Statistical Analysis Plan

Protocol Title:	Comprehensive Assessment of Erenumab Efficacy in Subjects With High Frequency Episodic Migraine With at Least 1 Previously Failed Preventive Treatment: a Global, Double-blind, Placebo-controlled Phase 4 Study
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	08MAR2021	NA
Amendment 1 (v2.0)	**02NOV2023**	Section 1: • updated the protocol version and date Section 2.1: • updated the secondary and exploratory endpoints regarding duration of migraine attack to align with the latest protocol • specified endpoints assessed for the first qualifying oral triptan-treated attack with complete data at 2-hour assessment • added endpoints assessed for the first qualifying oral triptan-only-treated attack with complete data at 2-hour assessment Section 2.2: • updated the primary clinical hypothesis to align with the latest protocol Section 3.1: • updated the study design to align with the latest protocol Section 5.1.1: • added Gepants and Ditans to acute headache medication • updated the criteria of combination acute headache medication overuse • updated the definition of migraine-free day • updated the definition of diary day • updated the definition of headache pain intensity (3-level) • updated the definition of monthly migraine day • updated the definition of monthly hours of at least moderate headache pain intensity • updated the definition of monthly hours of at least moderate headache pain intensity of qualifying oral triptan treated migraine attacks • updated the term to monthly average duration of at least moderate pain intensity in migraine attacks

		• added the definition of monthly average duration of at least moderate pain intensity in qualifying oral triptan treated migraine attacks Section 5.1.3: • updated the definition of most troublesome symptom Section 5.5: • added definition of on study Section 5.7: • corrected the option in eCRF to adverse event Section 6.2: • updated the definition of M-DBTP efficacy analyses set Section 5.1.3: • corrected the PRO name to MIBS-4 Section 9.6.2: • updated sort order for adverse event tables Table 3-1: • updated the hypothesis and footnote to align with the latest protocol Table 9-3: • removed covariates in the endpoint achievement of pain freedom at 2 hours post-triptan dose for the first attack at month 4 • added summary and analysis method for use of migraine rescue medication within 24 hours post-triptan dose for the first attack at month 4 • added summary and analysis method for change from baseline in the most troublesome symptom at month 3 in footnote c • removed use of migraine rescue medication within 24 hours post-triptan dose for the first attack at month 4 in footnote d

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List of Abbreviations

Abbreviation	Explanation
ANCOVA	Analysis of covariance
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CI	Confidence Interval
DBTP	Double-blind treatment period
E-DBTP	Exploratory double-blind treatment period
EAS	Efficacy analysis set
eDiary	Electronic diary
EM	Episodic migraine
FAS	Full analysis set
HFEM	High-frequency episodic migraine
HIT-6	Headache Impact Test-6
ICH	International Council for Harmonisation
IP	Investigational product
LSM	Least squares mean
M-DBTP	Main double-blind treatment phase
MFIQ	Migraine Functional Impact Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MIBS-4	4-item Migraine Interictal Burden Scale
MMD	Monthly migraine day
MO	Medication overuse
MTS	Most troublesome symptom
MSSS	Migraine Symptom Severity Score
NCT	National Clinical Trials
NRS	Numeric Rating Scale
PCS	Pain Catastrophizing Scale
PGI-S	Patient Global Impression of Severity
Q4W	Every 4 weeks
SAP	Statistical analysis plan
SAS	Safety analysis set

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 **superseded amendment 1** for study 20190008, Erenumab (AMG 334) dated **29 June 2022**. The scope of this plan includes the primary analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the treatment benefit of erenumab on headache duration of at least moderate pain intensity	• Change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2, and 3
Secondary	
• To evaluate the treatment benefit of erenumab on functional impairment	• Change from baseline in mean monthly function domain score as measured by the Migraine Functional Impact Questionnaire (MFIQ) over months 1, 2, and 3: − Impact on physical functioning − Impact on usual activities − Impact on emotional functioning − Impact on social functioning
• To evaluate the treatment benefit of erenumab on duration of migraine pain of at least moderate intensity	• Change from baseline in mean monthly average duration of at least moderate pain intensity **in** migraine attack**s** occurring over months 1, 2, and 3
• To evaluate the treatment benefit of erenumab on peak migraine pain intensity	• Change from baseline in mean monthly average peak migraine pain intensity as assessed by the 11-point Numeric Rating Scale (NRS) over months 1, 2, and 3

Exploratory	
Main Double-blind Treatment Period (month 1 to 3)	
• To evaluate the treatment benefit of erenumab on duration of oral triptan-treated migraine attacks	• Change from baseline in mean monthly hours of at least moderate pain intensity for **qualifying oral** triptan-treated

	migraine attacks over months 1, 2, and 3
• **To evaluate the treatment benefit of erenumab on duration of migraine pain of at least moderate intensity for oral triptan-treated migraine attacks**	• **Change from baseline in mean monthly average duration of at least moderate pain intensity in qualifying oral triptan-treated migraine attacks occurring over months 1, 2, and 3**
• To evaluate the treatment benefit of erenumab on migraine symptoms	• Change from baseline in Migraine Symptom Severity Score (MSSS) total score at assessment time points
	• Change from baseline in the most troublesome symptom (MTS) at month 3
	• Change in Patient Global Impression of Severity (PGI-S) total score at month 3
	• Change from baseline in mean monthly total migraine freedom days over months 1, 2, and 3
• To evaluate the treatment benefit of erenumab on interictal burden of migraine	• Change from baseline in Migraine Interictal Burden Scale (MIBS-4) total score at assessment time points
	• Achievement of no or mild interictal burden as measured by the MIBS-4 at assessment time points
• To evaluate the treatment benefit of erenumab on functional impairment	• Change from baseline in headache impact scores as measured by the Headache Impact Test (HIT-6) total score at assessment time points
	• Change from baseline in physical function domain score as measured by MFIQ at assessment time points
	• Change from baseline in usual activities domain score as measured by MFIQ at assessment time points
	• Change from baseline in social function domain as measured by MFIQ at assessment time points
	• Change from baseline in emotional function domain score as measured by MFIQ at assessment time points
	• Change from baseline in overall impact on usual activities global

