# Statistical Analysis Plan for Study 3101-304-002

# A Phase 3, Multicenter, Randomized, Double blind, Placebo-controlled, Parallel group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prophylaxis of Migraine in Participants with Episodic Migraine Who Have Previously Failed 2 to 4 Classes of Oral Prophylactic Treatments (ELEVATE)

## Version: 2.0

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# 1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for atogepant (AGN-241689) Study 3101-304-002, a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of oral atogepant for the prophylaxis of migraine in participants with episodic migraine who have previously failed 2 to 4 classes of oral prophylactic treatments (ELEVATE).

Study 3101-304-003 examines the efficacy and safety of atogepant in participants with episodic migraine who have previously failed 2 to 4 classes of oral prophylactic treatments.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis. Specifications of tables, figures, and data listings and statistical programming plan are contained in separate documents.

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

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 15.1.

# 2.0 Study Objectives and Design

The objective of this study is to prospectively assess the safety, tolerability, and efficacy of atogepant 60mg QD compared with placebo in the prophylaxis of episodic migraine in participants who previously failed 2 to 4 classes of oral prophylactic treatments.

## 2.1 Objectives, Hypotheses and Estimands

| Objectives | Hypotheses | Estimands |
|---|---|---|
| **Primary Efficacy** | | |
| To prospectively test for superiority of atogepant 60 mg QD versus placebo for the prevention of migraine in participants with episodic migraine who have previously failed 2 to 4 classes of oral medications for the prophylaxis of migraine | Null: atogepant 60 mg QD is equally effective to placebo in decreasing from baseline in mean monthly migraine days across the 12-week treatment period<br>Alternative: atogepant 60 mg QD is superior to placebo in decreasing from baseline in mean monthly migraine days across the 12-week treatment period | Efficacy is to be measured using change from baseline in mean monthly migraine days across the 12-week treatment period<br>*For the United States:*<br>The difference in the mean change from baseline in mean monthly migraine days across the 12-week treatment period between atogepant group and placebo in the Modified Intent-to-Treat (mITT) Population. Data after the discontinuation from double-blind treatment period will be excluded and assumed missing at random (MAR).<br>*For the European Union*<br>The difference in the mean change from baseline in mean monthly migraine days across the 12-week treatment period between atogepant group and placebo in the Off-treatment Hypothetical Estimand Population regardless of premature discontinuation of study drug. Data after starting a new migraine prophylaxis treatment use during the follow-up period will be excluded. |

| Objectives | Hypotheses | Estimands |
|---|---|---|
| **Secondary Efficacy** | | |
| To evaluate the effect of atogepant 60 mg QD versus placebo on the proportion of participants with at least 50% reduction from baseline in monthly migraine days | Null hypothesis: atogepant 60 mg QD is equally effective to placebo in the achievement of at least 50% reduction from baseline in monthly migraine days across the 12-week treatment period<br>Alternative hypothesis: atogepant 60 mg QD is superior to placebo in the achievement of at least 50% reduction from baseline in monthly migraine days across the 12-week treatment period | Efficacy is to be measured using the achievement of at least 50% reduction from baseline in monthly migraine days across the 12-week treatment period<br>*For the United States:*<br>The odds ratio in participants achieving at least 50% reduction in 3-month average of monthly migraine days between atogepant group and placebo in the mITT Population. Data after the discontinuation from double-blind treatment period will be excluded.<br>*For the European Union*<br>The odds ratio in participants achieving at least 50% reduction in 3-month average of monthly migraine days between atogepant group and placebo in the Off-treatment Hypothetical Estimand Population regardless of premature discontinuation of study drug. Data after starting a new migraine prophylaxis treatment use during the follow-up period will be excluded. |

| Objectives | Hypotheses | Estimands |
|---|---|---|
| To evaluate the effect of atogepant 60 mg QD versus placebo for the prophylaxis of headache | Null hypothesis: atogepant 60 mg QD is equally effective to placebo in decreasing from baseline in mean monthly headache days across the 12-week treatment period<br>Alternative hypothesis: atogepant 60 mg QD is superior to placebo in decreasing from baseline in mean monthly headache days across the 12-week treatment period | Efficacy is to be measured using change from baseline in mean monthly headache days across the 12-week treatment period<br>*For the United States:*<br>The difference in mean change from baseline in mean monthly headache days across the 12-week treatment period between atogepant group and placebo in the mITT Population. Data after the discontinuation from double-blind treatment period will be excluded and assumed missing at random (MAR).<br>*For the European Union*<br>The difference in the mean change from baseline in mean monthly headache days across the 12-week treatment period between atogepant group and placebo in the Off-treatment Hypothetical Estimand Population regardless of premature discontinuation of study drug. Data after starting a new migraine prophylaxis treatment use during the follow-up period will be excluded. |

| Objectives | Hypotheses | Estimands |
|---|---|---|
| To evaluate the effect of atogepant 60 mg QD versus placebo on acute medication use | Null hypothesis: atogepant 60 mg QD is equally effective to placebo in decreasing from baseline in mean monthly acute medication use days across the 12-week treatment period<br>Alternative hypothesis: atogepant 60 mg QD is superior to placebo in decreasing from baseline in mean monthly acute medication use days across the 12-week treatment period | Efficacy is to be measured using change from baseline in mean monthly acute medication use days across the 12-week treatment period<br>*For the United States:*<br>The difference in mean change from baseline in mean monthly acute medication use days across the 12-week treatment period between atogepant group and placebo in the mITT Population. Data after the discontinuation from double-blind treatment period will be excluded and assumed missing at random (MAR).<br>*For the European Union*<br>The difference in the mean change from baseline in mean monthly acute medication use days across the 12-week treatment period between atogepant group and placebo in the Off-treatment Hypothetical Estimand Population regardless of premature discontinuation of study drug. Data after starting a new migraine prophylaxis treatment use during the follow-up period will be excluded. |

| Objectives | Hypotheses | Estimands |
|---|---|---|
| To evaluate the effect of atogepant 60 mg QD versus placebo on the impact of migraine on daily activities as assessed by MSQ v2.1 Role Function-Restrictive domain score | Null hypothesis: atogepant 60 mg QD is equally effective to placebo in increasing from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12<br>Alternative hypothesis: atogepant 60 mg QD is superior to placebo in increasing from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 | Efficacy is to be measured using change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Week 12<br>*For the United States:*<br>The difference in mean change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 between atogepant group and placebo in the mITT Population. Data after the discontinuation from double-blind treatment period will be excluded and assumed missing at random (MAR).<br>*For the European Union*<br>The difference in mean change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 between atogepant group and placebo in the Off-treatment Hypothetical Estimand Population regardless of premature discontinuation of study drug. Data after starting a new migraine prophylaxis treatment use during the follow-up period will be excluded. |
| *For the United States only:*<br>To evaluate the effect of atogepant 60 mg QD versus placebo on Performance of Daily Activities | *For the United States only:*<br>Null hypothesis: atogepant 60 mg QD is equally effective to placebo in decreasing from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period<br>Alternative hypothesis: atogepant 60 mg QD is superior to placebo in decreasing from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period | Efficacy is to be measured using change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period<br>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 atogepant group and placebo in the mITT Population. Data after the discontinuation from double-blind treatment period will be excluded and assumed missing at random (MAR). |

| Objectives | Hypotheses | Estimands |
|---|---|---|
| To evaluate the effect of atogepant 60 mg QD and atogepant 60 mg QD versus placebo on physical impairment | Null hypothesis: atogepant 60 mg QD is equally effective to placebo in decreasing from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period<br>Alternative hypothesis: atogepant 60 mg QD is superior to placebo in decreasing from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period | Efficacy is to be measured using change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period<br>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 atogepant group and placebo in the mITT Population. Data after the discontinuation from double-blind treatment period will be excluded and assumed missing at random (MAR). |
| *For the European Union only:*<br>To evaluate the effect of atogepant 60 mg QD versus placebo on the impact of headaches on daily functioning as assessed by HIT-6 | *For the European Union only:*<br>Null hypothesis: atogepant 60 mg QD is equally effective to placebo in decreasing from baseline in the HIT-6 total score at Week 12<br>Alternative hypothesis: atogepant 60 mg QD is superior to placebo in decreasing from baseline in the HIT-6 total score at Week 12 | Efficacy is to be measured using change from baseline in the HIT-6 total score at Week 12<br>The difference in mean change from baseline in the HIT-6 total score at Week 12 between atogepant group and placebo in the Off-treatment Hypothetical Estimand Population regardless of premature discontinuation of study drug. Data after starting a new migraine prophylaxis treatment use during the follow-up period will be excluded. |

## 2.2 Study Design Overview

This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study planned to be conducted at approximately 125 sites globally (North America, Europe, and Asia/Pacific).

