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STATISTICAL ANALYSIS PLAN Amendment 2 Date: 22 May 2018

1. Title Page

STATISTICAL ANALYSIS PLAN

A PHASE 2/3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF MULTIPLE DOSING REGIMENS OF ORAL AGN-241689 IN EPISODIC MIGRAINE PREVENTION

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Protocol Number:	CGP-MD-01
Development Phase:	2/3
Product Name:	Atogepant (AGN-241689)
Study Statistician:	[redacted]
Sponsor:	Allergan, Inc. Clonshaugh Industrial Estate, Coolock, Dublin 17, Ireland

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Table 3–1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
ACM-I	Assessment of Chronic Migraine Impact
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BMI	body mass index
CFB	change from baseline
C-SSRS	Columbia-Suicide Severity Rating Scale
DBS	dry blood spot
DDE	Drug Dictionary Enhanced
eCRF	electronic case report form
ECG	electrocardiogram, electrocardiographic
EQ-5D-5L	European Quality of Life-5 Dimensional
EU	European Union
FWER	familywise error rate
HEOR	health economics and outcomes research
HIT-6	Headache Impact Test
INR	international normalized ratio
ITT	intent-to-treat
LS	least squares
LOCF	last observation carried forward
MAR	***missing-at-random***
MedDRA	Medication Dictionary for Regulatory Activities
MCMC	***Markov Chain Monte Carlo***
MI	***multiple imputation***
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
MPM	migraine/probable migraine
OR	odds ratio
PCS	potentially clinically significant
PGIC	Patient Global Impression of Change
PK	pharmacokinetics
PID	participant identification
PT	preferred term
QD	once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d'Unités (International System of Units)

Abbreviation/Term	Definition
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
US	United States
WHO	World Health Organization
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire – Specific Health Problem

4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the protocol amendment #***2*** dated ***11Sep2017*** of Study CGP-MD-01. Specifications of tables, figures, and data listings are contained in a separate document. The SAP for pharmacokinetic (PK) and health economics and outcomes research (HEOR) data will be prepared separately.

This document is organized into 3 main sections:

1. Study overview
2. Statistical Methodology and Study Endpoints
3. Data Handling and Analysis Conventions

4.1 Study Design Summary

This is a multi-center, randomized, double-blind, placebo-controlled, parallel group study conducted at approximately 75 sites in the United States. Approximately 810 participants will be randomized to one of six treatment arms (placebo, 10-mg once daily [QD], 30-mg QD, 30-mg twice daily [BID], 60-mg QD, and 60-mg BID) in a 2:1:2:1:2:1 ratio as follows:

- Placebo (n = 180)
- Atogepant 10-mg QD (n = 90)
- Atogepant 30-mg QD (n = 180)
- Atogepant 30-mg BID (n = 90)
- Atogepant 60-mg QD (n = 180)
- Atogepant 60-mg BID (n = 90)

To maintain the blind, investigational product will be administered orally BID for 12 weeks to all participants. Participants, therefore, will receive either placebo twice daily, a morning dose of atogepant with an evening dose of placebo, or atogepant twice daily.

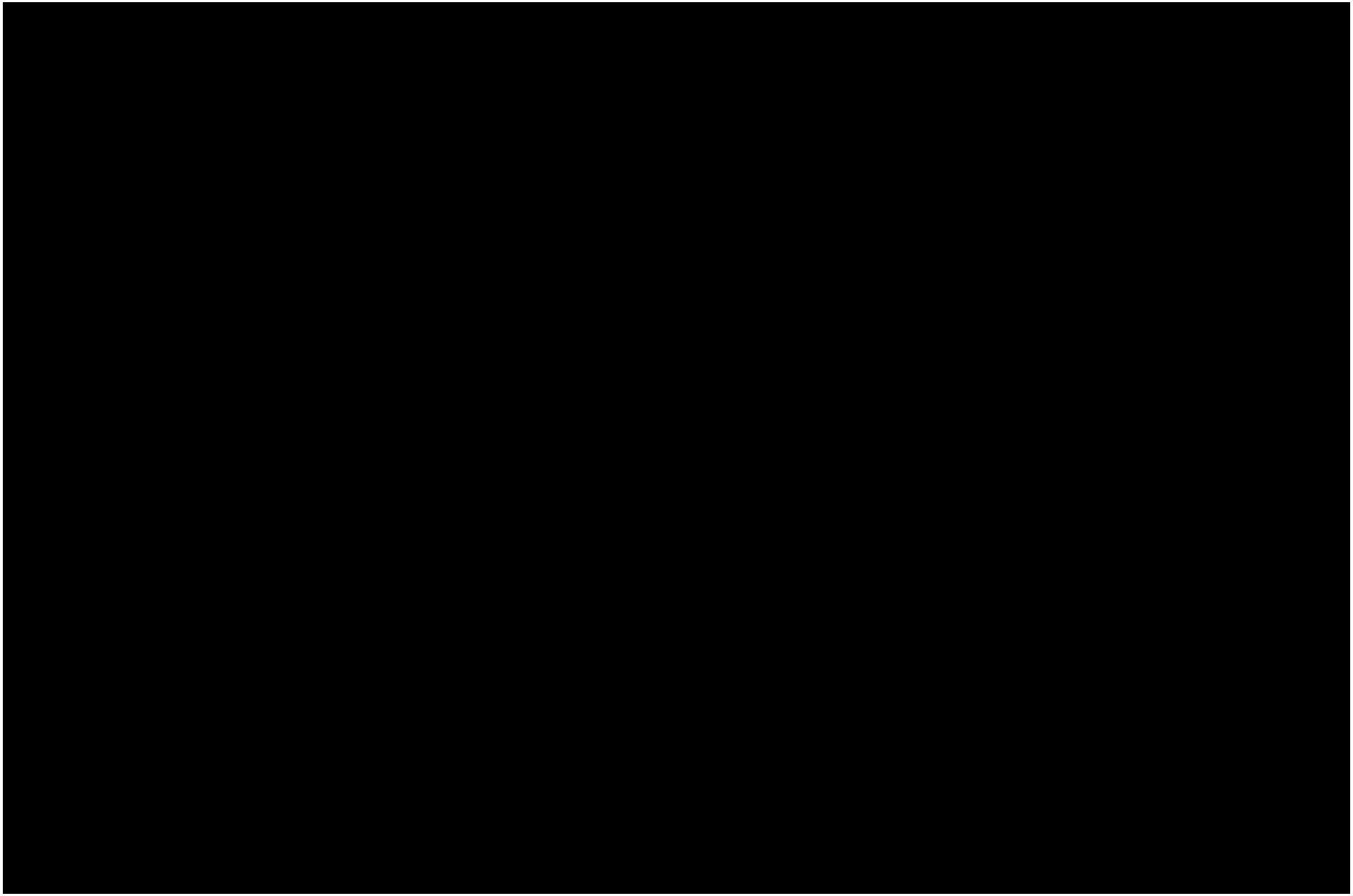
Subject participation will begin with a 4-week Screening/Baseline Period. Participants who complete the 4-week Screening/Baseline Period and meet all entry criteria will be randomized to the double-blind treatment period of the study at Visit 2 (randomization visit). The double-blind treatment period will last 12 weeks, with a subsequent Safety Follow-up Period of 4 additional weeks. There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline), Visit 2 (Randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Safety Follow-up). For details, please see Table 4–2, Schedule of Visit and Procedures.