	item score as measured by MFIQ at assessment time points
• To evaluate the treatment benefit of erenumab on headache-related cognitions and beliefs	• Change from baseline in pain catastrophizing as measured by the Pain Catastrophizing Scale (PCS) at month 3
• To evaluate the treatment benefit of erenumab on monthly migraine days (MMD)	• Change from baseline in mean MMD over months 1, 2, and 3
Following 2 endpoints will be calculated from months with at least 1 migraine attack	
• **To evaluate the treatment benefit of erenumab on duration of migraine pain of at least moderate intensity with at least 1 migraine attack**	• **Change from baseline in mean monthly average duration of at least moderate pain intensity per migraine attack occurring over months 1, 2, and 3**
• **To evaluate the treatment benefit of erenumab on peak migraine pain intensity with at least 1 migraine attack**	• **Change from baseline in mean monthly average peak migraine pain intensity as assessed by the 11-point Numeric Rating Scale (NRS) over months 1, 2, and 3**
Exploratory Double-blind Treatment Phase (month 4)	
• To evaluate the treatment benefit of erenumab on interictal burden of migraine	• Change from baseline in Migraine Interictal Burden Scale (MIBS-4) total score at month 4
For the first qualifying oral triptan-treated attack with complete data at 2-hour assessment:	
• To evaluate the treatment benefit of erenumab on achieving and sustaining pain freedom following treatment with an oral triptan	• Achievement of pain freedom at 2 hours post-triptan dose for the first attack at month 4
	• Achievement of 24-hour sustained pain freedom post-triptan dose for the first attack at month 4
	• Achievement of pain freedom at 30 and 60 minutes post-triptan dose for the first attack at month 4
• To evaluate the treatment benefit of erenumab on achieving pain relief following treatment with an oral triptan	• Achievement of pain relief at 30, 60, and 120 minutes post-triptan dose for the first attack at month 4
• To evaluate the treatment benefit of erenumab on achieving freedom from the most bothersome symptom following treatment with an oral triptan	• Achievement of freedom from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first attack at month 4
• To evaluate the treatment benefit of erenumab on achieving relief from the most bothersome	• Achievement of relief from the most bothersome symptom at 30,

symptom following treatment with an oral triptan	60, and 120 minutes post-triptan dose for the first attack at month 4
• To evaluate the treatment benefit of erenumab on migraine recurrence following treatment with an oral triptan	• Migraine recurrence within 24 hours post-triptan dose for the first attack at month 4
• To evaluate the treatment benefit of erenumab on use of migraine rescue medication following treatment with an oral triptan	• Use of migraine rescue medication within 24 hours post-triptan dose for the first attack at month 4
For the first qualifying oral triptan-only-treated attack with complete data at 2-hour assessment:	
• **To evaluate the treatment benefit of erenumab on achieving and sustaining pain freedom following treatment with oral triptan only**	• **Achievement of pain freedom at 30, 60, and 120 minutes post-triptan dose for the first triptan-only-treated attack in which complete data is obtained (at least 2 hours timepoint) at month 4**
• **To evaluate the treatment benefit of erenumab on achieving pain relief following treatment with oral triptan only**	• **Achievement of pain relief at 30, 60, and 120 minutes post-triptan dose for the first triptan-only-treated attack at month 4**
• **To evaluate the treatment benefit of erenumab on achieving freedom from the most bothersome symptom following treatment with oral triptan only**	• **Achievement of freedom from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first triptan-only-treated attack at month 4**
• **To evaluate the treatment benefit of erenumab on achieving relief from the most bothersome symptom following treatment with oral triptan only**	• **Achievement of relief from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first triptan-only-treated attack at month 4**

2.2 Hypotheses and/or Estimations

The primary clinical hypothesis is that preventive treatment with monthly administration of erenumab is superior to placebo in reducing **duration of moderate or severe** headache pain in subjects with high-frequency episodic migraine (HFEM) who have previously failed at least 1 migraine preventive treatment.

3. Study Overview

3.1 Study Design

Study 20190008 is a phase 4, interventional, prospective, double-blind, randomized, placebo-controlled, multicenter global study, evaluating the effects of erenumab on

aspects of migraine beyond MMD reduction in adult subjects with high-frequency episodic migraine (HFEM) who have previously failed at least 1 preventive treatment.

Subjects who meet eligibility criteria will be enrolled in a run-in period (2 weeks in duration) during which they will record oral triptan-treated migraine attacks in an episode electronic diary (eDiary). **At the end of the run-in period, subjects will be eligible to enter the 4-week baseline period only if they have 1 or more qualifying oral triptan-treated migraine attacks (defined as migraine attacks of at least moderate peak pain intensity that are treated with an oral triptan within 2 hours of pain reaching at least moderate severity) and if pain freedom is not achieved within 1 hour following oral triptan intake for > 50% of their qualifying migraine attacks.** During the baseline period subjects will keep a daily eDiary. At the end of the baseline period, subjects who meet specific eligibility criteria will be able to enter the double-blind treatment period (DBTP).

The 4-month DBTP has 2 phases:

- Main DBTP (M-DBTP, months 1-3) that will assess the effect of erenumab on metrics such as time spent in at least moderate pain, peak migraine severity, and functional impairment
- Exploratory DBTP (E-DBTP, month 4) that will assess the impact of erenumab on the acute response to treatment with oral triptans **therapy** as well as non-ictal burden

Throughout both phases of the DBTP, investigational product will be administered every 4 weeks (Q4W). Data entry will follow a daily eDiary collection during the M-DBTP and transition to an episode eDiary during the E-DBTP.

3.2 Sample Size

A total sample size of 576 subjects (288 subjects per group including 10% dropouts) provides at least a 90% power for the primary efficacy hypothesis. The statistical power for secondary efficacy hypotheses ranges from 81% to > 99% (Table 3-1).

Table 3-1. Sample Size Assumptions and Statistical Powers for Primary and Secondary Efficacy Endpoints for a Total Sample Size of 576 Subjects Including a 10% Attrition Rate due to Dropout

Hypothesis	Assumed Treatment Effect	Power

	(Common SD)	
Primary: Change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2, and 3	-16.7 (50)	96%
Secondary: Change from baseline in mean monthly		
MFIQ physical function **domain score** over months 1, 2, and 3	-9.2 (18.0)	> 99%
MFIQ usual activities **domain score** over months 1, 2, and 3	-7.5 (19)	> 99%
MFIQ emotional function **domain score** over months 1, 2, and 3	-11.5 (22)	> 99%
MFIQ social function **domain score** over months 1, 2, and 3	-6.9 (20)	97%
Average duration of at least moderate migraine pain intensity **in migraine attacks occurring** over months 1, 2, and 3[a]	-2.0 (8)	81%
Average peak migraine pain intensity over months 1, 2, and 3	-0.11 (0.44)	81%

MFIQ = Migraine Functional Impact Questionnaire
Note: All power calculations are based on a 2-sided significance level of 0.05. The assumed treatment effects and common standard deviations are derived or chosen from a subset of placebo-treated and erenumab-140mg-treated subjects in erenumab Study 20120296 with high-frequency episodic migraine (ie, 7 to 14 monthly migraine days) and having at least 4 moderate-to-severe migraine attacks at baseline.
[a] If a subject did not have any migraine attacks in a given month, the duration of at least moderate migraine pain intensity **was counted as 0**.

4. Covariates and Subgroups

4.1 Planned Covariates

For efficacy endpoints of the M-DBTP, all model-adjusted analyses of efficacy endpoints will include the corresponding baseline value for the endpoint being analyzed. The baseline value is calculated based on data collected during the 4-week baseline period or on day 1 prior to the first dose.