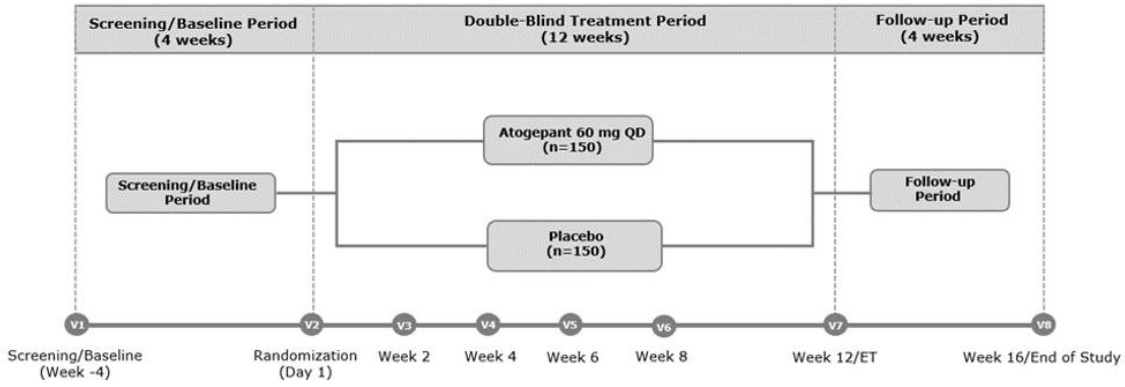
Participation will begin with a 4-week screening/baseline period. Participants who complete the 4-week screening/baseline period and meet all entry criteria will be randomized to the double-blind treatment period of the study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a subsequent safety follow-up period of 4 additional weeks. Total duration of study participation for one participant is approximately 20 weeks.

There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline Visit), Visit 2 (Randomization Visit), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Week 16/EOS/Follow-up). The Visit 8/EOS/follow-up period must be completed for all participants who take at least one dose of study intervention, except for participants rolling over into Study 3101-312-002 (long-term safety extension study). For these rollover participants Visit 8 is not required, because the final Follow-up Visit will be performed at the end of the long-term safety extension study. For participants who screen fail for the long-term safety extension study, the Follow-up Visit of Study 3101-304-002 must be completed.

Per study design (Protocol Sections 10.8.4 and 10.8.5), eDiary data will be collected for participants who early terminated from the double-blind treatment period during the 4 weeks between V7 (Early termination visit) and V8 (Follow-up Visit).

The schematic of the study is shown in Figure 1.

**Figure 1. Study Schematic**




## 2.3 Treatment Assignment and Blinding

Approximately 300 participants will be randomized to one of 2 treatment arms (placebo, and atogepant 60 mg QD) in a 1:1 ratio as follows:

- Placebo (n = 150)
- Atogepant 60 mg QD (n = 150)

Randomization will be stratified based on region (North America, Europe, and Asia/Pacific), number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) and number of classes of failed prior prophylactic treatments (2 and > 2). Block randomization will be applied with a block size of 4 (2 treatment arms × 2). Though the study was planned to include sites in Asia/Pacific, no participants were enrolled from this region.

A randomization cap of 20% will be instituted to ensure that the planned randomized participants include no more than 20% of participants with 4 to <8 migraine days at baseline. Approximately 50% of randomized participants will have failed > 2 classes of prior prophylactic treatments.

## 2.4 Sample Size Determination

A sample size of 150 randomized participants per treatment group will provide a 97% and 95% power to detect the treatment difference of -1.7 or -1.6 between atogepant and placebo for the primary efficacy endpoint for the United States or the EU, respectively. This sample size was selected to provide sufficient power for each of the secondary endpoints in Table 1 for the United States and in Table 2 for the EU.

## Table 1. Statistical Power for Primary and Secondary Endpoints for the United States

| Hypothesis Testing | Endpoint | Treatment Difference from Placebo | Standard Deviation | Statistical Power |
|---|---|---|---|---|
| Primary | Change from baseline in mean monthly migraine days across the 12-week treatment period | -1.7 | 3.5 | 97% |
| Secondary 1 | Achievement of at least 50% reduction in mean monthly migraine days across the 12-week treatment period | 29% Placebo rate, 60% atogepant rate | Not applicable | 99% |
| Secondary 2 | Change from baseline in mean monthly headache days across the 12-week treatment period | -1.7 | 3.7 | 95% |
| Secondary 3 | Change from baseline in mean monthly acute medication use days across the 12-week treatment period | -1.5 | 3.1 | 97% |
| Secondary 4 | Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 | 10.8 | 22.6 | 96% |
| Secondary 5 | Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period | -3.3 | 7.3 | 93% |
| Secondary 6 | Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period | -2.4 | 6.4 | 81% |

**Table 2. Statistical Power for Primary and Secondary Endpoints for the EU**

| Hypothesis Testing | Endpoint | Treatment Difference from Placebo[a] | Standard Deviation[a] | Statistical Power |
|---|---|---|---|---|
| Primary | Change from baseline in mean monthly migraine days across the 12-week treatment period | -1.6 | 3.5 | 95% |
| Secondary 1 | Achievement of at least 50% reduction in mean monthly migraine days across the 12-week treatment period | 30% Placebo rate, 59% atogepant rate | Not applicable | 99% |
| Secondary 2 | Change from baseline in mean monthly headache days across the 12-week treatment period | -1.6 | 3.7 | 92% |
| Secondary 3 | Change from baseline in mean monthly acute medication use days across the 12-week treatment period | -1.4 | 3.2 | 93% |
| Secondary 4 | Change from baseline in HIT-6 total score at Week 12 | -3.9 | 7.6 | 98% |
| Secondary 5 | Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 | 10.9 | 22.8 | 96% |

a. The assumptions applied for the EU were estimated using off-treatment hypothetical estimand approach based on Advance Study data.

The power calculations are based on the following assumptions:

1. Table 3 provides the results from two atogepant studies (CGP-MD-01 and 3101-301-002 [Advance Study]) and Liberty Study (Reuter 2018) for the primary endpoint. The treatment difference for atogepant 60mg QD versus placebo is assumed to be observed treatment difference in the atogepant Advance study, which is a relative conservative assumption in term of primary endpoint. The standard deviation assumptions were based on the variance in Liberty Study and monthly variance observed in Advance Study for the primary endpoint. In particular, the assumed treatment difference from placebo in change from baseline

in mean monthly migraine days across the 12-week treatment period is -1.7 days for the United States and is -1.6 days for the EU, and the standard deviation is 3.5 days. Detailed treatment difference and standard deviation assumptions for secondary endpoints are listed in Table 1 for the United States and in Table 2 for the EU, which are based on the results from the atogepant Advance study.

**Table 3. Observed Treatment Effect for Primary Endpoint in Atogepant Program and Liberty**

| Study | Population | Atogepant 60 mg QD Treatment Difference from Placebo | Standard Deviation |
|---|---|---|---|
| Advance | mITT population | -1.72 | 3.00 |
| | Participants with Prior exposure to migraine preventive treatment = Yes | -2.16 | 3.01 |
| | Participants with one treatment failures | -1.94 | 3.04 |
| | Participants with two or more treatment failures | -2.91 | 3.34 |
| CGP-MD-01 | Participants with Prior exposure to migraine preventive treatment = Yes | -1.41 | 2.97 |
| Liberty | Efficacy Population for Treatment Failure study | -1.93 (Average of 12 Weeks) | 3.47[a] |
| | Efficacy Population for Treatment Failure study | -1.6 (At month 3) | 4.6 |

a. SD was calculated using variance in liberty and correlation matrix from Advance study

2. A fixed-sequence procedure will be used for multiple comparisons to control the family-wise Type I error rate at a 0.05 level. The testing sequence is specified in Table 1 and Table 2. Once the primary endpoint for atogepant dose is significant at 0.05 (2-sided), the secondary endpoints will be tested sequentially. Statistical powers for secondary endpoints are conditional on success of prior endpoints (assuming independence among the endpoints) in the sequence.

3. The dropout rate is assumed to be 15% for endpoints other than AIM-D related endpoints. The dropout rate for AIM-D endpoints is 21%. A higher missing rate for AIM-D endpoints was observed in the Advance Study because the related measure was collected only in Today's eDiary instead of both Yesterday and Today's eDiary. If the participants provide less than 14 records of Today's eDiary within a 28-day period, it would lead to missing data.

