: United States. May 2000
https://www.cdc.gov/growthcharts/cdc_charts.htm

2000 CDC Growth Charts for the United States: Methods and Development:
https://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf.

[redacted]

12. Prioritization of Analyses

Prioritization of analyses has not been identified at this time.

13. Data Not Covered by This Plan

There are no plans for Global Biostatistical Science department to specifically analyze or summarize the following data points.

[redacted]

14. Appendices

Appendix A. Reference Values/Toxicity Grades

Adverse event severity and laboratory toxicity are graded based on NCI Common Toxicity Criteria version 4.03 or higher, which is available at the following:

https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix B. Concomitant Medications

Use of concomitant medications will be reviewed and, if deemed appropriate, the therapies of interest will be summarized as described in Section 9.6.10.

A list of selected concomitant medications has not been identified at this time for this study.

Appendix C. Clinical Outcome Assessment Forms/Instruments

- **Modified Pediatric Migraine Disability Assessment (PedMIDAS) Questionnaire**

  The modified PedMIDAS questionnaire can be found in the study protocol, Appendix 8.

- **Patient Global Impression of Change (PGIC)**

  PGIC questionnaire can be found in the study protocol, Appendix 9.

- **Columbia-suicide Severity Rating Scale**

  The children and adult (used for adolescent) C-SSRS questionnaire can be found in the study protocol, Appendix 10.

- **Pubertal Maturation Self-assessment (Tanner Staging) Scale**

  The Pubertal Maturation Self-assessment guidelines can be found in the study protocol, Appendix 11.

- **Patient Health Questionnaire for Adolescents**

  The patient health questionnaire can be found in the study protocol, Appendix 12.

- **Faces Pain Scale-Revised (FSP-R)**

  The FSP-R can be found in the study protocol, Appendix 13.

Appendix D. Health Economic Forms/Instruments

Not applicable for this study.



Appendix F. Analytical Windows

Table 1.1. Vital signs Analysis Visit Windows			
Analysis Visit	**Target Day**	**Visit Window (Study Day, Group 1)**	**Visit Window (Study Day, Group 2)**
Day 1	1	Last measurement ≤ Day 1	Last measurement ≤ Day 1
Week 4	29	16 to 43	16 to 43
Week 8	57	44 to 71	44 to 71
Week 12	85	72 to 99	· 72 to (week 12 DLBEP dose date) for subjects who receive DLBEP dose at week 12. · 72-99 for subjects who did not receive DLBEP dose at week 12
Week 16	113	100 to 127	· Week 12 DLBEP dose date + 1 to 127 for subjects who receive DLBEP dose at week 12. 100 to 127 for subjects who received at least one DLBEP dose and did not receive DLBEP dose at week 12 (eg, first DLBEP dose was postponed)
Week 20	141	128 to 155	128 to 155
Week 24	169	· 156 to (week 24 DLBEP dose date) for subjects who receive DLBEP dose at week 24. · 156 to 183 for subjects who did not receive DLBEP dose at week 24	156 to 183
Week 28	197	· Week 24 DLBEP dose date + 1 to 211 for subjects who	184 to 211

		receive DLBEP dose at week 24. · 184 to 211 for subjects who received at least one DLBEP dose and did not receive DLBEP dose at week 24 (eg, first DLBEP dose was postponed)	
Week 32	225	212 to 239	212 to 239
Week 36	253	240 to 267	240 to 267
Week 40	281	268 to 295	268 to 295
Week 44	309	296 to 323	296 to 323
Week 48	337	324 to 351	324 to 351
Week 52	365	352 to 379	352 to 379
Week 56	393	380 to 407	-
Week 60	421	408 to 435	-
Week 64	449	436 to 463	-
Safety follow-up	Based on visit name from RAVE or other source data; safety follow-up visit only applies to safety data and should be excluded from above analysis visit window in this table.		

Table 1.2. Chemistry and Hematology Laboratory Analysis Visit Windows

Analysis Visit	Target Day	Visit Window (Study Day, Group 1)	Visit Window (Study Day, Group 2)
Day 1	1	Last measurement ≤ Day 1	Last measurement ≤ Day 1
Week 4	29	16 to 43	16 to 43
Week 12	85	72 to 99	· 72 to (week 12 DLBEP dose date) for subjects who receive DLBEP dose at week 12. · 72-99 for subjects who did not receive DLBEP dose at week 12
Week 24	169	· 156 to (week 24 DLBEP dose date) for subjects who	156 to 183

		receive DLBEP dose at week 24. · 156 to 183 for subjects who did not receive DLBEP dose at week 24	
Week 36	253	240 to 267	-
Week 52	365	-	352 to 379
Week 64	449	436 to 463	-
Safety follow-up	Based on visit name from RAVE or other source data; safety follow-up visit only applies to safety data and should be excluded from above analysis visit window in this table.		