For pain freedom and pain relief related efficacy endpoints of the E-DBTP (month 4), the following covariates may be considered:

- Medication overuse status at month 3 (yes vs no)

- Time to triptan intake since reaching moderate/severe pain of the first qualifying attack at month 4 (< 1 hour vs ≥ 1 hour)
- Pain intensity prior to triptan intake is severe (yes [NRS ≥ 7] vs no) of the first qualifying attack at month 4

For most bothersome symptom related endpoints of the E-DBTP, the following symptom types may be included in the model:

- Nausea/Vomiting (yes vs no)
- Photophobia/phonophobia (yes vs no)

4.2 Subgroups

The primary and secondary endpoints of the M-DBTP will be analyzed in the following subgroups:

- Number of prior treatment failures (1, 2, and 3 or more treatment failures)
- Medication overuse status at baseline (yes vs. no)

Selected exploratory endpoints of the E-DBTP for the first qualifying triptan-treated attack may be analyzed by medication overuse status at month 3 (yes vs. no) (see Section 9.5.3).

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

5. Definitions

5.1 Definition of Terms Included in Study Endpoints

5.1.1 Efficacy Endpoints Based on Daily Diary Data Collection During M-DBTP

During the 4-week baseline period and the 12-week M-DBTP, headache start and stop date/time, pain feature/symptoms, acute headache medication and aura related information will be reported on a daily basis via optional any-time diar(ies) (available 24 hours) and mandatory evening diary (only available once daily from 17:00 to 23:59).

Acute Headache Medication (AHM)

Acute headache medications collected in the eDiary are classified separately as follows:

	Medication Group A
Acute headache medication (AHM)	Ergotamine-Based Migraine Medications
	Triptan-Based Migraine Medications
	Gepant-Based Migraine Medications
	Ditan-Based Migraine Medications

	Non-Opioid Acute Headache Medications
	Non-Opioid Butalbital Containing Medications
	Opioid-Containing Acute Headache Medications
	Opioid-Containing Butalbital Containing Medications

	Medication Group B
Acute headache medication (AHM)	Ergots
	Triptans
	Gepants
	Ditans
	Opiate or opioid-containing medication
	Opioid Combination-analgesic
	Non-opioid Combination-analgesic
	Simple analgesics/NSAIDs

Acute Migraine-specific Medication (AMSM)

A subset of acute headache medication consisting of triptan-based migraine medications and ergotamine-based migraine medications

Medication Overuse (MO)

Monthly acute headache medication days meeting at least one of the following criteria based on medication category B:

- ≥ 10 days of triptans
- ≥ 10 days of ergotamines
- ≥ 10 days of opiates or opioid-containing medications or opioid combination-analgesics
- ≥ 10 days of non-opioid combination-analgesics
- ≥ 15 days of simple analgesics/NSAIDs if no other acute headache medications were used
- ≥ 10 days of a combination of triptans, ergotamines, opiates or opioid-containing meds or opioid combination-analgesic, non-opioid combination-analgesic medications or simple analgesics/NSAIDs **whilst not satisfying medication overuse criteria in any of the individual medication categories alone**

Number of Diary Days in a Monthly Interval	Monthly Days with Medication Use
• ⩾ 14 days	**Prorate to 28-day equivalent without rounding** **Number of observed days with medication use*28/number of (diary days or medication days) within each monthly interval**
• < 14 days	**Set to missing**

Qualified Headache

A qualified headache is defined as

- A headache of duration ≥ 30 minutes, or
- A headache with acute headache medications (migraine-specific or not) taken during the headache (start time and end time inclusive) with any length of duration, or
- An aura during which an acute migraine-specific medication is administered

Headache Day

A calendar day (00:00 to 23:59) in which the subject experiences ≥ 1 qualified headache

Qualified Migraine Headache

A qualified migraine headache should meet at least one of the following criteria:

- A headache of duration ≥ 30 minutes, and meeting ≥ 1 of the following criteria (a and/or b):
  a) ≥ 2 of the following pain features:
    - Unilateral
    - Throbbing
    - Moderate to severe (based on the 3-level categorical pain severity)
    - Exacerbated with exercise/physical activity

  b) ≥ 1 of the following associated symptoms:
    - Nausea
    - Vomiting
    - Photophobia and phonophobia
- A headache during which an acute migraine-specific medication is administered regardless of the headache duration, pain features, and associated symptoms
- An aura during which an acute migraine-specific medication is administered

Migraine Day

A calendar day (00:00 to 23:59) in which the subject experiences ≥ 1 qualified migraine headache

Migraine-free Day

A calendar day (00:00 to 23:59) **of a diary day** in which the subject does not experience any headache and aura, photophobia, phonophobia, and nausea/vomiting**, and does not take any acute headache medication**

Diary Day

A calendar day (00:00 to 23:59) with complete headache, aura, and acute headache medication data recorded **via daily evening diary**

Information Day

A calendar day (00:00 to 23:59) which is either a headache day or a diary day

Migraine Attack in M-DBTP

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

- A migraine attack that is interrupted by sleep, or temporarily remits, and then recurs within 48 hours (recurrence time – headache start time ≤ 48 hours) will be counted as 1 attack
- An attack treated successfully with medication but with relapse within 48 hours (recurrence time – headache start time ≤ 48 hours) will be counted as 1 attack

Triptan-treated Migraine Attack in M-DBTP

A migraine attack with triptan taken during the attack (start time and end time inclusive)

Headache Pain Intensity (evaluated by NRS) in M-DBTP

Worst or peak pain intensity collected on a headache ranges from 0 to 10 with a higher score indicating more severe pain.

Pain intensity is reported when the headache end time is reported or in an evening diary on a daily basis for an ongoing headache. Therefore, there can be multiple pain intensity values reported for a headache that lasts for multiple days. In some circumstances, a headache which starts and ends on the same day may also have up to 2 pain intensity values reported when the headache ends after evening diary completion: 1) pain intensity is reported in the evening diary for the period between headache start time and diary completion time; 2) pain intensity is reported either in any-time diary or the next day's evening diary for the period between previous diary completion time and headache end time. The NRS headache pain intensity will be used to assess the monthly average peak pain intensity.

Headache Pain Intensity (3-level)

Worst or peak pain intensity collected on a headache in 3 levels (mild, moderate or severe) followed by the NRS pain intensity question when the preceding NRS headache pain intensity is reported to be ≥ 4**, worst or peak pain intensity (3 levels) is set as mild if NRS headache pain intensity is reported to be <4**.

Duration of Headache With at Least Moderate Pain Intensity

Duration of headache with at least moderate pain intensity (in hours and minutes) will be collected only when "Moderate" or "Severe" intensity is reported based on the 3-level headache pain intensity scale.