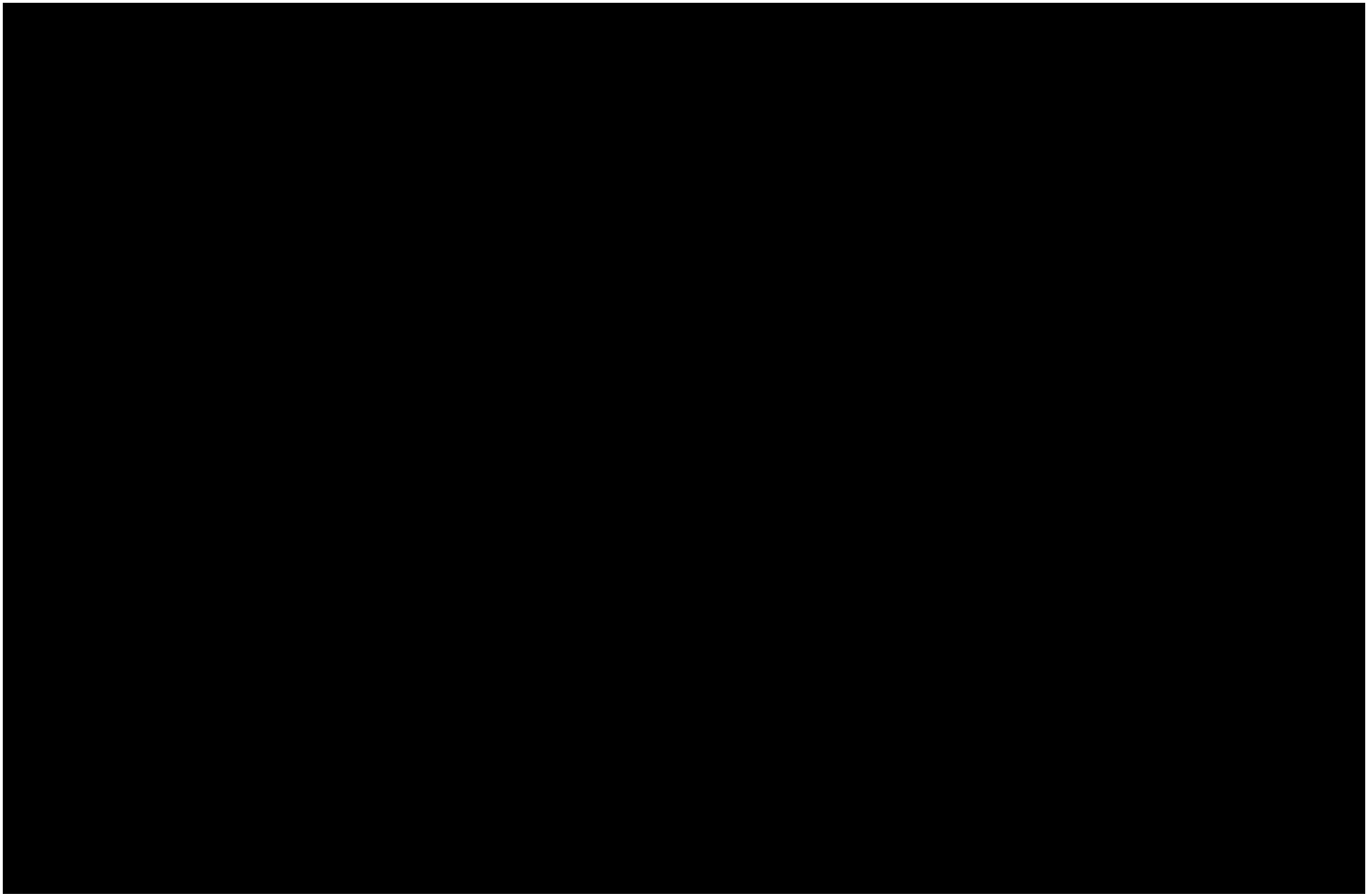
4.2 Study Objectives and Endpoints

Each study objective is presented with corresponding endpoint(s) below:

Table 4–1 Study Objectives and Corresponding Endpoints

Objectives	Endpoints
[redacted] • To prospectively test for superiority of the following doses and dose regimens of atogepant (10-mg QD, 30-mg QD, 30-mg BID, 60-mg QD, and 60-mg BID) versus placebo for the prevention of episodic migraine in this pivotal trial	[redacted] **Primary Efficacy Endpoint** P1. Change from baseline in the ***mean monthly*** migraine/probable migraine (MPM) headache days ***across the 12-week treatment period*** **Secondary Efficacy Endpoints** S1. Change from baseline in ***mean monthly*** headache days ***across the 12-week treatment period*** S2. Proportion of patients with at least a 50% reduction in ***mean monthly*** MPM headache days ***across the 12-week treatment period*** S3. ***Change from baseline in mean monthly acute medication use days across the 12-week treatment period***





5. Statistical Methodology and Study Endpoints

5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size

This statistical analysis plan (SAP) will be approved prior to database lock. The SAP expands the statistical section of the protocol and contains a detailed description of methods to analyze data collected in the study. The text portion of the SAP will be included in the CSR report as Appendix 16.1.9.

5.1.1 Statistical and Analytical Plans

Statistical analyses will be conducted using [redacted].

5.1.1.1 Common Conventions

5.1.1.1.1 Analysis Populations

The analysis populations will consist of participants as defined below:

Table 5–1 Analysis Populations

Population	Definition	Study Treatment
Screened	All screened participants who sign informed consent	—
Intent-to-Treat (ITT)	All randomized participants	Randomized assignment
Modified Intent-to-Treat (mITT)	All randomized participants who received ≥ 1 dose of study treatment, had an evaluable baseline period of diary data, and had ≥ 1 evaluable post-baseline 4-week (Weeks 1-4, 5-8, and 9-12) of diary data • For baseline, evaluable is defined as having at least 20 days of diary data during the 4-week baseline period • For each post-baseline 4-week treatment period, evaluable is defined as having at least 12 days of diary data for that particular period	Randomized assignment
Safety	All participants who received ≥ 1 dose of study treatment	Actual received[1]

[1] Participants will be summarized according to the study treatment received for majority of treatment period.

5.1.1.1.2 Study Treatments

The following treatment groups are defined for this study:

- Placebo
- Atogepant 10-mg QD
- Atogepant 30-mg QD
- Atogepant 30-mg BID
- Atogepant 60-mg QD

- Atogepant 60-mg BID

5.1.1.1.3 Statistical Methodology

The methodologies defined below apply as specified to individual endpoints defined in this SAP. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

Table 5–2 Statistical Methodology

Methodology	Description
R1 Categorical counts	• Number of participants in individual categories o Participants with ≥ 1 qualifying event counted once per individual category

R2 Categorical descriptives	• Number and percentage of participants in individual categories
	  o Participants with ≥ 1 qualifying event counted once per individual category
	• N1 if percentage denominator ≠ number of participants in the population (standard percentage denominator)
	  o N1 = participants with non-missing baseline value

R3 PCS descriptives	• Number and percentage of participants meeting potentially clinically significant (PCS) criteria
	  o Participants with ≥ 1 qualifying event counted once per PCS category
	• Percentage denominator = number of participants with non-missing non-PCS baseline and >=1 non-missing postbaseline assessment
	  o Unevaluable assessments considered missing

R4 Shift analysis	• Number and percentage of participants in individual baseline and postbaseline categories • Percentage denominator = number of participants in individual baseline categories • N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit
R5 Continuous descriptives	• N1, mean, standard deviation (SD), median, minimum, maximum • N1 = participants with non-missing value
R6 CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit

R7 CFB ANCOVA	• Continuous descriptives and standard error (SE) for baseline, postbaseline, and CFB values
	• Estimates derived from mixed model for CFB value controlling for factors (treatment group) and covariates (baseline value)
	  o Least squares (LS) means and standard errors
	  o LS mean differences, standard errors, and confidence intervals vs Placebo
	  o P-values from contrast t-test comparing atogepant treatment groups vs Placebo
	• N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit

R8 CFB MMRM	• Continuous descriptives and SE for baseline, postbaseline, and CFB values at each analysis visit o N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit • Estimates derived from mixed model for CFB value controlling for fixed factors (treatment group, analysis visit), covariates (baseline value), and interactions

Methodology		Description
		(treatment group by analysis visit, baseline value ***by analysis visit***), with an unstructured covariance matrix (compound symmetry covariance matrix if convergence fails) o LS means and standard errors o LS mean differences, standard errors, and confidence intervals vs Placebo o P-values from contrast t-test comparing atogepant treatment groups vs Placebo o N1 = participants with non-missing values at both baseline and at least one postbaseline analysis visit o ***When the time point of interest is across overall 12-week treatment period, the contrast is constructed to estimate the mean difference in average change from baseline of Month 1 – 3 in the model.***
R9	CFB figure	• Plot of CFB LS means and SE bars for Weeks 1-4, 5-8, and 9-12
R10	Responder	• Categorical descriptives for responders and nonresponders o Nonresponders include: ▪ Participants who do not meet responder criteria • ***N1 = all participants unless otherwise specified***
R11	***CDF*** Figure	• Plot of ***proportions of participants achieving a range of 0% to 100% reduction from baseline (i.e. improvement) in mean monthly MPM headache days across 12-week treatment period by treatment group*** o ***The figure is cumulative, so that participants whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%***
R12	GLMM	• Measures the relationship between the binary dependent variable with repeated measures and independent variables • Estimates derived from generalized linear mixed model (GLMM) for repeated measures which assumes a ***binomial*** distribution for the response and uses a logit link. • For the responder analysis in MPM headache days, the model includes: o Fixed factors (treatment group, analysis visit), covariates (baseline MPM headache days), and interactions (treatment group by analysis visit, baseline MPM headache days ***by analysis visit***), with an unstructured covariance matrix (compound symmetry covariance matrix if convergence fails). o Odds ratios, confidence intervals, and p-values comparing atogepant treatment groups vs Placebo o ***When the time point of interest is across overall 12-week treatment period, the contrast is constructed to estimate the geometric mean of odds ratio of Month 1 – 3 in the model.*** • Include participants with non-missing values at both baseline and at least one postbaseline analysis visit

CDF = cumulative distribution function; CFB = change from baseline; ANCOVA = analysis of covariance; MMRM = mixed model for repeated measures; GLMM = generalized linear mixed model.

Raw and derived data listings will be provided, and will be fully defined in the table, figure, and data listing specification document.

5.1.1.1.4 Missing Data

General missing data handling conventions are specified for methodologies in Section 5.1.1.1.3 and summarized as follows:

Table 5–3 Missing Data Handling by Endpoint Type

Parameter type	Timing	Missing Data Handling

Responder	Treatment Period	• Responder rate:
		  ○ All participants included
		• GLMM:
		  ○ If missing covariates (including baseline if applicable) or missing values at all postbaseline analysis visits: Participant excluded
		  ○ If ≥1 non-missing value at any postbaseline analysis visit: Participant included

CFB ANCOVA	Treatment Period	• If missing covariates (including baseline if applicable) ○ Participant excluded

CFB MMRM	Treatment Period	• If missing covariates (including baseline if applicable) or missing values at all postbaseline analysis visits
		  ○ Participant excluded
		• If ≥1 non-missing value at any postbaseline analysis visit:
		  ○ Participant included
		  ▪ Missing at random assumed

Pattern-mixture model ***(PMM)***	Treatment Period	• Sensitivity analysis for the primary efficacy endpoint to assess the robustness of the primary MMRM analysis to possible violation of the missing-at-random (MAR) assumption. • A pattern-mixture model approach based on the "copy reference" method (Carpenter et al, 2013) will be used for missing value imputation. Refer to Section ***6.4.3.1*** for details.

CFB = change from baseline; ANCOVA = analysis of covariance;
MMRM = mixed model for repeated measures; GLMM = generalized linear mixed model.

