Statistical Analysis Plan for Study M22-061

A Randomized, Double-blind, Parallel-group, Active Controlled Trial with Open-label Safety Extension to Evaluate the Tolerability, Safety, and Efficacy of Atogepant Versus Topiramate in Subjects Requiring Preventive Treatment of Migraine (TEMPLE)

Version 2.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for atogepant Study M22-061, A Randomized, Double-blind, Parallel-group, Active Controlled Trial with Open-label Safety Extension to Evaluate the Tolerability, Safety, and Efficacy of Atogepant versus Topiramate in Subjects Requiring Preventive Treatment of Migraine (TEMPLE).

Study M22-061 examines the tolerability, safety, and efficacy of atogepant in subjects requiring preventive treatment of migraine.

The analyses of pharmacokinetic and exploratory biomarkers endpoints will not be addressed in this SAP. Pharmacokinetic analyses will be covered in the pharmacokinetic SPP addendum.

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

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

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 14.1.

2.0 Study Objectives and Design

2.1 Study Objectives, Hypotheses, and Estimands

Primary

The primary objective of the trial is to evaluate the tolerability and safety of atogepant 60 mg QD compared to the highest tolerated dose of topiramate (50, 75, or 100 mg/day) in subjects who require preventive treatment of migraine.

The hypothesis corresponding to the primary endpoint is that atogepant 60 mg QD will have superior tolerability and safety compared to topiramate at the highest tolerated dose (50, 75, or 100 mg/day) during the 24-week double-blind (DB) treatment period.

The estimand corresponding to the primary endpoint is defined as the relative risk in the proportion of subjects with treatment-emergent adverse events (TEAEs) leading to treatment discontinuation during the DB treatment period between the atogepant group and the topiramate group in subjects who require preventive treatment of migraine. Subjects who discontinue trial treatment due to any reasons other than TEAEs (e.g., lack of efficacy, withdrawal of consent, lost to follow-up) will be classified as subjects without TEAEs leading to treatment discontinuation.

Key Secondary

The key secondary objective is to demonstrate a higher rate of subjects treated with atogepant versus topiramate achieving ≥ 50% improvement (reduction) in mean monthly migraine days (MMDs) during Months 4 to 6 of the DB treatment period.

The estimand corresponding to the key secondary endpoint is defined as follows: the relative risk in the proportion of subjects achieving ≥ 50% reduction in MMD across Months 4 to 6 of the DB treatment period between the atogepant group and the topiramate group in the modified intent-to-treat (mITT) population. Regardless of whether or not allowed rescue medications are taken, data are included in the analysis; use of acute migraine medications as rescue medications is considered in the definition of migraine/headache day as described in Section 3.7 of the protocol Operations Manual. Subjects who prematurely discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analyses. Subjects without an evaluable month of electronic diary (eDiary) data during the last 3 months of the DB treatment period (Months 4, 5, 6) will be treated as non-responders.

The estimands for additional key secondary endpoints include the following:

- The difference in the mean change from baseline in mean MMD across Months 4 to 6 of the DB treatment period between the atogepant group and the topiramate group in the mITT population regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analysis.
- The difference in the mean change from baseline in Headache Impact Test (HIT-6) total score at Week 24 between the atogepant group and the topiramate group in the mITT population regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analysis.
- The difference in the mean change from baseline in Migraine Specific Quality of Life Questionnaire (MSQ) Version 2.1 Role Function-Restrictive (RFR) domain score at Week 24 between the atogepant group and the topiramate group in the mITT population regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analysis.
- The relative risk in the proportion of subjects achieving a rating of "much better" or "very much better" at Week 24 assessed by Patient Global Impression of Change (PGIC) in the mITT population regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analysis. Subjects without a PGIC value at Week 24 will be treated as non-responders.
- The difference in the mean change from baseline in PROMIS Cognitive Function Abilities Subset Short Form 6a Version 2.0 score at Week 6 the DB treatment period between the atogepant group and the topiramate group in the mITT population regardless of premature discontinuation of study drug. Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analysis.

2.2 Study Design Overview

The trial is a multicenter, randomized, DB, double-dummy, parallel-group, active controlled, 24-week trial comparing the tolerability, safety, and efficacy of atogepant 60 mg QD and topiramate at the highest tolerated dose (50, 75, or 100 mg/day) in adult subjects with EM or CM who are eligible for conventional migraine prophylaxis, with a subsequent 52-week, open-label (OL) atogepant safety extension.

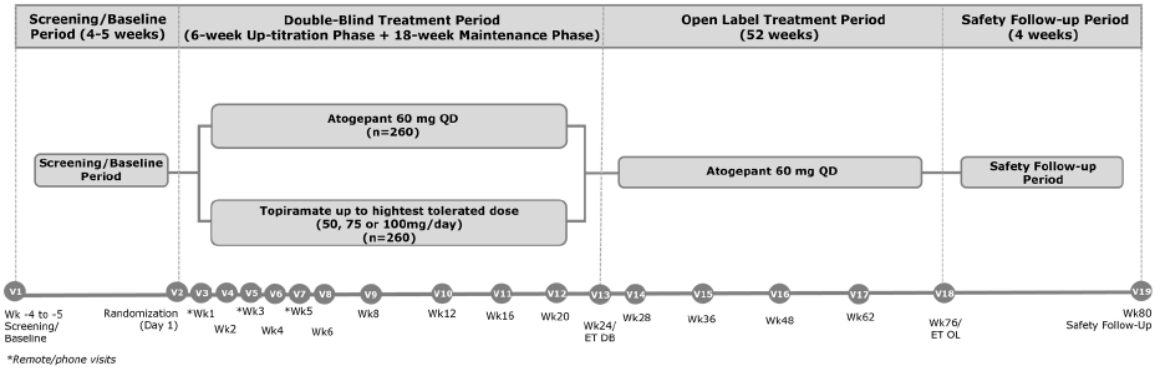
The trial will consist of a screening/baseline period (4 to 5 weeks), a 24-week DB treatment period including a topiramate up-titration phase (6 weeks) and maintenance phase (18 weeks), an OL treatment period (52 weeks), and a safety follow-up period (4 weeks) for a total trial duration of up to 85 weeks.

During the DB treatment period, due to the DB, double-dummy design, blinded atogepant or matching placebo and blinded topiramate or matching placebo will be administered separately. The dose of topiramate (or matching placebo) will not be blinded and can be adjusted as allowed by the protocol.

Subjects who prematurely discontinue study drug during the DB treatment period but do not withdraw consent should remain in the trial and continue collecting eDiary and ePRO data and attend scheduled trial visits remotely or in-person as defined in Simplified Schedule of Activities (SSA) in Appendix F of the protocol until the end of the 24-week DB treatment period.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



DB double blind; ET early termination; OL open label; QD once daily; wk week; V visit

For subjects who complete the double blind treatment period on blinded topiramate 75 mg/day or 100 mg/day, blinded topiramate may be down titrated at investigator discretion during the first week of the open label treatment period, in parallel with taking open label atogepant.

2.3 Treatment Assignment and Blinding

During the DB treatment period, approximately 520 eligible subjects will be randomized in a 1:1 ratio into one of the following 2 treatment arms:

- Atogepant 60 mg QD
- Topiramate at highest tolerated dose (50, 75, or 100 mg/day)

Randomization will be stratified by country and based on whether the subject can be classified as having CM ("Yes" if ≥ 15 headache days and ≥ 8 migraine days during the 28-day screening/baseline period, "No" otherwise).

Throughout the topiramate up-titration phase, blinded topiramate or matching placebo will be up-titrated from 25 mg/day to the target recommended dose of 100 mg/day (or to the highest tolerated dose) in weekly increments of 25 mg/day during Weeks 1 through 6. During the topiramate maintenance phase, subjects will be administered a consistent daily dose of 50 mg/day, 75 mg/day, or 100 mg/day of topiramate or matching placebo. Topiramate or matching placebo will be administered either once daily or divided into

individual AM and PM doses, depending on the total daily dose. Subjects who complete the DB treatment period on blinded topiramate 75 mg/day or 100 mg/day may taper off topiramate over 1 week at the investigator's discretion. The total daily dose of topiramate will be reduced by 50 mg during the tapering-off period. During the OL treatment period, all subjects will receive atogepant 60 mg QD.

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. For subjects who rescreen, the subject number assigned by the IRT at the initial Screening Visit should be used.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team) will remain blinded to each subject's DB treatment assignment until the primary analysis is complete. The investigator, trial site personnel, and the subject will remain blinded throughout the entire study. To maintain the blind, the matching placebo tablets and capsules provided for the trial will be identical in appearance to atogepant or topiramate, respectively.

2.4 Sample Size Determination

The planned total sample size of 520 randomized subjects (260 subjects per arm) will have at least 95% power to detect a 15% treatment difference in the primary endpoint, assuming 20% treatment discontinuation rate due to AEs with atogepant, and 35% with topiramate at a 0.025 one-sided significant level. The assumed rate of TEAEs leading to treatment discontinuation is based on atogepant long-term episodic Study 3101-302-002 and Study HER-MES[4] adjusted to use more conservative rates for sample size calculation.

The sample size of 260 subjects per arm will have approximately 99% power to detect a 20% treatment difference in the key secondary endpoint, achieving ≥ 50% reduction in monthly migraine days across last three months, assuming 51% response rate with atogepant, and 31% response rate with topiramate at a 0.025 one-sided significant level. The assumed response rates are based on Study HER-MES[4] and are adjusted to a more conservative rate in the atogepant arm for sample size calculation.