Monthly Migraine Days (MMD)

Number of migraine days during one monthly interval as defined below**.**

Number of Diary Days in a Monthly Interval	Monthly Migraine Days
• ≥ 14 days	Prorate to 28-day equivalent without rounding Number of observed migraine days*28/number of (diary days **or migraine days**) **within each monthly interval**
• < 14 days	Set to missing

Monthly Headache Days (MHD)

Number of headache days during one monthly interval as defined below**.**

Number of Diary Days in a Monthly Interval	Monthly Headache Days
• ≥ 14 days	Prorate to 28-day equivalent without rounding Number of observed headache days*28/number of information days Note: An information day is either a headache day or a diary day.
• < 14 days	Set to missing

Monthly Hours of at Least Moderate Headache Pain Intensity

Number of Diary Days in a Monthly Interval	**Monthly Hours of at Least Moderate Headache Pain Intensity**
• ≥ 14 days	Prorate to 28-day equivalent without rounding Sum of hours of headaches with at least moderate pain intensity *28/number of (diary days **or days with headache pain intensity**) **within each monthly interval**
• < 14 days	Set to missing

Monthly Hours of at Least Moderate Headache Pain Intensity of Qualifying Oral Triptan Treated Migraine Attacks

Number of Diary Days in a Monthly Interval	**Monthly Hours of at Least Moderate Headache Pain Intensity of Qualifying Oral Triptan Treated Migraine Attacks**
• ≥ 14 days	Prorate to 28-day equivalent without rounding Sum of hours of at least moderate pain intensity of qualifying **oral** triptan treated migraine attacks *28/number of (diary days **or migraine days**) **within each monthly interval**
• < 14 days	Set to missing

Monthly Average Duration of at Least Moderate Pain Intensity in Migraine Attacks

Number of Diary Days in a Monthly Interval	**Monthly Average Duration of at Least Moderate Pain Intensity in Migraine Attacks**
• ≥ 14 days	Sum of all the reported duration with at least moderate headache pain intensity within an attack divided by number of attacks in each month If there is no migraine during the monthly interval, then the monthly average duration will be set to 0.
• < 14 days	Set to missing

Monthly Average Duration of at Least Moderate Pain Intensity in Qualifying Oral Triptan Treated Migraine Attacks

Number of Diary Days in a Monthly Interval	**Monthly Average Duration of at Least Moderate Pain Intensity in Qualifying Oral Triptan Treated Migraine Attacks**
• **≥ 14 days**	**Sum of all the reported duration with at least moderate headache pain intensity within a qualifying oral triptan-treated attack divided by number of qualifying oral triptan-treated attacks in each month;** **If there is no migraine during the monthly interval, then the monthly average duration will be set to 0.**
• **< 14 days**	**Set to missing**

Monthly Average Peak Migraine Pain Intensity

Number of Diary Days in a Monthly Interval	**Monthly Average Peak Migraine Pain Intensity**
• ≥ 14 days	Sum of observed highest pain intensity scores (NRS) per migraine day divided by total number of migraine days with at least one measure of NRS; If there is no migraine day with NRS during the monthly interval, then the monthly average peak migraine pain intensity will be set to 0.
• < 14 days	Set to missing

5.1.2 Efficacy Endpoints Based on Episodic Diary Data Collection During E-DBTP

During the 2-week run-in period and the 1-month E-DBTP at month 4, subjects experiencing a qualified triptan-treated migraine attack will report medication usage, pain intensity, the most bothersome symptom and corresponding severity using the episodic diary. A qualifying headache for reporting is a headache reaching at least moderate pain intensity with initial triptan intake within 2 hours and also satisfying migraine headache criteria (ie, a qualified triptan-treated migraine attack). The initial triptan intake time (ie, time point 0) will trigger a 48-hour assessment window, during which the headache pain intensity, severity of the most bothersome symptom at 30, 60 and 120 minutes, 24 hours and 48 hours post triptan will be collected. Another 48-hour assessment window will be triggered if there is a new qualified triptan-treated migraine attack starts after the previous assessment window.

Headache Pain Intensity (NRS) in E-DBTP

Worst or peak pain intensity collected on a headache ranges from 0 to 10 with a higher score indicating more severe pain.

NRS Pain intensity is collected when a qualified headache reaching at least moderate pain intensity with triptan intake within 2 hours and for the following timed assessments at 30 minutes, 1-hour, 2-hour, 24-hour and 48-hour diaries.

Migraine Rescue Medication

Migraine rescue medication for each qualifying triptan-treated attack is defined as any additional acute headache medication(s) taken during the 48-hour assessment window.

Migraine Recurrence Within 24 Hours Post-triptan

Pain intensity NRS = 0 at any of the 30-minute, 60-minute, and 2-hour timed assessments and pain intensity NRS ≥ 4 at 24-hour timed assessment

Pain Relief at timed assessment post-triptan dose

Pain intensity NRS < 4 at the specific timed assessment (eg, 30 minutes, 60 minutes, or 2 hours post-triptan dose).

Pain freedom at timed assessment post-triptan dose

Pain intensity NRS = 0 at the specific timed assessment (eg, 30 minutes, 60 minutes or 2 hours post-triptan dose).

Achievement of 24-hour sustained pain freedom post-triptan dose

Pain intensity NRS = 0 at both 2-hour and 24-hour timed assessment without rescue medication taken post-triptan dose.

Most Bothersome Symptom

The most bothersome symptom can be selected among nausea, vomiting, sensitivity to light, or sensitivity to sound.

Severity of Most Bothersome Symptom (4-level)

Worst or peak severity collected on the most bothersome symptom according to 4 levels (none, mild, moderate or severe)

Achievement of freedom from the most bothersome symptom at timed assessment post-triptan dose

Symptom severity = none at the specific timed assessment (eg, 30 minutes, 60 minutes or 2 hours post-triptan dose).

Achievement of relief from the most bothersome symptom at timed assessment post-triptan dose

Reduction in symptom severity by at least one level down (eg, from severe to moderate, mild to none) at the specific timed assessment (eg, 30 minutes, 60 minutes or 2 hours post-triptan dose).

5.1.3 Efficacy Endpoints Based on Monthly Data Collection

Migraine Functional Impact Questionnaire (MFIQ)

The MFIQ version 2.0 is a self-administered 26-item instrument measuring the impact of migraine on broader functioning including 4 domains: Impact on Physical Functioning (5 items), Impact on Usual Activities (10 items), Impact on Social Functioning (5 items), and Impact on Emotional Functioning (5 items). In addition, there is 1 stand-alone global item assessing the overall impact on usual activities. Subjects respond to items using a 5-point scale assigned scores from 1 to 5, with 5 representing the greatest burden. Each domain score will be calculated as the sum of the item responses and the sum will be rescaled to a 0 to 100 scale, with higher scores representing greater burden. The recall period is the past 7 days and will be collected monthly at day 1, weeks 4, 8 and 12.

Migraine Symptom Severity Scale (MSSS)

The MSSS is a 7-item questionnaire that assesses frequency of pain and other symptoms associated with migraines. Responses are as follows: “never”, “rarely”, “less than half the time”, “half the time or more”, and “all or nearly all of the time”. The responses are given a value from 0 to 3: Never = 0, Rarely = 1, Less Than Half the Time = 2, Half the Time or More = 3, and All or Nearly All of the Time = 3. The MSSS score is the sum of the responses to the 7 items with a range from 0 to 21. MSSS will be collected monthly at day 1, weeks 4, 8 and 12.