The assumptions of sample size calculation such as SD and dropout rate will be monitored while the study is ongoing and sample size will be adjusted. This blinded analysis of variability in the pooled treatment groups will be performed using the primary efficacy analysis model for the primary endpoint as described in Section 9.3.2 but excluding the terms treatment and treatment by visit interaction from model terms.

# 3.0 Endpoints

## 3.1 Primary Efficacy Endpoint

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

## 3.2 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints for the United States:

- Achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period
- Change from baseline in mean monthly headache days across the 12-week treatment period
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period
- 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 treatment period
- Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period

Secondary efficacy endpoints for the EU:

- Achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period
- Change from baseline in mean monthly headache days across the 12-week treatment period
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period
- Change from baseline in the HIT-6 total score at Week 12
- Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12

## 3.3 Exploratory Efficacy Endpoint(s)

Exploratory efficacy endpoints for the United States and EU are provided below:

- Achievement of ≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100% improvement (decrease) in monthly migraine days at Weeks 1-4, 5-8, and 9-12
- Achievement of ≥ 25%, ≥ 30%, ≥ 75%, 100% improvement (decrease) in monthly migraine days across the 12-week treatment period
- 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 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 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 treatment period
- Change from baseline in monthly severe headache days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period
- Change from baseline in the HIT-6 total score at Weeks 4, and 8 (*European Union only*)
- Change from baseline in the HIT-6 total score at Weeks 4, 8, and 12 (*United States only*)
- Achievement of at least a 5-point improvement (decrease) from baseline in total HIT-6 score at Weeks 4, 8, and 12
- Achievement of a rating of "much better" or "very much better" at Week 12 assessed by the PGIC
- Achievement of a rating of "satisfied" or "extremely satisfied" at Weeks 4, 8, and 12 as assessed by the PSSM
- 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 EQ-5D-5L descriptive system index score at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, 12, and Week 16
- Change from baseline in the EQ-5D-5L VAS score at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, 12, and Week 16
- 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 to 4, 5 to 8, and 9 to 12
- Change from baseline in monthly Physical Impairment domain score of the AIM-D at Weeks 1 to 4, 5 to 8, and 9 to 12
- Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period (*EU only*)
- Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period (*EU only*)
- Change from baseline in monthly AIM-D total score at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
- Change from baseline in monthly activity level at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
- Change from baseline in monthly activity limitation at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
- Change from baseline in PROMIS-PI total score at Weeks 4, 8, and 12
- Change from baseline in PHQ-9 score at Week 12

### 3.4 Safety Endpoint(s)

The safety parameters include adverse events (AEs), clinical laboratory, vital sign, electrocardiographic (ECG), and C-SSRS. For 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.

All AEs and other safety data will be presented in the listings at the subject level.

## 4.0 Analysis Populations

The following population sets will be used for the analyses.

The Intent-to-Treat (ITT) Population includes all randomized participants.

The Safety Population includes all participants who received at least 1 dose of study intervention. All safety analyses will be performed using the Safety Population and based on the treatment actually received, regardless of assigned treatment according to the planned randomization. Participants will be summarized according to the study treatment received for the majority of treatment period.

The Modified Intent-to-Treat (mITT) Population includes all randomized participants who received at least 1 dose of study intervention, 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 during the double-blind (DB) treatment period. All efficacy analyses described will be performed using the mITT population unless specified otherwise and based on the randomization assignment, regardless of the actual treatment received.

The Off-treatment Hypothetical Estimand Population includes all randomized participants who received at least 1 dose of study treatment, 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, 9 to 12) of eDiary data during the DB treatment period and follow-up period, regardless of whether on study treatment or off study treatment. This population is used for the primary estimand in the support of the European submissions.

# 5.0 Participant Disposition

The number of participants screened will be summarized overall by region; the number of participants in the ITT, Safety, mITT, and Off-treatment Hypothetical Estimand Populations will be summarized by treatment group and study site, by treatment group and region, and by treatment group and country.

A summary of participant accountability will be provided where the number of participants in each of the following categories will be summarized for each treatment group and pooled across treatment groups:

- Participants enrolled (randomized) in the study;

- Participants in each region [North America and Europe], number of migraine days during the screening/baseline period [< 4, 4 to < 8, and ≥ 8], and number of classes of failed prior prophylactic treatments [2 and > 2]);
- Participants who took at least one dose of study drug;
- Participants who completed double-blind treatment period;
- Participants who prematurely discontinued the double-blind treatment period (including reasons for premature discontinuation);

"Actual" stratification will be re-derived using data from eDiary and eCRF based on algorithms detailed in the SPP Section 3.2. A summary table and list of participants with inconsistent randomization stratum against IWRS will be provided.

For end of study participation, the number and percentage of participants who completed the follow-up period (or did not with associated reasons) will be summarized overall and by treatment group. In addition, the number and percentage of participants who signed informed consent for long-term safety extension Study 3101-312-002 will be summarized.

# 6.0 Study Treatment Duration and Compliance

For the Safety Population, duration of treatment will be summarized for each treatment group. Duration of treatment is defined for each participant as last dose date minus first dose date + 1. Duration of treatment will be summarized using the number of participants treated, mean, standard deviation, median, minimum, and maximum. In addition, the number and percentage of participants in each treatment duration of ≥ 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 will be summarized. Participant-years, calculated by summing the duration of exposure across the respective set of participants and dividing this sum by 365.25, will be summarized by treatment group.

Treatment compliance for a specific period is defined as the number of study medications actually taken during that period divided by the number of study medications that should have been taken during the same period. Percent treatment compliance as well as the

associated compliance categories (< 80%, 80% - 120%, > 120%) will be summarized in each period between 2 consecutive visits, as well as in the entire treatment period from the first dose of the double-blind study interventions actually taken to the last dose of double-blind study intervention actually taken for the Safety Population.

# 7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics and baseline characteristics will be summarized overall and by treatment group for the Safety Population, mITT Population and Off-treatment Hypothetical Estimand Population. Disease characteristics, medical history, and prior and concomitant medication will be summarized for the Safety Population. Categorical variables will be summarized with the number and percentage of participants; percentage will be calculated based on the non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, Q1, Q3, minimum, and maximum).

## 7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age, weight, height, and body mass index (BMI). Categorical demographic variables include sex, ethnicity, race, race group (white, all other races), age group (< 20, 20-29, 30-39, 40-49, 50-59, 60-69, and ≥ 70), region (North America and Europe).

Disease characteristics are contained in migraine history, including diagnosis, duration of disorder, the use of migraine prevention medication in the past, number and percentage of participants who failed 2, 3, or 4 classes of prior prevention medications, number and percentage of participants who failed preventive medication by class, average number of migraine or headache days per month at baseline and in the last 3 months, acute medications taken to treat migraine headaches, and advice on lifestyle alterations.

Baseline efficacy parameters (monthly migraine days, monthly headache days, monthly acute medication use days, Migraine Specific Quality of Life Questionnaire [MSQ] v2.1

Role Function-Restrictive domain score, monthly performance of daily activities domain score of the Activity Impairment in Migraine - Diary [AIM-D], and monthly physical impairment domain score of the AIM-D) will be summarized by treatment group for mITT Population. Baseline efficacy parameters (monthly migraine days, monthly headache days, monthly acute medication use days, Headache Impact Test [HIT-6] total score, and Migraine Specific Quality of Life Questionnaire [MSQ] v2.1 Role Function-Restrictive domain score) will be summarized by treatment group for Off-Treatment Hypothetical Estimand Population.

## 7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of participants 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 descending frequency of the atogepant 60 mg QD group within each SOC. Participants reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term). In addition, non-drug therapies will be summarized overall and by treatment group.

## 7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by therapeutic class and generic name. Concomitant medication will be summarized for the double-blind treatment period and follow-up period. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continue to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug plus 30 days or Visit 8 whichever comes later. The number and percentage of participants

taking medications will be summarized by therapeutic class and generic name based on the World Health Organization Drug Dictionary Enhanced WHODD version March 2021 for both prior and concomitant medications. The number and percentage of participants with failed prior oral preventive migraine medications will be summarized by class and generic name. In addition, a table for concomitant medications used by ≥ 5% participants during the double-blind treatment period will be provided.

### 7.4 Protocol Deviations

The number and percentage of participants with significant protocol deviations will be summarized by study intervention group in the Intent-to-Treat Population.

A listing of participants with significant protocol deviations will be provided.

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

The primary efficacy endpoint (defined in Section 3.1) will be analyzed based on the mITT population in support of the submission in the US 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 discontinuation from the double-blind study period will be excluded and are assumed missing at random.