The assumptions for sample size calculation were monitored and updated based on blinded data review using a cutoff date of 01 August 2024. The pooled rate in TEAE leading to treatment discontinuation was 16.9%; the pooled rate for 50% responder rate was 48.9%. The sample size of 260 subjects per arm will have at least 98.9% power to detect a 13.8% treatment difference in the primary endpoint, assuming 10% treatment discontinuation rate due to AEs with atogepant, and 23.8% with topiramate at a 0.05 significance level. The assumed rate of AEs leading to treatment discontinuation in atogepant is based on Study M23-072 adjusted to use more conservative rate for sample size calculation.

The sample size of 260 subjects per arm will have approximately 93% power to detect a 15% treatment difference in the key secondary endpoint, achieving ≥ 50% reduction in monthly migraine days across last 3 months, assuming 56.4% response rate with atogepant and 41.4% response rate with topiramate at a 0.05 significant level. The assumed response rates are calculated based on a blinded pooled responder rate of approximately 48.9% and a presumed treatment difference of 15%.

3.0 Endpoints

3.1 Primary Endpoint

The primary endpoint is treatment discontinuation due to TEAEs during the 24-week DB treatment period.

3.2 Secondary Endpoints

3.2.1 Key Secondary Endpoints

Key secondary endpoints:

- Achievement of ≥ 50% improvement (reduction) in MMD during Months 4 to 6 of the DB treatment period.
- Change from baseline in MMD during Months 4 to 6 of the DB treatment period

- Change from baseline in HIT-6 total score at Week 24
- Change from baseline in MSQ Version 2.1 RFR domain score at Week 24
- Achievement of a rating of "much better" or "very much better" at Week 24 assessed by the PGIC
- Change from baseline in PROMIS Cognitive Function Abilities Subset Short Form 6a Version 2.0 score at Week 6

3.3 Additional Efficacy Endpoints

Additional efficacy endpoints include measurements assessed at visits as specified in the activities schedules in Appendix F of the protocol.

- Change from baseline in monthly migraine days for each monthly period
- Achievement of ≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100% improvement (reduction) in monthly migraine days for each monthly period
- Achievement of ≥ 25%, ≥ 30%, ≥ 75%, 100% improvement (reduction) in monthly migraine days during Month 4 to 6
- Change from baseline in monthly headache days during Month 4 to 6, and for each monthly period
- Change from baseline in monthly cumulative headache hours during Month 4 to 6, and for each monthly period
- Change from baseline in monthly acute medication use days during Month 4 to 6, and for each monthly period
- Change from baseline in monthly triptan use days during Month 4 to 6, and for each monthly period
- Change from baseline in monthly moderate/severe headache days during Month 4 to 6, and for each monthly period
- Change from baseline in monthly severe headache days during Month 4 to 6, and for each monthly period
- Change from baseline in the MSQ v2.1 Role Function-Preventive domain score at Weeks 4, 8, 12, 16, 20, and 24

- Change from baseline in the MSQ v2.1 RFR domain score at Weeks 4, 8, 12, 16, and 20
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, 12, 16, 20, and 24
- Change from baseline in the HIT-6 total score at Weeks 4, 8, 12, 16, and 20
- Achievement of at least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, 12, 16, 20, and 24.
- Change from baseline in Short Form-36 (SF-36) Version 2 Physical Component Score (PCS) and Mental Component Score (MCS) at Weeks 4, 8, 12, 16, 20, and 24
- Achievement of at least a 5-point increase from baseline to Week 4, 8, 12, 16, 20, and 24 in SF-36 Version 2 PCS and MCS
- Change from baseline in Patient Global Impression of Severity (PGI-S) score at Week 4, 8, 12, 16, 20, and 24
- Achievement of a rating of "much better" or "very much better" as assessed by the PGIC at Week 4, 8, 12, 16, and 20
- Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Week 4, 8, 12, 16, 20, and 24 as assessed by the Work Productivity and Activity Impairment (WPAI): Migraine
- Achievement of a rating of "satisfied" or "extremely satisfied" at Weeks 4, 8, 12, 16, 20 and 24 assessed by the Patient Satisfaction with Study Medication (PSSM)
- Change from baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Cognitive Function Abilities Subset Short Form 6a Version 2.0 score at Weeks 1, 2, 3, 4, 5, 8, 12, 16, 20, and 24 (to be conducted in a subset of subjects).

3.4 Safety Endpoints

Safety evaluations include AE monitoring, serious adverse event (SAE) monitoring, AEs of special interest (AESI) monitoring, clinical laboratory testing (hematology, chemistry,

and urinalysis), vital sign measurements, electrocardiogram (ECG) variables, and Columbia Suicide Severity Rating Scale (C-SSRS) responses as measures of safety and tolerability for the entire trial duration.

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 Screened Population includes all subjects who signed informed consent and received a subject number.

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

The Modified Intent-to-Treat (mITT) Population includes all randomized subjects 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 (1 month) period of eDiary data within 24 weeks after the first dose of study medication (Month 1 to Month 6), regardless of whether on study treatment or off study treatment. The mITT population will be used for all efficacy analyses, except for one sensitivity analysis for a key secondary endpoint. Subjects will be included in the analysis according to the treatment group to which they were randomized (as randomized).

The Safety Population 1 consists of all subjects who received at least 1 dose of study treatment during the DB treatment period. Subjects will be summarized according to the study treatment received for the majority of the treatment period.

The Safety Population 2 consists of all subjects who received at least 1 dose of study treatment during the OL treatment period.

5.0 Subject Disposition

The number of subjects in the ITT Population, mITT Population, Safety Population 1, and Safety Population 2 will be summarized by treatment group, by treatment group and country, and by treatment and study site. Enrollment failure subjects will be summarized among all screened subjects.

For the DB treatment period, a summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each treatment group and pooled across treatment groups on the ITT Population:

- Subjects enrolled (randomized) in the study
- Subjects who took at least one dose of study drug during the DB treatment period
- Subjects who completed the DB treatment period
- Subjects who discontinued study during the DB treatment period (including reasons for discontinuation)
- Subjects who completed the DB treatment period without premature discontinuation of study drug
- Subjects who completed the DB treatment period with premature discontinuation of study drug (including reasons for treatment discontinuation)
- Subjects who entered the OL treatment period

Subject disposition for the OL treatment period will be presented based on Safety Population 2. The number of subjects in each of the following categories will be summarized:

- Subjects who took at least one dose of atogepant during the OL treatment period
- Subjects who completed the OL treatment period
- Subjects who discontinued study during the OL treatment period (including reasons for discontinuation)

For the end of safety follow-up, the number of subjects in the ITT population in each of the following categories will be summarized for each treatment group and pooled across treatment groups based on whether or not subjects enter the OL treatment period:

- Subjects who completed safety follow-up period
- Subjects who discontinued the study (including reasons for the discontinuation)

6.0 Study Treatment Duration and Compliance

For all analyses related to exposure, only the active treatments from the atogepant and topiramate treatment groups will be summarized. The prescribed dose and actual dose of topiramate will be recorded separately for both the AM and PM daily.

For the topiramate treatment group, the number and percentage of subjects entering the up-titration phase, maintenance phase, and tapering-off phase of topiramate will be provided in a summary for the Safety Population 1.

The durations of the atogepant and topiramate treatments will be summarized for Safety Population 1 during the DB treatment period and the durations of the atogepant treatment will be summarized for Safety Population 2 during the OL treatment period. The duration of a treatment for a subject is defined as the last dose date minus the first dose date + 1 for a given period. During the DB treatment period, the duration of topiramate treatment will be summarized both with and without topiramate tapering-off phase, separately. The duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, Q1, Q3, minimum, and maximum. In addition, the number and percentage of subjects in each treatment duration of ≥ 1 day, ≥ 28 days, ≥ 56 days, ≥ 84 days, ≥ 90 days, ≥ 112 days, ≥ 140 days, and ≥ 168 days will be summarized for Safety Population 1 during the DB treatment period. The number and percentage of subjects in treatment duration of ≥ 1 day, ≥ 28 days, ≥ 56 days, ≥ 84 days, ≥ 90 days, ≥ 112 days, ≥ 140 days, ≥ 168 days, ≥ 180 days, ≥ 196 days, ≥ 224 days, ≥ 252 days, ≥ 270 days, ≥ 280 days, ≥ 308 days, ≥ 336 days, ≥ 360 days, ≥ 364 days, ≥ 392 days,

≥ 420 days, ≥ 448 days, ≥ 450 days, ≥ 476 days, ≥ 504 days, and ≥ 532 days will be summarized for the OL and DB + OL treatment periods for subjects who received atogepant during the trial. Participant-years, calculated by summing the duration of exposure across the respective set of subjects and dividing this sum by 365.25, will be summarized by treatment group.

For the topiramate treatment group, the modal and mean daily dose will be presented in an overall summary and detailed weekly throughout the up-titration phase. The initial and final daily dose will be summarized for the up-titration, maintenance, and tapering-off phases. The modal daily dose is defined as the most frequently taken daily dose for each subject within specified time intervals. The initial and final daily doses per subject are defined as the first and last daily dose taken within specified time intervals, respectively.