Most Troublesome Symptom (MTS)

The MTS will be measured by 5 questions on day 1 and the change in the MTS will be assessed by 2 questions at week 12. The baseline questions will be asking the subjects to select the most troublesome symptom during and/or between migraine headache attacks and to rate how often they experience the symptoms. The week 12 questions will be asking the subjects to rate how their previously identified most troublesome symptom during and/or between migraine headache attacks have changed since the start of the study on a scale of 1 (Very Much Improved) to 7 (Very Much Worse). Achieving 1 = Very Much Improved or 2 = Much Improved is considered as meaningful improvement.

Only subjects with non-missing baseline will be considered in the analysis. As per questionnaire design, if a subject answer ‘No’ for question 3 at baseline, subject will not be considered for between migraine headache attacks analysis.

Patient Global Impression of Severity (PGI-S)

The PGI-S is a single question that rates the severity of the subject's condition at the time of assessment. It is a 7-point scale that ranks severity of illness using one of the following response categories: 1 = Normal, not at all ill, 2 = Borderline ill, 3 = Mildly ill; 4 = Moderately ill, 5 = Markedly ill, 6 = Severely ill, and 7 = Most extremely ill. PGI-S will be collected at day 1 and week 12.

Migraine Interictal Burden Scale (MIBS-4)

The MIBS-4 measures interictal migraine-related burden with 4 questions that assess impairment in work or school, impairment in family and social life, difficulty making plans or commitments, and emotional/affective and cognitive distress. Each of the 4 questions is responded to using 1 of 6 response categories: "Don't know/NA" (Score = 0), "Never" (Score = 0), "Rarely" (Score = 1), "Some of the time" (Score = 2), "Much of the time" (Score = 3) or "Most or all of the time" (Score = 3). Response to each question is summed up to produce total score ranges from 0 to 12. The MIBS-4 total scores are categorized into 4 level of interictal burden: None (0), Mild (1 to 2), Moderate (3 to 4) and Severe (5 or higher). **MIBS-4** will be collected monthly at day 1, weeks 4, 8, 12 and 16.

Headache Impact Test (HIT-6)

The scoring of the HIT-6 total score will be performed using the QualityMetric's PRO CoRE Scoring Software. The HIT-6 total scores ranging from 36 to 78 can be categorized into 4 grades, representing little or no impact (49 or less), some impact (50 to 55), substantial impact (56 to 59), and severe impact (60 to 78) due to headache. HIT-6 will be collected monthly at day 1, weeks 4, 8 and 12.

Pain Catastrophizing Scale (PCS)

The PCS is a 13-item self-report measure consists of 3 subscales, which are Rumination (4 items), Magnification (3 items), and Helplessness (6 items). For each item, subjects are requested to provide a response in a 5-point Likert scale (0 "not at all," 1 "to a slight degree," 2 "to a moderate degree," 3 "to a great degree," 4 "all the time"). Higher scores in PCS indicate higher levels of catastrophizing. Response to each item is summed up to get the total score ranging from 0 to 52. PCS will be collected at day 1 and week 12.

5.1.4 Safety Endpoints

Serious Adverse Event (SAE)

An event categorized as "Adverse Event" with the indicator flag "Serious" equal to "Yes" on the Events eCRF starting on or after signing of the informed consent and up to the End of Study date.

Treatment-emergent Adverse Event (TEAE)

An event categorized as “Adverse Event” on the Events eCRF starting on or after first dose of investigational product, as determined by “Did event start before first dose of investigational product” equal to “No” or missing, and up to the End of Study date.

Serious TEAE

A TEAE with the indicator flag “Serious” equal to “Yes” on the Events eCRF.

Treatment-emergent Adverse Device Effect

A TEAE with the indicator flag “Is there a reasonable possibility that the event may have been caused by the investigational device” equal to “Yes” on the Events eCRF.

5.2 Study Dates

Informed Consent Date

The date on which subject signs the informed consent form.

Date of Ready for Daily Diary Entry in Baseline

The date on which an eDiary device is ready for daily diary entry after completion of run-in period.

Randomization Date

Randomization Date is defined as the date subject was allocated to a treatment group.

Enrollment Date

Enrollment Date is defined as the randomization date.

First IP Dose Date

First IP Dose Date is the date on which a subject is administered the first dose of IP following randomization as recorded on the IP Administration eCRF. The first IP dose may be the same day or after the randomization date.

Last IP Dose Date

Last IP Dose Date is the date on which a subject is administered the last dose of IP as recorded on the IP Administration eCRF.

End of Study (EOS) Date

End of study (EOS) date is defined as the last date on which the subject participates in the study as recorded on the End of Study eCRF.

5.3 Study Points of Reference

Run-in Assessment

Run-in assessment is designed to determine the entry eligibility for baseline period.

Baseline Assessment

Baseline assessment for the endpoint of the interest is defined as the last non-missing measurement taken or the monthly interval assessed (for endpoints derived from daily eDiary collection during baseline period) 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.

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 -1.

5.4 Study Time Intervals

5.4.1 Monthly Intervals for Efficacy Endpoints Derived From Daily Diary Collection

The (4-week) monthly intervals for efficacy endpoints derived from daily eDiary collection during baseline and months 1, 2, and 3 will be determined based on each subject's monthly IP dosing dates. When an IP is missed or discontinued, a 28-day monthly interval will be used. Any eDiary data occurring after EOS date will not be included in the analysis.

Applicable efficacy endpoints utilizing the monthly intervals in Table 5-1 include:

- Monthly migraine days (MMD)

- Monthly headache hours of at least moderate pain intensity
- Monthly average duration of at least moderate pain intensity per migraine attack
- Monthly average peak migraine pain intensity
- Monthly migraine-free days
- Monthly hours of at least moderate pain intensity of triptan-treated migraine attacks

Table 5-1. Monthly Intervals for Efficacy Endpoints Derived From Daily Diary Data Collection

Study Period	Assessment Timepoint	Monthly Interval	
		Start Date (Day) [a]	End Date (Day) [b]
Baseline Period	Baseline	Date of device ready for entry in baseline period	Day prior to study day 1
M-DBTP	Week 4 (Month 1)	Study Day 1	Week 4 dose date – 1
	Week 8 (Month 2)	Week 4 dose date	Week 8 dose date – 1
	Week 12 (Month 3)	Week 8 dose date	Week 12 dose date – 1

[a] Start Date (Day) = End date (day) of previous monthly interval + 1 if IP dose date is not available
[b] End Date (Day) = Start date (day) of current monthly interval + 27 if IP dose date is not available

5.4.2 Monthly Interval for Efficacy Endpoints Derived From Episodic Diary Collection

The first qualifying triptan-treated attack during the E-DBTP will be identified within the monthly interval defined in Table 5-2:

Table 5-2. Monthly Interval for Efficacy Endpoints Derived From Episodic Diary Data

Study Period	Monthly Interval	
	Start Date (Day)	End Date (Day)
E-DBTP	Week 12 dose date	MIN (Week 12 dose date + 27, EOS date)

5.4.3 Analysis Visits for Endpoints Derived Based on Monthly Data Collection

Since the actual visit for a subject may not exactly coincide with their targeted visit date, the actual visit date is mapped to the analysis visit as in Table 5-3, Table 5-4, and Table 5-5. Any data occurred after EOS date will not be included in the analysis.