The primary endpoint will be analyzed in the Off-treatment Hypothetical Estimand population in support of the European submissions 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.
- Participants who started a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data after starting the

new migraine prophylaxis treatment during the follow-up period excluded from the analysis.

- Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis.

The key secondary efficacy endpoint of key secondary endpoint (defined in Section 3.2) will be analyzed based on the mITT population or the Off-treatment Hypothetical Estimand 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, defined as a participant achieving at least a 50% reduction from baseline in the 3-month average of monthly migraine days.

  In support of the submission in the US:

  - Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.
  - Data after the premature discontinuation from the double-blind study period will be excluded. The average of monthly migraine days is calculated for each participant based on available monthly migraine days during the double-blind period, and then the participant is dichotomized as a responder or non-responder.

  In support of the European submissions:

  - Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.
  - Participants who started a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data after starting the new migraine prophylaxis treatment during the follow-up period excluded from the analysis.

- Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. The average of monthly migraine days is calculated for each participant based on available monthly migraine days, and then the participant is dichotomized as a responder or non-responder.

# 9.0 Efficacy Analyses

## 9.1 General Considerations

The efficacy endpoints for migraine day, headache day and acute medication use day are defined in protocol Section 8.1. All efficacy analyses will be conducted in the mITT Population in support of submission in the US and in the Off-treatment Hypothetical Estimand population in support of European submissions.

The primary analysis will be performed after all ongoing participants have completed the double-blind treatment period and follow-up period and the database has been locked. This will be the only and final analysis for the secondary efficacy endpoints as well as all other efficacy endpoints in the double-blind treatment period.

Unless otherwise specified, any participant who is randomized based on a wrong stratum will be analyzed according to the actual stratum the participant belong to.

## 9.2 Handling of Missing Data

Missing data will be handled 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) based on observed data collected during the double-blind treatment period (Primary efficacy approach for the US)
- ANCOVA model based on 3-month average of the monthly migraine days
- Within-group imputation based on observed data

- Copy-reference approach
- MMRM based on primary measures collected during the double-blind and follow-up periods (Primary efficacy approach for the EU)

## 9.3 Primary Efficacy Endpoint(s) and Analyses

### 9.3.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week 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

The attributes of the estimands corresponding to the primary efficacy endpoint are summarized in Table 4.

**Table 4. Summary of the Estimand Attributes of the Primary Efficacy Endpoint**

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Primary in support of the European submissions | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>Acute migraine medications as rescue medications are allowed to keep participants in the study | Change from baseline in mean monthly migraine days across the 12-week treatment period | The Off-treatment Hypothetical Estimand Population (see Section 4.0) | IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.<br>IE2: Participants who start a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data after starting the new migraine prophylaxis treatment during the follow-up period excluded from the analysis.<br>IE3: Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. | The difference in mean change from baseline in mean monthly migraine days across the 12-week treatment period between atogepant group and placebo |

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Primary in support of the submission in the US | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>Acute migraine medications as rescue medications are allowed to keep participants 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: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.<br>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 atogepant group and placebo |

**Primary analysis in support of the submission in the US**

The primary endpoint will be analyzed using a mixed model for repeated measures (MMRM) on the mITT population. The response variable is the change from baseline to each postbaseline month in monthly migraine days. The model will include treatment group, visit (derived as Weeks 1 - 4, Weeks 5 - 8, and Weeks 9 - 12), region, number of classes of failed prior prophylactic treatments (2 and >2), and treatment group by visit interaction as categorical fixed effects. It will also include the baseline monthly migraine days and baseline-by-visit interaction as covariates. Note that baseline monthly migraine is included in the primary model, therefore the stratification of number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) will be excluded in the primary model. The analysis will be performed based on evaluable postbaseline data using only the observed cases without missing data imputation. For submission in the US, only data collected during the double-blind period will be included in the analysis.

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

**Primary analysis in support of the European submissions**

Analysis of the primary endpoint will be conducted on the Off-treatment Hypothetical Estimand population based on treatment as randomized. The change from baseline to each postbaseline month in monthly migraine days will be analyzed using MMRM similar to the primary analysis specified for submission in the US. The analysis will be performed based on observed data collected from both double-blind treatment period and follow-up period.

### 9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

Sensitivity analyses of the primary analysis of the primary efficacy endpoint are given below. Four sensitivity analyses and one supplementary analysis will be provided for the estimand in support of the submission in the US. In addition, copy-reference approach for sensitivity analysis will be provided for the estimand in support of the European submissions.

**Sensitivity Analyses in Missing Data Handling**

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 treatment period for each participant. The ANCOVA model includes treatment, region, number of classes of failed prior prophylactic treatments (2 and >2) as fixed factors, and baseline monthly migraine days as a covariate. 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. There are no missing data for this analysis because participants who discontinued the treatment are assumed to maintain the same mean (observed while on treatment) for 3 months (12 weeks).

Within-group Imputation Based on Observed Data

A Sensitivity analysis will be performed based on imputation using participants from the same treatment group with observed data under the MAR assumption. Missing data for participants who prematurely discontinued are assumed to copy the profile of participants in the same treatment group with observed data. The details of imputation are as follows:

1. Create partial imputation dataset using MI based on the MCMC approach in each treatment group. Imputed dataset will consist of 100 copies of original dataset and is assumed to follow monotone missing pattern.
2. Impute missing data in each existing copy by treatment group using observed data in the corresponding treatment group based on monotone regression. Each of the 100 imputed datasets will then be analyzed using an ANCOVA model with treatment, region, number of classes of failed prior prophylactic treatments (2 and > 2) as fixed factors, and baseline monthly migraine days as a covariate.
3. The ANCOVA analysis results from 100 completed datasets are combined for overall estimation and inference using Rubin's rule[1] 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.

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.[2] 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) at 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 with the use of option IMPUTE = MONOTONE in the MCMC statement. Then the rest of the missing data will follow monotone missing pattern.

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

1. The reference-based approach uses the placebo group as the reference. The missing values in the reference group are imputed using the observed data in that group under the missing-at-random assumption. The missing pattern is defined by the participant's last visit with a non-missing value. The mean vector and the covariance matrix of the multivariate normal distribution are estimated for reference group. The imputation of missing data is not based on each of the reasons of early termination, because there may not be sufficient non-missing efficacy data in each of the reason categories to serve as a stable reference.
2. For atogepant treatment group, 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, region, number of classes of failed prior prophylactic treatments (2 and >2) as fixed factors, and baseline monthly migraine days as a covariate. The LS mean difference and corresponding SE is estimated from the model comparing each atogepant treatment group with the placebo group.

The ANCOVA analysis results from 100 completed datasets are combined for overall estimation and inference using Rubin's rule[1] 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.

**Supplementary Analyses of the Primary Efficacy Endpoint**

The estimand in support of the European submissions will serve as one supplementary analysis of the primary efficacy endpoint for the estimand in support of the submission in the US, and vice versa.

**Sensitivity Analysis for Possible Violation of Normality Assumption**

This sensitivity analysis uses MI in conjunction with robust regression to assess the robustness of the primary MMRM analysis to the possible violation of normality assumption. This method has been described and referred as ADAP [R].[3] 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 20 complete datasets.
2. Each of the 20 complete datasets will be analyzed using robust regression (M-estimation) to protect against either observed outliers in the original incomplete dataset, or imputed outliers in the completed datasets. For a given complete dataset, the average change from baseline in monthly 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, region, number of classes of failed prior prophylactic treatments (2 and >2) as fixed factors, and baseline monthly migraine days as a covariate. The mean difference and corresponding SE are estimated from the model comparing atogepant treatment group with the placebo group.
3. The robust analysis results from 20 completed datasets are combined for overall estimation and inference using Rubin's rule[1] 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 Secondary Efficacy Endpoints

See Section 3.2.

### 9.4.2 Main Analyses of Secondary Efficacy Endpoints

The attributes of the estimands corresponding to the key secondary efficacy endpoints are summarized in Table 5.