Treatment compliance for a specific period is defined as the ratio of the total doses (mg) of study medication actually taken to the total doses (mg) of study medication that should have been taken during that period. Percent treatment compliance as well as the associated compliance categories (< 80%, 80% - 120%, > 120%) will be summarized in each treatment period between 2 consecutive scheduled visits, as well as in the entire DB treatment period from the first to the last dose of DB study intervention actually taken (excluding the topiramate tapering-off phase) for the Safety Population 1. Additionally, the same summaries will be provided in the OL treatment period from the first to the last dose of the atogepant actually taken for Safety Population 2.

7.0 Subject Characteristics

Categorical variables will be summarized with the number and percentage of subjects; 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 Stratification Variables

Subjects will be randomized based on their country and whether they are identified as having CM. "Actual" status for whether a subject is identified as having CM will be rederived using data from eDiary based on algorithms detailed in the Statistical Programming Plan (SPP). A cross tabulation will be provided for randomization stratum from IRT and actual stratum from eDiary, accompanied by a listing of subjects with inconsistent randomization stratum values. Since the IRT and EDC have the same source of 'country', there will be no inconsistency between 'country' in the IRT and EDC.

7.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively overall and by treatment group for the ITT Population, Safety Populations 1 and 2, and mITT Population. Disease characteristics will be summarized for Safety Population 1. Unless otherwise specified, baseline refers to the last non-missing observation before the first dose of study drug or randomization if no study drug is administered.

Continuous demographic variables include age, weight, height, and body mass index (BMI).

Categorical demographic variables include:

- Sex (Female, Male)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple)
- Race group (White, All Other Races)
- Age group (< 20, 20-29, 30-39, 40-49, 50-59, 60-69, ≥ 70 years)
- Age group (< 40 years, 40 - 64 years, ≥ 65 years)
- BMI group (Underweight (< 18.5), Normal (≥ 18.5 - < 25), Overweight (≥ 25 - < 30), Obese (≥ 30))
- Alcohol user (current, former, never, unknown).

Disease characteristics are contained in migraine history, including diagnosis, duration of migraine in years, whether there was prior use of prophylaxis treatment for migraines, baseline MMDs categories (4 - < 8 days, 8 - < 15 days, and ≥ 15 days), and average number of migraine and headache days per month in the last 3 months prior to visit 1.

7.3 Medical History and Prior and Concomitant Medications

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 subjects in each medical history category (by MedDRA system organ class (SOC) and preferred term (PT)) will be summarized overall and by treatment group for Safety Population 1 and for those subjects in Safety Population 2 who entered the OL period. The SOC will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or PT).

Prior medications used before the DB treatment period will be summarized overall and by treatment group for Safety Population 1. A prior medication is defined as any medication taken prior to the date of the first dose of study drug.

Concomitant medications will be summarized overall and by treatment group based on the following four periods:

- The DB treatment period in Safety Population 1
- The DB follow-up period in Safety Population 1
- The OL treatment period in Safety Population 2
- The OL follow-up period in Safety Population 2

The DB treatment period starts from the day of the first dose of study drug taken and continues until the end of DB treatment visit. The end of DB treatment visit is defined as the scheduled subsequent visit after a subject stop taking the study drug within the DB

treatment period. The DB treatment period does not include the topiramate tapering-off phase.

For subjects who enter the OL treatment period, the DB follow-up period starts from the day following the end of DB treatment visit up to the day prior to the first dose of study drug during the OL treatment period. For subjects who do not enter the OL treatment period, the DB follow-up period starts from the day after the end of DB treatment visit until the end of study.

The OL treatment period starts from the day of the first dose of study drug taken in the OL treatment period until the end of OL treatment visit. The end of OL treatment visit is defined as Visit 18/OL ET.

The OL follow-up period starts from the day after the end of OL treatment visit and continues through to the end of study.

A medication is considered concomitant to a specific period if it was taken before the start date of the period and continued to be taken after the start date of the period or if it began being taken on or after the start date of the period but not after the end date of the period.

For each summary, the number and percentage of subjects will be summarized by generic name, based on the World Health Organization (WHO) Drug Dictionary. The actual version of the WHO Drug Dictionary will be noted in the statistical tables and clinical study report.

In addition, the non-drug therapies and procedures will be separately summarized for each of the following periods: prior to DB period, the DB treatment period, DB follow-up period, the OL treatment period, and the OL follow-up period. The criteria for defining non-drug therapies, prior and concomitant procedures for these periods align with the definition of concomitant medications. Listings of subjects with non-drug therapies, and prior and concomitant procedures will be provided.

7.3.1 Identifying Subjects Who Took a New Migraine Prophylaxis Treatment

To identify the subjects who started a new migraine prophylaxis treatment as specified in Section 8.0, the following criteria are used: A subject has taken prophylaxis medications during the DB treatment or DB follow-up periods with preferred names, and the concomitant medications are classified as "Migraine Prevention Medication" in concomitant medications eCRF.

7.4 Protocol Deviations

Protocol deviations include eligibility criteria violations, receipt of wrong treatment or incorrect dose of study treatment, development of withdrawal criteria without being withdrawn, and use of prohibited concomitant medications. Study-specific protocol deviations will be included as outlined in the Study Protocol Deviation and Issue Plan (SPDIP). A listing of subjects with protocol deviations will be provided.

For each of the following protocol deviation categories, along with additional protocol deviations detailed in the SPDIP, as well as across all categories, the number and percentage of randomized subjects with at least one protocol deviation will be summarized overall and by treatment group:

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

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

The primary endpoint (defined in Section 3.1) will be analyzed on Safety Population 1 and the following methods will be used to address potential intercurrent events:

- Subjects who discontinue study treatment due to any reasons other than AEs (e.g., lack of efficacy, withdrawal of consent, lost to follow-up, etc.) will be classified as subjects without TEAEs leading to treatment discontinuation.

The secondary endpoints (defined in Section 3.2) will be analyzed based on the mITT Population, and the following methods will be used to address the potential intercurrent events:

- A 50% responder is defined as a subject achieving at least a 50% reduction from baseline in mean MMD during Months 4 to 6 of the DB treatment period.
- Regardless of whether or not allowed rescue medications are taken, eDiary data are included in the analysis. Use of acute migraine medications as rescue medications is considered in the definition of migraine/headache day as described in Section 3.7 of the Operations Manual.
- Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis.
- Subjects who prematurely discontinue study treatment and use other prohibited migraine prophylactic treatment will have their off-treatment data after starting the new migraine prophylactic treatment excluded from the analysis.
- Subjects without an evaluable month of eDiary data during the last three months of the DB treatment period (Months 4, 5, 6) will be treated as non-responders.
- For the endpoint of achieving a rating of "much better" or "very much better" at Week 24 assessed by the PGIC, off-treatment data after starting a new migraine prophylaxis treatment will be excluded. Subjects without a PGIC value at Week 24 will be treated as non-responders.

Potential intercurrent events for other key secondary endpoints will be handled using the following methods:

- Regardless of whether or not allowed rescue medications are taken, data are included in the analysis. Use of acute migraine medications as rescue medications is considered in the definition of migraine/headache day as described in Section 3.7 of the Operations Manual.
- Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis.
- Subjects who prematurely discontinue study treatment and use other prohibited migraine prophylactic treatment will have their off-treatment data after starting the new migraine prophylactic treatment excluded from the analysis.

9.0 Efficacy Analyses

9.1 General Considerations

After all subjects have completed the DB treatment period and the Visit 13/DB ET, the primary analysis will be conducted based on the entire DB treatment period data. For this analysis, a database lock will occur, and randomization data will be released. Once all subjects have completed the OL treatment period, the final database lock will occur and the final analysis for safety data from both the DB and OL treatment periods will be performed.

The efficacy endpoints for migraine day, headache day and acute medication use day are defined in Appendix B.

All analyses on key secondary endpoints and additional efficacy endpoints will be performed on the mITT Population, except for one sensitivity analysis for the key secondary endpoint (Achievement of ≥ 50% improvement in MMD) as described in

Section 9.4.3. Baseline for efficacy variables is defined as the last non-missing efficacy assessment before the first dose of DB study drug for variables not derived from eDiary. Baseline for efficacy variables derived from eDiary will use data collected during the last 28 days of baseline period as described in Appendix C. The baseline of secondary efficacy endpoints will be summarized by each randomized treatment group and pooled across treatment groups based on the mITT population. All tests will be 2-sided at an alpha level of 0.05.

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

9.2 Handling of Missing Data

There will be no missing data for the primary endpoint of treatment discontinuation due to TEAEs during the 24-week DB treatment period. The analysis will be on Safety Population 1. For subjects in Safety Population 1 who prematurely discontinue DB study treatment due to TEAE, this variable will have value "Yes"; for subjects who complete the DB study treatment or discontinue DB study treatment due to reasons other than TEAE, this variable will have value "No."

For the key secondary endpoint of achievement of ≥ 50% improvement (reduction) in MMD during Months 4 to 6 of the DB treatment period, subjects without an evaluable month of electronic diary (eDiary) data during the last 3 months of the DB treatment period (Months 4, 5, 6) will be treated as non-responders. Therefore, every subject in the mITT will have a value for the main analysis of this endpoint. The same missing data handling will be applied to the key secondary endpoint of achievement of a rating of "much better" or 'very much better' at Week 24 assessed by PGIC. For other continuous key secondary endpoints, observed data will be used in the analyses.

Missing data will be handled using the following methods for the efficacy analyses of key secondary endpoints and additional efficacy endpoints utilizing repeated measurement models.