For by-visit summaries, if more than one visit with non-missing measurement (including the unscheduled visits, ie, CPEVENT = 'UNSCHED') fall within the same visit window, the following rules will be applied according to the order described below for selecting one visit per visit window for summary:

1. 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 visit window.
2. The visit closest to the target day among visits of the same type (all scheduled visits or all unscheduled visits) will be considered for analysis.
3. If two assessment dates are equidistant from the target date, the latter visit will be considered for analysis.

Table 5-3. MIBS-4 Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Baseline Period	Day 1 (Baseline)	1	Last measurement ≤ Day 1
M-DBTP	Week 4 (Month 1)	29	16 to 43
	Week 8 (Month 2)	57	44 to 71
	Week 12 (Month 3)	85	72 to 99
E-DBTP	Week 16 (Month 4)	113	100 to 127

Table 5-4. MFIQ, MSSS and HIT-6 Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Baseline Period	Day 1 (Baseline)	1	Last measurement ≤ Day 1
M-DBTP	Week 4 (Month 1)	29	16 to 43
	Week 8 (Month 2)	57	44 to 71
	Week 12 (Month 3)	85	72 to 99

Table 5-5. PGI-S, MTS and PCS Analysis Visit Windows

Study Period	Analysis Visit	Target Day	Visit Window (Study Day)
Baseline Period	Day 1 (Baseline)	1	Last measurement ≤ Day 1
M-DBTP	Week 12 (Month 3)	85	72 to 99

5.5 Subject Disposition

Randomized

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

Exposed to Investigational Product

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

Completing Investigational Product

Subjects are defined as completing investigational product if the primary reason for ending IP on End of IP eCRF is “Completed”.

Completing Study

Subjects are defined as completing study if they complete the entire 16 weeks of study evaluation**.** It will be derived from the End of Study eCRF with "Completed" as the primary reason for ending study.

On Study

Subjects are defined as on study for specific study week if their end of study date is on or after the first day of the analysis window.

5.6 Arithmetic Calculations

Duration of Migraine

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

Observed Portion	Missing Portion	Duration of Migraine (Years)
Year, Month, Day	NA	(Informed Consent Date – DXDT) / 365.25
Year, Month	Day	[Year(Informed Consent Date) – Year(DXDT)] + [Month(Informed Consent Date) – Month(DXDT)] / 12 [a]
Year	Month, Day	[Year(Informed Consent Date) – Year(DXDT)] [a]

[a] If it equals 0, add 1/12 years (ie, 1 month) to avoid a disease duration of 0.

Duration of IP Exposure

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

Change From Baseline in Monthly Measurement

Postbaseline monthly value – Baseline, as defined in Section 5.4. If the baseline or postbaseline value is missing, the change from baseline value will be set to missing.

Change From Baseline in Mean Monthly Measurement Over Multiple Months

Change from baseline in Mean Monthly Measurement is the arithmetic mean of the monthly change from baseline values for the months considered with observed data, if there is at least one observed monthly value.

Subject Incidence of TEAEs

The subject incidence for a given event during the study is defined as the number of subjects with at least one reported occurrence of the event divided by the number of subjects who received at least one dose of investigational product. For subjects with multiple occurrences of the same event, the event will only be counted once per subject.

5.7 Disease Characteristics

Treatment Failure of Prior Migraine Preventive Medications

Treatment failure of prior migraine preventive medications is determined by "Reason for Stopping" as "Lack of efficacy" or "Adverse **event**" or "Intolerance" on the Prior Migraine Prophylactic Medication eCRF.

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set consists of all subjects who were randomized in the study. Analysis of disposition, demographic and baseline characteristics, important protocol deviations, and protocol deviations related to COVID-19 control measures will utilize this analysis set.

6.2 M-DBTP Efficacy Analyses Set

The respective efficacy analysis set for each efficacy endpoint consists of a subset of subjects from full analysis set who receive at least 1 dose of investigational product and have **observed monthly hours of at least moderate headache pain intensity at baseline and at least 1 measurement during M-DBTP**. Subjects will be analyzed according to their randomized treatment, regardless of treatment received. Primary analysis of the efficacy endpoints during M-DBTP will utilize this efficacy analysis set.

6.3 E-DBTP Efficacy Analysis Set

The E-DBTP efficacy analysis set consists of a subset of subjects from full analysis set who receive week 12 dose. Subjects will be analyzed according to their randomized treatment, regardless of treatment received. Analysis of exploratory efficacy endpoints during E-DBTP will utilize this efficacy analysis set.

6.4 Safety Analysis Set

The safety analysis set will consist of all randomized subjects who receive at least 1 dose of investigational product. Subjects will be analyzed according to the randomized treatment unless a subject has received the incorrect dose during the entire DBTP, in which case, the subject will be analyzed according to the actual treatment received.

Analysis for safety endpoints and summary of investigational product administration will utilize the safety analysis set.

7. Planned Analyses

The primary analysis (or final analysis since there is only one milestone analysis for this study) will occur after all subjects have completed their week-16 visit (or discontinued

from the study). The DBTP treatment assignment will be unblinded and all efficacy and safety analyses will be conducted and reported by the DBTP treatment group.

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 provide all data to be used in the planned analyses. This study will use the RAVE database as well as eDiary data which is outside of the RAVE database.

8.3 Handling of Missing and Incomplete Data

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

For the endpoints derived from the daily diary data, please refer to proration approach specified in Section 5.1.1 on handling missing daily diary data. Missing monthly measurement after proration will be handled by statistical analysis approaches listed in Section 9.5.

For the endpoint derived from the episodic diary data, missing data at timed assessment will be handled by statistical analysis approaches listed in Section 9.5.

Missing items in each clinical outcome assessment questionnaire will be handled based on the scoring algorithm for each assessment. The missing value in the algorithm derived measurements (eg, total score, domain scores) will be handled by statistical analysis approaches listed in Section 9.5.

Missing data in safety endpoints will not be imputed except for incomplete start date of an AE or concomitant medication, which will be imputed as follows:

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

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 tabulated. If necessary, the incidence of other factors will be tabulated.

The reasons for early withdrawal from treatment and from study will be tabulated.

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 assessed 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. 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 will be used, 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

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

For the primary and secondary endpoints, the primary analysis method utilizing a repeated measures linear mixed effects model will include all observed data regardless of treatment adherence.

A sequential testing procedure will be used to maintain the family-wise type 1 error $\alpha = 0.05$ between the primary and secondary endpoints following the prespecified order below. An endpoint will only be tested for statistical significance if the endpoint tested in the previous step is statistically significant at 2-sided significance level of 0.05.