**Table 5. Summary of the Estimand Attributes of the Secondary Efficacy Endpoint**

| | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| **Estimand Label** | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Secondary 1 in support of the submission in the US | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>Acute migraine medications as rescue medications are allowed to keep patients in the study | Achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period (yes/no) | mITT Population (see Section 4.0) | IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.<br>IE2: Data after the discontinuation from double-blind treatment period are excluded.<br>The average of monthly migraine days is calculated for each participant based on available monthly migraine days during the double-blind period, and then the participant is dichotomized as a responder or non-responder. | The odds ratio in participants achieving at least a 50% reduction in 3-month average of monthly migraine days between atogepant group and placebo |

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | Treatment | Endpoint | Population | Handling of Intercurrent Events | Statistical Summary |
| Secondary 2 in support of the submission in the US | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>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 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.<br>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 treatment period between atogepant group and placebo |
| Secondary 3 in support of the submission in the US | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>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 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.<br>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 treatment period between atogepant group and placebo |

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | Treatment | Endpoint | Population | Handling of Intercurrent Events | Statistical Summary |
| Secondary 4 in support of the submission in the US | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>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.<br>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 atogepant group and placebo |
| Secondary 5 in support of the submission in the US | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>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 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.<br>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 |

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Secondary 6 in support of the submission in the US | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>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 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.<br>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 |

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | Treatment | Endpoint | Population | Handling of Intercurrent Events | Statistical Summary |
| Secondary 1 in support of the European submissions | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>Acute migraine medications as rescue medications are allowed to keep patients in the study | Achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period (yes/no) | The Off-treatment Hypothetical Estimand Population (see Section 4.0) | IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.<br>IE2: Participants who start a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data after starting the new migraine prophylaxis treatment during the follow-up period excluded from the analysis.<br>IE3: Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. The average of monthly migraine days is calculated for each participant based on available monthly migraine days, and then the participant is dichotomized as a responder or non-responder. | The odds ratio in participants achieving at least a 50% reduction in 3-month average of monthly migraine days between atogepant group and placebo |

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Secondary 2 in support of the European submissions | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>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 treatment period | The Off-treatment Hypothetical Estimand Population (see Section 4.0) | IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.<br>IE2: Participants who start a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data after starting the new migraine prophylaxis treatment during the follow-up period excluded from the analysis.<br>IE3: Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. | The difference in mean change from baseline in mean monthly headache days across the 12-week treatment period between each atogepant group and placebo |

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Secondary 3 in support of the European submissions | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>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 treatment period | The Off-treatment Hypothetical Estimand Population (see Section 4.0) | IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.<br>IE2: Participants who start a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data after starting the new migraine prophylaxis treatment during the follow-up period excluded from the analysis.<br>IE3: Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. | The difference in mean change from baseline in mean monthly acute medication use days across the 12-week treatment period between each atogepant group and placebo |

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | **Treatment** | **Endpoint** | **Population** | **Handling of Intercurrent Events** | **Statistical Summary** |
| Secondary 4 in support of the European submissions | Arm A: Placebo<br>Arm B: Atogepant 60 mg QD<br>Acute migraine medications as rescue medications are allowed to keep patients in the study | Change from baseline in the HIT-6 total score at Week 12 | The Off-treatment Hypothetical Estimand Population (see Section 4.0) | IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.<br>IE2: Participants who start a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data after starting the new migraine prophylaxis treatment during the follow-up period excluded from the analysis.<br>IE3: Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. | The difference in mean Change from baseline in the HIT-6 total score at Week 12 between each atogepant group and placebo |

| Estimand Label | Attributes of the Estimand | | | | |
|---|---|---|---|---|---|
| | Treatment | Endpoint | Population | Handling of Intercurrent Events | Statistical Summary |
| Secondary 5 in support of the European submissions | Arm A: Placebo<br>Arm B: Atogepant 60mg QD<br>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 | The Off-treatment Hypothetical Estimand Population (see Section 4.0) | IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis.<br>IE2: Participants who start a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data after starting the new migraine prophylaxis treatment during the follow-up period excluded from the analysis.<br>IE3: Participants who discontinue study treatment due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. | 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 |

The secondary endpoints for headache days, acute medication use days, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D will be analyzed in the same manner as that used to analyze the primary endpoint. For MSQ v2.1 Role Function Restrictive domain score and HIT-6 total score, the analysis will be performed similarly to the primary MMRM, with focus on the pairwise contrasts of atogepant dose group to placebo at Week 12. Some participants may have MSQ v2.1 or HIT-6 assessed at Visit 8, which will not be included in MMRM

models. Note that the stratification of number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) will be included in the secondary efficacy analyses if baseline values other than monthly migraine days are included in the corresponding models.

The 50% responder, defined as a participant with the achievement of at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each participant. A logistic regression model will be used to analyze the 50% responders across the 12-week treatment period. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, region, the stratification of number of classes of failed prior prophylactic treatments (2 and >2), and baseline monthly migraine days. The treatment difference in terms of odds ratio between each atogepant dose group and placebo will be estimated and tested from this model.

For the analyses in the mITT population, the 50% responder will be derived using data collected from the double-blind period. For the analyses in Off-treatment Hypothetical Estimand population, the 50% responder will be derived using data collected from the double-blind period and follow-up period; data after participants started a new prophylaxis treatment during the follow-up period will be excluded.

## 9.5 Exploratory Efficacy Analyses

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. Note that the stratification of number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) will be included in the additional efficacy analyses if baseline values other than monthly migraine days are included in the corresponding models. There is only one post-baseline assessment for MIDAS and PHQ-9, and thus ANCOVA model will be used to analyze MIDAS and PHQ-9 related endpoints with model terms including treatment group, region, the stratification of

number of classes of failed prior prophylactic treatments (2 and >2), number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) and corresponding baseline score. For the endpoints change from baseline in HIT-6, MSQ 2.1 and EQ-5D-5L descriptive system index score and vas score, Week 16 (follow up visit) will not be included in MMRM model fitting. Only descriptive statistics for Week 16 will be provided.

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, region, number of classes of failed prior prophylactic treatments (2 and >2), and treatment group-by-visit interaction as categorical fixed effects; baseline value and baseline-by-visit interaction will be included as covariates. If baseline values other than monthly migraine days is included in the model, then number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) will also be included in the corresponding analysis. Participants will be included as random effects with unstructured covariance matrix in the model to account for the correlation among 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 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, a logistic regression model will be used to model the probability of a response or event with model terms including treatment group, region, number of classes of failed prior prophylactic treatments (2 and >2), and corresponding baseline. If baseline values other than monthly

migraine days is included in the model, then number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) will also be included in the corresponding analysis. 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.

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%, ≥ 30%, ≥ 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 treatment period will be provided by treatment group.

## 9.6 Efficacy Subgroup Analyses

Subgroup analyses for primary efficacy endpoint will be performed based on the following subpopulations:

- Region: North America and Europe
- Participants who had baseline migraine days: 4 to < 8 and ≥ 8
- Participants who have failed 2 classes of prior oral prophylactic treatments
- Participants who have failed ≥ 3 classes of prior oral prophylactic treatments
- Participants who have failed 3 classes of prior oral prophylactic treatments

The same model as that of the primary MMRM model in primary efficacy analysis in Section 9.3.2 will be utilized based on mITT population in support of submission in the US and on the Off-treatment Hypothetical Estimand Population in support of European submissions. For each subgroup analysis, treatment effect and treatment comparison will

be estimated by the LS Means and their difference in LS Means, along with their SE and 95% confidence intervals (CIs).

# 10.0 Safety Analyses

## 10.1 General Considerations

Safety data will be summarized for the Safety Population. Safety summaries will be presented by treatment group. For the safety analysis, participants are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

A participant's actual treatment will be determined by the most frequent dose regimen received.

The safety parameters will include adverse events (AEs), clinical laboratory, vital sign, electrocardiographic (ECG), and C-SSRS. For clinical laboratory, vital sign, and ECG, 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 number of participants and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

## 10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Class (SOCs) and preferred terms (PTs) according to the version of 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 participant for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a participant, the highest severity and level of relationship to investigational product will be reported. Only AEs captured in Study 3101-304-002 will

be considered for TEAEs in this study. For participants rolling over into Study 3101-312-002 (extension study), AEs captured in the extension study will be summarized in the extension Study 3101-312-002 although some AEs might occur within 30 days after the last dose from Study 3101-304-002.

### 10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug. Events when the onset date is the same as the study drug start date are assumed to be treatment-emergent. An AE that occurs more than 30 days after the last dose of double-blind study treatment or Visit 8 whichever comes later will not be counted as a TEAE. All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in descending percentage in atogepant 60 mg QD group within each SOC.

The number and percentage of participants experiencing treatment-emergent AEs will be summarized.

TEAEs that started after the date of last dose of study treatment will be considered as newly emergent. The number and percentage of participants reporting newly emergent TEAEs in each treatment group will be summarized by system organ class and preferred term for participants who entered the safety follow-up period.

### 10.2.2 Adverse Event Overview

An overall of AEs will be presented consisting of the number and percentage of participants experiencing at least one event for each of the following AE categories.