- Descriptive statistics for efficacy endpoints will be based on observed cases only.
- A mixed model for repeated measures (MMRM) will be applied for continuous endpoints, using observed data without imputation of missing values.
- For generalized linear mixed model (GLMM) on repeated binary endpoints, observed data from the DB treatment period will be utilized, without imputing missing values.

9.3 Primary Endpoint and Analyses

The primary endpoint is treatment discontinuation due to TEAEs during the 24-week DB treatment period. Analysis of the primary endpoint will be conducted on Safety Population 1 (see Section 10.2).

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoints

Please refer to Section 3.2.1.

9.4.2 Main Analyses of Key Secondary Efficacy Endpoints

The attributes of the estimand corresponding to the key secondary efficacy endpoints are summarized in Table 1.

Table 1. Summary of the Estimand Attributes Corresponding to the Key Secondary Efficacy Endpoints

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Secondary 1	Arm A: Atogepant 60 mg QD Arm B: Topiramate (50, 75, or 100 mg/day) Acute migraine medications as rescue medications are allowed to keep subjects in the study	Achieving ≥ 50% reduction in mean MMD during Months 4 to 6 of the DB treatment period	Analysis Population: mITT Population. Target population: subjects who require preventive treatment of migraine	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. IE3: Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analyses. IE4: Subjects without an evaluable month of eDiary data during the last three months of the DB treatment period (Months 4, 5, 6) will be treated as non-responders.	The relative risk in subjects achieving at least 50% reduction in mean MMD during Months 4 to 6 of the DB treatment period between atogepant group and topiramate group using the Miettinen and Nurminen (MN) method, adjusting for CM status at baseline (Yes or No)

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Secondary 2	Arm A: Atogepant 60 mg QD Arm B: Topiramate (50, 75, or 100 mg/day) Acute migraine medications as rescue medications are allowed to keep subjects in the study	Change from baseline in mean MMD during Months 4 to 6 of the DB treatment period	Analysis Population: mITT Population. Target population: subjects who require preventive treatment of migraine	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. IE3: Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analyses.	The difference in mean change from baseline in mean monthly migraine days during Months 4 to 6 of the DB treatment period between each atogepant group and topiramate group

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Secondary 3	Arm A: Atogepant 60 mg QD Arm B: Topiramate (50, 75, or 100 mg/day) Acute migraine medications as rescue medications are allowed to keep subjects in the study	Change from baseline in HIT-6 total score at Week 24	Analysis Population: mITT Population. Target population: subjects who require preventive treatment of migraine	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. IE3: Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analyses.	The difference in mean change from baseline in the HIT-6 total score at Week 24 between atogepant group and topiramate group

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Secondary 4	Arm A: Atogepant 60 mg QD Arm B: Topiramate (50, 75, or 100 mg/day) Acute migraine medications as rescue medications are allowed to keep subjects in the study	Change from baseline in MSQ Version 2.1 Role Function Restrictive domain score at Week 24	Analysis Population: mITT Population. Target population: subjects who require preventive treatment of migraine	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. IE3: Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analyses.	The difference in mean change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 24 between atogepant group and topiramate group

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Secondary 5	Arm A: Atogepant 60 mg QD Arm B: Topiramate (50, 75, or 100 mg/day) Acute migraine medications as rescue medications are allowed to keep subjects in the study	Achievement of a rating of "much better" or "very much better" at Week 24 assessed by the PGIC	Analysis Population: mITT Population. Target population: subjects who require preventive treatment of migraine	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. IE3: Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analyses. IE4: Subjects without an evaluable PGIC data at Week 24 will be treated as non-responders.	The relative risk in the proportion of subjects achieving a rating of "much better" or "very much better" at Week 24 assessed by PGIC using the MN method, adjusting for CM status at baseline (Yes or No)

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Secondary 6	Arm A: Atogepant 60 mg QD Arm B: Topiramate (50, 75, or 100 mg/day) Acute migraine medications as rescue medications are allowed to keep subjects in the study	Change from baseline in PROMIS Cognitive Function – Abilities Subset – Short Form 6a Version 2.0 score at Week 6	Analysis Population: mITT Population. Target population: subjects who require preventive treatment of migraine	IE1: Regardless of whether allowed rescue medications are taken or not, data are included in the analysis. IE2: Subjects who discontinue study treatment due to all reasons other than starting a new migraine prophylactic treatment will have their data collected after discontinuation of study treatment, and those off-treatment data will be included in the analysis. IE3: Off-treatment data after starting a new migraine prophylaxis treatment will be excluded from the analyses.	The difference in mean change from baseline in PROMIS Cognitive Function – Abilities Subset – Short Form 6a Version 2.0 score at Week 6 between atogepant group and topiramate group

For key secondary endpoint of achieving ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period, the number and proportion (n, %) of subjects achieving ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period will be summarized based on mITT population. The relative risk as the primary measure in response rates of atogepant versus topiramate will be provided. Comparison of the 50% responders (i.e., adjusted relative risk, 95% confidence interval [CI], p-value) will be made between the atogepant group and the topiramate group using the MN method[1] adjusting for CM status at baseline (Yes or No).

Odds ratio and risk difference in 50% response rates of atogepant versus topiramate will also be provided. The odds ratio between the atogepant group and the topiramate group will be estimated and tested from a logistic regression model, which assumes a binary distribution for the response and uses a logit link, with model terms including treatment group and baseline MMDs. The risk difference between the atogepant group and the topiramate group will be calculated using the MN method,[1] adjusting for CM status at baseline (Yes or No). The 95% confidence interval (CI) and p-value will also be provided.

A mixed model for repeated measures (MMRM) will be used to analyze continuous key secondary endpoints. The model will include treatment group, visit (derived as month), CM status at baseline (Yes or No), and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. For the endpoint of change from baseline in MMD during Months 4 to 6 of the DB treatment period, CM status at baseline (Yes or No) will be excluded from the models as it's inherent in the baseline MMD. Model parameters were estimated using restricted maximum likelihood method incorporating all observed cases during the DB treatment period assuming data missing at random. An unstructured covariance matrix will be used to model the covariance of within-subject repeated measurements. The Kenward-Roger approximation[2] will be used to estimate the denominator degrees of freedom. In the event of non-convergence of the model using unstructured covariance matrix, a structured covariance matrix will be used in combination with empirical variance estimate (i.e., sandwich estimator) to address the potential mis-specified situation. Pairwise contrasts in the MMRM will be used to make pairwise comparisons of atogepant to topiramate. Treatment effect and treatment comparison will be estimated by the least squares (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.

For key secondary endpoint of achieving a rating of "much better" or "very much better" at Week 24 assessed by the PGIC, relative risk, odds ratio, and risk difference between the atogepant group and the topiramate group will be derived. These methods are in line with those utilized for achieving ≥ 50% improvement (reduction) in mean MMD during

Months 4 to 6 of the DB treatment period. However, the CM status at baseline (Yes or No) will be included in the logistic model, replacing the baseline MMDs.

9.4.3 Sensitivity Analyses of the Key Secondary Efficacy Endpoints

During the trial, subject details report provided by the IRT vendor (Endpoint) erroneously showed the actual treatment allocation, which potentially affected the confidentiality of the treatment allocation for 13 subjects (unblinded to AbbVie personnel for 2 subjects, potentially unblinded to AbbVie personnel for 9 subjects, and assumed unblinded to site personnel for 2 subjects). Detailed information on the affected subjects can be found in the SPP. To evaluate the impact of the unblinded subjects and to confirm the robustness of study results, two sensitivity analyses for all key secondary endpoints will be conducted excluding the impacted subjects. Both sensitivity analyses will utilize the same statistical methods used in the primary analysis for the key secondary endpoints. The first sensitivity analysis will exclude the 2 subjects confirmed unblinded by AbbVie and the 2 subjects reviewed by site personnel. The second sensitivity analysis will exclude all 13 impacted subjects.

Two additional sensitivity analyses for the key secondary endpoint of achievement of ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period are given below.

The first additional sensitivity analysis will be conducted using the ITT population. The modelling approach will be as same as our primary analysis model, with the only difference being the use of the ITT population instead of the mITT population used in the primary analysis model. Subjects in the ITT population who either do not receive the study drug during the DB period or receive a study drug but have no evaluable baseline eDiary data or do not have at least one evaluable post-baseline 4-week period of eDiary data will be classified as non-responders.

The second additional sensitivity analysis for the key secondary endpoint utilizes a GLMM. The GLMM will assume a binary distribution for the response and use a logit

link. The analysis model will include treatment group, visit, and treatment group-by-visit interaction as categorical fixed effects; baseline value of MMD and baseline-by-visit interaction will be included as covariates. An unstructured covariance matrix will be used to model the covariance of within-subject repeated measurements. In cases where the model encounters complete or quasi-complete separation issues at any particular visit, logistic regression models will be applied to analyze data to ensure valid inference. Firth's penalized likelihood method will be used to handle the separation issue at the particular visit. In the event of non-convergence of the model using unstructured covariance matrix, a structured covariance matrix will be used in combination with empirical variance estimate (i.e., sandwich estimator) to address the potential mis-specified situation. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. Treatment comparison will be estimated by the odds ratio between atogepant group and topiramate group across Month 4 to 6, along with its 95% confidence interval and p-value.