5.1.1.2 Demographics

5.1.1.2.1 Analysis Populations

The distribution of participants within the analysis populations will be summarized as follows:

Table 5–4 Analysis Population Summaries

Population	Description	Timing	Methodology
ITT, mITT, and Safety populations	Distribution in total and by treatment group	—	Categorical counts

5.1.1.2.2 Participant Disposition

Participant disposition encompasses the distribution of participants who complete, and discontinue each specified analysis period, along with eCRF-reported discontinuation reasons from each respective analysis period. Participant disposition will be summarized as follows:

Table 5–5 Participant Disposition Summaries

Parameter	Description	Timing	Methodology
Screening disposition [1]	***Number of screened participants*** in total	Screening Period	Categorical descriptives
Treatment Period	Distribution in the ITT Population in total	Treatment Period	Categorical

Parameter	Description	Timing	Methodology
disposition [1]	and by treatment group		descriptives
Follow-up period disposition[1]	Distribution in the ITT Population in total and by treatment group	Safety Follow-up Period	Categorical descriptives
[1] Participant disposition will be listed and participants who prematurely discontinued will be listed.			

5.1.1.2.3 Protocol Deviations

Protocol deviations will be defined in Protocol Deviation Requirement Specification, including importance classification. Protocol deviations will be summarized as follows:

Table 5–6 Protocol Deviation Summary

Parameter	Description	Timing	Methodology
Major protocol deviations[1]	Distribution in the ITT Population in total and by treatment group	—	Categorical descriptives

[1] Protocol deviations will be listed.

5.1.1.2.4 Demographics

Demographics will be summarized by treatment group for the Safety and mITT populations, as follows:

Table 5–7 Demographic Summaries

Parameter	Description	Timing	Methodology
Age[1]	Age (years) relative to informed consent date	Informed consent	Continuous descriptives
Age group	• <20 • 20 – 29 • 30 – 39 • 40 – 49 • 50 – 59 • 60 – 69 • >=70	Informed consent	Categorical descriptives

Sex, race, and ethnicity[1]	• eCRF categories
	• Race group
	  ○ White
	  ○ Non-white
		Screening Period	Categorical descriptives

[1] Participant demographics will be listed.

5.1.1.2.5 Baseline Characteristics

Baseline characteristics will be summarized in total and by treatment group for the Safety and ***m***ITT populations as follows:

Table 5–8 Baseline Characteristics Summaries

Parameter	Description	Timing	Methodology
Baseline characteristics[1]	• Height (m)	Latest assessment in Screening Period	Continuous descriptives

Parameter	Description	Timing	Methodology
	• Weight (kg) • Body mass index (BMI) o Weight (kg) / height (m)^2		
Baseline efficacy	Endpoints and timing fully described in Section 5.1.1.3 • Number of MPM headache days • Number of headache days • Number of ***acute medication*** use days Summary for mITT Population only	***The first 28 days of the screening period, starting with the day of the screening visit***	Continuous descriptives

[1] Participant baseline characteristics will be listed.
MPM = migraine/probable migraine.

5.1.1.2.6 Medical History

Medical history, encompassing abnormalities and surgeries reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or newer. Unique participants who report medical history events will be summarized by MedDRA system organ class (SOC) and preferred term (PT) in total and by treatment group for the Safety Population as follows:

Table 5–9 Medical History Summary

Parameter	Description	Timing	Methodology
Medical history[1]	Abnormalities and surgeries occurring before the Screening Visit	Screening Period	Categorical descriptives

SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.
[1] Participant medical history will be listed.

5.1.1.2.7 Migraine History

Migraine history, including diagnosis, duration of disorder, previous use of prophylaxis treatment, average frequency of migraines or headache days per month in past 3 months, and acute treatments will be reported in total and by treatment group for the Safety Population as follows:

Table 5–10 Medical History Summary

Parameter	Description	Timing	Methodology
Migraine Diagnosis[1]	With Aura, Without Aura, Both	Screening Period	Categorical descriptives
Duration of migraine[1]	In the Table summarize in Years, in the Listing show original data in Years and Months	Screening Period	Continuous descriptives
Previous Prophylaxis Migraine Treatment[1]	Yes or No	Screening Period	Categorical descriptives
Average number of migraine days per month in the last 3 months[1]		Screening Period	Continuous descriptives
Average number of headache days per month in the last 3 months[1]		Screening Period	Continuous descriptives

Parameter	Description	Timing	Methodology
Acute Migraine Treatment[1]	Categorize as Yes or No, and subcategorize the Yes by: • Triptan • Ergot or ergot combinations • NSAID • Opiate or opiate combination • Antiemetic agent • Barbituates • Other	Screening Period	Categorical descriptives

[1] Participant migraine history will be listed.

5.1.1.2.8 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced (DDE), version MAR2016 or newer. Unique participants who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 class and PT in total and by treatment group for the Safety Population as follows:

Table 5–11 Medication Summaries

Parameter	Description	Timing	Methodology
Prior medications[1]	Medications taken ≥ 1 time before the study treatment start date, regardless of medication end date	Screening Period	Categorical descriptives
Concomitant medications[1]	Medications taken ≥ 1 time on or after the study treatment start date, regardless of medication start date • Medications starting 1 day after treatment end date will be listed but excluded from analysis	Treatment Period	Categorical descriptives

ATC4 classes will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.
[1] Participant prior and concomitant medication will be listed.

5.1.1.3 Efficacy and Pharmacokinetic Analyses

Efficacy analyses will be based on the mITT Population.

The following efficacy assessments and terms are defined:

Assessment/Term	Description
[redacted]	[redacted]

For analyses of headache characteristics and acute medication use, the first 28 days of the screening period, starting with the day of the screening visit, will serve as the "baseline". Baseline assessments for applicable efficacy endpoints defined as follows:

Table 5–13 Efficacy Endpoint Baseline Definitions

Endpoint	Description	Timing
Baseline number of MPM headache days	The total number of reported MPM headache days divided by the total number of days with non-missing eDiary records during the 4-week baseline period and multiplied by 28. Refer to Section 6.4.1 for details.	The first 28 days from screening visit to the day before randomization
Baseline number of headache days	The total number of reported headache days divided by the total number of days with non-missing eDiary records during the 4-week baseline period and multiplied by 28. Refer to Section 6.4.1 for details.	The first 28 days from screening visit to the day before randomization
Baseline average headache day pain intensity	Baseline average headache day pain intensity is calculated for days with non-missing eDiary data during baseline period. Refer to Section 6.4.1 for details.	The first 28 days from screening visit to the day before randomization
Baseline cumulative headache hours	Average daily headache hours are calculated for days with non-missing eDiary data during baseline period. Baseline cumulative headache hours are calculated as average daily headache hours multiplied by 28. Refer to Section 6.4.1 for details.	The first 28 days from screening visit to the day before randomization
Baseline number of acute medication use days	The total number of reported acute medication use days divided by the total number of days with non-missing eDiary records during the 4-week baseline period and multiplied by 28. Refer to Section 6.4.1 for details.	The first 28 days from screening visit to the day before randomization
Baseline number of triptan use days	The total number of reported triptan use days divided by the total number of days with non-missing eDiary records during the 4-week baseline period and multiplied by 28. Refer to Section 6.4.1 for details.	The first 28 days from screening visit to the day before randomization

MPM = migraine/probable migraine.

5.1.1.3.1 Efficacy Endpoints

The efficacy endpoints are summarized in the table below. Analyses of HEOR endpoints (ACM-I total and domain scores, PGIC, WPAI-SHP V2.0, ***patient satisfaction with study medication, HIT-6,*** and EQ-5D-5L) will be specified in a separate HEOR SAP.

Table 5–14 Efficacy Analysis

Endpoint	Description	Timing	Methodology
Endpoint 1 P1	Change from baseline in ***mean monthly*** MPM headache days ***across the 12-week treatment period***	***Treatment period***	CFB MMRM ***Sensitivity Analyses:*** • ***PMM*** • ***Robust regression***

Endpoint	Description	Timing	Methodology
			(Refer to Section 6.4.3 for details)
Endpoint 2 S1	Change from baseline in ***mean monthly*** headache days ***across the 12-week treatment period***	***Treatment Period***	CFB MMRM
Endpoint 3 S2	Proportion of participants with at least a 50% reduction in ***mean monthly*** MPM headache days ***across the 12-week treatment period***	***Treatment Period***	Responder GLMM
Endpoint 4 S3	Change from baseline ***in mean monthly acute medication use days across the 12-week treatment period***	***Treatment Period***	CFB MMRM
[redacted]			

[1] Analysis visits defined in Section 6.2.1.
MPM = migraine/probable migraine. CFB = change from baseline; MMRM = mixed model for repeated measures; GLMM = generalized linear mixed model.
P1: primary efficacy parameter; S1-S***3***: secondary efficacy parameters. Endpoint ***5*** – ***12***: additional efficacy parameters

5.1.1.3.2 Pharmacokinetic Analyses

Pharmacokinetic analyses will be described in a separate SAP.