- Any treatment-emergent SAEs
- Any treatment-emergent AEs related to study drug according to the investigator
- Any serious treatment-emergent AEs
- Any treatment-emergent AEs leading to discontinuation of study drug

- All deaths

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

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

The incidence of common (≥ 2% of participants [after rounding] 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

An AE will be considered a treatment-emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any SAE criterion. TESAEs, TEAEs leading to premature discontinuation of study treatment, and TEAEs leading to death will be summarized by SOC and PT. Tabular listings will be provided for all AEs, all deaths, all SAEs, and TEAEs leading to premature discontinuation of study treatment.

### 10.2.5 Adverse Events of Special Interest

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study intervention or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESI(s) have been identified for the study intervention(s):

- Treatment-emergent suicidal ideations with intent, with or without a plan, (i.e., Type 4 or 5 on the C-SSRS) or any suicidal behaviors.
- Treatment-emergent elevated ALT or AST laboratory value ≥ 3 × ULN.
- Potential Hy's law cases: elevated ALT or AST laboratory value that is ≥ 3 × ULN and an elevated total bilirubin laboratory value that is ≥ 2 × ULN and, at the same time, an alkaline phosphatase laboratory value that is < 2 × ULN.

AESIs will be summarized. Listing of AESIs will be provided.

## 10.3 Laboratory Data

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

Each laboratory variable will be summarized 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 with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error will be presented for the mean change from baseline within each treatment group. 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 E. 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 E.

Changes in laboratory parameters will be tabulated using shift tables categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. A shift table will be provided to summarize shifts from baseline to the final post-baseline value.

Laboratory abnormalities will be evaluated based on potentially clinically significant (PCS) criteria (Table 15). For each laboratory PCS criterion, the number and percentage

of participants who have a laboratory value meeting the criteria will be summarized. Listings will be provided to summarize subject-level laboratory data for participants meeting PCS criteria. A listing of all AEs for participants with PCS Lab values will be provided.

In addition, ALT, AST, alkaline phosphatase, and total bilirubin will be categorized in Table 16. The number and percentage of participants meeting each of the criteria for postbaseline hepatic laboratory abnormalities listed in Table 16 will be summarized. The percentages will be calculated relative to the number of participants with at least 1 available postbaseline assessment. The numerator will be the total number of participants 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 participants with an adjudicated case (i.e., ALT $\geq 3 \times$ ULN and/or AST $\geq 3 \times$ 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 participants with at least 1 adjudicated case. The numerator will be the number of participants with at least 1 adjudicated case in the specific category of relationship. If a participant has more than 1 adjudicated case, he or she will be counted in the most relevant category of relationship.

Participants with an adjudicated case (i.e., ALT $\geq 3 \times$ ULN or AST $\geq 3 \times$ 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 participants who meet ALT $\geq 3 \times$ ULN or AST $\geq 3 \times$ 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.

A listing of possible Hy's Law cases, defined as those who meet all of the following conditions simultaneously, will be provided: ALT ≥ 3 × ULN or AST ≥ 3 × ULN that is associated with an increase in bilirubin ≥ 2 × ULN and alkaline phosphatase < 2 × ULN.

A listing of urine pregnancy test results will be provided for female participants of child-bearing potential with at least one positive result.

## 10.4 Vital Signs

Vital sign measurements of systolic and diastolic blood pressures (sitting and standing), pulse rate (sitting and standing), respiratory rate, temperature, weight, orthostatic systolic blood pressure, orthostatic diastolic blood pressure, and orthostatic pulse rate will be summarized. Orthostatic vital sign values (orthostatic systolic and diastolic blood pressures, and orthostatic pulse rate) are defined as the corresponding standing measurement minus sitting measurement of systolic and diastolic blood pressures and pulse rate respectively.

Each vital sign variable will be summarized 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, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error will be presented for the mean change from baseline within each treatment group.

Vital sign variables will be evaluated based on PCS criteria (Table 17). For each vital sign PCS criterion, the number and percentage of participants who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for participants meeting PCS criteria. In addition, a tabular display showing all AEs that occurred in participants who had PCS postbaseline vital sign values will be provided.

## 10.5 Other Safety Analyses

### 10.5.1 Electrocardiogram

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 Table 18. The number and percentage of participants with PCS postbaseline values will be tabulated by study treatment. The percentages will be calculated relative to the number of participants with an available non-PCS baseline value and at least 1 postbaseline assessment. The numerator will be the total number of participants with an available non-PCS baseline value and at least 1 PCS postbaseline ECG value during the study. A supportive listing of participants with PCS postbaseline values will be provided. A listing of all AEs for participants with PCS ECG values will also be provided.

To evaluate ECG postbaseline values of clinical interest, the number and percentage of participants with post-treatment QTcF > 450 msec, > 480 msec, and > 500 msec will be tabulated by treatment group.

The number and percentage of participants with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcF will be tabulated. Participants will be counted only once for the most severe category. A supportive listing of participants 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 participants with postbaseline QTcF increases > 30 msec will also be provided.

A shift table from baseline to the end of double-blind treatment 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.

A tabular display of participants 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 participants with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment group for the Safety Population. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior in the participant's lifetime history, in the past 6 months, in the double-blind treatment 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. A listing of all AEs occurring in participants who have suicidal ideation or suicidal behavior will also be provided.

## 11.0 Other Analysis

### 11.1 Healthcare Resource Utilization Questionnaire

Healthcare resource utilization questions will include use of migraine-specific healthcare resources due to migraine attack. The number and percentage of participants who visit to any general practitioner, specialist, emergency room, or hospital, and any diagnostic procedures prescribed by health care providers will be provided by treatment group over the past 12 weeks and since last visit, respectively, for the Safety Population. In addition, total number of days spent in the hospital for all admissions during a specific period will be provided by treatment group for Safety Population.

## 12.0 Interim Analyses

No interim analysis is planned for this study.

### 12.1 Data Monitoring Committee

An independent DSMB will be established to review unblinded safety data and summary reports, identify any safety issues and trends, and make recommendations to AbbVie, including modification or ET of the study, if emerging data show unexpected and clinically significant AEs of treatment.

Details of the DSMB memberships, standard operational procedures for data monitoring/review, frequency of review, and other pertinent details will be provided in a separate DSMB Charter.

## 13.0 Overall Type-I Error Control

A fixed-sequence procedure will be used for multiple comparisons to control the family-wise Type I error rate at a 0.05 level. Once the primary endpoint for atogepant dose is significant at 0.05 (2-sided), the secondary endpoints will be tested. The testing sequence is specified for the US and EU in Table 6 and Table 7.

## Table 6. Multiple Comparisons Procedure Definitions for the Submission in the US

| Nodes | Alternate Hypothesis | Weight | Initial Local Significance Level |
|---|---|---|---|
| P1 | Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period | 1 | α |
| S1 | Atogepant 60 mg is significantly different from placebo in the achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period | 0 | α×0=0 |
| S2 | Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period | 0 | α×0 = 0 |
| S3 | Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period | 0 | α×0=0 |
| S4 | Atogepant 60 mg is significantly different from placebo in change from baseline in the MSQ v2.1 Role Function Restrictive domain score at Week 12 | 0 | α×0=0 |
| S5 | Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period | 0 | α×0=0 |
| S6 | Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period | 0 | α×0=0 |

**Table 7. Multiple Comparisons Procedure Definitions for the European Submissions**

| Nodes | Alternate Hypothesis | Weight | Initial Local Significance Level |
|---|---|---|---|
| P1 | Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period | 1 | α |
| S1 | Atogepant 60 mg is significantly different from placebo in ≥ 50% reduction in 3-month average of monthly migraine days | 0 | α×0=0 |
| S2 | Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly headache days across the 12-week treatment period | 0 | α×0 = 0 |
| S3 | Atogepant 60 mg is significantly different from placebo in change from baseline in mean monthly acute medication use days across the 12-week treatment period | 0 | α×0=0 |
| S4 | Atogepant 60 mg is significantly different from placebo in change from baseline in the HIT-6 total score at Week 12 | 0 | α×0=0 |
| S5 | Atogepant 60 mg is significantly different from placebo in change from baseline in the MSQ v2.1 Role Function Restrictive domain score at Week 12 | 0 | α×0=0 |

# 14.0 COVID-19 Related Analyses

## 14.1 Efficacy Evaluation

**Efficacy Endpoints**

Table 8 and Table 9 describe the collection devices for primary and secondary endpoints for US and EU respectively. For US, the primary endpoint and 5 secondary endpoints are collected via eDiary and for EU, the primary endpoint and 3 secondary endpoints are collected via eDiary according to protocol design. Minimal disruption is expected for these endpoints because participants are expected to complete eDiary at home and submit the responses every day.