1. Primary endpoint: change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2, and 3
2. Secondary endpoints: change from baseline in mean monthly function over months 1, 2, and 3, as measured by the MFIQ using the Hochberg procedure
    - Impact on physical functioning

- Impact on usual activities
- Impact on emotional functioning
- Impact on social functioning

3. Secondary endpoint: change from baseline in mean monthly average duration of at least moderate pain intensity **in** migraine attack**s** over months 1, 2, and 3
4. Secondary endpoint: change from baseline in mean monthly peak migraine pain intensity over months 1, 2, and 3, as assessed by the 11-point NRS

9.2 Subject Accountability

The disposition of all randomized (enrolled) subjects will be tabulated by randomized treatment group. The summary will include the number of subjects who are randomized, the number and percent of subjects who receive/never receive double-blind IP, who complete double blind IP, discontinue double-blind IP and reasons for discontinuing, who complete the study, and who withdraw prematurely from the study before completion of the study and their reasons for withdrawal. Summary of subjects who discontinue investigational product/study due to COVID-19 control measures will be included.

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. IPDs will be summarized and listed by randomized treatment group.

Protocol Deviations (PDs) related to COVID-19 control measures will be summarized separately.

9.4 Demographic and Baseline Characteristics

Subject demographic and baseline characteristics will be summarized using descriptive statistics by randomized treatment group and overall study population using FAS. If multiple races have been reported for a subject, the subject will be categorized as multiple races as well as by combination of races.

At baseline, the following demographic and baseline characteristics will be summarized:

- Age
- Sex
- Ethnicity
- Race
- Height (cm)

- Weight (kg)
- Body mass index (BMI, kg/m^2)
- Targeted neurological disease diagnosis at baseline
- Disease duration of migraine with or without aura
- Age at onset of migraine
- Summary of prior migraine preventive medication and reasons for discontinuation
- Acute headache medication use during baseline period:
  a) Migraine-specific
  b) Non migraine-specific
- Monthly migraine days during baseline period
- Monthly headache days during baseline period
- Monthly hours of at least moderate headache pain intensity
- Monthly average duration of at least moderate pain intensity per migraine attack
- Monthly average peak migraine pain intensity
- Monthly total migraine freedom days
- Monthly hours of at least moderate pain intensity for triptan-treated migraine attacks
- MFIQ domain scores of function (physical, usual activities, social, and emotional)
- HIT-6 total score
- MTS
- MSSS total score
- PGI-S score
- MIBS-4 total score
- PCS total score

9.5 Efficacy Analyses

The primary and secondary efficacy analyses will utilize the M-DBTP EAS and the exploratory efficacy analyses will utilize the E-DBTP EAS. Subjects will be analyzed according to their randomized treatment group regardless of the actual treatment received during the study.

Detailed efficacy analysis methods and covariates included in the models are summarized in the table below.

Table 9-1. Primary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method
Change from baseline in mean monthly hours of at least moderate headache pain intensity over months 1, 2, and 3	1. Summary statistics by visit using observed data at each visit and the calculated mean monthly hours of headache pain over months 1, 2, and 3 2. Least squares means from a linear mixed effect model including treatment group, scheduled visit, interaction of treatment and scheduled visit and baseline value using observed data 3. Estimate treatment difference (AMG 334 – Placebo) from the model in #2.

Table 9-2. Secondary Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method
Change from baseline in mean monthly function as measured by the Migraine Functional Impact Questionnaire (MFIQ) over months 1, 2, and 3; Change from baseline in mean monthly average duration of at least moderate pain intensity **in** migraine attack**s** over months 1, 2, and 3; Change from baseline in mean monthly peak migraine pain intensity as assessed by the 11-point Numeric Rating Scale (NRS) over months 1, 2, and 3	1. Summary statistics by visit using observed data at each visit, and the calculated mean monthly values over months 1, 2 and 3 2. Least squares means from a linear mixed effect model including treatment group, scheduled visit, interaction of treatment and scheduled visit and baseline value using observed data 3. Estimate treatment difference (AMG 334 – Placebo) from the model in #2

Table 9-3. Exploratory Efficacy Endpoint Summary Table

Endpoint	Primary Summary and Analysis Method
Change from baseline in mean MMD over months 1, 2, and 3[a]	1. Summary statistics by visit using observed data at each visit and the calculated mean monthly migraine day over months 1, 2, and 3 2. Least squares means from a linear mixed effect model including treatment group, scheduled visit, interaction of treatment and scheduled visit and baseline value using observed data 3. Estimate treatment difference (AMG 334 – Placebo) from the model in #2.
Change from baseline in pain catastrophizing as measured by the Pain Catastrophizing Scale (PCS) at month 3[b]	1. Summary statistics using observed data at week 12 2. Analysis of covariance (ANCOVA) model including treatment group and baseline value using observed data 3. Estimate treatment difference (AMG 334 – Placebo) using the model in #2.
Achievement of no or mild interictal burden as measured by the MIBS-4 at assessment time points[c]	1. Summary statistics using observed data at the specific month 2. Logistic regression model including treatment group and baseline value will be used after subjects with missing outcome data are imputed as non-responders (NRI)

Endpoint	Primary Summary and Analysis Method
Achievement of pain freedom at 2 hours post-triptan dose for the first attack at month 4[d]	1. Summary statistics using observed data at the assessment time points 2. Logistic regression model including treatment group will be used after subjects with missing timed assessment are imputed as non-responders
Use of migraine rescue medication within 24 hours post-triptan dose for the first attack at month 4	**1. Summary statistics using observed data at the assessment time points** **2. Logistic regression model including treatment group using observed data**

[a] The same analyses methods will be applied to the endpoints:
Change from baseline in mean monthly hours of at least moderate pain intensity for qualifying oral triptan-treated migraine attacks over months 1, 2, and 3
Change from baseline in mean average duration of at least moderate pain intensity for qualifying oral triptan-treated migraine attacks occurring over months 1, 2, and 3
Change from baseline in Migraine Symptom Severity Score (MSSS) total score at assessment time points
Change from baseline in mean monthly total migraine freedom days over months 1, 2, and 3
Change from baseline in Migraine Interictal Burden Scale (MIBS-4) total score at assessment time points (the model will include data at month 1-4)
Change from baseline in headache impact scores as measured by the Headache Impact Test (HIT-6) total score at assessment time points
Change from baseline in physical function domain score as measured by MFIQ at assessment time points
Change from baseline in usual activities domain score as measured by MFIQ at assessment time points
Change from baseline in social function domain as measured by MFIQ at assessment time points
Change from baseline in emotional function domain score as measured by MFIQ at assessment time points
Change from baseline in overall impact on usual activities global item score as measured by MFIQ at assessment time points
Change from baseline in mean monthly average duration of at least moderate pain intensity per migraine attack in months with at least 1 migraine attack
Change from baseline in mean monthly peak migraine pain intensity as assessed by the 11-point Numeric Rating Scale (NRS) in months with at least 1 migraine attack

[b] The same analyses methods will be applied to the endpoints:
Change in Patient Global Impression of Severity (PGI-S) total score at month 3

[c] **The same analyses methods will be applied to the endpoints:**
Change from baseline in the most troublesome symptom (MTS) at month 3

[d] The same analyses methods will be applied to the endpoints:
Achievement of pain freedom at 30 and 60 minutes post-triptan dose for the first attack at month 4
Achievement of pain relief at 2 hours post-triptan dose for the first attack at month 4
Achievement of freedom from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first attack at month 4
Achievement of relief from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first attack at month 4
Achievement of 24-hour sustained pain freedom post-triptan dose for the first attack at month 4
Migraine recurrence during 24 hours post-triptan dose for the first attack at month 4

9.5.1 Analyses of Primary and Secondary Efficacy Endpoints

For the primary and secondary endpoints will be tested using a linear mixed model based on observed monthly data with appropriate contrasts for pairwise treatment comparisons.