5.1.1.3.3 Multiple Comparisons Procedure for Primary and Secondary Endpoints

The primary and secondary efficacy endpoints are identified ***as follows:***

- ***Primary (P1): Change from baseline in mean monthly MPM headache days across the 12-week treatment period***
- ***1st Secondary (S1): Change from baseline in mean monthly headache days across the 12-week treatment period***
- ***2nd Secondary (S2): Proportion of patients with at least a 50% reduction in mean monthly MPM headache days across the 12-week treatment period***

- ***3rd Secondary (S3): Change from baseline in mean monthly acute medication use days across the 12-week treatment period***

The overall familywise error rate (FWER) will be controlled at $\alpha = 0.05$ for each set of primary and secondary endpoint comparisons between each dose level of atogepant vs placebo. Specifically, the overall type I error rate for multiple comparisons across atogepant doses and the primary and secondary efficacy endpoints will be controlled at the 0.05 level using a graphical approach by Bretz et al (2011). The overall graphic approach procedure is defined in the ***Table 5–15*** and ***Figure 5-1***. ***In the graph, each of the nodes is corresponding to one null hypothesis, for example, 60BID/P1 represents the null hypothesis that there is no statistically significant difference comparing 60 mg BID versus placebo on the primary endpoint. The number inside each node is the proportion of overall alpha initially allocated to that hypothesis. The number on the edge between two nodes represents the proportion of local alpha propagated from one hypothesis to the other given the former null hypothesis is rejected.***

It is of Sponsor's interest to develop a QD regimen for registration unless the BID regimen provides meaningful additional benefit. Therefore, this study is designed to identify the dose regimen of QD or BID for the future development along with using its results for registration. To accomplish that objective, the weighting strategy is designed to allocate initial alpha equally to the QD and BID dose regimen. Within QD or BID dose regimen, atogepant doses will be tested in a hierarchical order from high to low dose. Specifically, for QD regimen, 50% of overall alpha (i.e. 0.025) is allocated to 60QD/P1. If 60QD/P1 is statistically significant, 3/5 of the local alpha (i.e. 0.015) will be propagated to test the lower dose on primary endpoint (30QD/P1); and the other 2/5 of the local alpha (i.e. 0.01) will be passed to the same dose comparison for the secondary endpoint (60QD/S1). The proportion of weights are chosen to first ensure sufficient power for the lower dose comparison on primary hypothesis and then reserve the rest of the alpha for the corresponding secondary endpoints so that their data can be used as part of the registration along with primary data. Then if 30QD/P1 is significant, 1/3 of the local alpha (i.e. 0.005) will be propagated to test 10QD/P1; and the other 2/3 of the local alpha (i.e. 0.01) will be passed to 30QD/S1. Similar weighting strategy applies to the BID regimen (60 mg BID and 30 mg BID).

Following statistical significance of primary endpoint for 60 mg QD and 30 mg QD, if 60QD/S1, 30QD/S1, 10QD/P1, or 10QD/S1 is significant, 100% of the local alpha will then be passed sequentially for the remaining secondary endpoints. Finally, if 60 mg QD or 30 mg QD can be shown significant across primary and all secondary endpoints, the associated alpha will be recycled to the primary hypothesis comparing the next lower dose. Similar alpha propagation applies to the secondary endpoints of BID regimen (60 mg BID and 30 mg BID). By this weighting strategy, secondary endpoints would be tested at the same alpha level of 0.01

for all 5 atogepant doses after the corresponding primary hypothesis is rejected (without considering alpha recycling). Under this strategy, no secondary hypothesis can be rejected until a primary hypothesis of the corresponding dose comparison is rejected. The primary endpoint will serve as the gatekeeper for the secondary endpoints. Weighted Bonferroni tests will be used for testing the hypotheses in the graph.

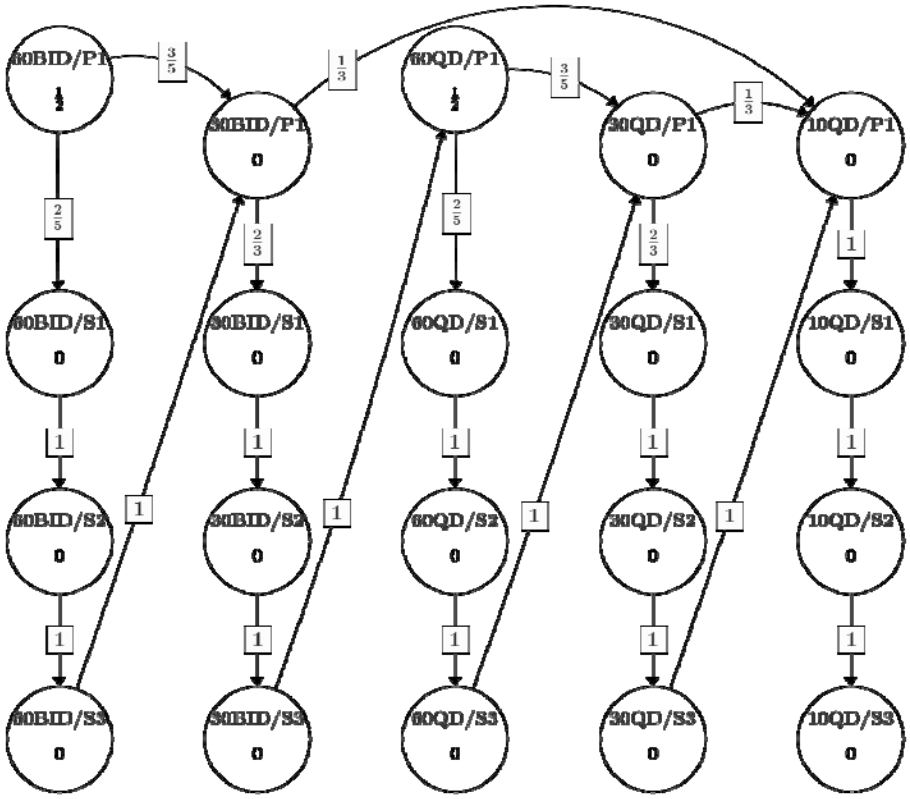
In addition, 10 mg QD dose comparison is tested with control of type I error. In case the other four higher doses are all rejected, 10QD/P1 will be tested at alpha level of 0.01. A lower expected alpha level is allocated to the 10QD/P1 is because this dose is included in the study as a potentially sub-optimal dose.

Table 5–15 Multiple Comparisons Procedure Definitions

Nodes	Alternate Hypothesis	Weight	*Initial* Local Significance Level
60mgBID P1	***60 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly MPM headache days across the 12-week treatment period (P1)***	***1/2***	***α*(1/2) = α/2***
30mgBID P1	***30 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly MPM headache days across the 12-week treatment period (P1)***	***0***	***α*0 = 0***
60mgQD P1	***60 mg QD atogepant is significantly different from placebo in change from baseline in mean monthly MPM headache days across the 12-week treatment period (P1)***	***1/2***	***α*(1/2) = α/2***
30mgQD P1	30 mg QD atogepant is significantly different from placebo in change from baseline in ***mean monthly*** MPM headache days ***across the 12-week treatment period*** (P1)	***0***	***α*0 = 0***
10mgQD P1	10 mg QD atogepant is significantly different from placebo in change from baseline in ***mean monthly*** MPM headache days ***across the 12-week treatment period*** (P1)	0	α*0 = 0
60mgBID S1	***60 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)***	***0***	***α*0 = 0***
30mgBID S1	***30 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)***	***0***	***α*0 = 0***
60mgQD S1	***60 mg QD atogepant is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period (S1)***	***0***	***α*0 = 0***
30mgQD S1	30 mg QD atogepant is significantly different from placebo in change from baseline in ***mean monthly*** headache days ***across the 12-week treatment period*** (S1)	0	α*0 = 0
10mgQD S1	10 mg QD atogepant is significantly different from placebo in change from baseline in ***mean monthly*** headache days ***across the 12-week treatment period*** (S1)	0	α*0 = 0
60mgBID S2	***60 mg BID atogepant is significantly different from placebo in proportion of patients with at least a 50% reduction in mean monthly MPM headache days across the 12-week treatment period***	***0***	***α*0 = 0***

Nodes	Alternate Hypothesis	Weight	*Initial* Local Significance Level
30mgBID S2	***30 mg BID atogepant is significantly different from placebo in proportion of patients with at least a 50% reduction in mean monthly MPM headache days across the 12-week treatment period***	***0***	***α*0 = 0***
60mgQD S2	***60 mg QD atogepant is significantly different from placebo in proportion of patients with at least a 50% reduction in mean monthly MPM headache days across the 12-week treatment period***	***0***	***α*0 = 0***
30mgQD S2	30 mg QD atogepant is significantly different from placebo in change from baseline in proportion of patients with at least a 50% reduction in ***mean monthly*** MPM headache days ***across the 12-week treatment period***	0	α*0 = 0
10mgQD S2	10 mg QD atogepant is significantly different from placebo in proportion of patients with at least a 50% reduction in ***mean monthly*** MPM headache days ***across the 12-week treatment period***	0	α*0 = 0
60mgBID S3	***60 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period***	***0***	***α*0 = 0***
30mgBID S3	***30 mg BID atogepant is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period***	***0***	***α*0 = 0***
60mgQD S3	***60 mg QD atogepant is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period***	***0***	***α*0 = 0***
30mgQD S3	30 mg QD atogepant is significantly different from placebo in change from baseline in ***mean monthly acute medication use days across the 12-week treatment period***	0	α*0 = 0
10mgQD S3	10 mg QD atogepant is significantly different from placebo in change from baseline in ***mean monthly acute medication use days across the 12-week treatment period***	0	α*0 = 0

Figure 5-1 Multiple Comparisons Procedure



5.1.1.4 Safety Analyses

Safety analyses will be based on the Safety Population.

Baseline assessments for applicable safety endpoints defined as follows:

Table 5–16 Safety Endpoint Baseline Definitions

Parameter	Description	Timing
• Clinical laboratory evaluations • Vital signs • Electrocardiograms (ECGs)	eCRF- or (standardized) vendor-provided assessments	Latest non-missing assessment before the first dose of study medication

5.1.1.4.1 Study Treatment Exposure and Compliance

Study treatment exposure and compliance will be summarized by treatment group for the Safety Population as follows:

Table 5–17 Study Treatment Summaries

Parameter	Description	Timing	Methodology

Parameter	Description	Timing	Methodology
Study treatment exposure (days)[1]	Treatment end date - treatment start date + 1	Treatment Period	Continuous descriptives
Participant-years of study treatment exposure (years)	Sum over participants of study treatment exposure	Treatment Period	—
Categorical study treatment exposure	• 1 day • 2-7 days • 8-14 days • 15-21 days • 22-28 days • 29-35 days • 36-42 days • 43-49 days • 50-56 days • 57-63 days • 64-70 days • 71-77 days • 78-84 days • > 84 days	Treatment Period	Categorical descriptives
Study treatment compliance (%)[2]	Summary by visit interval and overall $100 \times \frac{\text{Number of treatment units actually taken}}{\text{Number of treatment units expected to be taken}}$	Day 1 – Week 2, Week 2 – Week 4, Week 4 – Week 6, Week 6 – Week 8, Week 8 – Week 12, Overall during Treatment Period	Continuous descriptives
Categorical study treatment compliance (%)	Summary by the following compliance categories: • < 80% • 80% - 120% • > 120%	Day 1 – Week 2, Week 2 – Week 4, Week 4 – Week 6, Week 6 – Week 8, Week 8 – Week 12, Overall during Treatment Period	Categorical descriptives

[1] Treatment dosing data will be listed.
[2] Treatment duration and compliance will be listed.