The secondary endpoints, MSQ v2.1 Role Function Restrictive domain score at Week 12 and HIT-6 total score at Week 12, will be collected using eTablet as one electronic patient reported outcome (ePRO) at site. Participants are required to complete the ePRO measures remotely at Visit 7 (Week 12) according to remote-visit procedure.

To evaluate the missing rate for this endpoint at Week 12, the number of participants who missed at least one ePRO assessment due to COVID-19 will be summarized at each visit in the efficacy analysis population of Off-Treatment Hypothetical Estimand (mITT population for US and Off-treatment Hypothetical Estimand population for EU respectively).

**Table 8. Summary of Collection Devices for Primary and Secondary Endpoints for Submission in the US**

| Hypothesis Testing | Node | Endpoint | Collection Device |
|---|---|---|---|
| Primary | P1 | Change from baseline in mean monthly migraine days across the 12-week treatment period | eDiary |
| Secondary 1 | S1 | Change from baseline in mean monthly headache days across the 12-week treatment period | eDiary |
| Secondary 2 | S2 | Change from baseline in mean monthly acute medication use days across the 12-week treatment period | eDiary |
| Secondary 3 | S3 | Achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period | eDiary |
| Secondary 4 | S4 | Change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12 | eTablet |
| Secondary 5 | S5 | Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period. | eDiary |
| Secondary 6 | S6 | Change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period. | eDiary |

**Table 9. Summary of Collection Devices for Primary and Secondary Endpoints for European Submissions**

| Hypothesis Testing | Node | Endpoint | Collection Device |
|---|---|---|---|
| Primary | P1 | Change from baseline in mean monthly migraine days across the 12-week treatment period | eDiary |
| Secondary 1 | S1 | Change from baseline in mean monthly headache days across the 12-week treatment period | eDiary |
| Secondary 2 | S2 | Change from baseline in mean monthly acute medication use days across the 12-week treatment period | eDiary |
| Secondary 3 | S3 | Achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period | eDiary |
| Secondary 4 | S4 | Change from baseline in HIT-6 total score at Week 12 | eTablet |
| Secondary 5 | S5 | Change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12 | eTablet |

## 14.2 Safety and Other Evaluations

This section specifies analyses related to COVID-19 pandemic from the following aspects:

- Disposition
- Study visits and study procedures
- Protocol deviation
- Treatment interruption due to COVID-19
- TEAEs related with COVID-19 and supplemental signs and symptoms
- COVID-19 status (COVID-19 testing results or contact with a COVID-19 positive person)
- COVID-19 vaccine

Safety Population will be used for the planned analyses described above. The number of participants impacted by COVID-19 during the study will be summarized by treatment group and overall. In addition, the number of participants impacted by COVID-19 and

their corresponding disposition status in the double-blind treatment period and the follow-up period will be summarized respectively.

The number of participants who missed at least one entire visit, had impacted in-person clinic visits, and had remote visits using audio or video due to COVID-19 will be summarized by treatment group and overall. Furthermore, the number of participants who missed at least one assessment due to COVID-19 will be summarized by assessment category (laboratory, C-SSRS, urine pregnancy test, vital signs, ECG, and ePRO) and overall. Similar summaries will be provided by visit.

The number of participants with significant protocol deviation due to COVID-19 will be provided. The number of participants with study drug interruption due to COVID-19 will be provided as well. The number of participants with TEAEs related to COVID-19 infection and supplemental signs and symptoms will be provided.

The number and percentage of participants who received a COVID-19 vaccine will be tabulated by Anatomical Therapeutic Chemical (ATC) 4 class and preferred term (PT). The number and percentage of participants with TEAEs and serious TEAEs related to COVID-19 vaccine will be summarized by treatment and overall.

Supporting listings for the described analyses above will be provided.

# 15.0 Version History

This Statistical Analysis Plan (SAP) for Study 3101-304-002 is based on the protocol amendment 2 dated 01 December 2020. Summary of changes from SAP version 1.0 to SAP version 2.0 is provided in Table 10.

**Table 10. Summary of Changes from SAP Version 1.0 to SAP Version 2.0**

| Date | Section | Description |
|---|---|---|
| 08 JUL 2022 | 1.0 | Add a description for tables specification in separate document |
| 08 JUL 2022 | 1.0 | Add a statement for changes to planned analysis in the protocol |
| 15 JUL 2022 | 2.0 | Modify the title of Section 2.0 |
| 05 JUL 2022 | 2.0 | Add the objective of the study in Section 2.0 |
| 15 JUL 2022 | 2.3 | Delete block sharing description |
| 20 JUL 2022 | 2.3 | Delete 'Asia/Pacific' from the whole document |
| 12 JUL 2022 | 3.3 | Update efficacy endpoints analyses of HIT-6 and MSQ 2.1 at Week 16 |
| 05 AUG 2022 | 4.0 | Modify 'EU filing' to 'European submissions' in the whole document |
| 30 JUL 2022 | 5.0 | Update description of disposition summary |
| 30 JUL 2022 | 5.0 | Add a sub-group '< 4' to the factor 'number of migraine days during the screening/baseline period.' |
| 30 JUL 2022 | 5.0 | Delete disposition summary for mITT Population and Off-treatment Hypothetical Estimand Population |
| 09 JUL 2022 | 5.0 | Add comparing inconsistency between eDiary data and IWRS |
| 09 JUL 2022 | 6.0 | Update title for Section 6.0 |
| 05 AUG 2022 | 6.0 | Provide the definition of participant-years |
| 02 AUG 2022 | 7.1 | Add Baseline efficacy parameters descriptions |
| 29 JUL 2022 | 7.2 | Modify Medical History summary table description |
| 30 JUL 2022 | 7.2 | Add a section for non-drug therapy |
| 09 JUL 2022 | 7.3 | Modify concomitant medications summary table description |
| 30 JUL 2022 | 7.3 | Add ≥ 5% common concomitant medication summary table |
| 01 AUG 2022 | 7.4 | Move Protocol Deviations section from Appendix to Section 7.4 |
| 30 JUL 2022 | 8.0 | Delete 'of primary endpoint' |
| 07 JUL 2022 | 9.1 | Add the definitions of migraine day, headache day and acute medication use day. |
| 30 JUL 2022 | 9.3.2 | Add 'mITT Population' |
| 07 JUL 2022 | 9.3.3 | Add a sentence to summarize sensitivity and supplementary analyses |
| 30 JUL 2022 | 9.3.3 | Clarify no missing data in ANCOVA model |
| 01 AUG 2022 | 9.4 | Modify the title of Section 9.4 |
| 30 JUL 2022 | 9.4.2 | Clarify only providing descriptive statistics for MSQ 2.1 and HIT-6 data at Visit 8 |

| Date | Section | Description |
|---|---|---|
| 30 JUL 2022 | 9.4.2 | Modify 'individual' to 'Participant' |
| 10 JUL 2022 | 9.5 | Add PHQ-9, HIT-6 and MSQ 2.1 in the summary description |
| 30 JUL 2022 | 9.5 | Add factor 'region' in the GLMM model |
| 10 JUL 2022 | 9.5 | Add a description for models not converged. |
| 07 JUN 2022 | 9.6 | Revise this section for additional subgroup and model specifications |
| 10 JUL 2022 | 10.2 | Add a section to describe AEs obtained in 3101-312-002 study |
| 29 JUL 2022 | 10.2.1 | Modify AE summary table description |
| 10 JUL 2022 | 10.2.1 | Indicate the population as 'participants who entered the safety follow-up period' |
| 29 JUL 2022 | 10.2.2 | Delete 'Any severe treatment emergent AE' and 'Any treatment emergent AE leading to death' |
| 31 JUL 2022 | 10.2.3 | Delete 'by participant number and SOC and PT' |
| 28 JUL 2022 | 10.2.3 | Add '[after rounding]' |
| 31 JUL 2022 | 10.2.4 | Revise this section for TESAEs and Deaths |
| 31 JUL 2022 | 10.3 | Delete the sentences for local lab and lab due to SAE. |
| 01 AUG 2022 | 10.3 | Add descriptions for AEs with PCS listings of Lab, vital sign and CSSRS data. |
| 15 JUN 2022 | 10.3 | Revise '>' to '≥' for Hy's Law definition |
| 02 AUG 2022 | 10.4 | Provide the definitions of Orthostatic vital signs parameters |
| 08 JUL 2022 | 13.0 | Remove '(P1)' and '(S1)' |
| 08 AUG 2022 | 14.2 | Add a summary for Covid-19 analyses |
| 04 AUG 2022 | 15.0 | Revise protocol version and SAP version history |
| 05 AUG 2022 | 15.1 | Add a section for 'Changes to Planned Analyses in the Protocol' |
| 04 AUG 2022 | Appendix A | Add Appendix A for List of SAP Signatories |
| 04 AUG 2022 | Appendix C | Update the definition of AESI |
| 31 JUL 2022 | Appendix D | Delete SI Units for 'Glucose' and 'Protein.' Update PCS of 'Glucose' |
| 31 JUL 2022 | Appendix E | Remove 'Triglycerides' from lab parameters |
| 20 JUL 2022 | Appendix F | Update the List of Abbreviations |

**Table 11. SAP Version History Summary**

| Version | Date | Summary |
|---|---|---|
| 1.0 | 11 MAY 2021 | Initial Version |
| 2.0 | 21 AUG 2022 | Final Version |

## 15.1 Changes to Planned Analyses in the Protocol

Collection and Derivation of Primary and Secondary Efficacy Assessments in protocol Section 9.4.1.1.4 was updated. Original "12 days" criteria for using prorated approach were modified to "14 days."

