Statistical Analysis Plan for Study M22-056

A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study with An Active Treatment Extension to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Japanese Subjects with Episodic Migraine

Version 3.0

Date: 22 October 2024

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for Atogepant (AGN-241689) Study M22-056 A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study with An Active Treatment Extension to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Japanese Subjects with Episodic Migraine.

Study M22-056 examines the efficacy and safety of Atogepant (AGN-241689) in Japanese subjects with episodic migraine.

The analyses of pharmacokinetic and pharmacodynamic endpoints and exploratory biomarker endpoints will not be covered in this SAP.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later.

2.0 Study Objectives and Design

2.1 Study Objectives

The primary objective of the trial is to evaluate the safety, efficacy and tolerability of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg once daily for the prevention of migraine in Japanese subjects with episodic migraine, and to prospectively test for superiority of atogepant 10 mg, atogepant 30 mg, or atogepant 60 mg QD versus placebo for the prevention of migraine in Japanese subjects with episodic migraine.

The estimand corresponding to the primary efficacy objective is defined as follows:

- The difference in the mean change from baseline in mean monthly migraine days across the 12-week double-blind treatment period between each atogepant group and placebo in adult patients with episodic migraine who require

preventive treatment of migraine. Data collected during the double-blind treatment period are included in the analyses. Missing data for subjects who discontinued the study treatment due to any reason are assumed MAR, i.e., subjects with treatment discontinuation behave like other subjects who did not discontinue the study treatment. Use of acute migraine medication as rescue medications is considered in the definition of migraine/headache day (composite strategy).

The secondary objective is to demonstrate improvement in efficacy for treatment with atogepant when each of atogepant doses is compared to placebo with respect to the secondary endpoints.

The estimands corresponding to the secondary efficacy endpoints are:

- The difference in the mean change from baseline in mean monthly headache days across the 12-week treatment period between each atogepant group and placebo in adult patients with episodic migraine who require preventive treatment of migraine. Data after the discontinuation from double-blind treatment period are assumed MAR. Use of acute migraine medication as rescue medications is considered in the definition of migraine/headache day (composite strategy).
- The difference in the mean change from baseline in mean monthly acute medication use days across the 12-week treatment period between each atogepant group and placebo in adult patients with episodic migraine who require preventive treatment of migraine. Data after the discontinuation from double-blind treatment period are assumed MAR.
- The odds ratio in subjects achieving at least 50% reduction from baseline in 3-month average of monthly migraine days between each atogepant group and placebo in adult patients with episodic migraine who require preventive treatment of migraine. Use of acute migraine medication as rescue medications is considered in the definition of migraine/headache day (composite strategy).
- The difference in the mean change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12 between each atogepant group and placebo in adult patients with episodic migraine who require preventive

treatment of migraine. Data after the discontinuation from double-blind treatment period are assumed MAR.

- The difference in the mean change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period between each atogepant group and placebo in adult patients with episodic migraine who require preventive treatment of migraine. Data after the discontinuation from double-blind treatment period are assumed MAR.
- The difference in the mean change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period between each atogepant group and placebo in adult patients with episodic migraine who require preventive treatment of migraine. Data after the discontinuation from double-blind treatment period are assumed MAR.

2.2 Study Design Overview

This is a multicenter, randomized, double-blind, placebo controlled, parallel group Phase 2/3 study that evaluates the safety, efficacy, and tolerability of atogepant in Japanese subjects. The study consists of a 4-week screening and baseline period, a 12-week double-blind treatment period, a 12-week blinded active treatment extension period, and a follow-up Period 30 days after the last dose of study drug, for a total duration of approximately 32 weeks.

Subject participation will begin with a 4-week screening/baseline period. Subjects 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, and all completers move to the 12-week active treatment extension period with a subsequent follow-up Period 30 days after the last dose of study drug. For details, please see Figure 1, Study Schematic.

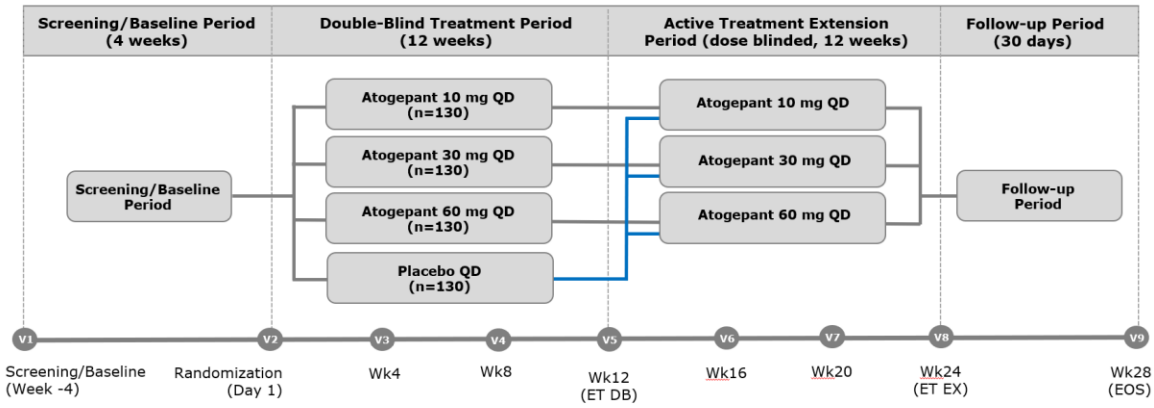
All completers of the double-blind treatment period may continue into the active treatment extension period (dose will be blinded). Subjects who are randomized to atogepant treatment groups in the double-blind treatment period will continue to be

assigned to the same dose treatment group in the active treatment extension period. Subjects in the placebo group in the double-blind treatment period will be re-randomized to either the atogepant 10 mg, atogepant 30 mg, or atogepant 60 mg treatment arm (dose blinded) in a 1:1:1 ratio in the active treatment extension period.

An eDiary will be used to record the daily total duration of headache, headache characteristics, associated symptoms, the worst pain severity, and acute medication use both in the screening/baseline period and double-blind treatment period until Visit 5.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



2.3 Treatment Assignment and Blinding

On Study Day 1 of the Double-Bline Treatment Period, approximately 520 subjects will be randomized to one of the following 4 arms in a 1:1:1:1 ratio:

- Placebo (n 130)
- Atogepant 10 mg (n 130)
- Atogepant 30 mg (n 130)
- Atogepant 60 mg (n 130)

The study will be enrolled so that approximately 70% of randomized subjects will have taken at least 1 prior migraine prevention medication with proven efficacy. Randomization will be stratified by site and by prior exposure (yes/no) to a migraine prevention medication with proven efficacy.

After finishing the double-blind treatment period, completers in the placebo arm will be re-randomized to atogepant 10 mg, atogepant 30 mg, or atogepant 60 mg arm (dose blinded) in a 1:1:1 ratio in the active treatment extension period.

2.4 Sample Size Determination

A sample size of 130 subjects per treatment group provides approximately 88%, 94% or 99% power to show statistically significant improvement between each of the three atogepant doses (10 mg, 30 mg, or 60 mg) and placebo for the primary efficacy endpoint, respectively, on the mITT analysis set. Assumptions used in the sample size calculation are based on results from the ADVANCE study in a US adult population.[1]

The assumed treatment difference between each atogepant dose versus placebo and the standard deviation for the primary endpoint are shown in Table 1. The dropout rate is assumed to be approximately 5.4% for the double-blind treatment period because the observed dropout rate was less than 5% for trials conducted in Japanese patients with EMs.[2-5] All statistical powers presented in this section were calculated adjusting for multiple comparisons using the Hochberg procedure with the family-wise Type I error rate being controlled at a 0.05 level (2-sided).

Table 1. Power and Sample Size Calculations for the Endpoint, Change from Baseline in Monthly Migraine Days Across the 12-Week Treatment Period

Randomized n/arm	Effective n/arm	Treatment Arm	Treatment Difference	Standard Deviation	Power for individual Dose	Probability (At Least one arm is significant)
130	123	60 mg	1.7	3	0.986	0.992
		30 mg	1.38	3	0.937	
		10 mg	1.21	3	0.877	

3.0 Endpoints

3.1 Primary Endpoint

The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week double-blind treatment period. Baseline is defined as the number of migraine days during the last 28 days prior to the randomization date.

3.2 Secondary Endpoints

The secondary efficacy endpoints are:

- Change from baseline in mean monthly headache days across the 12-week double-blind treatment period.
- Change from baseline in mean monthly acute medication use days across the 12-week double-blind treatment period.
- At least a 50% reduction in the 3-month average of monthly migraine days.
- Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12.
- Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM D across the 12-week double-blind treatment period.
- Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week double-blind treatment period.

3.3 Additional Efficacy Endpoints

Additional efficacy endpoints are:

- ≥ 25%, ≥ 50%, ≥ 75%, 100% improvement (decrease) in monthly migraine days at Weeks 1-4, 5-8, and 9-12.
- ≥ 25%, ≥ 75%, 100% improvement (decrease) in the 3-month average of monthly migraine days.
- Change from baseline in monthly migraine days at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly headache days at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly cumulative headache hours at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in monthly acute medication use days at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly triptan use days at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in monthly moderate/severe headache days at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in monthly severe headache days at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in weekly migraine days at Weeks 1-4.
- Having a migraine day on the day of initial dose and on each day of the 6 days post the initial dose.
- Change from baseline in monthly headache days with nausea and /or vomiting symptom across the 12-week double-blind treatment period
- Change from baseline in monthly headache days with photophobia across the 12-week double-blind treatment period
- Change from baseline in monthly headache days with phonophobia across the 12-week double-blind treatment period
- Change from baseline in the HIT-6 total score at Weeks 4, 8, and 12.
- At least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, and 12.

- Assessed by the PGIC as "much better" or "very much better" at Week 12.
- "Satisfied" or "extremely satisfied" with study medication for migraine prevention at Weeks 4, 8, and 12.
- Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Weeks 4, 8, and 12 as assessed by the WPAI:MIGRAINE.
- Change from baseline in the MIDAS total score at Week 12.
- Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Week 12.
- Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Week 12.
- Change from baseline in PGI-S score at Weeks 4, 8, and 12.
- Change from baseline in the MSQ v2.1 Role Function-Preventive domain score at Weeks 4, 8, and 12.
- Change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Weeks 4 and 8.
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, and 12.
- Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly Physical Impairment domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly AIM-D total score at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in monthly Activity Level at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in monthly Activity Limitation at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in PHQ-9 score at Week 12.
- Change from baseline in EQ-5D-5L descriptive system index score at Weeks 1 to 2, and at specified windows around Weeks 4, 8, and 12.

- Change from baseline in the EQ-5D-5L VAS score at Weeks 1 to 2, and at specified windows around Weeks 4, 8, and 12.
- Change from baseline in PROMIS-PI total score at Weeks 4, 8, and 12.

3.4 Safety Endpoints

Safety evaluations include AE monitoring, vital sign measurements, ECG variables, clinical laboratory testing (hematology, chemistry, and urinalysis), and C-SSRS as measures of safety and tolerability for the entire study duration.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The Screened Population consists of all subjects who signed informed consent.

The Intent-to-Treat (ITT) population includes all randomized subjects.

All efficacy analyses will be performed using the modified Intent-to-Treat (mITT) population, consisting of all randomized subjects who received at least 1 dose of study drug, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data. Refer to SAP Appendix B for the definition of evaluable baseline and post-baseline period. For efficacy analyses, subjects will be included in the analysis according to the treatment group to which they were randomized (as randomized).