5.1.1.4.2 Adverse Events

The following adverse event (AE) terms are defined:

Table 5–18 AE Terms

Term	Description
Treatment-emergent	An event that initially occurs or increases in severity on or after the treatment start date, where: • Treatment start date ≤ event start date ≤ (treatment end date + 30 or Visit 8, whichever comes later)
On-therapy	An event where: • Treatment start date ≤ event start date ≤ (treatment end date + 30 or Visit 8, whichever comes later)
Newly emergent	An event that initially occurs or increases in severity on or after the start date of safety follow-up period, where

Term	Description
	• Start date of the safety follow-up period ≤ event start date ≤ (treatment end date + 30 or Visit 8, whichever comes later)

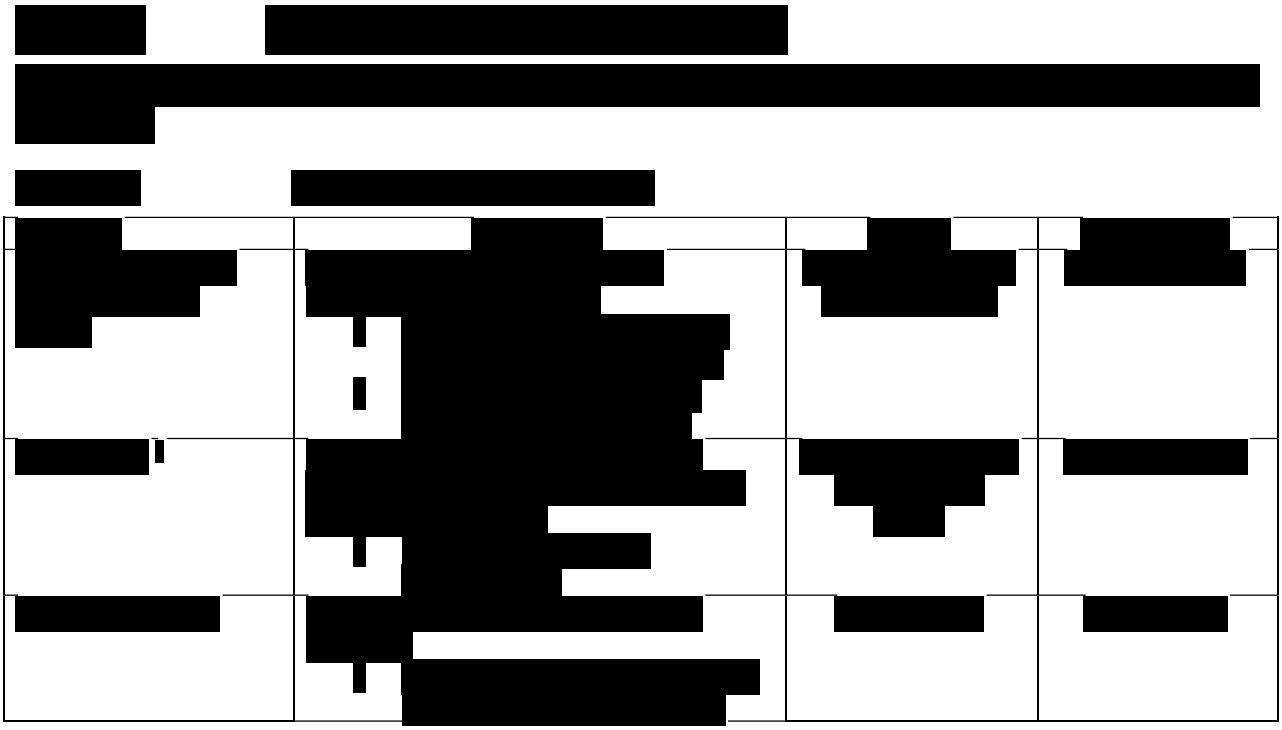
AEs, encompassing abnormalities and surgeries reported as occurring after the Screening Visit, will be coded using MedDRA version 19.0 or newer. Unique participants reporting AEs in the following AE categories will be summarized by treatment group for the Safety Population as follows:

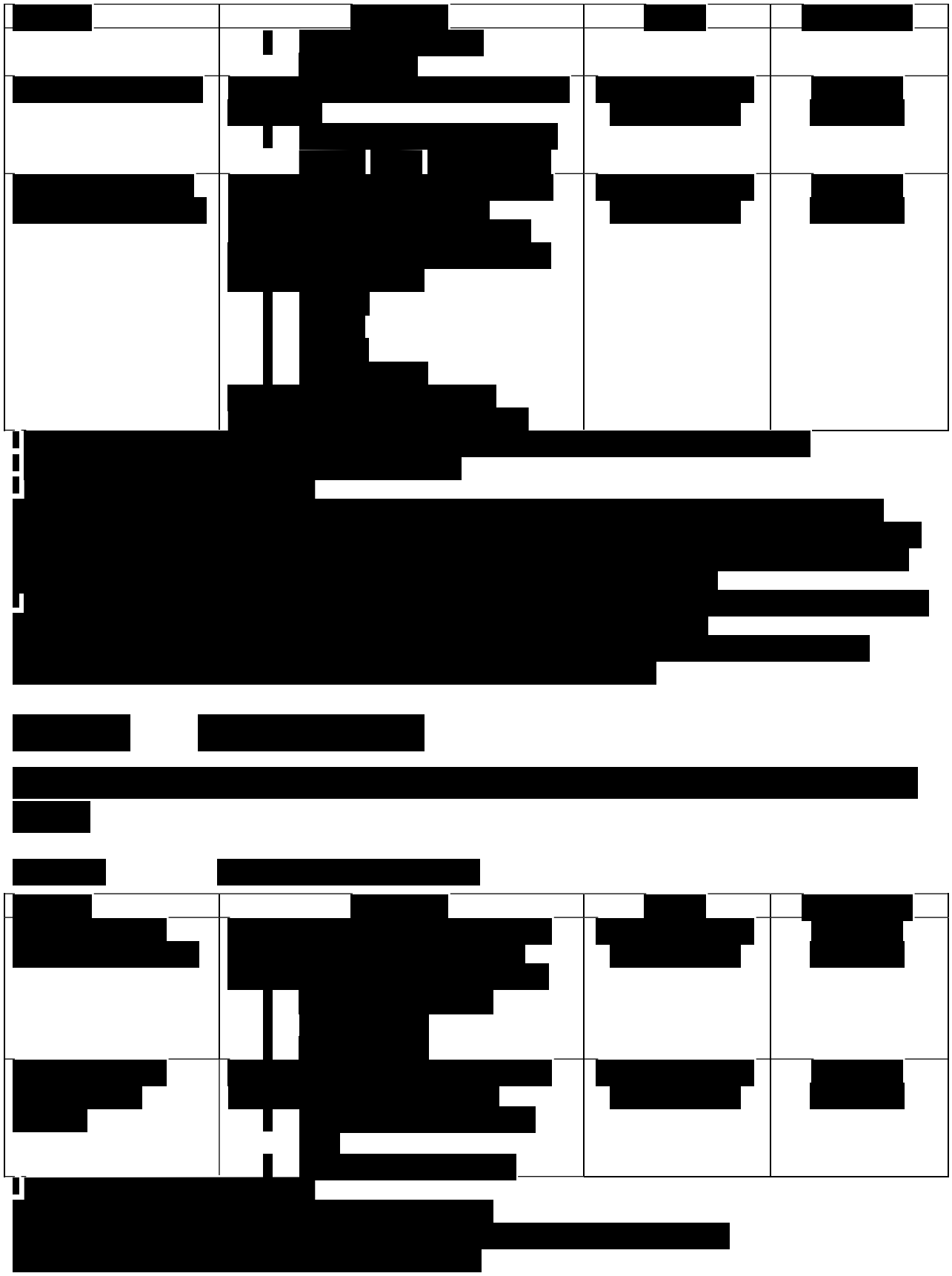
Table 5–19 AE Summaries

Parameter	Description	Timing	Methodology
Overall summary	Overall summary only for the following categories: • Treatment-emergent AEs (TEAEs) • Treatment-related TEAEs • On-therapy serious adverse events (SAEs) • On-therapy fatal SAEs • AEs leading to discontinuation	From treatment start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives
TEAEs	Overall summary and by SOC and PT	From treatment start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives
Common TEAEs	Summary by PT • Includes TEAEs occurring in ≥ 2% of participants in any treatment group	From treatment start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives
TEAEs by severity	Overall summary and by SOC, PT, and severity • Participants categorized overall and within each SOC and PT for the most severe occurrence	From treatment start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives
TEAE by relationship	Overall summary and by SOC, PT, and relationship • Participants categorized overall and within each SOC and PT for the most related occurrence	From treatment start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives
Newly emergent AE	Overall summary and by SOC and PT	From safety follow-up start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives
On-therapy SAE[1]	Overall summary and by PT	From treatment start date until 30 days	Categorical descriptives