The subgroup analyses for the primary efficacy endpoint (protocol Section 9.4.4) were updated in SAP Section 9.6.

# 16.0 References

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# Appendix A. List of SAP Signatories

| Name | Title | Role/Functional Area |
|---|---|---|
| [redacted] | Senior Manager, Statistics | Author |
| [redacted] | Director, Statistics | Clinical Statistics |
| [redacted] | Senior Director, Statistics | Therapeutic Area statistics Lead |
| [redacted] | Manager, Statistical Programming | Statistical Programming |
| [redacted] | Medical Director | Medical/Scientific Monitor |

## Appendix B. Derivation of Efficacy Variables

A.1 Derivation of Efficacy Endpoints Based on eDiary Data

For analysis purposes, four weeks (28 days) will be considered as one month. On a daily basis during the 4-week baseline period and throughout the double-blind treatment period, participants are to record eDiary information on the duration of headache, headache specific characteristics and symptoms, the pain severity, and use of any acute headache pain medication (see protocol Sections 8.1.1, 8.1.2, 8.1.3). Daily headache diary data consists of data from "today's diary" completed on that day and "yesterday's diary" completed on the following day. Participants are to report headache data in "today's diary" in the evening 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 participants miss "today's diary," they can report the whole-day headache data in "yesterday's diary" on the following day. In case participants miss "yesterday's diary," headache data from "today's diary" alone will be used as daily headache diary data. If both "today's diary" and "yesterday's dairy" are missing on one day, the daily headache diary data will be treated as missing.

Daily headache diary data will be merged from "today's diary" and "yesterday's diary" as following and will be used to derive 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 participant is considered to have taken a non-antiemetic acute headache medication if the participant 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 participant confirmed no headache for the Question 1 in eDiary, then the participant 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 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 participant 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 participant 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 participant 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.

## A.2 Derivation of Health Outcome Endpoints

AIM-D Related Endpoints Derivation

The AIM-D was developed as a daily eDiary with a recall period 24 hours. By design, it is collected in the today 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 12.

**Table 12. 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:
- Role Function-Preventive:
- Emotional Function:

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 13. 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 13. 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 participant's walking ability. The self-care dimension queries the participant's ability to wash or dress by himself. The usual activities dimension assesses the participant's performance in "work, study, housework, family or leisure activities." The pain/discomfort dimension measures how much pain or discomfort a participant has. The anxiety/depression dimension assesses how anxious or depressed a participant 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 participants 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 participant'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 7, except at Visit 8 (Week 16) where it will be administered on an eTablet. 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 14. Higher raw or T-scores indicate greater pain interference.

**Table 14. 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. Participants 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. Definition of Adverse Events of Special Interest

The definition of Adverse Events of Special Interest (AESI) is described in Section 10.2.5

## Appendix D. Potentially Clinically Significant Criteria for Safety

The potentially clinically significant criteria for clinical laboratory parameters, vital signs and ECG parameters are provided in the following tables.

Clinical laboratory parameters are provided in the following tables.

### Table 15. 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/min/1.73m$^2$ | < 60 mL/min/1.73m$^2$ | — |
| | 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 |
| | 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 | — | — | Positive [1] |
| | Protein | — | — | 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 trace or normal will be considered as positive.
2. Any results other than trace or negative will be considered as positive.

## Table 16. 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 |

| Laboratory Parameter | Categories |
|---|---|
| Concurrent Elevations[1] | ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 1.5 × ULN |
| | ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 2 × ULN |
| Potential Hy's Law[1] | ALT or AST ≥ 3 × ULN and Bilirubin Total ≥ 2 × ULN and ALP < 2 × ULN |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ALP = alkaline phosphatase; ULN = upper limit of normal (value provided by the laboratory).

1. Elevations are from the same day

**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 17. Potentially Clinically Significant Criteria for Vital Signs Parameters**

| Parameter | Flag | Criteria | |
|---|---|---|---|
| | | Observed Value | Change from Baseline |
| Systolic blood pressure, mmHg | High | ≥ 180 | Increase of ≥ 20 |
| | Low | ≤ 90 | Decrease of ≥ 20 |
| Diastolic blood pressure, mmHg | 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, mmHg | Low | ≤ -20 | — |
| Orthostatic DBP change, mmHg | 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 18. 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 |

## Appendix E. 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 the following table.

**Table 19. List of Selected Parameters Reported in Conventional Unit**

| *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)<br>(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 | Uric Acid | mg/dL | 1 |
| 18 | Hemoglobin | g/dL | 1 |

Patient narratives will also include the values in conventional units for the selected lab parameters in below table. That will be accomplished by presenting the values in conventional units within the parentheses next to the values in SI units.

## Table 20. 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 F. List of Abbreviations

| Abbreviation/Term | Definition |
|---|---|
| AE | adverse event |
| AESI | adverse events of special interest |
| AIM-D | Activity Impairment in Migraine –Diary |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| BMI | body mass index |
| bpm | beats per minute |
| CI | confidence interval |
| C-SSRS | Columbia–Suicide Severity Rating Scale |
| DBP | Diastolic blood pressure |
| DSMB | Data Safety Monitoring Board |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, 4th edition |
| eCRF | electronic case report form |
| ECG | electrocardiogram, electrocardiographic |
| ePRO | electronic Patient Reported Outcome |
| eDiary | electronic diary |
| eTablet | electronic tablet |
| EM | episodic migraine |
| EOS | end of study |
| EQ-5D-5L | European Quality of Life –5 Dimensional |
| ET | early termination |
| FWER | familywise error rate |
| GLMM | generalized linear mixed model |
| HIT-6 | Headache Impact Test |
| ITT | intent-to-treat |
| IWRS | interactive web response system |
| LLN | lower limit of normal value |
| LS | least squares |
| MAR | missing-at-random |
| MCMC | Markov chain Monte Carlo |

| Abbreviation/Term | Definition |
|---|---|
| MI | multiple imputation |
| MIDAS | Migraine Disability Assessment |
| MedDRA | Medication Dictionary for Regulatory Activities |
| mITT | modified intent-to-treat |
| MMRM | mixed-effects model for repeated measures |
| MNAR | missing-not-at-random |
| MSQ v2.1 | Migraine Specific Quality of Life Questionnaire, Version 2.1 |
| PCS | potentially clinically significant |
| PGIC | Patient Global Impression of Change |
| PGI-S | Patient Global Impression –Severity |
| PHQ-9 | Patient Health Questionnaire |
| PID | participant identification |
| PMM | pattern-mixture model |
| PRO | patient reported outcomes |
| PROMIS-PI | Patient-Reported Outcomes Measurement Information Systems Pain Interference – Short Form 6a |
| PSSM | Patient Satisfaction with Study Medication |
| PT | preferred term |
| Q1 | first quartile (25th percentile of the data) |
| Q3 | third quartile (75th percentile of the data) |
| QD | once daily |
| QTc | QT interval corrected for heart rate |
| QTcB | QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$) |
| QTcF | QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$) |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SBP | Systolic blood pressure |
| SD | standard deviation |
| SE | standard error |
| SI | Le Système International d'Unités (International System of Units) |
| SOC | standard of care |
| TBL | total bilirubin |
| TEAE | treatment-emergent adverse event |

| Abbreviation/Term | Definition |
|---|---|
| TESAE | treatment-emergent serious adverse event |
| ULN | upper limit of normal value |
| VAS | visual analogue scale |
| WHO | World Health Organization |
| WPAI: MIGRAINE | Work Productivity and Activity Impairment Questionnaire: Migraine Version V2.0 |