9.5 Additional Efficacy Endpoints and Analyses

Continuous variables will be analyzed using the MMRM method, primarily focusing on the comparison between the atogepant and topiramate groups. The model will include treatment group, visit, CM status at baseline (Yes or No), and treatment group by visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. For the endpoints of change from baseline in MMD, CM status at baseline (Yes or No) will be excluded from the models as it's inherent in the baseline MMD. Other model options align with the MMRM method introduced in Section 9.4.2. Comparisons will be made at each visit to determine the treatment effects between the atogepant and the topiramate groups for each endpoint. In addition, the average treatment effects between atogepant versus topiramate group across Month 4 to 6 will be provided for eDiary endpoints. Treatment effect and treatment comparison will be estimated by the LS Means and LS Mean difference, along with their SE and 95% confidence interval, and the p-value corresponding to the between-treatment group difference.

For variables where the data are essentially binary and have multiple postbaseline assessments, comparisons between the atogepant and topiramate groups will be conducted using a GLMM method. The GLMM will assume a binary distribution for the response and use a logit link. The analysis model will include treatment group, visit, CM status at baseline (Yes or No), and treatment group-by-visit interaction as categorical fixed effects; baseline value and baseline-by-visit interaction will be included as covariates. As there are no baseline assessments for the endpoints PSSM and PGIC, the baseline monthly migraine days and its interaction with visit will be included in the model. If baseline value is baseline MMD, then CM status at baseline (Yes or No) will be excluded from the models as it's inherent in the baseline MMD. Other model options align with the GLMM method introduced in Section 9.4.3. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. Treatment comparison will be estimated by the odds ratio between atogepant and topiramate groups, along with its 95% confidence interval, and p-value.

Similar to the primary analysis of the key secondary endpoint of achieving ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period, the relative risk, odds ratio, and risk difference will also be provided for binary outcomes of achieving ≥ 25%, ≥ 30%, ≥ 75%, and 100% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period. The relative risk and risk difference will be obtained from MN method,[1] adjusting for CM status at baseline (Yes or No). The odds ratio between atogepant group and topiramate will be estimated and tested from logistic regression model. A 95% confidence interval (CI) and p-value will also be provided.

Plots of fitted (least squares) mean changes and their standard errors for monthly migraine days, monthly headache days, monthly acute medication use days, HIT-6 total score, MSQ Version 2.1 RFR domain score, and PROMIS Cognitive Function Abilities Subset from the MMRM will be presented by treatment group.

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 Month 4 to 6 will be provided by treatment group.

9.6 Efficacy Subgroup Analyses

To evaluate the treatment effect across subgroup categories, the estimate of the between-group treatment effect (with a 95% CI) for atogepant versus topiramate for each key secondary endpoint will be provided within each category of the following classification variables:

- Chronic migraine (i.e., ≥ 15 headache days and ≥ 8 migraine days during the 28-day screening/baseline period): Yes or No
- Baseline MMDs categories: 4 - < 8 days, 8 - < 15 days, or ≥ 15 days
- Sex: Female or Male
- Age group: < 40 years, 40 - 64 years, or ≥ 65 years

The same statistical methods described in Section 9.4.2 will be utilized based on mITT population. For subgroup analysis based on the categories of chronic migraine and Baseline MMDs, the relative risk and risk difference will be calculated without adjusting for CM status at baseline. The logistic models will not include baseline MMDs or CM status at baseline as covariates. The MMRM will not include baseline value and baseline by visit interaction term. If models do not converge, descriptive statistics for subgroups will be provided.

10.0 Safety Analyses

10.1 General Considerations

The safety endpoints include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, and the C-SSRS. For the analyses during the DB treatment and follow-up periods, subjects will be assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized. For the analyses

during the OL treatment and follow-up periods analysis, all subjects will be allocated to the atogepant group.

Analyses of all AE will be performed separately for the Safety Population 1 during the DB treatment period and for the Safety Population 2 during the OL treatment period.

Other safety endpoints including clinical laboratory evaluations, vital sign measurements, and C-SSRS questionnaires will be summarized based on the following four periods:

- The DB treatment period in Safety Population 1
- The DB follow-up period in Safety Population 1
- The OL treatment period in Safety Population 2
- The OL follow-up period in Safety Population 2

ECG parameters will be summarized based on the DB treatment period in Safety Population 1 and the OL treatment period in Safety Population 2.

The definitions of these periods are detailed in Section 7.3. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of study drug will be used as the baseline for all analyses of that safety parameter. The baseline will be applied to safety analyses for all four periods. For subjects who prematurely discontinued study drug during the DB treatment period and have an EDBTD visit, the safety data from EDBTD visit will be considered as the end of the DB treatment.

In the summary for the OL treatment and follow-up periods, each of the clinical laboratory, vital sign, ECG parameters, and AEs, along with the entirety of Safety Population 2, the following subgroup (Atogepant OL subgroup) will also be summarized:

- Subjects without early discontinuation of study drug during the DB treatment period and enter the OL treatment period.

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

10.2 Summary and Analysis of the Primary Endpoint

The primary endpoint is the treatment discontinuation due to AEs during the 24-week DB treatment period. Analysis of the primary endpoint will be conducted on Safety Population 1.

The number and percentage (n, %) of subjects with treatment discontinuation during the DB treatment period will be summarized. The relative risk of AE-related treatment discontinuation rate for atogepant versus topiramate as the primary measure will be provided. Comparison of the primary endpoint (i.e., adjusted relative risk, 95% CI, *P* value) will be made between atogepant group and the topiramate group using the MN method,[1] adjusting for CM status at baseline (Yes or No).

Odds ratio and risk difference in AE-related treatment discontinuation rate for atogepant versus topiramate will be provided. The odds ratio between atogepant group and topiramate will be estimated and tested from a logistic regression model, which assumes a binary distribution for the response and uses a logit link, with model terms including treatment group and baseline MMDs. The risk difference between atogepant and topiramate group will be calculated using the MN method,[1] adjusting for CM status at baseline (Yes or No). The 95% CI and p-value will also be provided.

To evaluate the impact of the unblinded subjects and to confirm the robustness of study results, two sensitivity analyses for the primary endpoint will be conducted excluding the impacted subjects. Both sensitivity analyses will utilize the same statistical method previously described. The first sensitivity analysis will exclude the 2 subjects confirmed unblinded by AbbVie and the 2 subjects reviewed by site personnel. The second sensitivity analysis will exclude all 13 impacted subjects.

In addition, a Kaplan-Meier plot will be utilized for the time to the treatment discontinuation due to AE. Subjects who complete the 24-week DB treatment period without prematurely discontinuing the study treatment will be considered censored at 24 weeks. Subjects who discontinue the study treatment due to any reasons other than AEs will be considered censored at the time of treatment discontinuation.

Subgroup analysis for the primary endpoint will be provided within each category of the following classification variables:

- Chronic migraine (i.e., ≥ 15 headache days and ≥ 8 migraine days during the 28-day screening/baseline period): Yes or No
- Baseline MMDs categories: 4 - < 8 days, 8 - < 15 days, or ≥ 15 days
- Sex: Female or Male
- Age group: < 40 years, 40 - 64 years, or ≥ 65 years

For subgroup analysis based on the categories of chronic migraine and Baseline MMDs, the relative risk and risk difference will be calculated without adjusting for CM status at baseline and the logistic model for calculating odds ratio will not include baseline MMDs as a covariate.

The attributes of the estimands corresponding to the primary endpoint in support of all regions are summarized in Table 2.

Table 2. Summary of the Estimand Attributes Corresponding to the Primary Objectives

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
Primary	Arm A: Atogepant 60 mg QD Arm B: Topiramate (50, 75, or 100 mg/day) Acute migraine medications as rescue medications are allowed to keep subjects in the study	Treatment discontinuation due to AEs during the 24-week DB treatment period	Analysis population: Safety Population 1. Target population: subjects who require preventive treatment of migraine	IE1: Subjects who discontinue study treatment due to any reasons other than AEs (e.g., lack of efficacy, withdrawal of consent, lost to follow-up, etc) will be classified as subjects without AEs leading to treatment discontinuation.	The relative risk in subjects with treatment discontinuation due to AEs during the DB treatment period between atogepant group and topiramate group using the MN method, adjusting for CM status at baseline (Yes or No)

10.3 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report.

10.3.1 Treatment-Emergent Adverse Events

TEAE 1 and NEAE 1 are defined for the DB treatment period in Safety Population 1, while TEAE 2 and NEAE 2 are defined for the OL treatment period in Safety Population 2.

TEAE 1 for the DB treatment period is defined as any AE with an onset date on or after the date of first dose of study drug during the DB treatment period; and on or before the date of last dose of study drug during the DB treatment period (including tapering-off phase, if applicable) + 30 days; and before the date of first dose of study drug during the OL treatment period, if applicable.

In Safety Population 2, TEAE 2 for the OL treatment period is defined as any AE that starts on or after the date of the first dose of study drug during the OL treatment period but not after the date of the last dose of study drug during the OL treatment period plus 30 days.

In addition to the TEAE 1 for the DB treatment period, AE during the DB treatment period is defined as any AE with onset date on or after the date of first dose of study drug during the DB treatment period and before the date of first dose of study drug during the OL treatment period, if applicable.

Newly Emergent Adverse Event 1 (NEAE 1) for the DB treatment period is defined as any TEAE 1 with an onset date after the date of last dose of study drug in the DB treatment period (not including the tapering-off phase).

NEAE 2 for the OL treatment period is defined as any TEAE 2 with an onset date after the date of last dose of study drug in the OL treatment period.

AEs during the DB treatment period, TEAE 1, TEAE 2, NEAE 1 and NEAE 2 for the DB or OL treatment periods 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 alphabetical order within each SOC. The number and percentage of subjects experiencing AEs during the DB treatment period, TEAE 1, TEAE 2, NEAE 1 and NEAE 2 will be summarized.