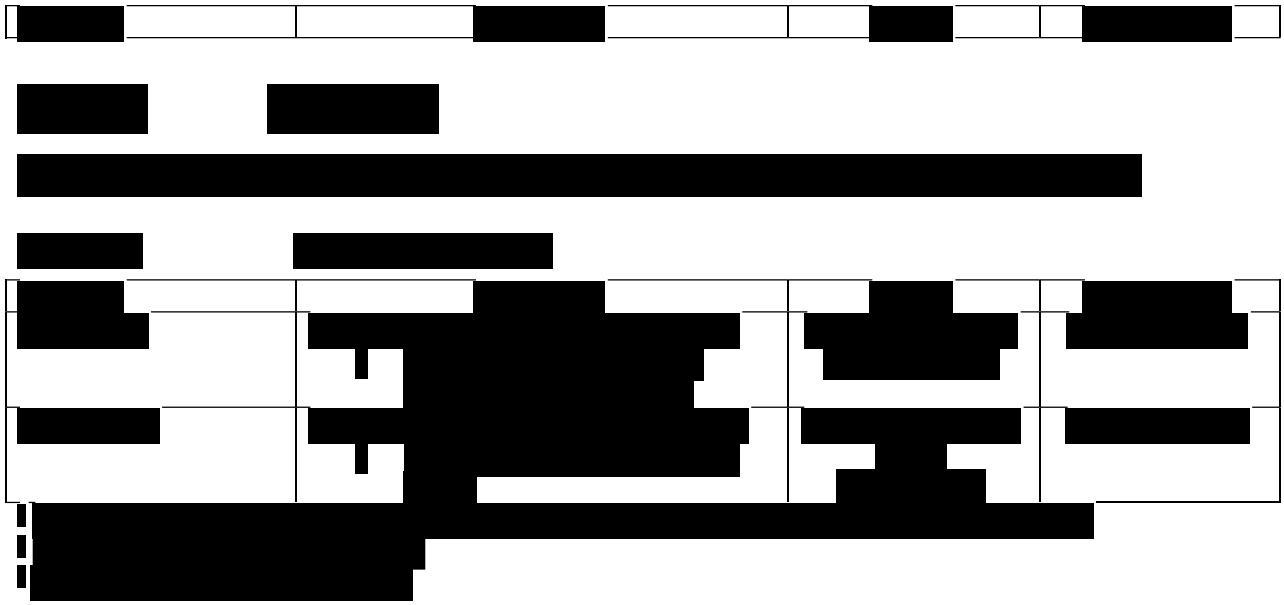
Parameter	Description	Timing	Methodology
		after treatment end date or Visit 8, whichever comes later	
Newly emergent SAE	Overall summary and by PT	From safety follow-up start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives
On-therapy fatal SAE[1]	Overall summary and by PT	From treatment start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives
Newly emergent fatal SAE	Overall summary and by PT	From safety follow-up start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives
AEs leading to discontinuation[1]	Overall summary and by PT	From treatment start date until 30 days after treatment end date or Visit 8, whichever comes later	Categorical descriptives

[1] Participants who report ≥ 1 AE in the AE category and all AEs for those participants will be listed.
SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.

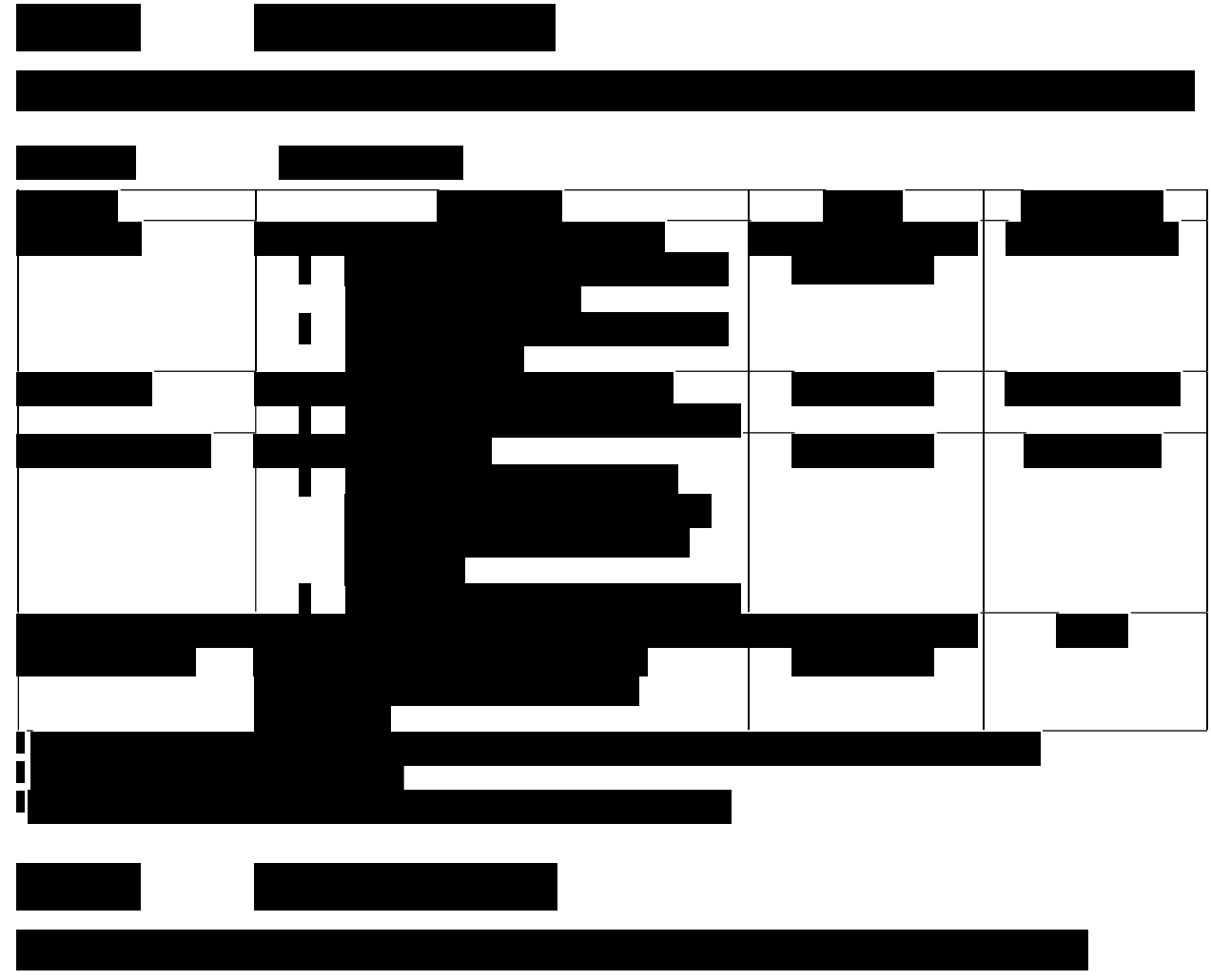




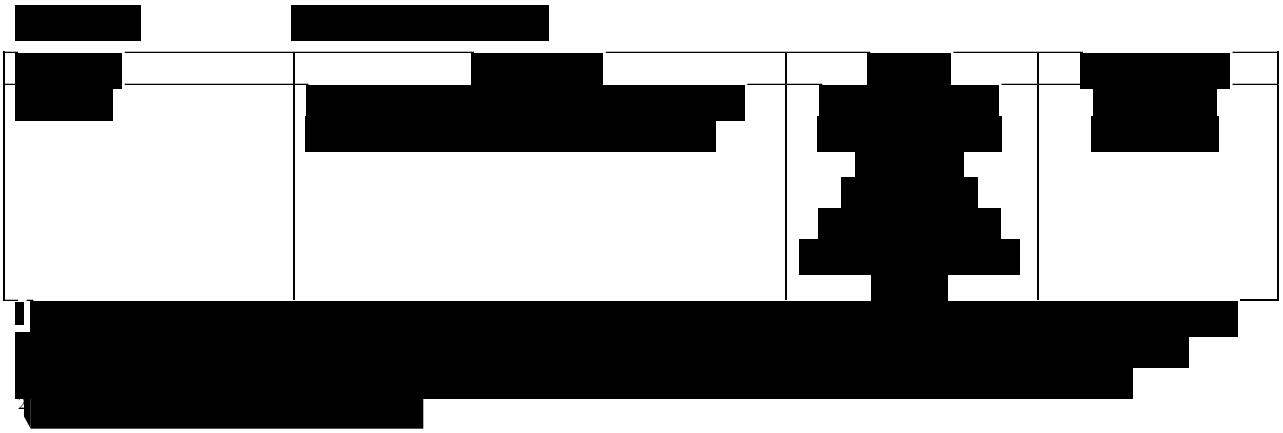
[redacted]



[redacted]



[redacted]



5.1.1.5 Subgroup Analyses

Not applicable.

5.1.1.6 Interim Analyses

Not applicable.

5.1.2 Determination of Sample Size

With this multiplicity strategy as described in Section 5.1.1.3.3, the assumptions and corresponding power assessments for the primary efficacy endpoint are shown in Table 5–25***. The treatment differences are assumed based on results from other episodic migraine prevention studies. The placebo-adjusted reduction in monthly migraine days observed from other episodic migraine prevention studies ranged from 1.1 to 2 days [topiramate (Silberstein 2004 and Brandes 2004), telcagepant (Ho 2014), and CGRP monoclonal antibodies Ph2 studies (Dodick 2014; Dodick 2014; Sun 2016), and their Ph3 studies results reported from American Headache Society & American Academy of Neuroscience 2017]. Power is calculated via 10,000 simulations based on multiplicity adjustment as described in Figure 5-1 for the 5 doses and primary and secondary endpoints.***

Table 5–25 Assumed Effect Size and Estimated Power for Primary Efficacy Endpoint

	60 mg BID (n=90)	*30 mg BID (n=90)*	*60 mg QD (n=180)*	*30 mg QD (n=180)*	*10 mg QD (n=90)*
Assumed Treatment difference vs. placebo (placebo n = 180)	***-1.6***	***-1.5***	***-1.5***	***-1.4***	***-1.2***
Effect size (Common SD[1] = 3.0)	***0.53***	***0.5***	***0.5***	***0.47***	***0.4***
Power	***97.0%***	***91.4%***	***99.3%***	***98.1%***	***80.3%***

[1] ***Common standard deviation is estimated based on blinded interim data assessments.***

QD = once daily; BID = twice daily; SD = standard deviation.