All safety analyses will be performed using the Safety Populations: Safety population 1 and Safety population 2. Safety Population 1 consists of all subjects who received at least 1 dose of study drug during the double-blind treatment period. Safety Population 2 consists of all subjects who received at least 1 dose of study drug during the active treatment extension period. For safety data analyses, the subjects will be analyzed according to actual treatment received (rather than as randomized). A subject's actual treatment will be determined by the first dose of study treatment.

5.0 Subject Disposition

The total number of subjects who were screened, enrolled (randomized), and treated will be summarized. Reasons for exclusion, including screen failure, will be summarized.

The number of randomized subjects will also be summarized by treatment group for the following factors:

- Randomization stratification factor (prior exposure [yes/no] to a migraine prevention medication with proven efficacy from IWRS;
- Prior exposure to migraine prevention medication with proven efficacy based on prior medication collected eCRF (derived as specified in Appendix E), which will be termed as "actual strata" in the SAP.

A listing of subjects with incorrect randomization stratum will be provided.

A summary of subject accountability by investigator will be provided where the number of subjects in each of the following categories will be tabulated for each treatment group:

- Subjects randomized in the study;
- Subjects who took at least one dose of study treatment;
- Subjects who completed study treatment;
- Subjects who prematurely discontinued study treatment;
- Subjects in the mITT population;
- Subjects in the Safety Populations 1 and 2.

The summary of subject accountability by investigator also will include the number of subjects who screened and the number of subjects who screen failed.

The number and percentage of subjects in the Safety Populations who prematurely discontinued study treatment will be summarized by reason for not completing study treatment overall and by treatment group.

6.0 Study Treatment Duration and Compliance

For the Safety Populations, duration of treatment will be summarized for each treatment group. The treatment groups for active treatment extension period will also include three additional columns for the lead-in placebo re-randomized group. Duration of treatment is defined for each subject as last dose date minus first dose date + 1. Duration of treatment for a treatment period is defined for each subject as last dose date minus first dose date + 1. Duration of treatment will be summarized separately for each period (double-blind treatment period and active treatment extension period) using the number of subjects treated, mean, standard deviation, median, Q1, Q3, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration interval for double-blind treatment period and active treatment extension period (≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥ 49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days) and overall (≥ 1 day, ≥ 7 days, ≥ 14 days, ≥ 21 days, ≥ 28 days, ≥ 35 days, ≥ 42 days, ≥ 49 days, ≥ 56 days, ≥ 63 days, ≥ 70 days, ≥ 77 days, ≥ 84 days, ≥ 91 days, ≥ 98 days, ≥ 105 days, ≥ 112 days, ≥ 119 days, ≥ 126 days, ≥ 133 days, ≥ 140 days, ≥ 147 days, ≥ 154 days, ≥ 161 days, ≥ 168 days) will be summarized by treatment group.

Subject-years, defined as exposure to the study treatment in years, will be summarized by treatment group for the Safety Populations.

Treatment compliance for a specified period is defined as the total number of study medications actually taken by a subject during that period divided by the number of study medications that were expected to be taken during the same period multiplied by 100. The total number of actual capsules taken during a specific period will be calculated from the study medication record.

Descriptive statistics for study medication dosing compliance together with the compliance categories (< 80%, 80% - 120%, > 120%) will be summarized by study treatment group for each period between 2 consecutive visits, for the period from the first dose of the double-blind study interventions actually taken to the last dose of double-blind

study intervention actually taken, as well as for the period from the first dose of the active treatment extension period interventions actually taken to the last dose of the active treatment extension period intervention actually taken for the Safety Populations 1 and 2, respectively.

7.0 Subject Characteristics

Demographics, baseline characteristics, medical history, and prior and concomitant medications will be summarized descriptively by treatment group for the Safety Populations and mITT population. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, first quartile (Q1), third quartile (Q3), minimum, and maximum).

7.1 Demographics and Baseline Characteristics

Demographic parameters (age; age group [< 20, 20-29, 30-39, 40-49, 50-59, 60-69, and ≥ 70]; age group [< 40 years, ≥ 40 - < 65 years, ≥ 65 years]; sex; race; race group [Asian, all other races]; ethnicity) will be summarized descriptively by treatment group for the Safety Populations and mITT Population.

Baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/ (height [m])^2, and body mass index classification [underweight (< 18.5), normal (≥ 18.5 - < 25), overweight (≥ 25 - < 30), and obese (≥ 30)]), will be summarized descriptively by study intervention group for the Safety Populations and mITT Population.

Baseline efficacy parameters (monthly migraine days, monthly migraine days category (< 8 days and ≥ 8 days), monthly headache days, monthly acute medication use days) and baseline health outcome parameters (monthly Performance of Daily Activities domain score of the AIM-D, monthly Physical Impairment domain score of the AIM-D, and

MSQ v2.1 Role Function-Restrictive domain score) will be summarized for mITT Population.

7.2 Medical History and Prior and Concomitant Medications

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 27.0 or newer. The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment group. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

Migraine history, including diagnosis, duration of disorder, use of migraine prevention medication in the past, average number of migraine or headache days per month in the last 3 months, acute medications taken to treat migraine headaches, and advice on lifestyle alternations will be reported in total and by study intervention group for the Safety Populations, respectively.

Prior medication is defined as any medication taken before the first dose of double-blind study treatment. Concomitant medication in the double-blind treatment period is defined as any medication taken on or after the date of the first dose of the double-blind study treatment but not after the date of either the last dose of study drug in the double-blind treatment period plus 30 days (if the subject discontinued from study drug in the double-blind treatment period) or the day of the first dose of study treatment in the active treatment extension period - 1, whichever comes later. Concomitant medication in the active treatment extension treatment period is defined as any medication taken on or after the date of the first dose of the active treatment extension study treatment but not after the date of the date of the last dose of study drug plus 30 days or Visit 8 whichever comes later. Prior and concomitant medications will be summarized separately.

Prior medication use will be summarized by the number and percentage of subjects in each treatment group receiving each medication within each Anatomical Therapeutic Chemical (ATC) 4 class for the Safety Populations.

Concomitant medication use will be summarized by the number and percentage of subjects in each treatment group receiving each medication within each ATC 4 class for the double-blind period and active treatment extension period for the Safety Populations, respectively. If a subject took a specific medication multiple times or took multiple medications within a specific therapeutic class, that subject would be counted only once for the coded drug name or therapeutic class.

Any prior and concomitant medications will be included in listings. The therapeutic class and drug name will be based on the World Health Organization (WHO) Drug Dictionary. The actual version of the WHO Drug Dictionary will be noted in the statistical tables and clinical study report.

7.3 Protocol Deviations

Protocol deviations include eligibility criteria violations, receipt of wrong treatment or incorrect dose of study treatment, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. A listing of subjects with protocol deviations will be provided.

For each of the following protocol deviation categories and across all categories, the number and percentage of randomized subjects with at least one protocol deviation will be summarized overall and by treatment group:

- Subject entered into the study even though did not satisfy entry criteria;
- Subject developed withdrawal criteria during the study but was not withdrawn;
- Subject received wrong treatment or incorrect dose of study treatment;
- Subject took prohibited concomitant medication.

8.0 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The primary efficacy endpoint of the change from baseline in mean monthly migraine days across the 12-week double-blind treatment period will be analyzed based on the mITT population and the following methods will be used to address potential intercurrent events:

- Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.
- Data after the premature treatment discontinuation from the double-blind study period will be assumed missing at random.

The secondary endpoints will be analyzed based on the mITT population and the following methods will be used to address the potential intercurrent events:

- Continuous secondary endpoints based on eDiary data will be handled using the same approach defined above for the primary endpoint in the corresponding analysis population.
- The 50% responder is defined as a subject achieving at least a 50% reduction from baseline in the 3-month average of monthly migraine days. The average of monthly migraine days is calculated for each subject based on available monthly migraine days during the double-blind period, and then the subject is dichotomized as a responder or non-responder.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted on the mITT Population in each period. As described in Section 12.0, the overall familywise error rate (FWER) will be controlled at a 0.05 significance level for the set of primary endpoint comparisons between each dose level of atogepant vs placebo. All other tests will be 2-sided at a nominally significance level of 0.05.

The primary analysis will be conducted after all subjects have completed the double-blind treatment period and a database lock has occurred. After all subjects have completed Visit 5, investigators and subjects will remain blinded to study treatment assignment until all subjects have completed the study.

For analyses by stratification factors used for randomization, any subject who is randomized within an incorrect stratum will be analyzed according to the actual stratum to which the subject belongs, unless otherwise indicated.

9.2 Handling of Missing Data

Missing data will be imputed using the following methods for the primary efficacy analysis. Details can be found in Section 9.3.2 and Section 9.3.3:

- Mixed model for repeated measures (MMRM): The repeated measures analysis will be conducted using a mixed model including observed measurements for the double-blind period. Parameter estimation is based on the assumption of data being missing at random and using the method of restrictive maximum likelihood (REML). MMRM will be the primary approach in the analysis of continuous variables.
- ANCOVA model based on 3-month average of the monthly migraine days;
- Copy-reference approach.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week double-blind treatment period. Baseline is defined as the number of migraine days during the last 28 days prior to the randomization date.

9.3.2 Main Analysis of Primary Efficacy Endpoint

Analysis of the primary endpoint will be conducted on the mITT population based on treatment as randomized. The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week double-blind treatment period. The primary null hypothesis is that atogepant treatment doses (atogepant 10 mg, atogepant 30 mg, or atogepant 60 mg once daily) are each equally effective to placebo in mean change from baseline in mean monthly migraine days across the 12-week double-blind treatment period. The alternative hypothesis is that at least 1 of the 3 doses of atogepant has a different effect than placebo.

The estimand corresponding to the primary efficacy objective are summarized in Table 2.

Table 2. Summary of the Estimand Corresponding to the Primary Efficacy Objective

Estimand Label	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Primary	Arm A: Placebo Arm B: Atogepant 10 mg QD Arm C: Atogepant 30 mg QD Arm D: Atogepant 60 mg QD Acute migraine medications as rescue medications are allowed to keep patients in the study	Change from baseline in mean monthly migraine days across the 12-week treatment period	The Modified Intent-to-Treat (mITT) Population (see Section 4.0)	IE1: Use of acute migraine medication as rescue medications is considered in the definition of migraine day (composite strategy). IE2: Data after the discontinuation from double-blind treatment period are excluded and assumed missing at random.	The difference in mean change from baseline in mean monthly migraine days across the 12-week treatment period between each atogepant group and placebo

The change from baseline to each postbaseline month in monthly migraine days will be analyzed using a mixed model for repeated measures (MMRM). The statistical model will include treatment group, visit (derived as month), prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group-by-visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. The stratum "prior exposure (yes/no)" will use the actual stratification factor derived from prior medication collected by eCRF. An unstructured covariance matrix will be used to model the covariance of within-subject repeated measurements. If the model does not converge, then the Toeplitz covariance structure will be used. If the model with the Toeplitz covariance structure does not converge, then the compound symmetry covariance structure will be used. The Kenward-Roger approximation[6] will be used to estimate the denominator degrees of freedom. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. Only data collected during the double-blind period will be included in the analysis. Subjects are always analyzed based on the treatment group assigned by randomization.

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.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

The sensitivity analyses for missing data handling will be conducted and summarized in this section based on the mITT Population.