Table 1.3. ECG Analysis Visit Windows

Analysis Visit	Target Day	Visit Window (Study Day, Group 1)	Visit Window (Study Day, Group 2)
Day 1	1	Last measurement ≤ Day 1	Last measurement ≤ Day 1
Week 4	29	16 to 43	16 to 43
Week 12	85	72 to 99	· 72 to (week 12 DLBEP dose date) for subjects who receive DLBEP dose at week 12. · 72-99 for subjects who did not receive DLBEP dose at week 12
Week 24	169	· 156 to (week 24 DLBEP dose date) for subjects who receive DLBEP dose at week 24. · 156 to 183 for subjects who did not receive DLBEP dose at week 24	-
Week 52	365	-	352 to 379
Week 64	449	436 to 463	-

Table 1.4. Physical Measurement Analysis Visit Windows (weight and height)

Analysis Visit	Target Day	Visit Window (Study Day, Group 1)	Visit Window (Study Day, Group 2)
Day 1	1	Last measurement ≤ Day 1	Last measurement ≤ Day 1
Week 12	85	-	· 72 to (week 12 DLBEP dose date) for subjects who receive DLBEP dose at week 12.
			· 72-99 for subjects who did not receive DLBEP dose at week 12
Week 24	169	· 156 to (week 24 DLBEP dose date) for subjects who receive DLBEP dose at week 24.	-
		· 156 to 183 for subjects who did not receive DLBEP dose at week 24	
Week 36	253	-	240 to 267
Week 48	337	324 to 351	-
Week 52	365	-	352 to 379
Week 64	449	436 to 463	-
Safety follow-up	Based on visit name from RAVE or other source data; safety follow-up visit only applies to safety data and should be excluded from above analysis visit window in this table.		

Table 1.5. C-SSRS Analysis Visit Windows

Analysis Visit	Target Day	Visit Window (Study Day, Group 1)	Visit Window (Study Day, Group 2)
Day 1	1	Last measurement ≤ Day 1	Last measurement ≤ Day 1
Week 4	29	16 to 43	16 to 43
Week 8	57	44 to 71	44 to 71
Week 12	85	72 to 99	· 72 to (week 12 DLBEP dose date) for subjects who receive DLBEP dose at week 12.

			· 72-99 for subjects who did not receive DLBEP dose at week 12
Week 16	113	100 to 127	· Week 12 DLBEP dose date + 1 to 127 for subjects who receive DLBEP dose at week 12. 100 to 127 for subjects who received at least one DLBEP dose and did not receive DLBEP dose at week 12 (eg, first DLBEP dose was postponed)
Week 20	141	128 to 155	128 to 155
Week 24	169	· 156 to (week 24 DLBEP dose date) for subjects who receive DLBEP dose at week 24. · 156 to 183 for subjects who did not receive DLBEP dose at week 24	156 to 183
Week 28	197	· Week 24 DLBEP dose date + 1 to 211 for subjects who receive DLBEP dose at week 24. · 184 to 211 for subjects who received at least one DLBEP dose and did not receive DLBEP dose at week 24 (eg, first DLBEP dose was postponed)	184 to 211
Week 32	225	212 to 239	212 to 239
Week 36	253	240 to 267	240 to 267
Week 40	281	268 to 295	268 to 295
Week 44	309	296 to 323	296 to 323

Week 48	337	324 to 351	324 to 351
Week 52	365	352 to 379	352 to 379
Week 56	393	380 to 407	-
Week 60	421	408 to 435	-
Week 64	449	436 to 463	-

Table 1.6. PGIC Analysis Visit Windows

Analysis Visit	Target Day	Visit Window (Study Day, Group 1)	Visit Window (Study Day, Group 2)
Week 12	85	72 to 99	· 72 to (week 12 DLBEP dose date) for subjects who receive DLBEP dose at week 12. · 72-99 for subjects who did not receive DLBEP dose at week 12
Week 24	169	· 156 to (week 24 DLBEP dose date) for subjects who receive DLBEP dose at week 24. · 156 to 183 for subjects who did not receive DLBEP dose at week 24	-
Week 32	225	-	212 to 239
Week 44	309	296 to 323	-
Week 52	365	-	352 to 379
Week 64	449	436 to 463	-

Appendix G. Handling of Dates, Incomplete Dates and Missing Dates

Handling of Dates, Incomplete Dates and Missing Dates described in Section 8.3 and Section 8.3.1.