5.2 Changes in the Conduct of the Study or Planned Analyses

5.2.1 Changes in the Conduct of the Study

Not applicable.

5.2.2 Changes to Analyses Prior to Database Lock

Not applicable.

6. Data Handling and Analysis Conventions

6.1 Study Treatment Conventions

6.1.1 Analysis Days

Treatment day is defined as follows:

Table 6–1 Analysis Day Definitions

Term	Description

Treatment Day	Relative to treatment start date
	If analysis date ≥ treatment start date:
	• Day = analysis date – treatment start date + 1
	  o Day 1 = treatment start date
	If analysis date < treatment start date:
	• Day = analysis date – treatment start date
	  o Day -1 = day before treatment start date
	  o There is no Day 0

6.1.2 Missing/Incomplete Treatment End Date

If the investigator is unable to provide the treatment end date, treatment end date will be imputed to the last available dosing record date.

6.2 Analysis Visit Windows

6.2.1 Efficacy

The analysis visit windows for efficacy endpoints based on daily eDiary data are defined as follows:

Table 6–2 Efficacy Analysis Visit Definitions for eDiary Data

Analysis Phase	Analysis Visit (Derived)	eDiary Window
Pretreatment	Baseline	The first 28 days from screening visit
Treatment	Weeks 1 – 4	Treatment Day [1, 28]
	Weeks 5 – 8	Treatment Day [29, 56]
	Weeks 9 – 12	Treatment Day [57, 84]

6.2.2 Safety

The analysis visit windows for safety endpoints are defined as follows:

Table 6–3 Safety Analysis Visit Definitions

Analysis Phase	Analysis Visit (Derived)	Scheduled Study Visit (eCRF)	Window
Pretreatment	Baseline	Visit 2 (Randomization)	Treatment Day ≤ 1
Treatment	Week 2	Visit 3	Treatment Day [2, 20]
	Week 4	Visit 4	Treatment Day [21,34]
	Week 6	Visit 5	Treatment Day [35, 48]
	Week 8	Visit 6	Treatment Day [49, 69]
	Week 12	Visit 7/ET	Treatment Day [70, the last double-blind visit]
	End of treatment		Last available assessment during double blind treatment period
	Week 16 (Safety follow-up)	Visit 8	Treatment Day [the last double-blind visit +1, the last study visit]
	End of study		Last available assessment after treatment start date, i.e. occurs at final visit (expected Day 112) or ET

Safety follow-up visit will be presented in analysis tables for clinical laboratory values and vital signs.
End of Treatment is defined as the last available assessment during double-blind treatment period, i.e. on or before the treatment end date. End of Treatment results will be presented in analysis tables for clinical laboratory values and vital signs.
End of Study is defined as the last available assessment during the study, including double-blind and safety follow-up period. End of Study results will be presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs.
ET = early termination.

The following general conventions for repeated or unscheduled assessments will apply unless otherwise specified:

- The latest non-missing assessment within any analysis window will be flagged as the analysis value for any summaries by analysis visit
- All postbaseline assessments will be considered for PCS categorization
- All assessments will be included in respective listings

6.3 Missing/Incomplete Date Conventions

Dates may be imputed with year, month, and day values under certain scenarios:

Table 6–4 Imputation Scenarios

	Complete			
Scenario	Year	Month	Day	Imputable
1	Yes	Yes	Yes	Complete
2	Yes	Yes	—	Yes
3	Yes	—	Yes	No[1]
4	Yes	—	—	Yes
5	—	Yes	Yes	No[1]

Scenario	Complete			Imputable
	Year	Month	Day	
6	—	Yes	—	No[1]
7	—	—	Yes	No[1]
8	—	—	—	Yes

[1] Not allowed per database design.

Dates will be imputed initially toward a specified target date for imputable scenarios 2, 4, and 8, and adjusted against the latest reasonable dates. The initial imputed date is determined by the following algorithm:

Table 6–5 Initial Imputed Date Algorithm

Available Year (YYYY)	Available Month (MM)			
	Missing	< Target Month	= Target Month	> Target Month
Missing	Target Date	—		
< Target Year	YYYY-12-31	YYYY-MM-LD		
= Target Year	Target Date	YYYY-MM-LD	Target Date	YYYY-MM-01
> Target Year	YYYY-01-01	YYYY-MM-01		

YYYY = available start date year; MM = available start date month; LD = last day of the month.

6.3.1 Missing/Incomplete AE Start Date

AE start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date
- Complete end date

6.3.2 Missing/Incomplete Medication Start Date

Medication start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date – 1
- Complete end date

6.3.3 Missing/Incomplete AE/Medication End Date

AE and medication end dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment end date + 30
- Death date

6.4 Efficacy Endpoint Conventions

6.4.1 Derivation of Efficacy Endpoints Based on eDiary Data

For analysis purposes, four weeks (28 days) will be considered as one month. On a daily basis during the 4-week baseline period and throughout the double-blind treatment period, participants are to record eDiary information on the duration of headache, headache specific characteristics

and symptoms, the pain severity, and use of any acute headache pain medication. Daily headache diary data consists of data from "today's dairy" completed on that day and "yesterday's diary" completed on the following day. Participants are to report headache data in "today's diary" in the evening 19:00 to 23:59 and to complete "yesterday's diary" on the following day to add the remaining headache data of previous evening until midnight. In case participants miss "today's diary", they are able to report the whole-day headache data in "yesterday's diary" on the following day. In case participants miss "yesterday's diary", headache data from "today's diary" alone will be used as daily headache diary data. If both "today's diary" and "yesterday's dairy" are missing on one day, the daily headache diary data will be treated as missing.

Daily headache diary data will be merged from "today's diary" and "yesterday's diary" as following and will be used to derive MPM headache day and headache day.

- Daily headache total duration: summation of headache durations from "today's diary" and "yesterday's diary"
- Daily headache pain severity: the worst pain severity from "today's diary" and "yesterday's diary"
- Daily headache characteristics and symptoms: present if present in one of "today's diary" and "yesterday's diary"
- Daily acute headache medication usage: combination of acute headache medications usage from "today's diary" and "yesterday's diary"

For analysis purpose endpoint, the number of headache days during the first 28 days of the baseline phase, starting with the day of the screening visit, will serve as the "baseline", and change from baseline will be calculated for consecutive 28-day periods beginning with Day 1 (ie, Weeks 1-4, 5-8 and 9-12, corresponding to Days 1-28, 29-56 and 57-84). In order to be randomized, a participant should be in the baseline phase for at least 28 days and must report diary data for at least 20 days during the 28-day baseline period.

The 4-week ***(monthly)*** MPM headache days is defined as the total number of reported MPM headache days in the diary divided by the total number of days with diary records during each 4-week period and multiplied by 28. A minimum of 12 days' diary data during each ***postbaseline*** 4-week treatment period is required in order for the MPM headache migraine days to be evaluable for that particular period. If a subject does not have at least 12 days of diary data for any 4-week treatment period, the MPM headache days for that particular period will be considered as missing. MPM headache days will be derived for each participant at baseline and for each ***postbaseline*** 4-week treatment period (Weeks 1-4, 5-8, 9-12). The same method to derive MPM headache days will be used to derive headache days***, acute medication use days, and triptan use days***.

If a subject reports 'Yes' to the intake of allowed medication(s) to treat an acute migraine but does not list any of them in the diary, then the acute medication use days will not be counted in this situation.

6.4.2 Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in mean monthly MPM headache days across the 12-week treatment period. The endpoint will be analyzed using MMRM. The response variable is the change from baseline to each postbaseline month in monthly MPM headache days. The model will include baseline monthly MPM headache days as a covariate, treatment group and visit (month) as fixed factors, and treatment group-by-visit and baseline-by-visit as interaction terms. The analysis will be performed based on evaluable postbaseline data using only the observed cases without imputation of missing values.

Restricted maximum likelihood method will be used. The within-patient correlation will be modeled using the unstructured covariance matrix. If the model does not converge, then the compound symmetry covariance structure will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Contrasts will be constructed to obtain the average treatment effects across the 12-week treatment period to compare each atogepant treatment group versus the placebo group. Each treatment effect and treatment comparisons will be estimated by the LS Means and their differences in LS Means, along with their SE and 95% confidence intervals, and the p-value corresponding to the between-treatment group difference.

6.4.3 Sensitivity Analysis

6.4.3.1 Pattern-Mixture Model

The sensitivity analysis will use a pattern-mixture model (PMM) approach based on the ***reference-based*** copy reference method (Carpenter et al, 2013) for missing value imputation. ***This approach considers a missing-not-at-random (MNAR) mechanism for missing data and is to assess the impact of potential deviation of MAR assumption in the primary analysis.***

Note that the missingness is assumed monotonic. Any intermediate missing values, if any, will be imputed at first. If the intermediate missing value exists at the first postbaseline month, it is imputed using the average of baseline and next available postbaseline values; otherwise, intermediate missing values are imputed using last observation carried forward (LOCF) approach.