ANCOVA Model Based on 3-month Average of the Monthly Migraine Days

A supportive analysis will be performed on the primary endpoint using an ANCOVA model. The response variable for the ANCOVA model is the change from baseline in the

calculated average monthly migraine days during the 12-week double-blind treatment period for each participant. The ANCOVA model includes fixed effects for treatment, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline score. The treatment difference for atogepant dose versus placebo will be estimated and reported along with the corresponding 95% CI and nominal p-value for superiority testing.

Copy-Reference Approach

Copy-reference approach is one type of pattern-mixture models (PMM), under which data could be missing-not-at-random (MNAR), with repeated analyses combined via the reference based multiple imputation (MI) procedure.[7] This approach is to assess the robustness of the MMRM analysis to possible violation of the missing-at-random (MAR) assumption in the primary analysis.

Step 1. A few intermittent missing values will be imputed by the Markov Chain Monte Carlo (MCMC) first. The MCMC imputation assumes missing-at-random (MAR) for intermittent missing data. The MCMC method will be implemented using SAS Proc MI statement "MCMC impute monotone." This is achieved using the option IMPUTE MONOTONE in the MCMC statement. Then the rest of the missing data will follow a monotone missing pattern.

Step 2. Implementation of the copy reference method are as follows:

- 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 subject's last visit with a non-missing value. The mean vector and the covariance matrix of the multivariate normal distribution are estimated for the reference group. The imputation of missing data is not based on each of the reasons for early termination, because there may not be enough non-missing efficacy data in each of the reason categories to serve as a stable reference.

- For atogepant treatment groups, missing values are imputed based on the distribution estimated from the reference group (placebo group).

The first PROC MI will be performed 100 times using MCMC method for partial imputation of the data with a non-monotone missing pattern. The output dataset will then be used as the input dataset for the next PROC MI. Note that the output dataset already contains 100 copies of the original dataset. With the next invocation of MI procedure, the missing data will be filled in (Step 1 and 2) for the existing copies. This is achieved with the use of NIMPUTE 1 and a BY Imputation statement. Finally, each of the 100 imputed datasets will be analyzed using an analysis of covariance (ANCOVA) model. For a given imputed dataset, the average change from baseline in monthly migraine 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, baseline monthly migraine days and prior exposure (yes/no) to a migraine prevention medication with proven efficacy as covariates. The LS mean difference and corresponding SE is estimated from the model comparing each atogepant treatment group with the placebo group.

The ANCOVA analysis results from 100 completed datasets are combined for overall estimation and inference using Rubin's rule[8] 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.

Sensitivity Analysis for Possible Violation of Normality Assumption

An additional sensitivity analysis, MI in conjunction with robust regression, will be performed in case of non-normality for the primary efficacy endpoint. This method has been described and referred to as ADAP [R] in Mehrotra et al. 2012.[9] The details of the 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 test for

normality is applied to the de-correlated and scaled residuals and normality test is rejected if p-value from the Kolmogorov-Smirnov 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 100 complete datasets.
2. Each of the 100 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 migraine 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, prior exposure (yes/no) to a migraine prevention medication with proven efficacy as fixed factors, and baseline score. The mean difference and corresponding SE are estimated from the model comparing each atogepant treatment group with the placebo group.

The robust analysis results from 100 completed datasets are combined for overall estimation and inference using Rubin's rule[8] to produce a pooled estimate of treatment difference, its SE, and corresponding p-value for the test of null hypothesis of no treatment effect.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoints

Secondary efficacy endpoints are listed in Section 3.2.

9.4.2 Main Analyses of Key Secondary Efficacy Endpoints

The estimands corresponding to the key secondary efficacy objectives are summarized in Table 3.

Table 3. Summary of the Estimand Corresponding to the Key Secondary Efficacy Objectives

Estimand Label	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Secondary 1	Arm A: Placebo Arm B: Atogepant 10 mg QD Arm C: Atogepant 30 mg QD Arm D: Atogepant 60 mg QD Acute migraine medications as rescue medications are allowed to keep patients in the study.	Change from baseline in mean monthly headache days across the 12-week double-blind treatment period.	mITT population (see Section 4.0)	IE1: Use of acute migraine medication as rescue medications is considered in the definition of headache day (composite strategy). IE2: Data after the discontinuation from double-blind treatment period are excluded and assumed missing at random.	The difference in mean change from baseline in mean monthly headache days across the 12-week double-blind treatment period between each atogepant group and placebo.
Secondary 2	Arm A: Placebo Arm B: Atogepant 10 mg QD Arm C: Atogepant 30 mg QD Arm D: Atogepant 60 mg QD Acute migraine medications as rescue medications are allowed to keep patients in the study.	Change from baseline in mean monthly acute medication use days across the 12-week double-blind treatment period.	mITT population (see Section 4.0)	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Data after the discontinuation from double-blind treatment period are excluded and assumed missing at random.	The difference in mean change from baseline in mean monthly acute medication use days across the 12-week double-blind treatment period between each atogepant group and placebo.

Estimand Label	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Secondary 3	Arm A: Placebo Arm B: Atogepant 10 mg QD Arm C: Atogepant 30 mg QD Arm D: Atogepant 60 mg QD Acute migraine medications as rescue medications are allowed to keep patients in the study.	At least a 50% reduction in the 3-month average of monthly migraine days.	mITT population (see Section 4.0)	IE1: Use of acute migraine medication as rescue medications is considered in the definition of migraine day (composite strategy). IE2: Data after the discontinuation from double-blind treatment period are excluded. The average of monthly migraine days is calculated for each subject based on available monthly migraine days during the double-blind period, and then the subject is dichotomized as a responder or non-responder.	The odds ratio in subjects achieving at least 50% reduction in 3-month average of monthly migraine days between each atogepant group and placebo.
Secondary 4	Arm A: Placebo Arm B: Atogepant 10 mg QD Arm C: Atogepant 30 mg QD Arm D: Atogepant 60 mg QD Acute migraine medications as rescue medications are allowed to keep patients in the study.	Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12.	mITT population (see Section 4.0)	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Data after the discontinuation from double-blind treatment period are excluded and assumed missing at random.	The difference in mean Change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12 between each atogepant group and placebo.

Estimand Label	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Secondary 5	Arm A: Placebo Arm B: Atogepant 10 mg QD Arm C: Atogepant 30 mg QD Arm D: Atogepant 60 mg QD Acute migraine medications as rescue medications are allowed to keep patients in the study.	Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week double-blind treatment period.	mITT population (see Section 4.0)	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Data after the discontinuation from double-blind treatment period are excluded and assumed missing at random.	The difference in mean Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period between each atogepant group and placebo.
Secondary 6	Arm A: Placebo Arm B: Atogepant 10 mg QD Arm C: Atogepant 30 mg QD Arm D: Atogepant 60 mg QD Acute migraine medications as rescue medications are allowed to keep patients in the study.	Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week double-blind treatment period.	mITT population (see Section 4.0)	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Data after the discontinuation from double-blind treatment period are excluded and assumed missing at random.	The difference in mean Change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period between each atogepant group and placebo.

9.5 Additional Efficacy Endpoints and Analyses

Additional efficacy endpoints can be found in Section 3.3.

For variables with a continuous response range, analyses will be performed similarly to that used for the primary analysis, with focus again on the pairwise contrasts of each dose group to placebo. Baseline in the primary MMRM model will be replaced with corresponding endpoint baseline. There is only one post-baseline assessment for MIDAS, and thus ANCOVA model will be used to analyze MIDAS related endpoints with model terms including treatment group, prior exposure (yes/no), and the corresponding baseline score.

For weekly data analysis purposes, baseline is defined to be the baseline derived on a monthly basis divided by 4 and change from baseline in the weekly migraine days will be calculated for consecutive 7-day periods beginning with Day 1. Subsequent to treatment start date, the number of headache days will be counted in successive and non-overlapping 1-week (ie, 7-day) windows. Headaches that continue into a subsequent 1-week period will be counted (with recorded severity and duration) as occurring in each period. If any postbaseline eDiary window for a subject has at least 4, but less than 7 days, of reported data, the prorated approach will be used. If a subject reports less than 4 days of headache data, the subject's observed counts in that particular 7-day eDiary window will be set to missing for that window.

For variables where the data are essentially binary, comparisons between treatment groups will be done using a generalized linear mixed model for variables with multiple postbaseline assessments. A generalized linear mixed model will assume a binary distribution for the response and uses a logit link. The analysis model will include treatment group, visit, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group-by-visit interaction as categorical fixed effects; baseline value and baseline-by-visit interaction will be included as covariates. Subjects will be included as random effects with unstructured covariance matrix in the model to account for the correlation among repeated measurements. The analysis will be performed

based on all postbaseline values using only the observed cases without imputation of missing values. As there is no baseline assessment for the endpoint patient's satisfaction with study medication, baseline monthly migraine days will be included in the model.

For binary endpoints with only one postbaseline assessment (for example, PGIC responder) or responders across 12-week double-blind treatment period or active treatment extension period, a logistic regression model will be used to model the probability of a response or event with model terms including treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and corresponding baseline. As there is no baseline assessment for PGIC, baseline monthly migraine days will be used in the logistic regression model as a covariate for PGIC responder analyses.

For daily efficacy variables, the number and percentage of subjects with a migraine day will be summarized by each day under consideration. A generalized linear mixed model as described above will be used to analyze the proportion of subjects with a migraine day as repeated measures from the initial dose day to 6 days after. Here baseline value is the daily rate for subjects with a migraine day during the baseline period.

In addition, the percentage reduction in the proportion of subjects with a migraine day will be provided by each day under consideration. It is defined as:

$$100 \times (1 - \frac{\text{proportion of subjects with a migraine day on a specific day}}{\text{baseline daily rate of subjects with a migraine day}}).$$

The percentage of subjects with a migraine day will be calculated relative to the number of subjects in mITT population with available eDiary record on the day of consideration. The numerator will be the number of subjects with a migraine day on that day. The baseline daily rate of subjects with a migraine day will be calculated as the average of monthly migraine days (prorated if less than 28 days of baseline data are reported) at baseline period for subjects in mITT population divided by 28.

Plots of fitted (least squares) mean changes and their standard errors for monthly migraine days, monthly headache days and monthly acute medication use days from the MMRM will be presented by treatment group and 4-week interval.

Plots of achievement of ≥ 25%, ≥ 50%, ≥ 75%, and 100% improvement (decrease) in monthly migraine days will be presented by treatment group and 4-week interval, respectively.

In addition, cumulative distribution graph of percent improvement (decrease) in mean monthly migraine days across 12-week double-blind treatment period will be provided by treatment group and prior exposure (yes/no) to a migraine prevention medication with proven efficacy.

9.6 Efficacy Subgroup Analyses

Subgroup analysis based on age group (< 40 years, ≥ 40 - < 65 years, ≥ 65 years), sex (male, female), BMI classification (underweight or normal [< 25] and overweight or obese [≥ 25]), baseline monthly migraine days (< 8 days, and ≥ 8 days), prior exposure (yes/no) to a migraine prevention medication with proven efficacy, number of migraine prevention medication failures with proven efficacy (category details below), migraine diagnosis history (migraine with aura, migraine without aura, and migraine both with and without aura), and prior exposure to calcitonin gene-related peptide (CGRP) antagonists (yes/no) will be performed for the following efficacy endpoints

- Change from baseline in mean monthly migraine days across the 12-week double-blind treatment period.
- Change from baseline in mean monthly headache days across the 12-week double-blind treatment period.
- Change from baseline in mean monthly acute medications use days across the 12-week double-blind treatment period.
- At least a 50% reduction in 3-month average of monthly migraine days.

The between-group treatment effect (with a 95% CI) for each atogepant dose vs placebo for the specified efficacy endpoints will be estimated within each category of the subgroup. If models do not converge, descriptive statistics for subgroups will be provided.

Subgroup by number of migraine prevention medication failures with proven efficacy are specified as the following categories:

- Failed 0 medication,
- Failed 1 or more medication(s) with the same mechanism of action,
- Failed 2 or more medications with different mechanisms of action,
- Never used.

10.0 Safety Analyses

10.1 General Considerations

For the purposes of safety analysis, the start of the active treatment extension period is marked by the date of the first dose of study medication received in the active treatment extension period (Visit 6, Visit 7, or Visit 8).

Safety data will be summarized for the Safety Populations 1 and 2. Safety summaries will be presented by treatment groups. For the safety analysis, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

The safety parameters will include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, and the C-SSRS. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of treatment will be used as the baseline for all analyses of that safety parameter.

Continuous variables will be summarized by the number of subjects, and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects.

Descriptive statistics for safety endpoints will be provided by treatment period (double-blind treatment period or active treatment extension period), separately. For selected safety endpoints, analyses will be provided across both treatment periods to show the trend over time.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any AE with an onset after the first dose of study treatment and no more than 30 days after the last dose of study treatment. Events where the onset date is the same as the study treatment start date are assumed to be treatment-emergent, unless the study treatment start time and the AE start time are collected and the AE start time is prior to the study treatment start time. If an incomplete onset date is collected for an AE, then the AE will be assumed to be treatment-emergent unless there is evidence that confirms that the AE was not treatment-emergent (e.g., the AE end date was prior to the date of the first dose of study treatment).

An AE is considered a TEAE for the double-blind treatment period if the onset date is after the first dose of study treatment and no more than 1) 30 days after the last dose of double-blind study treatment or 2) the day before the date of the first dose of the active treatment extension study medication, whichever is earlier. An AE is considered a TEAE for the active treatment extension period if the AE begin on or after the date of the first

dose of the active treatment extension period study medication and no more than 30 days after the last dose of active treatment extension study treatment. TEAEs that start after the date of last dose of study treatment for each treatment period will be considered as newly emergent for the corresponding treatment period.

All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term for the double-blind treatment period and active treatment extension period based on the Safety Population 1 and Safety Population 2, respectively. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing newly emergent treatment-emergent AEs will be summarized by period. The analysis population for the double-blind treatment period and active treatment extension period will be subjects in Safety Population 1 who entered the safety follow-up period without study treatment in the active treatment extension period and subjects who entered the safety follow-up period in Safety Population 2, respectively.

10.2.2 Adverse Event Overview

An overview of AEs will be presented by treatment period consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study treatment according to the investigator
- Any severe treatment-emergent AE
- Any serious treatment-emergent AE
- Any treatment-emergent AE leading to discontinuation of study treatment
- Any treatment-emergent AE leading to death
- All deaths

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by treatment group, for each treatment period and overall, by SOC and PT; by maximum relationship to study treatment as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

The incidence of common (≥ 2% of subjects in any treatment group) TEAEs will be summarized by preferred term, and treatment group. A similar 5% table will be provided as well.

10.2.4 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Treatment Discontinuation

Treatment-emergent serious adverse events (TESAEs) and TEAEs leading to premature discontinuation of study treatment will be summarized by SOC and PT for each treatment period. TESAEs will also be summarized by SOC and PT overall.

For TEAEs leading to premature discontinuation of study treatment, summaries by SOC and PT will be provided as follows:

- TEAEs with start date and treatment discontinuation date in the double-blind period
- TEAEs with start date and treatment discontinuation date in the extension period
- TEAEs leading to treatment discontinuation during the extension period, i.e., the treatment discontinuation date occurred in the extension period regardless of whether the TEAE started in the double-blind period or the extension period.

Tabular listings will be provided for all deaths, all SAEs and TEAEs leading to premature discontinuation of study treatment.

10.2.5 Adverse Events of Special Interest

Adverse events of special interest are categorized as follows:

- Treatment-emergent suicidal ideations with intent, with or without a plan, (ie, Type 4 or 5 on the C-SSRS) or any suicidal behaviors.
- Treatment-emergent elevated ALT or AST lab value ≥ 3 × ULN.
- Potential Hy's law cases: elevated ALT or AST lab value that is ≥ 3 × ULN and an elevated total bilirubin lab value that is ≥ 2 × ULN and, at the same time, an alkaline phosphatase lab value that is < 2 × ULN.
- Related summaries can be found in C-SSRS summary tables and lab section.

10.3 Analysis of Laboratory Data

The clinical laboratory tests defined in the protocol operations manual (e.g., hematology, clinical chemistry, and urinalysis) will be summarized.

Each laboratory variable will be summarized by treatment group for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, Q1, Q3, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment time point will be presented for selected clinical laboratory parameters listed in Appendix D. A description of reporting the lab values in conventional units in patient narratives (along with the standard reporting in SI units) is presented at the end of Appendix D.

Laboratory abnormalities will be evaluated based on Potentially Clinically Significant (PCS) criteria (Appendix C, Table C-1). For each laboratory PCS criterion, the number

and percentage of subjects who have a laboratory value meeting the criteria will be summarized by treatment group. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCS criteria.

The number and percentage of subjects meeting each of the criteria for postbaseline hepatic laboratory abnormalities listed in Appendix C, Table C-2 will be summarized. The percentages will be calculated relative to the number of subjects with at least 1 available postbaseline assessment. The numerator will be the total number of subjects having at least 1 postbaseline value that meets the specific category during the study. A supportive listing will also be provided.

The number and percentage of subjects with an adjudicated case (i.e., ALT ≥ 3 × ULN and/or AST ≥ 3 × ULN) will be summarized by treatment group and by relationship of ALT or AST elevation to study medication. The percentages will be calculated relative to the number of subjects with at least 1 adjudicated case. The numerator will be the number of subjects with at least 1 adjudicated case in the specific category of relationship. If a subject has more than 1 adjudicated case, he or she will be counted in the most relevant category of relationship.

Subjects with an adjudicated case (i.e., ALT ≥ 3 × ULN or AST ≥ 3 × ULN) will be listed with their ALT and AST assessments, adjudication dates, relationship of ALT or AST elevation to study medication, and confounding factor(s). Additional listings will be provided for subjects who meet ALT ≥ 3 × ULN or AST ≥ 3 × ULN and/or potential Hy's law and have one of the following categories: at least 1 abnormal liver biochemistry risk factor, at least 1 liver disease sign and symptom, at least 1 liver diagnostic test performed, consultation with a specialist for liver evaluation, liver lab tests performed, and drug screen performed, respectively.

Potential Hy's Law criteria within a 24-hour window is defined by a postbaseline evaluation of alanime aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × ULN, along with total bilirubin (TBL) ≥ 2 × ULN and a non-elevated alkaline phosphatase (ALP) < 2 × ULN, all based on blood draws collected within a

24-hour period. Patients who meet the potential Hy's Law criteria from the first dose of study drug to the end of study will be summarized. Supportive tabular displays will also be provided.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressures (sitting and standing), pulse rate (sitting and standing), respiratory rate, body weight, orthostatic systolic blood pressure, orthostatic diastolic blood pressure, and orthostatic pulse rate will be summarized.

Each vital sign variable will be summarized by treatment group for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, Q1, Q3, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable by treatment group, with the number of observations, baseline mean, and visit mean. The change from baseline mean, and standard error will be presented for the mean change from baseline within each treatment group.

Vital sign variables will be evaluated based on potentially clinically significant (PCS) criteria (Appendix C). For each vital sign PCS criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCS criteria.

10.5 Other Safety Analyses

10.5.1 Electrocardiograms

Descriptive statistics for ECG parameters (i.e., heart rate, PR interval, QRS interval, RR interval, QT interval, and QTc interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint will be presented by treatment group.

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in Appendix C, Table C-4. The number and

percentage of subjects with PCS postbaseline values will be tabulated by study treatment. The percentages will be calculated relative to the number of subjects with at least 1 postbaseline assessment. The numerator will be the total number of subjects with an more extreme (worse) postbaseline value than the baseline value. If a subject did not have a baseline value but met the criterion post-baseline, then the subject is counted in the numerator. Subject is counted once if the criterion is met more than once. A supportive listing of subjects with PCS postbaseline values will be provided. A listing of all AEs for subjects with PCS ECG values will also be provided.

The number and percentage of subjects meeting each of the criteria for postbaseline ECG values of clinical interest listed in Appendix C, Table C-5 will be summarized. Subjects will be counted only once for the most severe category. A supportive listing of subjects with postbaseline QTcF increases > 30 msec will be provided, including the PID number, study center, and all QTc values (including changes from baseline). A listing of all AEs for subjects with postbaseline QTcF increases > 30 msec will also be provided.

A shift table from baseline to the end of double-blind treatment period and active treatment extension period in the investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant for Safety Population 1 and Safety Population 2, respectively. A tabular display of subjects with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

10.5.2 Columbia-Suicide Severity Rating Scale

For C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment group for the Safety Populations 1 and 2. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior in the subject's lifetime history, in the past 6 months, in the double-blind treatment period, active treatment extension period, and in the follow up period will also be presented by treatment group. Supportive listings will be provided and

will include the PID number, study center number, treatment group, lifetime history, and postbaseline values. Intensity of suicidal ideation and suicidal behavior type will also be included in these listings.

11.0 Interim Analyses

No interim analysis of efficacy data is planned for this study.

An external DMC composed of persons independent of AbbVie and with relevant expertise in their field will review unblinded safety data from the ongoing study. A separate DMC charter will be prepared and will describe the roles and responsibilities of the DMC, frequency of data reviews, planned interim analyses and relevant data to be assessed, and expectations for blinded communications.

12.0 Overall Type-I Error Control

The Hochberg procedure[10] will be used to control the overall Type I error rate at a 0.05 level (2-sided) for multiple comparisons of each atogepant dose with placebo for the primary endpoint. Detailed procedure is provided below.

Let $p_{(1)}$, $p_{(2)}$, and $p_{(3)}$ denote the nominal p-values in increasing order from the 3 comparisons of atogepant doses versus placebo.

Step 1: If $p_{(3)}$ is ≤ 0.05, then all the 3 comparisons are considered statistically significant at the 2-sided significance level of 0.05 and stop here; otherwise, go to Step 2.

Step 2: If $p_{(2)}$ is ≤ 0.025, then the corresponding 2 comparisons for $p_{(2)}$ and $p_{(1)}$ are considered statistically significant at the 2-sided significance level of 0.05 and stop here; otherwise, go to Step 3.

Step 3: If $p_{(1)}$ is ≤ 0.01667, then the corresponding comparison for $p_{(1)}$ is considered statistically significant at the 2-sided significance level of 0.05; otherwise, stop here.

Adjusted p-values using Hochberg procedure will also be provided.

13.0 Version History

Table 4. SAP Version History Summary

Version	Date	Summary
1.0	18 March 2020	Initial version
2.0	25 September 2023	This version of the SAP was completely re-written based on Protocol Amendment 5.
3.0	22 October 2024	Corrected typos and inconsistencies throughout the document. Removed the listing for positive urine pregnancy test per AbbVie CSR simplification standard. For Japan submission purpose • Section 3.3 added endpoints CFS in monthly headache days with nausea and/or vomiting symptom, photophobia and phonophobia • Section 9.6 added efficacy subgroup analyses: number of migraine prevention medication failures with proven efficacy (category details below), migraine with or without aura diagnosis (migraine with aura, migraine without aura, and migraine both with and without aura), and prior exposure to calcitonin gene-related peptide (CGRP) antagonists (yes/no) Removed AESI summary by SOC and PT as data is not collected in the AE eCRF. Updated the text to refer to C-SSRS and lab section for summary. Removed temperature from vital sign summary. Updated SI unit and PCS low for estimated glomerular filtration rate in Table C-1 per standard lab transfer unit. Added more details in estimand description and handling of the intercurrent events in Section 2.1, Section 9.3.2, and Section 9.4.2.

14.0 References

1. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the preventive treatment of migraine. N Engl J Med. 2021;385(8):695-706.
2. Sakai F, Ozeki A, Skljarevski V. Efficacy and safety of galcanezumab for prevention of migraine headache in Japanese patients with episodic migraine: A phase 2 randomized controlled clinical trial. Cephalalgia. 2020;3:1-10.
3. Sakai F, Suzuki N, Kim BK, et al. Efficacy and safety of fremanezumab for episodic migraine prevention: Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in Japanese and Korean patients. Headache. 2021;61(7):1102-11.
4. Sakai F, Takeshima T, Tatsuoka Y, et al. A Randomized Phase 2 Study of Erenumab for the Prevention of Episodic Migraine in Japanese Adults. Headache. 2019;59(10):1731-42.
5. Takeshima T, Sakai F, Hirata K, et al. Erenumab treatment for migraine prevention in Japanese patients: Efficacy and safety results from a Phase 3, randomized, double-blind, placebo-controlled study. Headache. 2021;61(6):927-35.
6. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53(3):983-97.
7. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: A framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71.
8. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: Wiley; 1987.
9. Mehrotra DV, Li X, Liu J, et al. Analysis of longitudinal clinical trials with missing data using multiple imputation in conjunction with robust regression. Biometrics. 2012;68(4):1250-9.
10. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75(4):800-2.

Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
[redacted]	[redacted]	Author
[redacted]	[redacted]	Clinical Statistics
[redacted]	[redacted]	Statistical Programming
[redacted]	[redacted]	Medical/Scientific Monitor
[redacted]	[redacted]	Medical/Scientific Monitor
[redacted]	[redacted]	Medical/Scientific Monitor

Appendix B. Derivation of Efficacy Variables and Health Outcome Endpoints

B.1 Derivation of Efficacy Endpoints Based on eDiary Data

A migraine day, a headache day, an acute medication use day, and a triptan use day are defined in Section 3.7 of the Operations Manual.

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, subjects 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 diary" completed on that day and "yesterday's diary" completed on the following day. Subjects are to report headache data in "today's diary" in the evening at any time from 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 subjects miss "today's diary," they can report the whole-day headache data in "yesterday's diary" on the following day. In case subjects 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 migraine 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 the derivation of headache day, the subject is considered to have taken a non-antiemetic acute headache medication if the subject has taken such a medication in either "today's diary" or "yesterday's diary."

Moderate/severe headache day is defined as a headache day during which the maximum pain severity is either moderate or severe. Severe headache day is defined as a headache day during which the maximum pain severity is severe.

If a subject confirmed no headache for the Question 1 in eDiary, then the subject will not answer subsequent questions related to headache symptoms, duration, and acute headache mediation use by design. Thus, the acute medication use for that diary ('today' or 'yesterday') will be treated as 'No' when deriving acute medication use day.

The monthly migraine days is defined as the total number of recorded migraine days in the eDiary divided by the total number of days with eDiary records during each monthly period and multiplied by 28. For baseline, a minimum of 20 days' eDiary data during the 4-week baseline period is required for the migraine days to be evaluable. For each postbaseline 4-week treatment period, a minimum of 14 days' eDiary data during that period is required for the migraine days to be evaluable. If a subject does not have at least 14 days of diary data for a monthly treatment period, the migraine days for that period will be considered as missing. Migraine days will be derived for each subject at baseline and for each postbaseline monthly treatment period (Weeks 1-4, 5-8, 9-12). The same method to derive monthly migraine days will be used to derive monthly headache days, monthly acute medication use days, monthly triptan use days, monthly cumulative headache hours, monthly moderate/severe headache days, and monthly severe headache days.

If a subject confirmed that acute medications were taken and entered medications in the eDiary, then the acute medication use day will be set to 'Yes.' 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 and vice versa.

B.2 Derivation of Health Outcome Endpoints

AIM-D Related Endpoints Derivation

The AIM-D was developed as a daily eDiary with a recall period of 24 hours. By design, it is collected in the today's diary only. The scoring of the following endpoints is completed in 2 steps.

- Monthly Performance of Daily Activities domain score of the AIM-D
- Monthly Physical Impairment domain score of the AIM -D
- Monthly AIM -D total score

Step 1: Calculate AIM-D daily domain score and total score

Daily performance of daily activities score will be calculated based on the summation of items 1-5 and 10 and 11, ranging from 0-35. A daily performance of daily activities domain score will be calculated if 4 or more item scores have non-missing responses. When the response category "I did not have <errands, leisure or social, strenuous activities> planned" (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding performance of daily activities domain score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 7, provided that 4 or more item scores are available; otherwise, it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (35).

Daily physical impairment scores will be calculated based on the summation of items 6-9, ranging from 0-20. A daily physical Impairment score will be calculated if 2 or more item scores have non-missing responses. The corresponding physical Impairment score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 4, provided that 2 or more item scores are available; otherwise, it will be set to missing. The raw daily score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (20).

A daily total score will be calculated based on the summation of items 1-11, ranging from 0-55. A Total Score will be calculated if 6 or more items scores have non-missing responses. When the response category "I did not have <errands, leisure or social, strenuous activities> planned" (items 2, 4, and 5), is selected, the response will be considered missing. The corresponding Total Score will be calculated by summing the non-missing item scores and dividing by the number of non-missing items and then multiplying by 11, provided that 6 or more item scores are available; otherwise, it will be set to missing. The raw score will be transformed to a 0-100 scale by multiplying by 100 and dividing by the highest raw score (55).

Step 2: Calculate Monthly Scores and Baseline Score

Monthly scores will be calculated using the average daily scores only if there are at least 14 non-missing daily scores in the corresponding monthly (28-day) period. The corresponding monthly scores will be calculated by summing the non-missing daily domain scores and dividing by the number of non-missing daily domain, provided that 14 or more daily scores are available; otherwise, it will be set to missing.

Activity Level and Activity Limitation

Monthly activity level score will be calculated by summing the non-missing daily scores and dividing by the number of these scores, provided that 14 or more daily scores are available in the corresponding monthly (28-day) period; otherwise, it will be set to missing. Same rule will be applied to the calculation of monthly activity limitation score.

MSQ Related Endpoints Derivation

MSQ v2.1 consists of 14 items with a 4-week recall period. The scoring of the MSQ is completed in following 3 steps.

Step 1: Final item value assignment.

Precoded item values and final item values for each MSQ item response are shown in Table B-1.

Table B-1. Item Values for MSQ Item Responses

Response Categories	Precoded Item Value	Final Item Value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

Step 2: Computation of raw domain (dimension) scores.

Once a final item value has been assigned to each item, a raw score can be computed for each MSQ domain. Role Function Restrictive domain includes Items 1 - 7, Role Function Preventive domain includes Items 8 - 11, and Emotional Function domain includes Items 12 - 14. The raw score for each domain is the algebraic sum of the final item values for all items in that domain.

Missing data handling: if a respondent answered at least half of the items in a domain (or half plus one in the case of scales with an odd number of items), a missing item value can be estimated using the average of the other completed items within the same dimension.

In detail, for MSQ v2.1 Role Function Restrictive domain, the 7 individual item responses using final item value will be summed, resulting in the raw domain score ranging from 7 to 42 with higher scores indicating better quality of life. If there are missing item responses, the raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by 7 provided that 4 or more items in the domain are completed; otherwise it will be set to missing. For MSQ v2.1 Role Function Preventive and Emotional domains, the raw domain scores will be calculated similarly using final item

value respectively. If there are missing item responses, the corresponding raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by the number of questions in that domain provided that 2 or more domain items are completed; otherwise it will be set to missing.

Step 3: Linear transformation to a 0 to 100 scale.

The transformation formula for each MSQ 2.1 domain is listed below

- Role Function -Restrictive: $\frac{(raw\ score-7)*100}{35}$
- Role Function-Preventive: $\frac{(raw\ score-4)*100}{20}$
- Emotional Function: $\frac{(raw\ score-3)*100}{15}$

HIT-6 Total Score Derivation

For HIT-6 total score, pre-coded item values and final item values for each item response are shown in Table B-2. Total score is calculated by summing 6 sub-item responses, resulting in the total score ranging from 36 to 78 with higher scores indicating greater impact. If any sub item is missing, then total score will be missing.

Table B-2. Item Values for HIT-6 Item Responses

Response Categories	Precoded Item Value	Final Item Value
Never	0	6
Rarely	1	8
Sometimes	2	10
Very Often	3	11
Always	4	13

The HIT-6 instrument has a recall period of 4 weeks for 3 of the 6 items.

MIDAS Related Endpoints Derivation

MIDAS total score is derived as the sum of first 5 of questions (i.e., the sum of days missing work or school, Productivity at work or school reduced, Not do household work, Productivity in household work reduced, Miss family social or leisure activities). If any sub item is missing, the MIDAS total score will be missing.

The MIDAS absenteeism score is derived as the sum of Questions 1, 3 and 5. If any sub item is missing, then the MIDAS absenteeism score will be missing. The MIDAS presenteeism score is derived as the sum of Questions 2 and 4. If any sub item is missing, then the MIDAS presenteeism score will be missing.

WPAI:MIGRAINE Related Endpoints Derivation

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

- Q1 currently employed (working for pay).
- Q2 missed work hours because of problems associated with your migraine
- Q3 missed work hours due to other reason.
- Q4 hours actually worked.
- Q5 migraine affected productivity while working.
- Q6 migraine affected regular daily activity.

Scores:

Multiply scores by 100 to express in percentages.

- Percent work time missed due to migraine (absenteeism): Q2/(Q2 + Q4)
- Percent impairment while working due to migraine (presenteeism): Q5/10
- Percent overall work impairment due to migraine (overall work productivity loss): Q2/(Q2 + Q4) + (1- (Q2/(Q2 + Q4))) × (Q5/10)
- Percent activity impairment due to migraine (regular activity impairment): Q6/10

If the response to Q1 ("Currently employed?") is No or missing, absenteeism, presenteeism, and overall work productivity loss will all be set to missing.

EQ-5D-5L Score Derivation

The EQ-5D-5L is made up of two components: health state description and evaluation. The description component consists of five dimensions: mobility, self-case, usual activities, pain/discomfort, and anxiety/depression. The mobility dimension queries the subject's walking ability. The self-care dimension queries the subject's ability to wash or dress by himself. The usual activities dimension assesses the subject's performance in "work, study, housework, family or leisure activities." The pain/discomfort dimension measures how much pain or discomfort a subject has. The anxiety/depression dimension assesses how anxious or depressed a subject is. The respondents rate their level of severity for each dimension using a 5-level scale (EQ-5D-5L) by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The second component of the EQ-5D-5L is a visual analogue scale (EQ-VAS) by which subjects can rate their overall health from 0 (worst imaginable health state) to 100 (best imaginable health state).

With the EQ-5D-5L, rating levels can be coded as numbers 1, 2, 3, 4 or 5 which correspond to "have no problems," "have slight problems," "have moderate problems,"

"have severe problems," and "unable to do/have extreme problems," respectively. As a result, a subject's health state can be defined by a 5-digit number by combining the numeric levels from the 5 dimensions, ranging from 11111 ("have no problems" in all 5 dimensions) to 55555 ("unable to do/have extreme problems" in all 5 dimensions). The index value for the EQ-5D-5L will be derived using an international standardized protocol.

EQ-5D-5L will be captured on eDiary during 7 days in the screening/baseline period and during specific time periods for Visit 1 to 5. The index score and VAS score for a specific period will be calculated as the average of available scores in that period respectively if at least 50% of daily scores are available; otherwise, the scores will be set as missing. For example, for a period of 14 days, at least 7 assessments are required; and for a period of 7 days, at least 4 assessments are required.

PROMIS-PI T-Score Derivation

The PROMIS-PI measures self-reported interference of pain on relevant aspects of daily life (i.e., social, cognitive, emotional, physical, recreational) over the past 7 days. A 5-level response scale for all 6 items ranges from 1 to 5, corresponding to item response of "Not at all" to "Very much." The raw score of PROMIS-PI is the sum of all 6 items, ranging from 6 to 30. If one or more items are missing, the raw score will be set to missing. A raw score can be standardized into a T-score with a mean of 50 and standard deviation of 10 using Table B-3. Higher raw or T-scores indicate greater pain interference.

Table B-3. PROMIS-PI Raw Score Transformation

Raw Score	T-Score	Raw Score	T-Score	Raw Score	T-Score	Raw Score	T-Score
6	41.1	13	56.6	20	63.0	27	69.8
7	48.6	14	57.6	21	63.8	28	71.0
8	50.7	15	58.6	22	64.8	29	72.6
9	52.2	16	59.5	23	65.7	30	76.3
10	53.4	17	60.4	24	66.7		
11	54.5	18	61.2	25	67.6		
12	55.6	19	62.1	26	68.7		

Patient Health Questionnaire (PHQ-9)

The PHQ-9 consists of the 9 diagnostic criteria for depressive disorders in the past 2 weeks from the DSM-IV. Subjects are asked to indicate the frequency with which they have been bothered by 9 symptoms of depressive disorders over the previous 2 weeks, on a 4-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 27 (from best to worst). A score of 15 to 19 is considered as moderately severe depression and 20 to 27 as severe depression. A Total Score will be calculated using (sum of non-missing items) × 9 / (number of non-missing items) if 5 or more items scores have non-missing responses.

Appendix C. Potentially Clinically Significant Criteria for Safety Endpoints

The criteria for Potentially Clinically Significant (PCS) laboratory findings are described in Table C-1 and Table C-2. The PCS criteria for vital sign findings are described in Table C-3, and the PCS criteria for ECG parameters are described in Table C-4.

Table C-1. Potentially Clinically Significant Criteria for Clinical Laboratory Parameters

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/sec/1.73m^2	< 1	—
	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

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
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.

Table C-2. Criteria for Hepatic Laboratory Abnormalities

Laboratory Parameter	Categories
ALT	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN

Laboratory Parameter	Categories
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
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

Laboratory Parameter	Categories
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

Vital sign values will be considered PCS if they meet both the observed value criterion and the change from baseline value criterion, if both criteria are available, or meet either the observed value criterion or the change from baseline value criterion that is detailed in the following table.

Table C-3. Potentially Clinically Significant Criteria for Vital Signs Parameters

Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%
Orthostatic SBP change, mm Hg	Low	≤ -20	—
Orthostatic DBP change, mm Hg	Low	≤ -15	—
Orthostatic Pulse rate change, bpm	High	≥ 25	—

SBP Systolic blood pressure; DBP Diastolic blood pressure; bpm beats per minute

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in the following table.

Table C-4. Potentially Clinically Significant Criteria for ECG Parameters

Parameter	Unit	Criterion
QRS interval	msec	≥ 150
PR interval	msec	≥ 250
QTc (QTcB or QTcF) interval	msec	> 500
QTc (QTcB or QTcF) interval	msec	Increase from baseline > 60

Table C-5. ECG Post-baseline Values of Clinical Interest

Parameter	Unit	Criterion
QTcF	msec	> 450
		> 480
		> 500
		Increase > 30 but ≤ 60
		Increase > 60

Appendix D. Reporting Selected Laboratory Parameters in Conventional Unit

All clinical laboratory parameters will be reported in the International System (SI) units as standard practice. In addition, descriptive statistics for values and changes from baseline in conventional units at all assessed visits will be reported for selected laboratory parameters as listed in Table D-1 below.

Table D-1. List of Selected Parameters to be Reported in Conventional Units

Number	Laboratory Parameter	Conventional Unit	Decimal Places
1	Alanine Aminotransferase (SGPT)	U/L	0
2	Albumin	g/dL	1
3	Alkaline Phosphatase	U/L	0
4	Aspartate Aminotransferase (SGOT)	U/L	0
5	Bilirubin, Direct (Conjugated)	mg/dL	1
6	Bilirubin, Indirect (Unconjugated)	mg/dL	1
7	Bilirubin, Total	mg/dL	1
8	Blood Urea Nitrogen	mg/dL	0
9	Calcium	mg/dL	1
10	Cholesterol, HDL	mg/dL	0
11	Cholesterol, LDL	mg/dL	0
12	Cholesterol, LDL direct and calculated (combined) (This lab parameter could be the same as #11)	mg/dL	0
13	Cholesterol, Total	mg/dL	0
14	Creatine Kinase	U/L	0
15	Creatinine	mg/dL	1
16	Glucose	mg/dL	0
17	Insulin	uIU/mL	1
18	Triglycerides	mg/dL	0
19	Uric Acid	mg/dL	1
20	Hemoglobin	g/dL	1

Patient narratives will also include the values in conventional units for the selected lab parameters (Table D-1). That will be accomplished by presenting the values in conventional units within the parentheses next to the values in SI units. As shown in Table D-2 below for 'Bilirubin, Total' parameter, for which 'umol/L' is the SI unit and 'mg/dL' is the conventional unit.

Table D-2. Presenting Laboratory Data Using SI and Conventional Units in Narratives

LABORATORY DATA						
		Normal Range		VISIT01	VISIT05	VISIT07
Lab Test	Test Name	Low	High	2012-07-03	2012-08-07	2012-09-04
CHEMISTRY	Bilirubin, Total (µmol/L(mg/dL))	0 (0)	18.81 (1.1)	6.84 (0.4)	5.13 (0.3)	5.13 (0.3)

Appendix E. Identifying Prior Exposure (yes/no) to a Migraine Prevention Medications with Proven Efficacy Based on Prior Medications Reported in eCRF

According to Appendix F in the protocol, a list of migraine-preventive medications with proven efficacy was identified by the clinical team and coding team as shown in Table E.

If a subject has taken medications before the screening visit with preferred names in Table E, and the prior medications are classified as "Migraine Prevention Medication" in the prior and concomitant medications eCRF, then the prior exposure to migraine prevention medications with proven efficacy will be "Yes" for this subject, otherwise, it is set as "No."

Table E. A List of Migraine-Preventive Medications with Proven Efficacy

Protocol Pharmacologic Category	Drug Class	Preferred Name
Antiepileptic	valproic acid	CLONAZEPAM;VALPROIC ACID
Antiepileptic	valproic acid	VALPROIC ACID
Antiepileptic	sodium valproate	VALPROATE MAGNESIUM
Antiepileptic	sodium valproate	CLONAZEPAM;VALPROATE SEMISODIUM
Antiepileptic	sodium valproate	VALPROATE SEMISODIUM
Antiepileptic	sodium valproate	VALPROATE SODIUM
Antiepileptic	sodium valproate	VALPROATE SODIUM;VALPROIC ACID
Antiepileptic	Topiramate	PHENTERMINE HYDROCHLORIDE;TOPIRAMATE
Antiepileptic	Topiramate	PHENTERMINE;TOPIRAMATE
Antiepileptic	Topiramate	TOPIRAMATE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;CHLORDIAZEPOXIDE

Protocol Pharmacologic Category	Drug Class	Preferred Name
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;CHLORDIAZEPOXIDE HYDROCHLORIDE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;CODEINE PHOSPHATE;DEXTROPROPOXYPHENE HYDROCHLORIDE;METAMIZOLE SODIUM
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;DIAZEPAM
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;DIAZEPAM;PERPHENAZINE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;GABAPENTIN
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;LIDOCAINE HYDROCHLORIDE;PREDNISONE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;MECOBALAMIN
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;MEDAZEPAM
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;PERPHENAZINE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;PREGABALIN
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;PRIDINOL HYDROCHLORIDE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;PROPRANOLOL HYDROCHLORIDE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE HYDROCHLORIDE;TRIFLUOPERAZINE HYDROCHLORIDE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;CHLORDIAZEPOXIDE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;CODEINE;DEXTROPROPOXYPHENE; METAMIZOLE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;DIAZEPAM

Protocol Pharmacologic Category	Drug Class	Preferred Name
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;DIAZEPAM;PERPHENAZINE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;GABAPENTIN
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;KETAMINE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;LIDOCAINE;PREDNISONE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;MECOBALAMIN
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;MEDAZEPAM
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;PERPHENAZINE
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;PREGABALIN
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;PRIDINOL
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;PROPRANOLOL
Tricyclin antidepressant	Amitriptyline	AMITRIPTYLINE;TRIFLUOPERAZINE
Tricyclin antidepressant	Nortriptyline	NORTRIPTYLINE
Tricyclin antidepressant	Nortriptyline	NORTRIPTYLINE;PREGABALIN
Tricyclin antidepressant	Nortriptyline	NORTRIPTYLINE;PERPHENAZINE
Tricyclin antidepressant	Nortriptyline	NORTRIPTYLINE HYDROCHLORIDE
Tricyclin antidepressant	Nortriptyline	NORTRIPTYLINE HYDROCHLORIDE;PREGABALIN
Tricyclin antidepressant	Nortriptyline	NORTRIPTYLINE HYDROCHLORIDE;PERPHENAZINE
Beta-blockers	Metoprolol	ACETYLSALICYLIC ACID;ATORVASTATIN CALCIUM;METOPROLOL SUCCINATE;RAMIPRIL

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-blockers	Metoprolol	ACETYLSALICYLIC ACID;ATORVASTATIN;METOPROLOL;RAMIPRIL
Beta-blockers	Metoprolol	ACETYLSALICYLIC ACID;METOPROLOL
Beta-blockers	Metoprolol	ACETYLSALICYLIC ACID;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	AMLODIPINE BESILATE;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	AMLODIPINE BESILATE;METOPROLOL TARTRATE
Beta-blockers	Metoprolol	AMLODIPINE;METOPROLOL
Beta-blockers	Metoprolol	AMLODIPINE;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	AMLODIPINE;METOPROLOL TARTRATE
Beta-blockers	Metoprolol	ATORVASTATIN CALCIUM;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	ATORVASTATIN CALCIUM;METOPROLOL TARTRATE;RAMIPRIL
Beta-blockers	Metoprolol	ATORVASTATIN;METOPROLOL
Beta-blockers	Metoprolol	ATORVASTATIN;METOPROLOL;RAMIPRIL
Beta-blockers	Metoprolol	BENIDIPINE HYDROCHLORIDE;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	BENIDIPINE;METOPROLOL
Beta-blockers	Metoprolol	CHLORTALIDONE;CILNIDIPINE;METOPROLOL
Beta-blockers	Metoprolol	CHLORTALIDONE;METOPROLOL
Beta-blockers	Metoprolol	CHLORTALIDONE;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	CHLORTALIDONE;METOPROLOL SUCCINATE;TELMISARTAN
Beta-blockers	Metoprolol	CHLORTALIDONE;METOPROLOL TARTRATE
Beta-blockers	Metoprolol	CHLORTALIDONE;METOPROLOL;TELMISARTAN
Beta-blockers	Metoprolol	CILNIDIPINE;METOPROLOL
Beta-blockers	Metoprolol	CILNIDIPINE;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	CILNIDIPINE;METOPROLOL SUCCINATE;TELMISARTAN
Beta-blockers	Metoprolol	CILNIDIPINE;METOPROLOL TARTRATE
Beta-blockers	Metoprolol	CILNIDIPINE;METOPROLOL TARTRATE;TELMISARTAN
Beta-blockers	Metoprolol	CILNIDIPINE;METOPROLOL;TELMISARTAN

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-blockers	Metoprolol	FELODIPINE;METOPROLOL
Beta-blockers	Metoprolol	FELODIPINE;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	HYDRALAZINE HYDROCHLORIDE;HYDROCHLOROTHIAZIDE; METOPROLOL TARTRATE
Beta-blockers	Metoprolol	HYDRALAZINE;HYDROCHLOROTHIAZIDE; METOPROLOL
Beta-blockers	Metoprolol	HYDROCHLOROTHIAZIDE;METOPROLOL
Beta-blockers	Metoprolol	HYDROCHLOROTHIAZIDE;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	HYDROCHLOROTHIAZIDE;METOPROLOL TARTRATE
Beta-blockers	Metoprolol	ISOSORBIDE MONONITRATE;METOPROLOL
Beta-blockers	Metoprolol	ISOSORBIDE MONONITRATE;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	IVABRADINE HYDROCHLORIDE;METOPROLOL TARTRATE
Beta-blockers	Metoprolol	IVABRADINE;METOPROLOL
Beta-blockers	Metoprolol	LEVAMLODIPINE BESILATE;METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	LEVAMLODIPINE;METOPROLOL
Beta-blockers	Metoprolol	METOPROLOL
Beta-blockers	Metoprolol	METOPROLOL FUMARATE
Beta-blockers	Metoprolol	METOPROLOL SUCCINATE
Beta-blockers	Metoprolol	METOPROLOL SUCCINATE;METOPROLOL TARTRATE
Beta-blockers	Metoprolol	METOPROLOL SUCCINATE;OLMESARTAN MEDOXOMIL
Beta-blockers	Metoprolol	METOPROLOL SUCCINATE;RAMIPRIL
Beta-blockers	Metoprolol	METOPROLOL SUCCINATE;TELMISARTAN
Beta-blockers	Metoprolol	METOPROLOL TARTRATE
Beta-blockers	Metoprolol	METOPROLOL TARTRATE;NIFEDIPINE
Beta-blockers	Metoprolol	METOPROLOL TARTRATE;OLMESARTAN MEDOXOMIL
Beta-blockers	Metoprolol	METOPROLOL TARTRATE;RAMIPRIL

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-blockers	Metoprolol	METOPROLOL TARTRATE;TELMISARTAN
Beta-blockers	Metoprolol	METOPROLOL TARTRATE;TRIMETAZIDINE HYDROCHLORIDE
Beta-blockers	Metoprolol	METOPROLOL;MORPHINE
Beta-blockers	Metoprolol	METOPROLOL;NIFEDIPINE
Beta-blockers	Metoprolol	METOPROLOL;OLMESARTAN
Beta-blockers	Metoprolol	METOPROLOL;OLMESARTAN MEDOXOMIL
Beta-blockers	Metoprolol	METOPROLOL;RAMIPRIL
Beta-blockers	Metoprolol	METOPROLOL;TELMISARTAN
Beta-blockers	Metoprolol	METOPROLOL;TRIMETAZIDINE
Beta-blockers	Bisoprolol	ACETYLSALICYLIC ACID;BISOPROLOL FUMARATE;CANDESARTAN CILEXETIL;HYDROCHLOROTHIAZIDE;ROSUVASTATIN CALCIUM
Beta-blockers	Bisoprolol	ACETYLSALICYLIC ACID;BISOPROLOL;CANDESARTAN;HYDROCHLOROTHIAZIDE;ROSUVASTATIN
Beta-blockers	Atenolol	ACETYLSALICYLIC ACID;ATENOLOL;HYDROCHLOROTHIAZIDE;RAMIPRIL;SIMVASTATIN
Beta-blockers	Atenolol	ALPRAZOLAM;ATENOLOL
Beta-blockers	Atenolol	AMILORIDE HYDROCHLORIDE;ATENOLOL;HYDROCHLOROTHIAZIDE
Beta-blockers	Atenolol	AMILORIDE;ATENOLOL;CHLORTALIDONE
Beta-blockers	Atenolol	AMILORIDE;ATENOLOL;HYDROCHLOROTHIAZIDE
Beta-blockers	Atenolol	AMLODIPINE BESILATE;ATENOLOL
Beta-blockers	Atenolol	AMLODIPINE BESILATE;ATENOLOL;CHLORTALIDONE
Beta-blockers	Atenolol	AMLODIPINE;ATENOLOL
Beta-blockers	Atenolol	AMLODIPINE;ATENOLOL;CHLORTALIDONE
Beta-blockers	Atenolol	ATENOLOL
Beta-blockers	Atenolol	ATENOLOL HYDROCHLORIDE

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-blockers	Atenolol	ATENOLOL HYDROCHLORIDE;BENDROFLUMETHIAZIDE; HYDRALAZINE
Beta-blockers	Atenolol	ATENOLOL HYDROCHLORIDE;CHLORTALIDONE
Beta-blockers	Atenolol	ATENOLOL;BENDROFLUMETHIAZIDE
Beta-blockers	Atenolol	ATENOLOL;BENDROFLUMETHIAZIDE; HYDRALAZINE
Beta-blockers	Atenolol	ATENOLOL;CHLORTALIDONE
Beta-blockers	Atenolol	ATENOLOL;CHLORTALIDONE;HYDRALAZINE
Beta-blockers	Atenolol	ATENOLOL;CHLORTALIDONE;HYDRALAZINE HYDROCHLORIDE
Beta-blockers	Atenolol	ATENOLOL;CHLORTALIDONE;NIFEDIPINE
Beta-blockers	Atenolol	ATENOLOL;CHLORTALIDONE;NITRENDIPINE
Beta-blockers	Atenolol	ATENOLOL;HYDROCHLOROTHIAZIDE
Beta-blockers	Atenolol	ATENOLOL;HYDROCHLOROTHIAZIDE;LOSARTAN
Beta-blockers	Atenolol	ATENOLOL;HYDROCHLOROTHIAZIDE;LOSARTAN POTASSIUM
Beta-blockers	Atenolol	ATENOLOL;INDAPAMIDE
Beta-blockers	Atenolol	ATENOLOL;ISOSORBIDE MONONITRATE
Beta-blockers	Atenolol	ATENOLOL;LERCANIDIPINE
Beta-blockers	Atenolol	ATENOLOL;LERCANIDIPINE HYDROCHLORIDE
Beta-blockers	Atenolol	ATENOLOL;LEVAMLODIPINE
Beta-blockers	Atenolol	ATENOLOL;LEVAMLODIPINE BESILATE
Beta-blockers	Atenolol	ATENOLOL;LOSARTAN
Beta-blockers	Atenolol	ATENOLOL;LOSARTAN POTASSIUM
Beta-blockers	Atenolol	ATENOLOL;NIFEDIPINE
Beta-blockers	Atenolol	ATENOLOL;NITRENDIPINE
Beta-blockers	Nadolol	BENDROFLUMETHIAZIDE;NADOLOL
Beta-blockers	Nadolol	NADOLOL
Beta-blockers	Propranolol	ALPRAZOLAM;PROPRANOLOL
Beta-blockers	Propranolol	ALPRAZOLAM;PROPRANOLOL HYDROCHLORIDE

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-blockers	Propranolol	AMOBARBITAL SODIUM;ATROPA BELLA-DONNA EXTRACT;CLAVICEPS PURPUREA EXTRACT;PROPRANOLOL
Beta-blockers	Propranolol	AMOBARBITAL;ATROPA BELLA-DONNA;CLAVICEPS PURPUREA;PROPRANOLOL
Beta-blockers	Propranolol	ATROPINE SULFATE;CRATAEGUS SPP. LEAF WITH FLOWER;PROPRANOLOL HYDROCHLORIDE;VALERIANA OFFICINALIS ROOT
Beta-blockers	Propranolol	ATROPINE;CRATAEGUS SPP.;PROPRANOLOL;VALERIANA OFFICINALIS
Beta-blockers	Propranolol	BENDROFLUMETHIAZIDE;HYDRALAZINE HYDROCHLORIDE;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	BENDROFLUMETHIAZIDE;HYDRALAZINE; PROPRANOLOL
Beta-blockers	Propranolol	BENDROFLUMETHIAZIDE;PROPRANOLOL
Beta-blockers	Propranolol	BENDROFLUMETHIAZIDE;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	BENZALKONIUM CHLORIDE;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	BENZALKONIUM;PROPRANOLOL
Beta-blockers	Propranolol	CAFFEINE;PHENYTOIN SODIUM;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	CAFFEINE;PHENYTOIN;PROPRANOLOL
Beta-blockers	Propranolol	CAFFEINE;PROPRANOLOL
Beta-blockers	Propranolol	CHLORTALIDONE;NIFEDIPINE;PROPRANOLOL
Beta-blockers	Propranolol	CHLORTALIDONE;NIFEDIPINE;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	CLONAZEPAM;PROPRANOLOL
Beta-blockers	Propranolol	CLONAZEPAM;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	DIAZEPAM;PROPRANOLOL
Beta-blockers	Propranolol	DIAZEPAM;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	DIHYDRALAZINE SULFATE;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	DIHYDRALAZINE;PROPRANOLOL

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-blockers	Propranolol	ETIZOLAM;PROPRANOLOL
Beta-blockers	Propranolol	ETIZOLAM;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	HYDRALAZINE HYDROCHLORIDE;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	HYDRALAZINE;PROPRANOLOL
Beta-blockers	Propranolol	HYDROCHLOROTHIAZIDE;PROPRANOLOL
Beta-blockers	Propranolol	HYDROCHLOROTHIAZIDE;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	HYDROCHLOROTHIAZIDE;PROPRANOLOL HYDROCHLORIDE;TRIAMTERENE
Beta-blockers	Propranolol	HYDROCHLOROTHIAZIDE;PROPRANOLOL; TRIAMTERENE
Beta-blockers	Propranolol	NIFEDIPINE;PROPRANOLOL
Beta-blockers	Propranolol	NIFEDIPINE;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	PENTAERITHRITYL TETRANITRATE;PROPRANOLOL
Beta-blockers	Propranolol	PENTAERITHRITYL TETRANITRATE;PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	PROPRANOLOL
Beta-blockers	Propranolol	PROPRANOLOL HYDROCHLORIDE
Beta-blockers	Propranolol	PROPRANOLOL HYDROCHLORIDE;SPIRONOLACTONE
Beta-blockers	Propranolol	PROPRANOLOL;SPIRONOLACTONE
Beta-blockers	Timolol	ACECLIDINE HYDROCHLORIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	ACECLIDINE;TIMOLOL
Beta-blockers	Timolol	AMILORIDE HYDROCHLORIDE;HYDROCHLOROTHIAZIDE; TIMOLOL MALEATE
Beta-blockers	Timolol	AMILORIDE;HYDROCHLOROTHIAZIDE;TIMOLOL
Beta-blockers	Timolol	BENDROFLUMETHIAZIDE;TIMOLOL
Beta-blockers	Timolol	BENDROFLUMETHIAZIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	BENZALKONIUM CHLORIDE;SODIUM HYDROXIDE;SODIUM PHOSPHATE DIBASIC;SODIUM PHOSPHATE MONOBASIC (ANHYDROUS);TIMOLOL MALEATE

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-blockers	Timolol	BENZALKONIUM CHLORIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	BENZALKONIUM;SODIUM HYDROXIDE;SODIUM PHOSPHATE;SODIUM PHOSPHATE MONOBASIC (ANHYDROUS);TIMOLOL
Beta-blockers	Timolol	BENZALKONIUM;TIMOLOL
Beta-blockers	Timolol	BIMATOPROST;BRIMONIDINE TARTRATE;TIMOLOL MALEATE
Beta-blockers	Timolol	BIMATOPROST;BRIMONIDINE;TIMOLOL
Beta-blockers	Timolol	BIMATOPROST;TIMOLOL
Beta-blockers	Timolol	BIMATOPROST;TIMOLOL MALEATE
Beta-blockers	Timolol	BRIMONIDINE TARTRATE;DORZOLAMIDE HYDROCHLORIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	BRIMONIDINE TARTRATE;DORZOLAMIDE;LATANOPROST; TIMOLOL MALEATE
Beta-blockers	Timolol	BRIMONIDINE TARTRATE;DORZOLAMIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	BRIMONIDINE TARTRATE;TIMOLOL
Beta-blockers	Timolol	BRIMONIDINE TARTRATE;TIMOLOL MALEATE
Beta-blockers	Timolol	BRIMONIDINE;DORZOLAMIDE;LATANOPROST; TIMOLOL
Beta-blockers	Timolol	BRIMONIDINE;DORZOLAMIDE;TIMOLOL
Beta-blockers	Timolol	BRIMONIDINE;TIMOLOL
Beta-blockers	Timolol	BRINZOLAMIDE;TIMOLOL
Beta-blockers	Timolol	BRINZOLAMIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	DORZOLAMIDE HYDROCHLORIDE;TIMOLOL
Beta-blockers	Timolol	DORZOLAMIDE HYDROCHLORIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	DORZOLAMIDE;TIMOLOL
Beta-blockers	Timolol	DORZOLAMIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	EUCALYPTUS GLOBULUS OIL;MENTHA X PIPERITA OIL;PINUS MUGO OIL;TIMOLOL MALEATE;TOCOPHERYL ACETATE

Protocol Pharmacologic Category	Drug Class	Preferred Name
Beta-blockers	Timolol	EUCALYPTUS GLOBULUS;MENTHA X PIPERITA;PINUS MUGO;TIMOLOL;TOCOPHEROL
Beta-blockers	Timolol	HYALURONATE SODIUM;TIMOLOL MALEATE
Beta-blockers	Timolol	HYALURONIC ACID;TIMOLOL
Beta-blockers	Timolol	HYDROCHLOROTHIAZIDE;TIMOLOL
Beta-blockers	Timolol	HYDROCHLOROTHIAZIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	HYPROMELLOSE;TIMOLOL
Beta-blockers	Timolol	HYPROMELLOSE;TIMOLOL MALEATE
Beta-blockers	Timolol	LATANOPROST;TIMOLOL
Beta-blockers	Timolol	LATANOPROST;TIMOLOL MALEATE
Beta-blockers	Timolol	PILOCARPINE HYDROCHLORIDE;TIMOLOL MALEATE
Beta-blockers	Timolol	PILOCARPINE NITRATE;TIMOLOL MALEATE
Beta-blockers	Timolol	PILOCARPINE;TIMOLOL
Beta-blockers	Timolol	PILOCARPINE;TIMOLOL MALEATE
Beta-blockers	Timolol	TAFLUPROST;TIMOLOL
Beta-blockers	Timolol	TAFLUPROST;TIMOLOL MALEATE
Beta-blockers	Timolol	TIMOLOL
Beta-blockers	Timolol	TIMOLOL HEMIHYDRATE
Beta-blockers	Timolol	TIMOLOL MALEATE
Beta-blockers	Timolol	TIMOLOL MALEATE, R-ENANTIOMER
Beta-blockers	Timolol	TIMOLOL MALEATE, S-ENANTIOMER
Beta-blockers	Timolol	TIMOLOL MALEATE;TRAVOPROST
Beta-blockers	Timolol	TIMOLOL;TRAVOPROST
Calcium channel blocker	Flunarizine	DIHYDROERGOCRISTINE MESILATE;FLUNARIZINE DIHYDROCHLORIDE
Calcium channel blocker	Flunarizine	DIHYDROERGOCRISTINE;FLUNARIZINE
Calcium channel blocker	Flunarizine	DOMPERIDONE;FLUNARIZINE DIHYDROCHLORIDE;PARACETAMOL
Calcium channel blocker	Flunarizine	DOMPERIDONE;FLUNARIZINE;PARACETAMOL

Protocol Pharmacologic Category	Drug Class	Preferred Name
Calcium channel blocker	Flunarizine	FLUNARIZINE
Calcium channel blocker	Flunarizine	FLUNARIZINE BETADEX
Calcium channel blocker	Flunarizine	FLUNARIZINE DIHYDROCHLORIDE
Calcium channel blocker	Flunarizine	FLUNARIZINE DIHYDROCHLORIDE;NICERGOLINE
Calcium channel blocker	Flunarizine	FLUNARIZINE DIHYDROCHLORIDE;PROPRANOLOL HYDROCHLORIDE
Calcium channel blocker	Flunarizine	FLUNARIZINE;NICERGOLINE
Calcium channel blocker	Flunarizine	FLUNARIZINE;PROPRANOLOL
Calcium channel blocker	Lomerizine	LOMERIZINE
Calcium channel blocker	Lomerizine	LOMERIZINE HYDROCHLORIDE
Calcium channel blocker	Verapamil	CAPTOPRIL;VERAPAMIL
Calcium channel blocker	Verapamil	CAPTOPRIL;VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	DIAZEPAM;VERAPAMIL
Calcium channel blocker	Verapamil	DIAZEPAM;VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	DIGOXIN;TRIMETOZINE;VERAPAMIL
Calcium channel blocker	Verapamil	DIGOXIN;TRIMETOZINE;VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	HYDROCHLOROTHIAZIDE;TRIAMTERENE; VERAPAMIL
Calcium channel blocker	Verapamil	HYDROCHLOROTHIAZIDE;TRIAMTERENE; VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	HYDROCHLOROTHIAZIDE;VERAPAMIL

Protocol Pharmacologic Category	Drug Class	Preferred Name
Calcium channel blocker	Verapamil	HYDROCHLOROTHIAZIDE;VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	ISOSORBIDE DINITRATE;VERAPAMIL
Calcium channel blocker	Verapamil	ISOSORBIDE DINITRATE;VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	PENTOBARBITAL;VERAPAMIL
Calcium channel blocker	Verapamil	PENTOBARBITAL;VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	PROSCILLARIDIN;VERAPAMIL
Calcium channel blocker	Verapamil	PROSCILLARIDIN;VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	QUINIDINE BISULFATE;VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	QUINIDINE;VERAPAMIL
Calcium channel blocker	Verapamil	TRANDOLAPRIL;VERAPAMIL
Calcium channel blocker	Verapamil	TRANDOLAPRIL;VERAPAMIL HYDROCHLORIDE
Calcium channel blocker	Verapamil	VERAPAMIL
Calcium channel blocker	Verapamil	VERAPAMIL HYDROCHLORIDE
Angiotensin receptor blocker (ARB)	Candesartan	AMLODIPINE BESILATE;CANDESARTAN CILEXETIL
Angiotensin receptor blocker (ARB)	Candesartan	AMLODIPINE BESILATE;CANDESARTAN CILEXETIL;HYDROCHLOROTHIAZIDE
Angiotensin receptor blocker (ARB)	Candesartan	AMLODIPINE;ATORVASTATIN;CANDESARTAN

Protocol Pharmacologic Category	Drug Class	Preferred Name
Angiotensin receptor blocker (ARB)	Candesartan	AMLODIPINE;CANDESARTAN
Angiotensin receptor blocker (ARB)	Candesartan	AMLODIPINE;CANDESARTAN CILEXETIL
Angiotensin receptor blocker (ARB)	Candesartan	AMLODIPINE;CANDESARTAN CILEXETIL;HYDROCHLOROTHIAZIDE
Angiotensin receptor blocker (ARB)	Candesartan	AMLODIPINE;CANDESARTAN; HYDROCHLOROTHIAZIDE
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN CILEXETIL
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN CILEXETIL;FELODIPINE
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN CILEXETIL;HYDROCHLOROTHIAZIDE
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN CILEXETIL;HYDROCHLOROTHIAZIDE; ROSUVASTATIN CALCIUM
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN CILEXETIL;ROSUVASTATIN CALCIUM
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN;FELODIPINE
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN;HYDROCHLOROTHIAZIDE

Protocol Pharmacologic Category	Drug Class	Preferred Name
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN;HYDROCHLOROTHIAZIDE; ROSUVASTATIN
Angiotensin receptor blocker (ARB)	Candesartan	CANDESARTAN;ROSUVASTATIN
Angiotensin converting enzyme (ACE) inhibitor	Lisinopril	LISINOPRIL
Angiotensin converting enzyme (ACE) inhibitor	Lisinopril	LISINOPRIL DIHYDRATE
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine	DESVENLAFAXINE
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine	DESVENLAFAXINE BENZOATE
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine	DESVENLAFAXINE FUMARATE
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine	DESVENLAFAXINE SUCCINATE
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine	DESVENLAFAXINE SUCCINATE MONOHYDRATE
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Venlafaxine	VENLAFAXINE

Protocol Pharmacologic Category	Drug Class	Preferred Name
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Venlafaxine	VENLAFAXINE BESYLATE MONOHYDRATE
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Venlafaxine	VENLAFAXINE HYDROCHLORIDE
Miscellaneous	Pizotifen	NICOTINAMIDE;PIZOTIFEN MALATE;PYRIDOXINE HYDROCHLORIDE;RIBOFLAVIN SODIUM PHOSPHATE;THIAMINE HYDROCHLORIDE
Miscellaneous	Pizotifen	NICOTINAMIDE;PIZOTIFEN MALATE;PYRIDOXINE HYDROCHLORIDE;RIBOFLAVIN;THIAMINE HYDROCHLORIDE
Miscellaneous	Pizotifen	NICOTINAMIDE;PIZOTIFEN MALATE;PYRIDOXINE;RIBOFLAVIN;THIAMINE
Miscellaneous	Pizotifen	NICOTINAMIDE;PIZOTIFEN;PYRIDOXINE; RIBOFLAVIN;THIAMINE
Miscellaneous	Pizotifen	PIZOTIFEN
Miscellaneous	Pizotifen	PIZOTIFEN HYDROCHLORIDE
Miscellaneous	Pizotifen	PIZOTIFEN MALATE