10.3.2 Adverse Event Overview

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

- Any TEAE
- Any TEAE related to study treatment according to the investigator
- Any severe TEAE
- Any serious TEAE
- Any AE during the DB treatment period
- Any TEAE leading to discontinuation of study treatment
- Any TEAE leading to death
- All deaths

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

TEAE 1 and TEAE 2 will be summarized by SOC and PT; by maximum relationship to study treatment as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum severity and SOC and PT; and by subject number and SOC and PT for the DB and OL treatment periods, separately. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

The incidence of common (≥ 2% of subjects [after rounding] in any treatment group) TEAE 1 and TEAE 2 will be summarized by preferred term, and treatment group for the DB and OL treatment periods, separately.

AEs during the DB treatment period will be summarized by SOC and PT, and by treatment group.

10.3.4 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 criteria. An AE during the DB treatment period will be considered a SAEs during the DB treatment period if the AE additionally meets any SAE criterion. TESAEs, SAEs during the DB treatment period, TEAEs leading to premature discontinuation of study treatment during the DB and OL treatment periods, AEs leading to treatment discontinuation during the OL treatment period, and TEAEs leading to death will be summarized by SOC and PT for both the DB and OL treatment periods. Tabular listings will be provided for all deaths, all SAEs, TEAEs leading to premature discontinuation of study treatment, and TEAEs leading to early discontinuation from the trial.

10.3.5 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 AESIs will be monitored during the trial:

- 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 $\geq 3 \times$ ULN.
- Potential Hy's law cases: elevated ALT or AST laboratory value that is $\geq 3 \times$ ULN and an elevated total bilirubin laboratory value that is $\geq 2 \times$ ULN and, at the same time, an alkaline phosphatase laboratory value that is $< 2 \times$ ULN.

AESIs will be summarized.

10.4 Analysis of Laboratory Data

Each laboratory variable will be summarized for all time points (starting with Baseline) according to the four periods specified in Section 10.1, 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 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 Table 12. A description of reporting the lab values in conventional units in patient narratives (along with the standard reporting in SI units) is listed in Table 13.

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. Shift tables will be provided to summarize shifts from baseline to the post-baseline values during the DB treatment period and the OL treatment period.

Laboratory abnormalities will be evaluated based on potentially clinically significant (PCS) criteria (Table 7). For each laboratory PCS criterion, the number and percentage of subjects who have a laboratory value meeting the criteria will be summarized for the four periods. Listings will be provided to summarize subject-level laboratory data for subjects meeting PCS criteria. A listing of all AEs for subjects with PCS Lab values will be provided.

In addition, ALT, AST, alkaline phosphatase, and total bilirubin will be categorized in Table 8. The number and percentage of subjects meeting each of the criteria for postbaseline hepatic laboratory abnormalities listed in Table 8 will be summarized. The percentages will be calculated relative to the number of subjects with at least 1 available postbaseline assessment. The numerator will be the total number of subjects having at

least 1 postbaseline value that meets the specific category during the study. A supportive listing will also be provided.

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

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

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.

10.5 Analysis of 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) according to the four periods specified in Section 10.1, 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 during the DB treatment and DB follow-up periods. Similarly, the summary will be presented for atogepant group during the OL treatment and OL follow-up periods.

Vital sign variables will be evaluated based on PCS criteria (Table 9). For each vital sign PCS criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized for the four periods. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCS criteria. In addition, a tabular display showing all AEs that occurred in subjects who had PCS postbaseline vital sign values will be provided.

In addition, a cumulative distribution function plot for the percentage change from baseline in body weight (kg) at the end of DB treatment period will be provided.

10.6 Other Safety Analyses

10.6.1 Electrocardiogram

Descriptive statistics for ECG parameters (i.e., heart rate, PR interval, QRS interval, RR interval, QT interval, and QTcF interval) at baseline, postbaseline, and changes from baseline values at each postbaseline timepoint, in alignment with the DB treatment period and the OL treatment periods specified in Section 10.1, will be presented.

ECG parameter values are considered PCS if ECG values meet either the actual value or change from baseline PCS high criteria listed in Table 10. The number and percentage of subjects with PCS postbaseline values will be tabulated by study treatment for the DB and OL treatment periods. The percentages will be calculated relative to the number of subjects with an available non-PCS baseline value and at least 1 postbaseline assessment. The numerator will be the total number of subjects with an available non-PCS baseline value and at least 1 PCS postbaseline ECG value during the study. A supportive listing of subjects with PCS postbaseline values will be provided. A listing of all AEs for subjects with PCS ECG values will also be provided.

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

The number and percentage of subjects with an increase > 30 msec but ≤ 60 msec, and with an increase > 60 msec in QTcF will be tabulated. Subjects will be counted only once for the most severe category. A supportive listing of subjects with postbaseline QTcF increases > 30 msec will be provided, including the subject identification (SID) number, study center, and all QTcF values (including changes from baseline). A listing of all AEs for subjects with postbaseline QTcF increases > 30 msec will also be provided.

A shift table from baseline to the end of DB 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. Similar tables for the OL treatment period will also be provided. A tabular display of subjects with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

10.6.2 Columbia-Suicide Severity Rating Scale

For C-SSRS, the number and percentage of subjects with suicidal ideation or suicidal behavior as recorded on the C-SSRS will be summarized by treatment group in the subject's lifetime history, in the past 6 months, in the DB treatment and DB follow-up periods for the Safety Population 1 and in the OL treatment and OL follow-up periods for the Safety Population 2. The distribution of responses for the most severe suicidal ideation and the most severe suicidal behavior will also be presented by treatment group. Supportive listings will be provided and will include the SID 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 subjects who have suicidal ideation or suicidal behavior will also be provided.

11.0 COVID-19 Related Analyses

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

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

All COVID-19 related analyses will use the safety population 1 for the DB period and the safety population 2 for the OL period, respectively. The number of subjects impacted by COVID-19 during the study will be summarized by treatment group and overall. In addition, the number of subjects impacted by COVID-19 and their corresponding

disposition status in the DB treatment period and the OL treatment period will be summarized respectively.

The number of subjects 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.

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

The number and percentage of subjects 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 subjects with TEAEs and serious TEAEs related to COVID-19 vaccine will be summarized by treatment and overall.

Supporting listings for the analyses described above will be provided.

12.0 Interim Analyses

An independent DSMB will review safety data throughout the trial and make recommendations to the sponsor, including modification or ET of the trial.

12.1 Data Safety Monitoring Board

An external DSMB composed of clinicians and statisticians independent of AbbVie and with relevant expertise in their field will review unblinded data from the ongoing trial. The DSMB is responsible for safeguarding the interests of trial subjects, assessing the safety of the study drug during the trial, as well as for monitoring the integrity and interpretability of the trial. The DSMB will provide recommendations to the sponsor, including modification or ET of the trial, if emerging data show unexpected and clinically significant AEs related to study treatment.

A separate DSMB charter will be prepared outside of the protocol and will further describe the roles and responsibilities of the DSMB members, frequency and scope of the data reviews, and expectations for blinded communications.

13.0 Overall Type-I Error Control

The overall type I error rate for multiple comparisons of the primary and secondary efficacy endpoints will be controlled at a 2-sided 0.05 significant level as follows:

- A fixed-sequence procedure is used for multiple comparisons of primary and key secondary endpoints. The primary endpoint is tested first at a 0.05 significance level; if significant, then the key secondary endpoints will be tested sequentially according to the prespecified order listed below unless specified otherwise at level 0.05. Once 1 hypothesis is tested not significantly, all subsequent hypotheses cannot be formally rejected.
  - Treatment discontinuation due to AEs during the 24-week DB treatment period.
  - Achievement of ≥ 50% improvement (reduction) in mean MMD during Months 4 to 6 of the DB treatment period.
  - Change from baseline in mean MMD during Months 4 to 6 of the DB treatment period.
  - Change from baseline in HIT-6 total score at Week 24.
  - Change from baseline in MSQ Version 2.1 RFR domain score at Week 24.
  - Achievement of a rating of "much better" or "very much better" at Week 24 assessed by the PGIC.
  - Change from baseline in PROMIS Cognitive Function Abilities Subset Short Form 6a Version 2.0 score at Week 6.

14.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	08 November 2023	Initial version
2.0	23 April 2025	• Removed key secondary endpoints in support of France HTA submission. • Expand secondary endpoints. • Revised the estimands of secondary endpoints. • Removed country comparisons between IRT and EDC. • Provided definition of new migraine preventive treatment. • Removed the listing for urine pregnancy test • Added sub-group analyses for all secondary endpoints. • Two additional sensitivity analyses were added for the primary endpoint and all key secondary endpoints. • Modified the GLMM fitting process and GLMM description • Added Kaplan-Meier plots for time to treatment discontinuation during the DB period. • Removed interim analysis. • Modified multiplicity controls. • Updated sample size determination. • Updated PROMIS-CF transformation scores.

14.1 Changes to Planned Analyses in the Protocol

There are no changes from the protocol-planned analyses.

15.0 References

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4. Reuter U, Ehrlich M, Gendolla A, et al. Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia. 2022;42(2):108-18.
5. Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: A framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71.
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Appendix A. List of SAP Signatories

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

Appendix B. Definitions of Electronic Diary Data

Migraine Day

A migraine day is defined as any calendar day on which a headache which meets criteria A, B, and C or meets criteria D and E, as listed below occurs, per participant eDiary. Calendar days begin at midnight and last until 11:59 PM (23:59).

A. Headache has at least two of the following four characteristics:
   - Unilateral location
   - Pulsating quality
   - Moderate or severe pain intensity
   - Aggravated by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

AND

B. At least one of the following:
   - Nausea and/or vomiting
   - Photophobia and phonophobia
   - Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

AND

C. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (i.e., triptan, ditan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified

OR

D. Any headache which fulfils one criterion from (1) and at least one criterion from (2) or fulfils at least two criteria from (1) and no criteria from (2).

   1. Headache characteristics:

      - Unilateral location
      - Pulsating quality
      - Moderate or severe pain intensity
      - Aggravated by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

   2. Symptoms:

      - Nausea and/or vomiting
      - Photophobia and phonophobia
      - Typical aura (i.e., visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

AND

E. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (i.e., triptan, ditan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified.

Headache Day

A headache day is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (e.g., ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration will be specified. Calendar days begin at midnight and last until 11:59 PM (23:59).

Acute Medication Use Day

An acute medication use day is defined as any day on which a subject reports, per eDiary, the intake of allowed medication(s) to treat a migraine. The allowed medications include

the following categories of drugs: triptans, ergots, ditans, opioids, analgesics (including acetaminophen), nonsteroidal anti-inflammatory drugs (including aspirin), and antiemetics.

A triptan use day is defined as any day on which a subject reports intake of a triptan to treat a migraine per subject eDiary.

Appendix C. Derivation of Efficacy Variables

C.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, subjects are to record eDiary information on the duration of headache, headache specific characteristics and symptoms, the pain severity, and use of any acute headache pain medication. Daily headache diary data consists of data from "today's diary" completed on that day and "yesterday's diary" completed on the following day. Subjects are to report headache data in "today's diary" in the evening at any time from 19:00 to 23:59 and to complete "yesterday's diary" on the following day to add the remaining headache data of previous evening until midnight. In case subjects miss "today's diary," they can report the whole-day headache data in "yesterday's diary" on the following day. In case subjects miss "yesterday's diary," headache data from "today's diary" alone will be used as daily headache diary data. If both "today's diary" and "yesterday's diary" are missing on one day, the daily headache diary data will be treated as missing.

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

- Daily headache total duration: summation of headache durations from "today's diary" and "yesterday's diary"
- Daily headache pain severity: the worst pain severity from "today's diary" and "yesterday's diary"
- Daily headache characteristics and symptoms: present if present in one of "today's diary" and "yesterday's diary"
- Daily acute headache medication usage: combination of acute headache medications usage from "today's diary" and "yesterday's diary."
- For the derivation of headache day, the subject is considered to have taken a non-antiemetic acute headache medication if the subject has taken such a medication in either "today's diary" or "yesterday's diary."

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

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

The monthly migraine days is defined as the total number of recorded migraine days in the eDiary divided by the total number of days with eDiary records during each monthly period and multiplied by 28. For baseline, a minimum of 20 days' eDiary data during the 4-week baseline period is required for the migraine days to be evaluable. For each postbaseline 4-week treatment period, a minimum of 14 days' eDiary data during that period is required for the migraine days to be evaluable. If a subject does not have at least 14 days of diary data for a monthly treatment period, the migraine days for that period will be considered as missing. Migraine days will be derived for each subject at baseline and for each postbaseline monthly treatment period (Month 1, 2, 3, 4, 5, and 6). The same method to derive monthly migraine days will be used to derive monthly headache days, monthly acute medication use days, monthly triptan use days, monthly cumulative headache hours, monthly moderate/severe headache days, and monthly severe headache days.

If a subject confirmed that acute medications were taken and entered medications in the eDiary, then the acute medication use day will be set to 'Yes.' If a subject reports 'Yes' to the intake of allowed medication(s) to treat an acute migraine but does not list any of them in the diary, then the acute medication use days will not be counted in this situation and vice versa.

C.2 Derivation of Health Outcome Endpoints

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 the 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 4.

Table 4. Item Values for MSQ Item Responses

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

Step 2: Computation of raw domain (dimension) scores

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

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

In detail, for MSQ v2.1 Role Function Restrictive domain, the 7 individual item responses using final item value will be summed, resulting in the raw domain score ranging from 7 to 42 with higher scores indicating better quality of life. If there are missing item responses, the raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by 7 provided that 4 or more items in the domain are completed; otherwise, it will be set to missing. For MSQ v2.1 Role Function Preventive and Emotional domains, the raw domain scores will be calculated similarly using final item value respectively. If there are missing item responses, the corresponding raw domain score will be calculated by summing the non-missing item responses using final item value and dividing by the number of non-missing items and then multiplying by the number of questions in that domain provided that 2 or more domain items are completed; otherwise, it will be set to missing.

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

The transformation formula for each MSQ 2.1 domain is listed below:

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

HIT-6 Total Score Derivation

For HIT-6 total score, pre-coded item values and final item values for each item response are shown in Table 5. 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 the total score will be missing.

Table 5. 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.

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.

PROMIS-CF T-Score Derivation

The Patient Reported Outcomes Measurement Information System (PROMIS®) Cognitive Function and Cognitive Function Abilities Subset item banks assess patient perceived cognitive deficits (i.e., mental acuity, concentration, verbal and nonverbal memory, verbal fluency, and perceived changes) 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-CF 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 6. Higher raw or T-scores indicate a better cognitive function.

SF-36 V2 T-Score Derivation

The SF-36 v2 yields scores for eight health domain scales, including physical functioning (PF), bodily pain (BP), role limitations due to physical health problems (RP), role

limitations due to personal or emotional problems (RE), general mental health (MH), social functioning (SF), energy/fatigue or vitality (VT), and general health perceptions (GH). Two summary scores, physical component summary (PCS) and mental component summary (MCS), are generated based on the eight scales. All items, scales, and summary measures are scored so that a higher score indicates a better health state. The scoring of the questions is as follows.

Physical Functioning (PF) - items 3a through 3j (10 items):

- 1 Yes, limited a lot
- 2 Yes, limited a little
- 3 No, not limited at all

Role-Physical (RP) - items 4a through 4d (4 items):

- 1 all the time
- 2 most of the time
- 3 some of the time
- 4 a little of the time
- 5 none of the time

Bodily Pain (BP) - items 7 and 8 (2 items):

- For item 7
  - 6.0 none
  - 5.4 very mild
  - 4.2 mild
  - 3.1 moderate
  - 2.2 severe
  - 1.0 very severe
- For item 8
  - 6 not at all when item 7 none

- 5 not at all when item 7 ≠ none
- 4 a little bit
- 3 moderate
- 2 quite a bit
- 1 extremely

- For item 8, if item 7 is not answered
  - 6.0 not at all
  - 4.75 a little bit
  - 3.5 moderate
  - 2.25 quite a bit
  - 1.0 extremely

General Health (GH) - items 1 and 11a through 11d (5 items):

- For item 1
  - 5.0 excellent
  - 4.4 very good
  - 3.4 good
  - 2.0 fair
  - 1.0 poor
- For items 11a and 11c
  - 1 definitely true
  - 2 mostly true
  - 3 don't know
  - 4 mostly false
  - 5 definitely false
- For items 11b and 11d
  - 5 definitely true
  - 4 mostly true
  - 3 don't know

- 2 mostly false
- 1 definitely false

Vitality (VT) - items 9a, 9e, 9g, and 9i (4 items):

- For items 9a and 9e
  - 5 all the time
  - 4 most of the time
  - 3 some of the time
  - 2 a little of the time
  - 1 none of the time
- For items 9g and 9i
  - 1 all the time
  - 2 most of the time
  - 3 some of the time
  - 4 a little of the time
  - 5 none of the time

Social Functioning (SF) - items 6 and 10 (2 items):

- For item 6
  - 5 not at all
  - 4 slightly
  - 3 moderately
  - 2 quite a bit
  - 1 extremely
- For item 10
  - 1 all the time
  - 2 most of the time
  - 3 some of the time

- 4 a little of the time
- 5 none of the time

Role-Emotional (RE) - items 5a through 5c (3 items):

- 1 all of the time
- 2 most of the time
- 3 some of the time
- 4 a little of the time
- 5 none of the time

Mental Health (MH) - items 9b, 9c, 9d, 9f, and 9h (5 items):

- For items 9b, 9c, and 9f
  - 1 all of the time
  - 2 most of the time
  - 3 some of the time
  - 4 a little of the time
  - 5 none of the time
- For items 9d and 9h
  - 5 all of the time
  - 4 most of the time
  - 3 some of the time
  - 2 a little of the time
  - 1 none of the time

Reported Health Transition (HT) - item 2:

- 1 much better now than one year ago
- 2 somewhat better now than one year ago
- 3 about the same as one year ago

- 4 somewhat worse now than one year ago
- 5 much worse now than one year ago

This item is not scored as part of any SF-36v2 Health Survey scale or measure and should be treated as ordinal level data. It can be used to analyze the percentage of respondents who select each response choice for this item or to estimate change reported for each response category.

The total raw scores for each health domain scale are calculated as follows.

Scale	Sum of Questions	Score Range
PF	3a + 3b + 3c + 3d + 3e + 3f + 3g + 3h + 3i + 3j	10 – 30
RP	4a + 4b + 4c + 4d	4 – 20
BP	7 + 8	2 – 12
GH	1 + 11a + 11b + 11c + 11d	5 – 25
VT	9a + 9e + 9g + 9i	4 – 20
SF	6 + 10	2 – 10
RE	5a + 5b + 5c	3 – 15
MH	9b + 9c + 9d + 9f + 9h	5 – 25

The scale total raw scores are then transformed to a 0 - 100 scale using the following formula:

$$\frac{(Actual\ raw\ score - lowest\ possible\ raw\ score)}{Possible\ raw\ score\ range} \times 100$$

In order to meaningfully compare results from different health domain scales and directly interpret the domain scale scores in relation to the distribution of scores in the 1998 US general population, the health domain scale 0 - 100 scores can be transformed to norm-based scores (NBS):

1. First, a z-score for each scale is computed by subtracting the 1998 US general population mean for each health domain scale from the 0 100 score for that scale,

and then dividing the difference by the corresponding scale standard deviation. The formulas for computing the z-score for each standard form health domain scale are as follows:

PF: z (PF 83.29094)/23.75883

RP: z (RP 82.50964)/25.52028

BP: z (BP 71.32527)/23.66224

GH: z (GH 70.84570)/20.97821

VT: z (VT 58.31411)/20.01923

SF: z (SF 84.30250)/22.91921

RE: z (RE 87.39733)/21.43778

MH: z (MH 74.98685)/17.75604

where the scale acronym in each formula represents the 0 100 score for that scale.

2. Second, the standard form z-scores are transformed into norm-based scores by multiplying each z-score by 10 and adding 50 to the resulting product.

Scoring of the physical and mental component summary measures (PCS and MCS) are as follows:

1. Aggregate the eight health domain scale z-scores using the physical or mental factor score coefficients from the 1990 US general population. The formulas are:

$$Aggregate\ PCS$$

$$(PFz \times .42402) + (RPz \times .35119) + (BPz \times .31754)$$

$$+ (GHz \times .24954) + (VTz \times .02877) + (SFz \times .00753)$$

$$+ (REz \times .19206) + (MHz \times .22069)$$

$$Aggregate\ MCS$$

$$(PFz \times .22999) + (RPz \times .12329) + (BPz \times .09731)$$

$$+ (GHz \times .01571) + (VTz \times .23534) + (SFz \times .26876)$$

$$+ (REz \times .43407) + (MHz \times .48581)$$

Transform aggregate component scores to norm-based T-scores by multiplying the aggregated component scale scores by 10 and adding 50 to the resulting products.

If multiple instances occur on the same day, then the sum of the MCS and PCS scores will be calculated and the instance with the lowest sum score will be selected. If the lowest sum score is observed for multiple instances, then the instance with the latest timestamp will be selected.

Missing values in individual questions of SF-36 v2 questionnaire are handled as follows. Given that the ePRO device will be used to collect data, logic checks will be implemented to avoid unanswered questions or the selection of multiple options for one question.

- Using Full Missing Data Estimation (Full MDE) method, an estimate of health domain scale scores for group-level analyses can be obtained even if only one item in a scale is answered. The missing scale item responses would be assumed to be the same as the response to the one answered item on that scale.

But for PF scale, the best estimate is attained through item response theory, which is provided by the QualityMetric Health Outcomes Scoring Software 2.0.

- Under Full MDE, a PCS score can be computed if at least 7 scales (one of which must be the PF scale) have been scored and an MCS score can be computed if at least 7 scales (one of which must be the MH scale) have been scored.

Appendix D. Definition of Adverse Events of Special Interest

The definition of Adverse Events of Special Interest (AESI) is described in Section 10.3.5.

Appendix E. Potentially Clinically Important Criteria for Safety Endpoints

The potentially clinically significant (PCS) criteria for clinical laboratory parameters are described in Table 7, the criteria for hepatic laboratory abnormalities are described in Table 8, the PCS criteria for vital sign findings are described in Table 9, the PCS criteria for ECG parameters are described in Table 10.

Table 7. Potentially Clinically Significant Criteria for Clinical Laboratory Parameters

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
Chemistry	Albumin	g/L	< 0.8 × LLN	> 1.2 × ULN
	Alanine aminotransferase	U/L	—	≥ 3.0 × ULN
	Alkaline phosphatase	U/L	—	≥ 3.0 × ULN
	Aspartate aminotransferase	U/L	—	≥ 3.0 × ULN
	Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Bilirubin, total	µmol/L	—	≥ 1.5 × ULN
	Blood urea nitrogen	mmol/L	—	> 1.5 × ULN
	Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
	Cholesterol, total	mmol/L	—	> 1.6 × ULN
	Creatinine	µmol/L	—	> 1.5 × ULN
	Creatine kinase	U/L	—	> 2.0 × ULN
	Estimated glomerular filtration rate	mL/sec/1.73m^2	< 1 mL/sec/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
	Triglycerides	mmol/L	—	> 2.0 × ULN
	Uric acid	µmol/L	—	> 1.2 × ULN

Category	Parameter	SI Unit	PCS Criteria	
			PCS Low	PCS High
Hematology	Basophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Eosinophils, absolute cell count	10^9/L	—	> 2.0 × ULN
	Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
	Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
	Lymphocytes, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Monocytes, absolute cell count	10^9/L	< 0.5 × LLN	> 2.0 × ULN
	Neutrophils, absolute cell count	10^9/L	< 0.7 × LLN	> 1.3 × ULN
	Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
	Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
	White blood cell count	10^9/L	< 0.9 × LLN	> 1.5 × ULN
Urinalysis	pH	pH	< 0.9 × LLN	> 1.1 × ULN
	Glucose	mmol/L	—	At least 1+
	Protein	g/L	—	At least 1+
	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)

Table 8. Criteria for Hepatic Laboratory Abnormalities

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

Laboratory Parameter	Categories
Alkaline Phosphatase	≥ 1 × ULN
	≥ 1.5 × ULN
	≥ 2 × ULN
	≥ 3 × ULN
	≥ 5 × ULN
	≥ 10 × ULN
	≥ 20 × ULN
Concurrent Elevations[a]	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[a]	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)

a. 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 9. Potentially Clinically Significant Criteria for Vital Signs Parameters

Parameter	Flag	Criteria	
		Observed Value	Change from Baseline
Standing/Sitting Systolic blood pressure, mmHg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Standing/Sitting Diastolic blood pressure, mmHg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Standing/Sitting Pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%
	Low	—	Decrease of ≥ 5%
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 10. Potentially Clinically Significant Criteria for ECG Parameters

Parameter	Unit	Actual Value	Change from Baseline
QRS interval	msec	≥ 150	-
PR interval	msec	≥ 250	-
QTcF interval	msec	> 500	-
QTcF interval	msec	-	Increase > 60

Table 11. Clinical Interest Criteria for ECG Parameters

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

Appendix F. 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 12. 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) (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	Triglycerides	mg/dL	0
18	Uric Acid	mg/dL	1
19	Hemoglobin	g/dL	1

Patient narratives will also include the values in conventional units for the selected lab parameters (Table 12). That will be accomplished by presenting the values in

conventional units within the parentheses next to the values in SI units. As shown in Table 13 below for 'Bilirubin, Total' parameter, for which 'umol/L' is the SI unit and 'mg/dL' is the conventional unit.

Table 13. Presenting Laboratory Data Using SI and Conventional Units in Narratives

LABORATORY DATA						
		Normal Range		VISIT01	VISIT02	VISIT04
Lab Test	Test Name	Low	High	03 July 2024	07 August 2024	04 September 2024
CHEMISTRY	Bilirubin, Total (µmol/L (mg/dL))	0 (0)	18.81 (1.1)	6.84 (0.4)	5.13 (0.3)	5.13 (0.4)

Appendix G. List of Abbreviations

Abbreviation/Term	Definition
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
bpm	beats per minute
CI	confidence interval
CM	chronic migraine
CP	conditional power
C-SSRS	Columbia–Suicide Severity Rating Scale
DB	double-blind
DBP	Diastolic blood pressure
DMC	data monitoring committee
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
ET	early termination
FWER	familywise error rate
GLMM	generalized linear mixed model
HIT-6	Headache Impact Test
ITT	intent-to-treat
IRT	interactive response technology
LLN	lower limit of normal value
LS	least squares

Abbreviation/Term	Definition
MAR	missing-at-random
MedDRA	Medication Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MDE	Missing Data Estimation
MMD	monthly migraine days
MMRM	mixed effects model for repeated measures
MN	Miettinen O, Nurminen M
MNAR	missing-not-at-random
MSQ v2.1	Migraine Specific Quality of Life Questionnaire, Version 2.1
NEAE	newly emergent adverse event
OL	open-label
PCS	potentially clinically significant
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression –Severity
PRO	patient reported outcomes
PROMIS-CF	Patient-Reported Outcomes Measurement Information System Cognitive Function – 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
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RFR	Role Function-Restrictive
SAE	serious adverse event
SAP	statistical analysis plan
SBP	Systolic blood pressure
SD	standard deviation
SE	standard error
SF-36 PCS	Short Form-36 (SF-36) Version 2 Physical Component Score
SF-36 MCS	Short Form-36 (SF-36) Version 2 Mental Component Score
SI	Le Système International d'Unités (International System of Units)
SID	subject identification

Abbreviation/Term	Definition
SOC	System Organ Classes
SPP	Statistical Programming Plan
SSA	Simplified Schedule of Activities
SSR	sample size re-estimation
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TSAE	treatment supplementary adverse events
ULN	upper limit of normal value
WHO	World Health Organization
WPAI: MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine Version V2.0

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