The details of missing data imputation using the copy reference method are as follows:

1. ***The reference-based approach uses the placebo group as the reference. The missing values in the reference group are imputed using the observed data in that group under the missing-at-random assumption. The missing pattern is defined by the participant's last visit with a non-missing value. The mean vector and the covariance matrix of the multivariate normal distribution are estimated for reference group.***
2. ***For atogepant treatment groups, missing values are imputed based on the distribution estimated from the reference group (from Step 1).***
3. ***The MI (Step 1 and 2) will be performed 20 times and result in 20 imputed datasets. Each of the 20 imputed datasets will be analyzed using ANCOVA model. For a given imputed dataset, the average change from baseline in monthly MPM headache days is calculated across the 3 post-baseline months and is used as the response variable in the model. The model includes treatment group as a fixed factor and baseline monthly MPM headache days as a covariate. The LS mean difference and corresponding SE is estimated from the model comparing each atogepant treatment group with the placebo group.***
4. ***The ANCOVA analysis results from 20 completed datasets are combined for overall estimation and inference using Rubin's rule (1987) to produce a pooled estimate of LS mean difference, its SE, and corresponding p-value for the test of null hypothesis of no treatment effect.***

6.4.3.2 Robust Regression

The sensitivity analysis uses MI in conjunction with robust regression to assess the robustness of the primary MMRM analysis to the possible violation of normality assumption. This method has been described and referred as ADAP [R] in Mehrotra et al. 2012. The details of method are as follows.

The normality test is performed on the residuals which are generated by the same MMRM as used for the primary efficacy analysis. The residuals are scaled by the inverse Cholesky root of its estimated variance-covariance matrix. The Kolmogorov-Smirnov (K-S) test for normality is applied to the de-correlated and scaled residuals and normality test is rejected if p-value from the K-S test is less than 0.01.

If the normality test is rejected, sensitivity analysis below will be performed:

1. ***Create complete datasets using MI based on the Markov chain Monte Carlo (MCMC) approach. Imputed data will consist of 20 complete datasets.***
2. ***Each of the 20 complete datasets will be analyzed using robust regression (M-estimation) to protect against either observed outliers in the original incomplete dataset, or imputed outliers in the completed datasets. For a given complete dataset, the average change from baseline in monthly MPM headache days is calculated across the 3 post-baseline months and is used as the response variable in the robust regression model. The model includes treatment group as a fixed factor and baseline monthly MPM headache days as a covariate. The mean difference and corresponding SE is estimated from the model comparing each atogepant treatment group with the placebo group.***
3. ***The robust analysis results from 20 completed datasets are combined for overall estimation and inference using Rubin's rule (1987) to produce a pooled estimate of treatment difference, its SE, and corresponding p-value for the test of null hypothesis of no treatment effect.***

6.5 Safety Endpoint Conventions

6.5.1 Adverse Events

6.5.1.1 Missing Intensity or Relationship

If the investigator is unable to provide the actual values, the following imputations will be applied:

Table 6–6 Missing AE Intensity and Relationship Imputation Algorithms

Missing Value	Imputation	Timing
Intensity	Mild	Screening Period
	Severe	Treatment Period
Relationship	—	Screening Period
	Related	Treatment Period

6.5.2 Clinical Laboratory Assessments

6.5.2.1 Potentially Clinically Significant Criteria

Laboratory assessments values meeting any of the following PCS low or PCS high criteria will be categorized as PCS:

Table 6–7 Clinical Laboratory PCS Criteria

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	**PCS High**
Chemistry	Albumin	g/L	< 0.8 × LLN	> 1.2 × ULN
	Alanine aminotransferase	U/L	—	≥ 3.0 × ULN
	Alkaline phosphatase	U/L	—	≥ 3.0 × ULN
	Aspartate aminotransferase	U/L	—	≥ 3.0 × ULN
	Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Bilirubin, total	µmol/L	—	≥ 1.5 × ULN
	Blood urea nitrogen	mmol/L	—	> 1.5 × ULN
	Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Cholesterol, total	mmol/L	—	> 1.6 × ULN
	Creatinine	µmol/L	—	> 1.5 × ULN
	Creatine kinase	U/L	—	> 2.0 × ULN
	Estimated glomerular filtration rate	mL/min/1.73m^2	< 0.8 × LLN	—
	Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 2.0 × ULN
	Lactate dehydrogenase (LDH)	U/L	—	> 3.0 × ULN
	Phosphorus	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
	Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Triglycerides	mmol/L	—	> 2.0 × ULN
	Uric acid	µmol/L	—	> 1.2 × ULN
Hematology	Basophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Eosinophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
	Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
	Lymphocytes, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Monocytes, absolute cell count	10^9/L	< 0.5 × LLN	> 2.0 × ULN
	Neutrophils, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
	Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
	White blood cell count	10^9/L	< 0.9 × LLN	> 1.5 × ULN
Urinalysis	pH	pH	< 0.9 × LLN	> 1.1 × ULN
	Glucose	mmol/L	—	Positive [1]
	Protein	g/L	—	Positive [2]
	Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value; ULN = upper limit of normal value; normal value provided by laboratory.
SI = Le Système International d'Unités (International System of Units).
[1] Any results other than negative will be considered as positive.
[2] Any results other than trace or negative will be considered as positive.

6.5.2.2 Hepatic Laboratory Abnormalities

The following laboratory parameters will be summarized:

Table 6–8 Criteria for Hepatic Laboratory Abnormalities

Laboratory Parameter	Categories
ALT	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
ALT or AST	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Bilirubin Total	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN

Laboratory Parameter	Categories
Alkaline Phosphatase	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Concurrent Elevations[1]	ALT or AST >= 3 × ULN **AND** Bilirubin Total ≥ 1.5 × ULN
	ALT or AST >= 3 × ULN **AND** Bilirubin Total ≥ 2 × ULN
Potential Hy's Law[1]	ALT or AST ≥ 3 × ULN **AND** Bilirubin Total ≥ 2 × ULN AND ALP < 2 × ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ALP = alkaline phosphatase; ULN = upper limit of normal (value provided by the laboratory).
[1] Elevations are from the same day

6.5.2.3 Continuous Descriptives and Shift Table Parameters

The following laboratory parameters will be summarized:

Table 6–9 Clinical Descriptive and Shift Table Parameters

Category	Parameters
Hematology	Hemoglobin; hematocrit; red blood cell count; red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration); white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils); platelet count
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol. The estimated glomerular filtration rate will be calculated by the central laboratory.
Urinalysis	Urine dipstick for specific gravity, pH

6.5.2.4 Character Values

Character values (eg, < 5, negative) will be reviewed prior to database lock and converted to numeric for analysis as appropriate. These conversions will be documented in the ADaM specifications.

6.5.3 Vital Signs

6.5.3.1 Potentially Clinically Significant Criteria

Vital sign values meeting both the actual value and change from baseline PCS criteria will be categorized as PCS:

Table 6–10 Vital Sign PCS Criteria

Parameter	Unit	PCS Category	PCS Criteria	
			Actual Value	Change from Baseline
Systolic BP	mmHg	High	≥ 180	Increase ≥ 20
		Low	≤ 90	Decrease ≥ 20
Diastolic BP	mmHg	High	≥ 105	Increase ≥ 15
		Low	≤ 50	Decrease ≥ 15
Pulse rate	bpm	High	≥ 120	Increase ≥ 15
		Low	≤ 50	Decrease ≥ 15
Weight	kg	High	—	Increase ≥ 7%
		Low	—	Decrease ≥ 7%
Orthostatic SBP change	***mm Hg***	***Low***	***≤ -20***	
Orthostatic DBP change	***mm Hg***	***Low***	***≤ -15***	
Orthostatic Pulse rate change	***bpm***	***High***	***≥ 25***	

BP = blood pressure; bpm = beats per minute.

Orthostatic pulse rate change equals standing pulse rate minus sitting pulse rate; orthostatic systolic blood pressure change equals standing systolic blood pressure minus sitting systolic blood pressure; and orthostatic diastolic blood pressure change equals standing diastolic blood pressure minus sitting diastolic blood pressure.

6.5.3.2 Continuous Descriptives and Shift Table Parameters

The following vital sign parameters will be summarized:

Table 6–11 Vital Sign Descriptive and Shift Table Parameters

Parameters			
Systolic BP	Respiratory rate	Weight	
Diastolic BP	Temperature	BMI	
Pulse rate	***Orthostatic SBP***	***Orthostatic DBP***	
Orthostatic Pulse rate			

BP = blood pressure.

Orthostatic pulse rate change equals standing pulse rate minus sitting pulse rate; orthostatic systolic blood pressure change equals standing systolic blood pressure minus sitting systolic blood pressure; and orthostatic diastolic blood pressure change equals standing diastolic blood pressure minus sitting diastolic blood pressure.

6.5.4 Electrocardiograms

6.5.4.1 QTc Derivation

QTc Bazett (QTcB) and QTc Fridericia (QTcF) are derived as follows:

Table 6–12 QTc Derivation

Parameter	Derivation if RR available	Derivation if RR unavailable

Parameter	Derivation if RR available	Derivation if RR unavailable
QTcB	$\frac{QT}{\text{square root of RR}}$	$\frac{QT}{\text{square root of 60/HR}}$
QTcF	$\frac{QT}{\text{cubic root of RR}}$	$\frac{QT}{\text{cubic root of 60/HR}}$

QTcB = QTc Bazett; QTcF = QTcF Fridericia.

6.5.4.2 Potentially Clinically Significant Criteria

ECG values meeting either the actual value or change from baseline PCS high criteria will be categorized as PCS:

Table 6–13 ECG PCS Criteria

Parameter	Unit	PCS High Criteria	
		Actual Value	Change from Baseline
QRS interval	msec	≥ 150	—
PR interval	msec	≥ 250	—
QTcB, QTcF	msec	> 500	Increase > 60

QTcB = QTc Bazett; QTcF = QTcF Fridericia.

6.5.4.3 Continuous Descriptives and Shift Table Parameters

The following ECG parameters will be summarized:

Table 6–14 ECG Descriptive and Shift Table Parameters

Parameters		
Heart rate	QRS interval	QT interval
	PR interval	QTcB
	RR interval	QTcF

QTcB = QTc Bazett; QTcF = QTcF Fridericia.

6.6 Imputed Value Listing Conventions

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in endpoint derivation. In instances where imputed values will be presented, imputed values will be flagged. Actual rules will be fully defined in the table, figure, and data listing specification document.

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