The model will include treatment, scheduled visit, treatment by visit interaction, and baseline value as covariates. If applicable, the first-order autoregressive covariance structure is assumed. Least squares means (LSMs) for each treatment group, standard errors, associated 95% CIs, difference of LSMs compared to placebo group, associated 95% CIs and nominal two-sided p-values will be tabulated by visit and treatment, as well as for the mean monthly values over months 1, 2, and 3 of the DBTP. No sensitivity analyses will be performed for the primary and secondary endpoints.

Subgroup analysis described below will be performed for the primary and secondary endpoints:

1. Treatment failure of prior migraine prophylactic medications (1, 2, and 3 or more treatment failures)
2. Medication overuse at baseline (yes vs. no)

The purpose of the subgroup analyses is to explore if the treatment effect varies across subgroups of interest. Subgroup analyses are performed for primary and secondary efficacy endpoints using the same method as primary analysis method but performed within each interested subgroup.

The heterogeneity of the treatment effect across the subgroups will be evaluated by examining the treatment-by-subgroup interaction at primary time point and an interaction p-value will be presented. The primary analysis model with the addition of treatment-by-subgroup interaction will be used.

9.5.2 M-DBTP Analyses of Exploratory Efficacy Endpoints

For exploratory efficacy endpoints during the M-DBTP, summary statistics and primary analysis method will be conduct in the same way as that for the primary and secondary endpoints.

The continuous exploratory efficacy endpoints at each assessment time point or over months 1, 2, and 3 of the 3-month M-DBTP will be analyzed using the

linear mixed effects model that includes treatment group, baseline values, scheduled visit, and the interaction of treatment and scheduled visit without any imputation for missing data.

The efficacy endpoints for PCS total score and PGI-S score will be analyzed using analysis of covariance model including treatment and baseline value as covariates. The efficacy endpoints for **MTS** (achievement of “Very Much Improved” or “Much Improved”) and the MIBS (achievement of no or mild interictal burden) will be analyzed using logistic regression model with missing data imputed using NRI **up to End of Study Date**. No sensitivity analyses will be performed for the exploratory endpoints.

9.5.3 E-DBTP Analyses of Exploratory Efficacy Endpoints

The dichotomous efficacy endpoints for assessing qualifying triptan-treated attacks only in E-DBTP will be analyzed using logistic regression model with missing data imputed as non-responders (NRI) **up to End of Study Date**. Odds ratios of treatment group and placebo with associated 95% CIs and p-values will be reported. The efficacy endpoint for Migraine Interictal Burden Scale at month 4 will be analyzed using the linear mixed effects model that includes treatment group, baseline values, scheduled visit, and the interaction of treatment and scheduled visit without any imputation for missing data.

The following exploratory endpoints of the E-DBTP for the first qualifying triptan-treated attack will be analyzed by medication overuse status at month 3 (yes vs. no):

- Achievement of pain freedom at 2 hours post-triptan dose for the first attack at month 4
- Achievement of pain relief at 2 hours post-triptan dose for the first attack at month 4
- Achievement of relief from the most bothersome symptom at 30, 60, and 120 minutes post-triptan dose for the first attack at month 4
- Achievement of 24-hour sustained pain freedom post-triptan dose for the first attack at month 4
- Migraine recurrence within 24 hours post-triptan dose for the first attack at month 4
- Use of migraine rescue medication within 24 hours post-triptan dose for the first attack at month 4

9.6 Safety Analyses

9.6.1 Analyses of Safety Endpoints

For safety endpoints, all randomized subjects who received at least one dose of IP (ie, Safety Analysis Set) will be analyzed based on the randomized treatment unless a subject has received the incorrect dose during the entire study.

No statistical testing comparing treatment groups will be performed in the safety analyses.

9.6.2 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later will be used to code all adverse events (AEs) 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 summary tables described below will be summarized by treatment group using subject incidence.

The subject incidence of AEs will be summarized for all treatment-emergent adverse events (TEAEs), serious AEs, AEs leading to withdrawal of investigational product, fatal AEs, and adverse events of interest (EOI) including

- 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)
- Constipation AMQ (Narrow and Broad)
- Alopecias AMQ (Narrow and Broad)
- COVID-19 SMQ (Narrow)

Subject incidence of all TEAEs, SAEs, AEs leading to withdrawal of investigational product, fatal AEs, and device related AEs will be tabulated by SOC in alphabetical order and PT in descending order of frequency **based on the AMG 334 140 mg dose, then Placebo dose and then alphabetically**.

Subject incidence of EOI (standardized MedDRA queries [SMQ] and/or Amgen medical queries [AMQ]) will also be summarized according to their categories and PT in descending order of frequency.

In addition, summarizes of all TEAEs and SAEs occurring in at least 3% of the subjects by PT in any treatment arm will be provided in descending order of frequency **based on**

the AMG 334 140 mg dose, then Placebo dose and then alphabetically. Summaries of all TEAEs and SAEs will be tabulated by SOC, PT, and grade.

9.6.3 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group. 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.

9.6.4 Exposure to Concomitant Medication

The number and proportion of subjects receiving acute headache medications will be summarized by acute medication category for each treatment group based on medication data collected in eDiary.

9.7 Other Analyses

Not Applicable.

10. Changes From Protocol-specified Analyses

There are one deviation from protocol:

- The efficacy analysis set mentioned in protocol was changed to M-DBTP efficacy analysis set and E-DBTP efficacy analysis set to meet the target population of primary, secondary and exploratory endpoints.

11. Literature Citations / References

Holroyd KA, Drew JB, Cottrell CK, Romanek KM, Heh V. Impaired functioning and quality of life in severe migraine: the role of catastrophizing and associated symptoms. *Cephalalgia*. 2007;27:1156–1165.

Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and Validation. *Psychol Assess*. 1995;7:524–532.

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

12. Data Not Covered by This Plan

There are no plans to specifically analyze or summarize the following data points.

13. Appendices

Appendix A. Reference Values/Toxicity Grades

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

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf