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Protocol for Study M22-056

Episodic Migraine: Evaluate the Efficacy, Safety, and Tolerability of Atogepant for the Prevention of Migraine in Japanese Subjects

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

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1 SYNOPSIS

Title: A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study with An Active Treatment Extension to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Japanese Subjects with Episodic Migraine	
Background and Rationale:	Atogepant is a potent, selective oral calcitonin gene-related peptide receptor antagonist being developed for migraine prevention. Atogepant has been approved in the United States for preventive treatment of migraine in adults at doses of 10 mg, 30 mg, and 60 mg/day QD for episodic migraine, and 60 mg QD for chronic migraine. In the EU, atogepant is approved for the prophylaxis of migraine in adults who have at least 4 migraine days per month with the recommended dose of 60 mg QD. This randomized, double-blind, placebo-controlled Phase 2/3 study is designed to evaluate the safety and efficacy of atogepant 10 mg, 30 mg, and 60 mg QD and to assess the dose response in Japanese subjects with episodic migraine. In addition, the extension phase after the completion of the double-blind phase provides opportunities for all subjects to have active treatment.
Objectives and Endpoints:	**Primary objective:** To evaluate the safety, efficacy, and tolerability of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg QD for the prevention of migraine in Japanese subjects with episodic migraine, and to prospectively test for superiority of atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg QD versus placebo for the prevention of migraine in Japanese subjects with episodic migraine. The following primary endpoint will be evaluated: • Change from baseline in mean monthly migraine days across the 12-week double-blind treatment period. **Secondary objective:** To demonstrate improvement in efficacy for treatment with atogepant when each of atogepant doses is compared to placebo with respect to the secondary endpoints. The following secondary endpoints will be evaluated: • Change from baseline in mean monthly headache days across the 12-week double-blind treatment period. • Change from baseline in mean monthly acute medication use days across the 12-week double-blind treatment period. • At least a 50% reduction in the 3-month average of monthly migraine days. • Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12 • Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week double-blind treatment period.

	• Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week double-blind treatment period. The following safety endpoint will be evaluated: • Safety evaluations include AE monitoring, vital sign measurements, ECG variables, clinical laboratory testing (hematology, chemistry, and urinalysis), and C-SSRS as measures of safety and tolerability for the entire study duration.
Investigators:	Investigator information on file at AbbVie.
Study Sites:	Approximately 50 sites in Japan.
Study Population and Number of Subjects to be Enrolled:	Approximately 520 subjects with migraine (with or without aura) will be randomized into the study.
Investigational Plan:	This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 2/3 study that will evaluate the efficacy, safety and tolerability of atogepant in Japanese subjects. The study consists of a 4-week screening and baseline period, a 12-week double-blind treatment period, a 12-week active treatment extension period (dose blinded), and a follow-up Period 30 days after the last dose of study drug, for a total duration of approximately 32 weeks. Subjects will be randomized in a 1:1:1:1 ratio to receive daily dosing of placebo, atogepant 10 mg, atogepant 30 mg, or atogepant 60 mg for 12 weeks. All subjects who complete the 12-week double-blind treatment period will continue into the 12-week active treatment extension period where the study drug dose will be blinded. Subjects randomized to atogepant treatment groups in the double-blind treatment period will continue to receive the same study drug dose in the active treatment extension period. Subjects in the placebo group in the double-blind treatment period are re-randomized to the active treatment extension period in a 1:1:1 ratio to receive blinded treatment of atogepant 10 mg, 30 mg, or 60 mg.
Key Eligibility Criteria:	Adult subjects age 18 to 80 years with at least a 1-year history of migraine (with or without aura) are eligible. Subjects meets the following criteria: • < 50 years of age at the time of migraine onset; • history of 4 to 14 migraine days per month in the 3 months prior to screening; and • 4 to 14 migraine days in the baseline period and completed at least 20 out of 28 days at the baseline period per the eDiary.

Study Drug and Duration of Treatment:	Treatment duration is approximately 24 weeks. During the 12-week double-blind treatment period, subjects will be randomized in a 1:1:1:1 ratio to one of 4 treatment groups: • Atogepant 10 mg QD • Atogepant 30 mg QD • Atogepant 60 mg QD • Placebo During the 12-week active treatment extension period, subjects will receive atogepant 10, 30, or 60 mg QD.
Date of Protocol Synopsis:	18 July 2024

2 INTRODUCTION

2.1 Background and Rationale

Atogepant is a potent, selective oral CGRP receptor antagonist being developed for migraine prevention. Atogepant has been approved in the United States for preventive treatment of migraine in adults at doses of 10 mg, 30 mg, and 60 mg/day QD for episodic migraine, and 60 mg QD for chronic migraine.[1] In the EU, atogepant is approved for the prophylaxis of migraine in adults who have at least 4 migraine days per month with the recommended dose of 60 mg QD.

In Japan, the overall prevalence of migraine in the past year was reported as 8.4% with 5.8 % of migraine cases were without aura and 2.6% or occurrences of migraine were with aura.[2] Similar to Western countries, migraine is more prevalent among women in Japan and women were observed to have a 5.9-fold higher risk of migraine than men.[3] Approximately one third of patients with migraine have 4 or more migraine attacks per month and 85.5% of the third who have at least 4 attacks were eligible for prevention based on an expert consensus.[4] However, most of those patients do not use any preventive medication.[5] Migraine is the second leading cause of years lived with disability globally with an estimated global prevalence of 14.1%.[6] Migraine was ranked seventh highest among specific causes of disability globally.[7]

Migraine is typically characterized by attacks of throbbing, unilateral headache of moderate or severe pain intensity, associated with nausea, vomiting, and/or sensitivity to light (photophobia), and sound (phonophobia). Approximately 25% of individuals experience migraine headaches that are preceded by focal neurological dysfunction (aura). Improving diagnosis and optimizing treatments for migraine have been recognized as critically important to overcoming current barriers to reduce the global burden of migraine.

Currently there are no biological markers for migraine and diagnosis is based on clinical history, examination, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnoses and subsequent treatment. Episodic migraine is a syndrome diagnosis applied to patients with migraine (with or without aura) who have 1 to 14 headache days per month. Chronic migraine is a specific ICHD-3 diagnosis applied to a subset of patients with ≥ 15 headache days per month.[8-10] This study evaluates the efficacy, safety and tolerability of atogepant in subjects with episodic migraine.

Why Is This Study Being Conducted?

Based on the results of the Phase 3 Study 3101-301-002, the present study is being performed to prospectively assess the safety, tolerability, and efficacy of atogepant 10 mg, 30 mg, and 60 mg QD compared with placebo in the prevention of episodic migraine in Japanese subjects. This randomized, double-blind, placebo-controlled Phase 2/3 study is designed to confirm the efficacy of these dose regimens and to assess the dose response in Japanese subjects with episodic migraine. An active study drug extension phase will be conducted in subjects who complete the double-blind treatment phase and provides opportunities for all subjects to receive active treatment. This Phase 2/3 study is intended to support registration applications of atogepant for migraine prevention in Japan.

2.2 Benefits and Risks to Subjects

Based on currently available data, atogepant has demonstrated efficacy in significantly reducing the number of migraine and headache days at doses of 10, 30, and 60 mg QD in episodic migraine and 60 mg QD in chronic migraine; and has been safe and well tolerated. The most common adverse drug reactions in clinical trials are nausea, constipation, fatigue/somnolence, decreased appetite, and decreased body weight.

Asymptomatic AST and ALT elevations above 3 × the ULN were rarely observed during the clinical trials in adults and there was a balance in the incidence of these elevations between atogepant treatment arms and placebo. No cases of severe liver injury or concurrent bilirubin elevations (≥ 2 × ULN) were observed during the clinical trials in adults. Hepatotoxicity events are under close surveillance and monitoring during this study. An external hepatic event adjudication committee should provide blinded surveillance, monitoring, and adjudication of events of post-treatment elevations of ALT and/or AST ≥ 3 × ULN in this study. In addition, an independent DSMB should review safety data throughout the study and make recommendations to the sponsor including modification or early termination of the study.

A newly identified risk of hypersensitivity, including anaphylaxis, dyspnea, rash, pruritus, urticaria, and facial edema, with the use of atogepant has been identified based on postmarketing safety reports. Serious hypersensitivity reactions, such as anaphylaxis, are rare, idiosyncratic in nature, and treatable with well-established treatment options as part of the standard of care.

As such, considering atogepant's established efficacy and safety profile and the measures planned to minimize risk to subjects participating in this study, the benefits of treatment with atogepant outweigh the risks, including serious hypersensitivity reactions, such as anaphylaxis.

The protocol is designed to ensure that safety is assessed adequately throughout the study. Although this is a 12-week placebo-controlled trial with a 12-week active treatment extension (with atogepant dose blinded), if a study subject experiences a migraine attack during the study, the subject is allowed to treat the migraine with their acute migraine treatment. Overall, the assessment of benefit/risk of atogepant is favorable.

For further details regarding atogepant, please refer to the current atogepant Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

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

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

- The difference in the mean change from baseline in mean monthly migraine days across the 12-week double-blind treatment period between each atogepant group and placebo in the mITT population. Data collected during the double-blind treatment period are included in the analyses. Missing data for subjects who discontinued the study treatment due to any reason are assumed MAR, i.e., subjects with treatment discontinuation behave like other subjects who did not discontinue the study treatment.

Secondary

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

The estimands corresponding to the secondary efficacy endpoints are:

- The difference in the mean change from baseline in mean monthly headache days across the 12-week treatment period between each atogepant group and placebo in the mITT population. Data after the discontinuation from double-blind treatment period are assumed MAR.
- The difference in the mean change from baseline in mean monthly acute medication use days across the 12-week treatment period between each atogepant group and placebo in the mITT population. Data after the discontinuation from double-blind treatment period are assumed MAR.
- The odds ratio in subjects achieving at least 50% reduction from baseline in 3-month average of monthly migraine days between each atogepant group and placebo in the mITT population.
- The difference in the mean change from baseline in MSQ v2.1 Role Function Restrictive domain score at Week 12 between each atogepant group and placebo in the mITT population. Data after the discontinuation from double-blind treatment period are assumed MAR.
- The difference in the mean change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period between each atogepant group and placebo in the mITT population. Data after the discontinuation from double-blind treatment period are assumed MAR.
- The difference in the mean change from baseline in mean monthly Physical Impairment domain score of the AIM -D across the 12-week treatment period between each atogepant group and placebo in the mITT population. Data after the discontinuation from double-blind treatment period are assumed MAR.

3.2 Primary Endpoint

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

3.3 Secondary Endpoints

The secondary efficacy endpoints are:

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

3.4 Additional Efficacy Endpoints

Additional efficacy endpoints and HEOR (Health Economics and Outcomes Research) endpoints are:

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

- At least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, and 12.
- Assessed by the PGIC as "much better" or "very much better" at Week 12.
- "Satisfied" or "extremely satisfied" with study medication for migraine prevention at Weeks 4, 8, and 12.
- Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Weeks 4, 8, and 12 as assessed by the WPAI:MIGRAINE.
- Change from baseline in the MIDAS total score at Week 12.
- Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Week 12.
- Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Week 12.
- Change from baseline in PGI-S score at Weeks 4, 8, and 12.
- Change from baseline in the MSQ v2.1 Role Function-Preventive domain score at Weeks 4, 8, and 12.
- Change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Weeks 4 and 8.
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, and 12.
- Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly Physical Impairment domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12.
- Change from baseline in monthly AIM-D total score at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in monthly Activity Level at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in monthly Activity Limitation at Weeks 1-4, 5-8, 9-12, and average across the 12-week double-blind treatment period.
- Change from baseline in PHQ-9 score at Week 12.
- Change from baseline in EQ-5D-5L descriptive system index score at Weeks 1 to 2, and at specified windows around Weeks 4, 8, and 12.
- Change from baseline in the EQ-5D-5L VAS score at Weeks 1 to 2, and at specified windows around Weeks 4, 8, and 12.
- Change from baseline in PROMIS-PI total score at Weeks 4, 8, and 12.

3.5 Safety Endpoints

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

3.6 Pharmacokinetic Endpoints

A graphical evaluation of the PK and PD data of atogepant may be performed for the identification of possible trends. The PK may be evaluated using the existing population PK model, updated with data from this study. Individual predictions of atogepant exposure (including but not limited to steady state $AUC_{0\text{-}Tau}$, C_{max} and C_{min}) will be evaluated graphically for potential relationships with efficacy and/or safety endpoints. If graphical evaluation identifies possible trends, exploratory PK/PD analyses may be performed for the evaluation and quantification of potential relationships via nonlinear mixed-effects modeling. Efficacy endpoints to be evaluated include migraine days and responder rates. A standalone pharmacometric analysis plan will be written, and the analyses results may be reported separately from the integrated clinical study report.

3.7 Biomarker Research Endpoints

Optional biospecimens (whole blood DNA, plasma, and saliva) may be collected to support the biomarker research objectives of the study drug. Please refer to Appendix H for the schedule of biomarker research sample collections. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. Assessments may include, but are not limited to, biomarkers related to the pathway(s) targeted by the study drug, or those believed to be related to the disease being studied. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to episodic migraine and/or in the development of new therapies and diagnostic tests. This research is exploratory in nature and the results may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual (Appendix J), Section 3.9.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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

Approximately 520 subjects will be randomized to one of the following 4 treatment arms in a 1:1:1:1 ratio:

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

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

Subject participation will begin with a 4-week screening/baseline period. Subjects who complete the 4-week screening/baseline period and meet all entry criteria will be randomized to the double-blind treatment period of the study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, and all completers move to the 12-week active treatment extension period with a subsequent follow-up Period 30 days after the last dose of study drug. For details, please see Appendix H, Schedule of Activities.

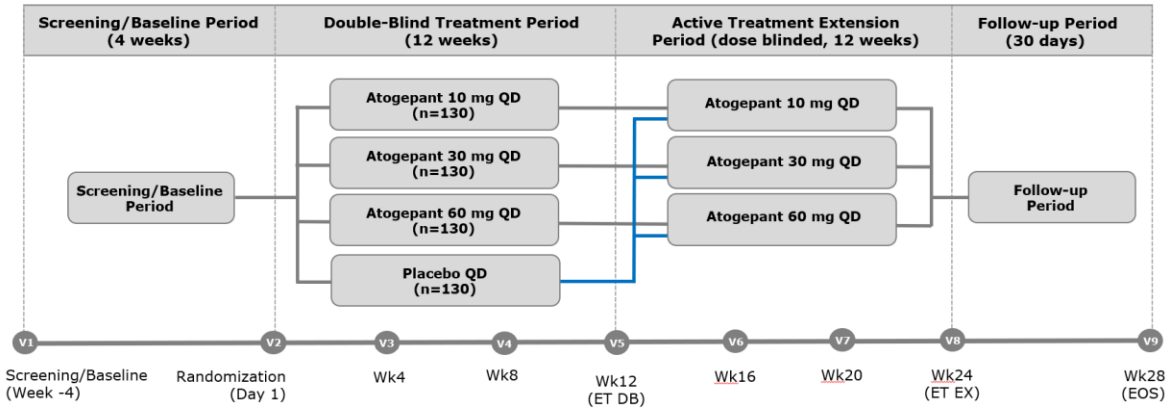
All completers of the double-blind treatment period may continue into the active treatment extension period (dose will be blinded). Subjects who are randomized to atogepant treatment groups in the double-blind treatment period will continue to be assigned to the same dose treatment group in the active treatment extension period. Subjects in the placebo group in the double-blind treatment period will be re-randomized to atogepant 10 mg, atogepant 30 mg, and atogepant 60 mg arms (dose blinded) in a 1:1:1 ratio to enter into the active treatment extension period.

An eDiary will be used to record the daily total duration of headache, headache characteristics, associated symptoms, the worst pain severity, and acute medication use both in the screening/baseline period and double-blind treatment period until Visit 5. Training for the eDiary will be provided for qualified subjects during Visit 1.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual.

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Design Diagram



4.2 Discussion of Study Design

Choice of Control Group

The 12-week double-blind treatment period utilizes a placebo control group. The use of placebo control is critical to the study design, allowing for further characterization of the safety profile of atogepant while also ensuring that results assessing efficacy can be interpreted. In this study, a placebo treatment group is included to comply with worldwide regulatory preferences since placebo-controlled superiority studies have been shown to be conducive to higher quality studies and to provide more reliable outcomes. Additionally, from a scientific point of view, randomized double-blind comparisons versus placebo are needed to permit adequate evaluations of efficacy.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with migraine. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

In non-Japanese subjects with migraine, the efficacy benefits of atogepant outweigh the risks. This favorable benefit-risk ratio supports the study of atogepant in Japanese subjects with episodic migraine. The purpose of this study is to determine if the benefit-risk profile of atogepant is similar in Japanese subjects as observed in non-Japanese subjects with episodic migraine.

Selection of Doses in the Study

This study evaluates 3 doses of atogepant, 10 mg, 30 mg, and 60 mg, which were selected based on the results from the Phase 3 registrational Study 3101-301-002 in US subjects with episodic migraine. In Study 3101-301-002, atogepant 10 mg, 30 mg, and 60 mg QD demonstrated statistically significant and clinically meaningful improvement compared with placebo in the preventive treatment of migraine in subjects with episodic migraine. Additionally, a clear dose-response relationship was evident, with the atogepant 60 mg dose consistently providing greater improvement across all primary and secondary efficacy endpoints compared with the 30 mg and 10 mg doses. Atogepant administered at doses of

10 mg, 30 mg, and 60 mg QD was well-tolerated and no safety concerns were identified. In addition, in Study 3101-101-002, atogepant was safe and well tolerated in healthy Japanese subjects within the dose range tested (10 mg QD, 30 mg QD, 60 mg QD, and 120 mg (i.e., 60 mg BID). The current study will evaluate atogepant 10 mg, 30 mg, and 60 mg, as a QD regimen to assess the dose response and to confirm the efficacy, safety, and tolerability in Japanese subjects.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent**, approved by an IEC/IRB, prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Male or female subjects ages 18 to 80 years, inclusive, at Visit 1.
- 3. No clinically significant laboratory values OR any of the following laboratory values at Visit 1:
  - ALT or AST > 1 × ULN OR;
  - total bilirubin > 1 × ULN (except for subjects with a diagnosis of Gilbert's disease) OR;
  - serum albumin < 2.8 g/dL.

Disease/Condition Activity

- 4. At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3, 2018 (Appendix D).
- 5. Age of the subject at the time of migraine onset < 50 years.
- 6. History of 4 to 14 migraine days per month (see Operations Manual [Appendix J], Section 3.7 for definition) on average in the 3 months prior to Visit 1 in the investigator's judgment.
- 7. 4 to 14 migraine days in the 28-day baseline period per eDiary.
- 8. Must have completed at least 20 out of 28 days in the eDiary during baseline period and is able to read, understand, and complete the study questionnaires and eDiary per investigator's judgment.

Subject History

- 9. No difficulty with distinguishing migraine headaches from tension-type or other headaches.

- 10. No history of migraine accompanied by diplopia or decreased level of consciousness, hemiplegic migraine, or retinal migraine as defined by ICHD-3, 2018.
- 11. No current diagnosis of chronic migraine, new persistent daily headache, trigeminal autonomic cephalgia (e.g., cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018.
- 12. No history of ≥ 15 headache days per month (see Operations Manual [Appendix J], Section 3.7 for definition of headache day) on average across the 3 months prior to Visit 1 in the investigator's judgment.
- 13. No history of ≥ 15 headache days (see Operations Manual [Appendix J], Section 3.7 for definition of headache day) in the 28-day baseline period per eDiary.
- 14. No history of an inadequate response to > 4 medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine (see Appendix F for classification of inadequate response to migraine-preventive medications).
- 15. No ECG with clinically significant abnormalities at Screening (Visit 1) as determined by the investigator.
- 16. No QTcF > 450 msec for males and QTcF > 470 msec for females at Visit 1 based on the final ECG report.
- 17. No clinically significant cardiovascular or cerebrovascular disease per the investigator's opinion including, but not limited to:
    - Clinically significant ischemic heart disease (e.g., unstable angina pectoris).
    - Clinically significant cardiac rhythm or conduction abnormalities (e.g., atrial fibrillation, second- or third-degree heart block) or risk factors for Torsade de Pointes (e.g., heart failure, hypokalemia, bradycardia).
    - Myocardial infarction, transient ischemic attack, or stroke within 6 months prior to Visit 1.
    - Heart failure defined as New York Heart Association functional classification system, Class III or IV (Appendix G).
- 18. No hypertension as defined by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Visits 1 or Visit 2. Vital sign measurements that exceed these limits may be repeated only once.
- 19. No clinically significant hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease:
    - If there is a history of such a disease, but the condition has been stable for more than 1-year prior to Visit 1, and is judged by the investigator as not likely to interfere with the subject's participation in the study, the subject may be included.
    - Subjects on dialysis for renal failure are excluded.
- 20. No history of acute hepatitis within 6 months of screening (Visit 1); chronic liver disease (including nonalcoholic fatty liver disease, viral chronic hepatitis, and cirrhosis); or a positive result on hepatitis B surface antigen or anti hepatitis C antibody testing.

- 21. No confounding psychiatric conditions, dementia, epilepsy or significant neurological disorders other than migraine, in the opinion of the investigator.
- 22. No subject has any other concurrent pain condition that, in the opinion of the investigator, may significantly impact the current headache disorder (e.g., fibromyalgia, facial pain).
- 23. No significant risk of self-harm based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator; subjects must be excluded if they report suicidal ideation with intent, with or without a plan, (i.e., Type 4 or 5 on the C-SSRS) in the past 6 months or report suicidal behavior in the 6 months prior to Visit 1 or Visit 2 assessments.
- 24. No history of malignancy in the 5 years prior to Visit 1, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.
- 25. No history of any GI prior procedures or GI conditions (e.g., diarrhea syndromes, inflammatory bowel disease) that may affect the absorption or metabolism of study drug; subjects with prior gastric bariatric treatments (e.g., Lap Band) which have been reversed are not excluded.
- 26. At Visit 1, subject is not a user of recreational or illicit drugs or has had no history within the past year of drug or alcohol abuse or dependence.
- 27. No positive result on the urine drug screen at Visit 1 unless explained by concomitant medication use (e.g., opioids prescribed for migraine pain).
- 28. Subject is not currently participating or has participated in a study with an investigational compound or device within 30 days prior to Visit 1 (this includes studies using marketed compounds or devices).
- 29. No previous exposure to:
  - Atogepant (AGN-241689 or MK 8031) OR
  - Injectable monoclonal antibodies blocking the CGRP pathway (e.g., erenumab, galcanezumab, fremanezumab, eptinezumab) within the last 6 months OR
  - Ubrogepant (has taken more than 3 doses of ubrogepant)
  - Rimegepant (has taken more than 3 doses of rimegepant)
  - Zavegepant (has taken more than 3 doses of zavegepant)
- 30. No history of hypersensitivity or clinically significant adverse reaction to a CGRP receptor antagonist or hypersensitivity to any component of the study drugs (atogepant or placebo).
- 31. Subject is not employed by or is an immediate family member (parents, spouses, siblings or children) of one of the investigators, study staff, or the sponsor.
- 32. Subject does not have a condition or is in a situation which in the investigator's opinion may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
- 33. No medical or other reasons (e.g., unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study) that, in the investigator's opinion, might indicate that the subject is unsuitable for the study.

Contraception

- 34. For all females of childbearing potential; a **negative serum pregnancy test** at Visit 1 and a **negative urine pregnancy test** at Visit 2 (Day 1) prior to the first dose of study drug.
- 35. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control** from at least 30 days before Study Day 1 until 30 days after the last dose of study drug. Female subjects of nonchildbearing potential do not need to use birth control.
- 36. If female, subject is not **pregnant or breastfeeding, and is not considering becoming pregnant** or donating eggs during the study or for at least 30 days after the last dose of study drug.
- 37. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Study Day 1 through 30 days after the last dose of study drug, to practice the protocol-specified contraception.
- 38. If male, subject is not considering **fathering a child or donating sperm** during the study or for at least 30 days after the last dose of study drug.

Concomitant Medications

- 39. No requirement for any medication, diet (i.e., grapefruit juice), or nonpharmacologic headache intervention that is on the list of prohibited concomitant medications or treatments that cannot be discontinued or switched to an allowable alternative medication or treatment (see Section 5.3 and Appendix E). This includes concomitant medications with demonstrated efficacy for the prevention of migraine (e.g., amitriptyline, topiramate, propranolol).
- 40. No usage of opioids or barbiturates > 2 days/month; triptans, ergots, or ditans ≥ 10 days/month; or simple analgesics (e.g., aspirin, NSAIDs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline period (barbiturates are excluded 30 days prior to screening and through the duration of the study) (see Appendix E). (Note: triptans, ergots and ditans are to be considered as a group)
- 41. No usage of therapeutic or cosmetic botulinum toxin injections (e.g., Dysport®, BOTOX®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to screening (Visit 1) and throughout the trial.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Nonchildbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of nonchildbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:

- Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy
- Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.

2. Postmenopausal female
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a FSH level ≥ 30 IU/L.

- Females, of Childbearing Potential
  - Review and document pregnancy avoidance recommendations with females of childbearing potential
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 30 days
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal,* transdermal,* injectable) associated with inhibition of ovulation-initiated at least 30 days prior to Visit 2 (Day 1).
    - Progestogen-only hormonal birth control (oral, injectable,* implantable*) associated with inhibition of ovulation-initiated at least 30 days prior to Visit 2 (Day 1).
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - IUD.
    - IUS.
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Note: the methods with asterisk (*) are not approved in Japan for the indication of contraception.

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential, must agree to use male condoms, even if the male subject has undergone a successful vasectomy, from Study Day 1 through at least 30 days after the last dose of study drug. Male subjects must also refrain from donating sperm during this period.

5.3 Prohibited Medications and Therapy

The following medications are prohibited 30 days prior to Visit 1 (unless otherwise indicated) and throughout the study period:

- Strong CYP3A4 inhibitors, including but not limited to: systemic (oral/IV) itraconazole, ketoconazole, clarithromycin, telithromycin,* nefazodone,* and HIV protease inhibitors.
- Strong and moderate CYP3A4 inducers, including but not limited to: barbiturates (e.g., phenobarbital and primidone), systemic (oral/IV) dexamethasone, efavirenz, carbamazepine, phenytoin, rifampin*/rifampicin, rifabutin, and St. John's wort.
- Strong OATP1B1 and OATP1B3 inhibitors (e.g., gemfibrozil,* cyclosporine, atorvastatin, pitavastatin, telmisartan) (see Appendix E).
- Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions (e.g., warfarin).
- Medications with demonstrated efficacy for the prevention of migraine (e.g., amitriptyline, topiramate, propranolol) (see Appendix F).
- CBD oil, cannabis.
- Injectable monoclonal antibodies blocking the CGRP pathway (e.g., erenumab, galcanezumab, fremanezumab, eptinezumab*) within 6 months prior to Visit 1 and through the study period.
- Oral or intranasal CGRP inhibitors such as rimegepant* or ubrogepant* or zavegepant* within 3 months prior to Visit 1 and through the study period.
- Therapeutic or cosmetic botulinum toxin injections (e.g., Dysport®, Botox®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to Visit 1 and throughout the study period.
- Acupuncture, non-invasive neuromodulation devices (e.g., transcutaneous supraorbital neurostimulator, single pulse transcranial magnetic stimulator, vagus nerve stimulator), cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache, within 4 weeks prior to entry into the baseline phase at Week 4 or at any time during the study (including the Week 4 to Day 1 baseline phase).
- Herbal and traditional medicine is prohibited from the time the ICF is signed until the end of the study.

Note: the methods with asterisk (*) are not approved in Japan for the indication.

Subjects should refrain from consuming Seville oranges, grapefruit or grapefruit juice from the time the consent form is signed until completion of the study. Subjects should also refrain from making significant changes to their diet or caffeine intake during the study.

Alcohol intake should be limited to no more than 1 drink per day throughout the study. A drink is defined as 360 mL of beer, 150 mL of wine, or 45 mL of liquor.

The decision to administer a prohibited medication/treatment is done with the safety of the study subject as the primary consideration. When possible, the sponsor should be notified before the prohibited medication/treatment is administered.

5.4 Prior and Concomitant Therapy

Medications that are not specifically prohibited in Section 5.3 are allowed with the following clarifications and restrictions:

The following medications for the acute treatment of migraine are allowed during the study:

- Any triptan
- Any ergot derivative
- Any ditan
- Any opioid
- Any other form of analgesic (including acetaminophen)
- Any NSAID agent
- Any antiemetic agent

Aspirin up to 325 mg/day is allowed for cardiac prophylaxis.

SSRI or SNRI will be permitted provided that treatment is stable for at least 60 days prior to screening (Visit 1) and continues without change in dose throughout the study.

- Venlafaxine and desvenlafaxine are prohibited 30 days prior to screening and throughout the study period.

Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual (Appendix J, Section 4.2) for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

Early Discontinuation of Subjects

A premature discontinuation will occur when a subject who signed the ICF and has been randomized ceases participation in the study, regardless of circumstances, before completion of the study. A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the sponsor.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.

ALT or AST Elevations

Study drug must be interrupted if any of the following criteria are met:

- ALT or AST ≥ 3 × ULN and the subject is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
- ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN
- ALT or AST ≥ 3 × ULN and INR > 1.5
- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

The subject may be rechallenged with study drug only after careful evaluation of the case including thorough evaluation of potential alternative etiologies and approval of the sponsor TA MD. For subjects who are not rechallenged with study drug, they should be discontinued from the study and complete an ET visit and Follow-up visit (30 days after the last dose of study drug). Subjects should receive appropriate follow-up as per standard of care.

Withdrawal Criteria

Subjects may voluntarily withdraw from the study at any time.

The subjects must withdraw from the study at any time for:

- Female subjects who become pregnant (Section 6.1).
- Subjects who meet study drug discontinuation criteria related to abnormal liver function tests (Section 6.1) and advised not to be rechallenged will be withdrawn from the study and should refrain from taking study drug. The subject should return to the clinic for the ET visit and the Follow-up visit.
- Subjects who reply with "yes" to Type 4 or 5 in the suicidal ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS at Visits 3 through 8 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the ET and the Follow-up visits.
- Subjects who experience any serious AE of hypersensitivity or anaphylactic reaction.
- Subjects who experience a nonserious AE of hypersensitivity unless there is clear alternative etiology.
- Subjects with a condition and/or a situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study must be withdrawn from treatment.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

Study Termination

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

Subjects will be followed for 30 days following discontinuation of the study drug. The 30-day follow-up visit should not take place sooner than 30 days after the last dose of the study drug. The allowable visit window is +3 days (30 to 33 days after the last study drug date).

Notification of early subject discontinuation from the study/study drug and the reason for discontinuation should be made to the sponsor and should be documented on the appropriate case report form. All randomized subjects who prematurely discontinue from the study/study drug, regardless of cause, should be seen for final study assessments. The final assessments should be defined as completion of the evaluations scheduled for the ET and the Follow-up visits.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker research to continue, samples will not be analyzed, no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s), and the samples should be destroyed. A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Study dugs refer to drugs that are used (or can be used) in this study to assess the safety and the efficacy of the investigational product (Table 1).

Atogepant or matching placebo manufactured by AbbVie will be taken orally QD beginning on Day 1 and should be taken at approximately the same time each day. The study drug will be taken with or without food. If subjects should forget to take their atogepant or matching placebo dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember as long as it is at least 12 hours before their next scheduled dose. Otherwise, they should take the next dose at the next scheduled dosing time.

The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit and documentation of their dosing compliance.

AbbVie will provide study drug for atogepant or matching placebo. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

Atogepant and matching placebo will be packaged in blisters with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug accountability procedures.

Table 1. Study Drug

Study drug	Manufacturer	Mode of Administration	Dosage Form	Strength
Atogepant	AbbVie	Oral	Tablet	10, 30, 60 mg
Placebo	AbbVie	Oral	Tablet	-

Digital Health Tools Accountability

The investigator or his/her representative will verify that the digital health tools are received intact and in the correct amounts. A proof of receipt or similar document will be kept in the site files as a record of what was received.

In addition, sites will maintain records of traceability, accountability, and return including but not limited to date received/dispensed/returned, subject number, and the identification of the person dispensing/returning the digital health tools.

5.8 Randomization/Drug Assignment

Drug Allocation Ratio

Approximately 520 subjects will be randomized to one of the following 4 treatment arms in a 1:1:1:1 ratio:

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

Approximately 70% of randomized subjects will have taken at least 1 prior migraine prevention medication with proven efficacy (see Appendix F). Randomization will be stratified by prior exposure (yes/no) to a migraine prevention medication with proven efficacy (see Appendix F).

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

Method for Assignment to Drug Groups/Randomization

All subjects will be centrally assigned to randomized study drug using an IRT. Before the study is initiated, log-in information and directions for the IRT will be provided to each site.

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the double-blind treatment period. After all subjects have completed Visit 5, investigators and subjects will remain blinded from study treatment assignment until all subjects have completed the study. To maintain the blind, the atogepant tablets and placebo tablets provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

5.10 External Committees

Data Safety Monitoring Board (DSMB)

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 study. The DSMB is responsible for safeguarding the interests of trial subjects, assessing the safety of the interventions 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 study, if emerging data show unexpected and clinically significant AEs of treatment.

In order to maintain sponsor blinding, an external statistical data analysis center is responsible for performing the analyses described in the DSMB charter as well as additional analyses requested by the DSMB and facilitating interpretation and answering questions that arise before, during or after DSMB review.

The DSMB will regularly review unblinded safety data from the ongoing study according to the schedule provided in the DSMB charter, including as appropriate, AEs, laboratory values, vital sign, values, and ECG results.

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.

Hepatic Events Adjudication Committee

A Hepatic Events Adjudication Committee Charter should be established and should describe the process for the blinded surveillance, monitoring, and adjudication by the Hepatic Events Adjudication Committee of events of post-treatment elevations of ALT and/or AST ≥ 3 × ULN in the atogepant program. The purpose of this committee charter should be to provide a standardized process for the adjudication of data associated with these events in order to determine whether the elevation was related to atogepant.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via EDC. The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events: Atogepant

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is

considered an AE in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any of the following events are reported, then the following supplemental report must be completed.

Event	Supplemental Report
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Cardiovascular procedures (SAE Supplemental Procedure eCRF)**	MACE eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE **A hepatic-related SAE** **ALT/AST $\geq$ 3 × ULN**	Hepatic AE eCRF Hepatic Supplemental Lab eCRF

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious adverse event within 24 hours of the site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

All subjects with an SAE must be followed up and the outcomes reported. The investigator must supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and discharge summaries).

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.

Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for SAR and SUSAR:

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable RSI), and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements, including reporting to Eudravigilance database in accordance with EU Clinical Trial Regulation.

AEs will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study:

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

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate, or severe. The investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 30 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on efficacy analyses and some key safety analyses. Complete and specific details of the statistical analysis will be described in the SAP.

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

7.2 Definition for Analysis Populations

The ITT population will consist of all randomized subjects.

All efficacy analyses will be performed using the mITT population, consisting of all randomized subjects who received at least 1 dose of study drug, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data. For efficacy analyses, data will be analyzed according to subjects' randomization assignments, regardless of actual treatment received.

All safety analyses will be performed using the safety population, consisting of all subjects who received at least 1 dose of study drug during the double-blind treatment period. The safety population in the active treatment extension period consists of all subjects who received at least 1 dose of study drug during the active treatment extension period. For safety data analyses, the subjects will be analyzed according to actual treatment received (rather than as randomized).

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The primary efficacy endpoint of the change from baseline in mean monthly migraine days across the 12-week double-blind treatment period (defined in Section 3.2) will be analyzed based on the mITT population and the following methods will be used to address potential intercurrent events:

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

The secondary endpoints (defined in Section 3.3) will be analyzed based on the mITT population and the following methods will be used to address the potential intercurrent events:

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

7.4 Statistical Analyses for Efficacy

Collection and Derivation of Efficacy Assessments

On a daily basis during the 28-day baseline period and throughout the double-blind treatment period, subjects are to record into an eDiary information on the daily total duration of headache, headache specific characteristics and symptoms, the worst pain severity, and use of any acute headache pain medication. Subjects will be able to report headache data, including absence of headache, for the day of the eDiary report and for the day immediately prior to the day of the eDiary report, as long as information reported is for a time subsequent to the subject's most recent report. This is defined as a one-day "missing-recall" window.

Following randomization on Day 1, there are 3 visits at 4-week intervals during the double-blind treatment period. In practice, there may or may not be exact 4-week durations between 2 consecutive visits and the visits might not align with each 28-day period recorded in the eDiary (i.e., Weeks 1 to 4, 5 to 8, and 9 to 12, corresponding to Days 1 to 28, 29 to 56, and 57 to 84). Therefore, for data analysis purposes, the number of migraine days during the last 28 days prior to the randomization date will serve as the "baseline," and change from baseline will be calculated for consecutive 28-day periods beginning with the date of first dose of study drug.

In order to be randomized, a subject should be in the baseline phase for at least 28 days and should report eDiary data for at least 20 days (including missing recall) during the 28-day baseline period. If less than 28 days of baseline data are reported, the number of headache days and other such counting variables for "baseline" will be prorated to standardize the count to a 28-day equivalent. Subsequent to treatment start, the number of headache days will be counted in successive and non-overlapping 4-week (i.e., 28-day) windows. Headaches that continue into a subsequent 4-week period will be counted (with recorded severity and duration) as occurring in each period.

If any postbaseline eDiary window for a subject has at least 14 but less than 28 days of reported data, the prorated approach should be used. If a subject reports less than 14 days of headache data, the subject's observed counts in that particular 28-day eDiary window will be set to missing for that window. These prorating rules should be applied to all efficacy analyses of eDiary data unless otherwise stated.

Summary and Analysis of the Primary Endpoint

The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week double-blind treatment period. To test the primary hypotheses that each dose of atogepant is

superior to placebo for the primary endpoint, the change from baseline in monthly migraine days at each monthly period will be analyzed using a MMRM with treatment group, visit, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and treatment group-by-visit interaction as categorical fixed effects. It will also include the baseline score and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-subject repeated measurements. The Kenward-Roger[11] approximation will be used to estimate the denominator degrees of freedom. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values.

Pairwise contrasts in the MMRM model will be used to make the pairwise comparisons of each atogepant dose to placebo.

Copy-reference approach as 1 sensitivity analysis will be performed on the primary endpoint to assess the robustness of the MMRM analysis to possible violation of the MAR assumption. This sensitivity analysis is one type of PMM, under which data could be MNAR, with repeated analyses combined via the reference-based MI procedure. Subjects who discontinued in the atogepant groups are assumed to have no treatment effect after the discontinuation. Subjects are assumed to copy the profile of placebo arm and missing values are imputed based on the distribution estimated from the placebo group under the MAR using copy reference approach. An additional sensitivity analysis, MI in conjunction with robust regression, will be performed in case of non-normality for the primary efficacy endpoint.

A supportive analysis will be performed on the primary endpoint using an ANCOVA model. The response variable for the ANCOVA model is the change from baseline in the calculated average monthly migraine days during the 12-week treatment period for each subject. The ANCOVA model includes terms for treatment, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline score. The treatment difference for atogepant doses versus placebo will be estimated and reported along with the corresponding 95% CI and nominal p-value for superiority testing. Details of the sensitivity and supportive analyses will be provided in the SAP.

Summary and Analysis of Secondary Endpoints

The secondary efficacy variables are identified in Section 3.3. No multiplicity adjustment will be provided for the secondary efficacy endpoints in this study.

The secondary endpoints for headache days, acute medication use days, MSQ v2.1 Role Function-Restrictive domain score at Week 12, Performance of Daily Activities domain score of the AIM-D, and Physical Impairment domain score of the AIM-D will be analyzed in the same manner as that used to analyze the primary endpoint.

The 50% responders, defined as subjects with at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each individual, and will be analyzed by a logistic regression model. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, prior exposure (yes/no) to a migraine prevention medication with proven efficacy, and baseline value.

Summary and Analysis of Additional Efficacy Endpoints

In general, other efficacy analyses are performed at the nominal significance level, without adjusting for multiplicity.

Other efficacy variables will be analyzed as follows:

- For selected diary variables with a continuous response range, the baseline score will be included as a covariate in an MMRM analysis of the change from baseline. These analyses will be performed similarly to the primary MMRM, with focus again on the pairwise contrasts of each dose group to placebo.
- For weekly data analysis purposes, baseline is defined to be the baseline derived in monthly basis divided by 4, and change from baseline in the weekly migraine days will be calculated for consecutive 7-day periods beginning with Day 1. Subsequent to treatment start, the number of headache days will be counted in successive and non overlapping 1-week (i.e., 7-day) windows. Headaches that continue into a subsequent 1-week period will be counted (with recorded severity and duration) as occurring in each period. If any postbaseline eDiary window for a subject has at least 4, but less than 7-days, of reported data, the prorated approach will be used. If a subject reports less than 4 days of headache data, the subject's observed counts in that particular 7-day eDiary window will be set to missing for that window.
- For variables where the data are essentially binary, comparisons between treatment groups will be done with logistic regression for variables with only one postbaseline assessment or using a generalized linear mixed model for variables with multiple postbaseline assessments.

Descriptive statistics will be provided by visit for each efficacy variable by treatment group. Analysis of some variables will be limited to descriptive summary statistics.

Details will be specified in the SAP.

Subgroup Analysis for Efficacy

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a 95% CI) for each atogepant dose vs placebo for the specified efficacy endpoints will be estimated within each category of the following classification variable:

- Prior exposure to a migraine prevention medication with proven efficacy (Yes, No)

Subgroup analysis will be performed for the following efficacy endpoints:

- Change from baseline in mean monthly migraine days across the 12-week double-blind treatment period.
- Change from baseline in mean monthly headache days across the 12-week double-blind treatment period.
- Change from baseline in mean monthly acute medications use days across the 12-week double-blind treatment period.
- At least a 50% reduction in 3-month average of monthly migraine days.
- At least a 75% reduction in 3-month average of monthly migraine days.
- 100% reduction in 3-month average of monthly migraine days.

7.5 Statistical Analyses for Safety

All safety analyses will be performed using the safety population.

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

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

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

7.6 Interim Analysis

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

7.7 Overall Type I Error Control

The Hochberg procedure[12] will be used to control the overall Type I error rate at a 0.05 level (2-sided) for multiple comparisons of each atogepant dose with placebo for the primary endpoint. Detailed procedure is provided below.

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

- Step 1: If $p_{(3)}$ is ≤ 0.05, then all the 3 comparisons are considered statistically significant at the 2-sided significance level of 0.05 and stop here; otherwise, go to Step 2.
- Step 2: If $p_{(2)}$ is ≤ 0.025, then the corresponding 2 comparisons for $p_{(2)}$ and $p_{(1)}$ are considered statistically significant at the 2-sided significance level of 0.05 and stop here; otherwise, go to Step 3.
- Step 3: If $p_{(1)}$ is ≤ 0.01667, then the corresponding comparison for $p_{(1)}$ is considered statistically significant at the 2-sided significance level of 0.05; otherwise, stop here.

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

7.8 Sample Size Determination

Approximately 520 subjects will be randomized to one of the 4 treatment groups (placebo, atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 60 mg once daily) in a 1:1:1:1 ratio.

A sample size of 130 subjects per treatment group provides approximately 88%, 94% or 99% power to show statistically significant improvement between each of the 3 atogepant doses (10 mg, 30 mg, or 60 mg) and placebo for the primary efficacy endpoint, respectively, on the mITT analysis set. Assumptions in this sample size calculation are based on the ADVANCE study in a US adult population.[13]

The assumed treatment difference between each atogepant dose versus placebo and the standard deviation for the primary endpoint are shown in Table 2. The dropout rate is assumed to be approximately 5.4% for the double-blind treatment period because the observed dropout rate was less than 5% for trials conducted in Japanese patients with EMs.[14-17] All statistical powers presented in this section were calculated adjusting for multiple comparisons using the Hochberg procedure with the family-wise Type I error rate being controlled at a 0.05 level (2-sided).

Table 2. Power and Sample Size Calculations for the Endpoint, Change from Baseline in Monthly Migraine Days Across the 12-Week Treatment Period

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

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, ICH guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH GCP, and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end of study is defined as the date of end of study participation by the last subject in the last country where the study was conducted.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ACE	Angiotensin converting enzyme
AE	adverse event
AESI	adverse event of special interest
Ag	antigen
AIM-D	Activity Impairment in Migraine – Diary
ALT	alanine aminotransferase
ANA	Antinuclear antibody
ANCOVA	analysis of covariance
ARB	Angiotensin receptor blocker
ASC-12	12-item Allodynia Symptom Checklist
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BID	twice daily
BP	blood pressure
BUN	Blood urea nitrogen
CBD	Cannabidiol
CGRP	calcitonin gene-related peptide
CI	confidence interval
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CPH	chronic paroxysmal hemicrania
CRP	C-reactive protein
CSD	cortical spreading depression
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DL	detection limit
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form

Abbreviation	Definition
EDC	electronic data capture
eDiary	electronic diary
EQ-5D-5L	European Quality of Life - 5-Dimensional - 5 Level
ET	early termination
eTablet	electronic tablet
FDA	Food and Drug Administration
FHM	familial hemiplegic migraine
FHM1	familial hemiplegic migraine type 1
FHM2	familial hemiplegic migraine type 2
FHM3	familial hemiplegic migraine type 3
FSH	follicle-stimulating hormone
GBD2010	*Global Burden of Disease Study 2010*
GC	Global Campaign
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GFR	glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	gastrointestinal
GLP	glucagon-like peptide
HaNDL	headache and neurological deficits with cerebrospinal fluid lymphocytosis
HDL	high density lipoprotein
HIT-6	Headache Impact Test
HIV	human immunodeficiency virus
IBMS	International Burden of Migraine Study
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IgG	immunoglobulin G
IHS	International Headache Society
IL	interleukin
IMP	Investigational Medicinal Product
INR	international normalized ratio

Abbreviation	Definition
IRB	Institutional Review Board
IRT	interactive response technology
ITSE	International Team for Specialist Education
ITT	intent-to-treat
IU	International Unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
LDH	Lactate dehydrogenase
LDL	low-density lipoprotein
MACE	major adverse cardiac event
MAR	missing at random
Max	maximum
MI	multiple imputation
MIDAS	Migraine Disability Assessment
Min	minimum
mITT	modified intent-to-treat
MMRM	mixed-effect model for repeated measures
MNAR	missing not at random
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSQ v2.1	Migraine Specific Quality of Life Questionnaire, version 2.1
N/A	not applicable
NEFA	nonsterified fatty acids
NO	nitric oxide
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression – Severity
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic

Abbreviation	Definition
PMM	pattern mixture model
PRO	patient-reported outcome
PROMIS	Patient Reported Outcomes Measurement Information System
PROMIS-PI	Patient Reported Outcomes Measurement Information System Pain Interference - Short Form 6a
PSSM	Patient Satisfaction with Study Medication
PT	Prothrombin time
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SD	standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHM	sporadic hemiplegic migraine
SNRI	serotonin-norepinephrine reuptake inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
VARS	Visual Aura Rating Scale
VAS	visual analogue scale
VLDL	very LDL
vs.	versus
WBC	White blood cell
WPAI:MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine v2.0

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M22-056: A Phase 2/3, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel-Group Study with An Active Treatment Extension to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prevention of Migraine in Japanese Subjects with Episodic Migraine

Protocol Date: 18 July 2024

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development
[redacted]	[redacted]	Statistics

APPENDIX D. INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS, 3RD EDITION

1. Migraine
1.1 Migraine without aura
1.2 Migraine with aura
1.2.1 Migraine with typical aura
1.2.1.1 Typical aura with headache
1.2.1.2 Typical aura without headache
1.2.2 Migraine with brainstem aura
1.2.3 Hemiplegic migraine
1.2.3.1 Familial hemiplegic migraine (FHM)
1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
1.2.3.1.4 Familial hemiplegic migraine, other loci
1.2.3.2 Sporadic hemiplegic migraine (SHM)
1.2.4 Retinal migraine
1.3 Chronic migraine
1.4 Complications of migraine
1.4.1 Status migrainosus
1.4.2 Persistent aura without infarction
1.4.3 Migrainous infarction
1.4.4 Migraine aura-triggered seizure
1.5 Probable migraine
1.5.1 Probable migraine without aura
1.5.2 Probable migraine with aura
1.6 Episodic syndromes that may be associated with migraine
1.6.1 Recurrent gastrointestinal disturbance
1.6.1.1 Cyclical vomiting syndrome
1.6.1.2 Abdominal migraine
1.6.2 Benign paroxysmal vertigo
1.6.3 Benign paroxysmal torticollis

Coded elsewhere:

Migraine-like headache secondary to another disorder (*symptomatic migraine*) is coded as a secondary headache attributed to that disorder.

General comment

Primary or secondary headache or both? Three rules apply to migraine-like headache, according to circumstances.

1. When a *new headache with the characteristics of migraine* occurs for the first time in close temporal relation to another disorder known to cause headache, or fulfils other criteria for causation by that disorder, the new headache is coded as a secondary headache attributed to the causative disorder.
2. When *pre-existing migraine* becomes *chronic* in close temporal relation to such a causative disorder, both the initial migraine diagnosis and the secondary diagnosis should be given. 8.2 *Medication-overuse headache* is a particularly important example of this: both the migraine diagnosis (episodic or chronic) and the diagnosis 8.2 *Medication-overuse headache* should be given when medication overuse is present.
3. When *pre-existing migraine* is made *significantly worse* (usually meaning a twofold or greater increase in frequency and/or severity) in close temporal relation to such a causative disorder, both the initial migraine diagnosis and the secondary headache diagnosis should be given, provided that there is good evidence that the disorder can cause headache.

Introduction

Migraine is a common disabling primary headache disorder. Many epidemiological studies have documented its high prevalence and socio-economic and personal impacts. In the *Global Burden of Disease Study 2010* (GBD2010), it was ranked as the third most prevalent disorder in the world. In GBD2015, it was ranked the third-highest cause of disability worldwide in both males and females under the age of 50 years.

Migraine has two major types: 1.1 Migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms; 1.2 *Migraine with aura* is primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. Some patients also experience a prodromal phase, occurring hours or days before the headache, and/or a postdromal phase following headache resolution. Prodromal and postdromal symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain.

When a patient fulfils criteria for more than one type, subtype or subform of migraine, all should be diagnosed and coded. For example, a patient who has frequent attacks with aura but also some attacks without aura should be coded as 1.2 *Migraine with aura* and 1.1 *Migraine without aura*. However, since the diagnostic criteria for 1.3 *Chronic migraine* subsume attacks of all

types, subtypes or subforms, additional coding is unnecessary for episodic subtypes of migraine.

1.1 Migraine without aura

Previously used terms: Common migraine; hemicrania simplex

Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks[1] fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)[2,3]
C. Headache has at least two of the following four characteristics:
    1. unilateral location
    2. pulsating quality
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 *Migraine without aura* but have had fewer than five attacks should be coded 1.5.1 *Probable migraine without aura*.
2. When the patient falls asleep during a migraine attack and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children and adolescents (aged under 18 years), attacks may last 2–72 hours (the evidence for untreated durations of less than two hours in children has not been substantiated).

Comments: Migraine headache in children and adolescents (aged under 18 years) is more often bilateral than is the case in adults; unilateral pain usually emerges in late adolescence or early adult life. Migraine headache is usually frontotemporal. Occipital headache in *children* is rare and calls for diagnostic caution. A subset of otherwise typical patients have facial location of pain, which is called 'facial migraine' in the literature; there is no evidence that these patients form a separate subgroup of migraine patients. Prodromal symptoms may begin hours or a day or two before the other symptoms of a migraine attack without aura. They include various combinations of fatigue, diffculty in concentrating, neck stiffness, sensitivity to light and/or sound, nausea, blurred vision, yawning and pallor. Postdromal symptoms, most commonly feeling tired or weary, difficulty with concentration and neck stiffness, may follow resolution of the headache, persisting for up to 48 hours; these are less well studied.

Migraine attacks can be associated with cranial autonomic symptoms and symptoms of cutaneous allodynia.

In young children, photophobia and phonophobia may be inferred from their behaviour.

A minority (<10%) of women have attacks of migraine in association with the majority of their menstrual cycles; most of such attacks are without aura. Attacks during menstruation tend to be longer and accompanied by more severe nausea than attacks outside the menstrual cycle. ICHD-3 offers criteria for A1.1.1 *Pure menstrual migraine without aura*, A1.1.2 *Menstrually related migraine without aura* and A1.1.3 *Non-menstrual migraine without aura*, but in the Appendix because of uncertainty over whether they should be regarded as separate entities. Criteria are also offered for A1.2.0.1 *Pure menstrual migraine with aura*, A1.2.0.2 *Menstrually related migraine with aura* and A1.2.0.3 *Non-menstrual migraine with aura* to encourage better characterization of these uncommon subforms if they are separate entities.

Very frequent migraine attacks are distinguished as 1.3 *Chronic migraine*. When there is associated medication overuse, both of the diagnoses 1.3 *Chronic migraine* and 8.2 *Medication-overuse headache* should be applied. 1.1 *Migraine without aura* is the disease most prone to accelerate with frequent use of symptomatic medication.

Regional cerebral blood flow imaging shows no changes suggestive of cortical spreading depression (CSD) during attacks of 1.1 *Migraine without aura*, although blood flow changes in the brainstem may occur, as may cortical changes secondary to pain activation. This contrasts with the pathognomonic spreading oligaemia of 1.2 *Migraine with aura*. While the bulk of the literature suggests that CSD does not occur in 1.1 *Migraine without aura*, some recent studies disagree. Furthermore, it has been suggested that glial waves or other cortical phenomena may be involved in 1.1 *Migraine without aura*. The messenger molecules

nitric oxide (NO), serotonin (5-hydroxytryptamine; 5-HT) and calcitonin gene-related peptide (CGRP) are involved. While the disease was previously regarded as primarily vascular, the importance of sensitization of pain pathways, and the possibility that attacks may originate in the central nervous system, have gained increasing attention over the last decades.

At the same time, the circuitry of migraine pain, the trigeminovascular system, and several aspects of its neurotransmission peripherally and in the trigeminal nucleus caudalis, central mesencephalic grey and thalamus, have been recognized. Highly receptor- specific acute medications including 5-$HT_{1B/D}$ receptor agonists (triptans), 5-HT_{1F} receptor agonists and CGRP receptor antagonists have demonstrated efficacy in the acute treatment of migraine attacks. Because of their high receptor-specificity, their mechanisms of action provide new insight into migraine mechanisms. It is now clear that 1.1 *Migraine without aura* is a neurobiological disorder, while clinical as well as basic neuroscience studies continue to advance our knowledge of migraine mechanisms.

1.2 Migraine with aura

Previously used terms: Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnee; complicated migraine.

Description: Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
   1. visual
   2. sensory
   3. speech and/or language
   4. motor
   5. brainstem
   6. retinal
C. At least three of the following six characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes
   2. two or more aura symptoms occur in succession
   3. each individual aura symptom lasts 5-60 minutes[1]
   4. at least one aura symptom is unilateral[2]
   5. at least one aura symptom is positive[3]
   6. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 x 60 minutes. Motor symptoms may last up to 72 hours.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.
3. Scintillations and pins and needles are positive symptoms of aura.

Comments: Many patients who have migraine attacks with aura also have attacks without aura; they should be coded as both 1.2 *Migraine with aura* and 1.1 *Migraine without aura*.

Field testing has compared the diagnostic criteria for 1.2 *Migraine with aura* in the main body of ICHD-3 beta with those for A1.2 *Migraine with aura* in the Appendix. The latter performed better in distinguishing migraine with aura from transient ischaemic attacks. These are now adopted in ICHD-3, which no longer has Appendix criteria for this disorder.

The aura is the complex of neurological symptoms that occurs usually before the headache of 1.2 *Migraine with aura*, but it may begin after the headache phase has commenced or continue into the headache phase.
Visual aura is the most common type of aura, occurring in over 90% of patients with 1.2 *Migraine with aura*, at least in some attacks. It often presents as a fortification spectrum: a zigzag figure near the point of fixation that may gradually spread right or left and assume a laterally convex shape with an angulated scintillating edge, leaving absolute or variable degrees of relative scotoma in its wake. In other cases, scotoma without positive phenomena may occur; this is often perceived as being of acute onset but, on scrutiny, usually enlarges gradually. In children and adolescents, less typical bilateral visual symptoms occur that may represent an aura. A visual aura rating scale with high specificity and sensitivity has been developed and validated.
Next in frequency are sensory disturbances, in the form of pins and needles moving slowly from the point of origin and affecting a greater or smaller part of one side of the body, face and/or tongue. Numbness may occur in its wake, but numbness may also be the only symptom.
Less frequent are speech disturbances, usually aphasic

but often hard to categorize.
Systematic studies have demonstrated that many patients with visual aura occasionally have symptoms in the extremities and/or speech symptoms. Conversely, patients with symptoms in the extremities and/or speech or language symptoms almost always also experience visual aura symptoms at least during some attacks. A distinction between migraine with visual aura, migraine with hemiparaesthetic aura and migraine with speech and/or language aura is probably artificial, and therefore not recognized in this classification: they are all coded as 1.2.1 *Migraine with typical aura.*
When aura symptoms are multiple, they usually follow one another in succession, beginning with visual, then sensory, then aphasic; but the reverse and other orders have been noted. The accepted duration for most aura symptoms is one hour, but motor symptoms are often longer lasting.
Patients with aura symptoms arising from the brainstem are coded as 1.2.2 *Migraine with brainstem aura*, but they almost always have additional typical aura symptoms. When the aura includes motor weakness, the disorder should be coded as 1.2.3 *Hemiplegic migraine* or one of its subforms. 1.2.3 *Hemiplegic migraine* is classified as a separate subtype because of genetic and pathophysiological differences from 1.2.1 *Migraine with typical aura*. Patients with 1.2.3 *Hemiplegic migraine* often have brainstem symptoms in addition.

Patients often find it hard to describe their aura symptoms, in which case they should be instructed to time and record them prospectively. The clinical picture then becomes clearer. Common mistakes are incorrect reports of lateralization, of sudden rather than gradual onset and of monocular rather than homonymous visual disturbances, as well as of duration of aura and mistaking sensory loss for weakness. After an initial consultation, use of an aura diary may clarify the diagnosis.
Migraine aura is sometimes associated with a headache that does not fulfill criteria for 1.1 *Migraine without aura*, but this is still regarded as a migraine headache because of its relation to the aura. In other cases, migraine aura may occur without headache.
Before or simultaneously with the onset of aura symptoms, regional cerebral blood flow is decreased in the cortex corresponding to the clinically affected area and often over a wider area. Blood flow reduction usually starts posteriorly and spreads anteriorly, and is usually above the ischaemic threshold. After one to several hours, gradual transition into hyperaemia occurs in the same region. Cortical spreading depression of Leao is the likely underlying mechanism.

The previously defined syndromes, *migraine with prolonged aura* and *migraine with acute-onset aura*, have been abandoned. It is not rare for aura to last more than one hour but, in most such cases, patients have at least two of the other characteristics of criterion C. Even when most of a patient's attacks do not fulfil criterion C, it is usual that other attacks fulfil criteria for one of the recognized subtypes or subforms of 1.2 *Migraine with aura*, and this should be the diagnosis. The few other cases should be coded to 1.5.2 *Probable migraine with aura*, specifying the atypical feature (prolonged aura or acute-onset aura) in parenthesis. The diagnosis is usually evident after a careful history alone, although there are rare secondary mimics including carotid dissection, arteriovenous malformation and seizure.
Prodromal symptoms may begin hours or a day or two before the other symptoms of a migraine attack with aura. They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light and/or sound, nausea, blurred vision, yawning and pallor. The term 'prodrome', which has replaced 'premonitory phase' or 'premonitory symptoms', does not include aura. Postdromal symptoms, most commonly feeling tired or weary, difficulty with concentration and neck stiffness, may follow resolution of the headache, persisting for up to 48 hours; these are less well studied.

1.2.1 Migraine with typical aura

Description: Migraine with aura, in which aura consists of visual and/or sensory and/or speech/language symptoms, but no motor weakness, and is characterized by gradual development, duration of each symptom no longer than one hour, a mix of positive and negative features and complete reversibility

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
B. Aura with both of the following:
    1. fully reversible visual, sensory and/or speech/ language symptoms
    2. no motor, brainstem or retinal symptoms.

1.2.1.1 Typical aura with headache

Description: Migraine with typical aura in which aura is accompanied or followed within 60 minutes by headache with or without migraine characteristics.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.1 *Migraine with typical aura* and criterion B below
B. Headache, with or without migraine characteristics, accompanies or follows the aura within 60 minutes.

1.2.1.2 Typical aura without headache

Description: Migraine with typical aura in which aura is neither accompanied nor followed by headache of any sort.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.1 *Migraine with typical aura* and criterion B below
B. No headache accompanies or follows the aura within 60 minutes.

Comments: In some patients, a typical aura is always followed by migraine headache, but many patients have, in addition, attacks with aura followed by a less distinct headache or even without headache. A number of patients have, exclusively, 1.2.1.2 *Typical aura without headache*.

In the absence of headache fulfilling criteria for 1.1 *Migraine without aura*, the precise diagnosis of aura and its distinction from mimics that may signal serious disease (e.g., transient ischaemic attack) becomes more difficult and often requires investigation. When aura occurs for the first time after age 40, when symptoms are exclusively negative (e.g., hemianopia) or when aura is prolonged or very short, other causes, particularly transient ischaemic attacks, should be ruled out.

1.2.2 Migraine with brainstem aura

Previously used terms: Basilar artery migraine; basilar migraine; basilar-type migraine.

Description: Migraine with aura symptoms clearly originating from the brainstem, but no motor weakness.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
B. Aura with both of the following:
    1. at least two of the following fully reversible brainstem symptoms:
        a. dysarthria[1]
        b. vertigo[2]
        c. tinnitus
        d. hypacusis[3]
        e. diplopia[4]
        f. ataxia not attributable to sensory deficit
        g. decreased level of consciousness (GCS ≤13)[5]
    2. no motor[6] or retinal symptoms.

Notes:

1. Dysarthria should be distinguished from aphasia.
2. Vertigo does not embrace and should be distinguished from dizziness.
3. This criterion is not fulfilled by sensations of ear fullness.
4. Diplopia does not embrace (or exclude) blurred vision.
5. The Glasgow Coma Scale (GCS) score may have been assessed during admission; alternatively, deficits clearly described by the patient allow GCS estimation.
6. When motor symptoms are present, code as 1.2.3 *Hemiplegic migraine*.

Comments: Originally the terms *basilar artery migraine* or *basilar migraine* were used but, since involvement of the basilar artery is unlikely, the term *migraine with brainstem aura* is preferred.

There are typical aura symptoms in addition to the brainstem symptoms during most attacks. Many patients who have attacks with brainstem aura also report other attacks with typical aura and should be coded for both 1.2.1 *Migraine with typical aura* and 1.2.2 *Migraine with brainstem aura*.
Many of the symptoms listed under criterion B1 may occur with anxiety and hyperventilation, and are therefore subject to misinterpretation.

1.2.3 Hemiplegic[1] migraine

Description: Migraine with aura including motor weakness.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
B. Aura consisting of both of the following:
    1. fully reversible motor weakness[2]
    2. fully reversible visual, sensory and/or speech/ language symptoms.

Notes:

1. The term *plegic* means paralysis in most languages, but most attacks are characterized by motor weakness.
2. Motor symptoms generally last less than 72 hours but, in some patients, motor weakness may persist for weeks.

Comment: It may be difficult to distinguish weakness from sensory loss.

1.2.3.1 Familial hemiplegic migraine (FHM)

Description: Migraine with aura including motor weakness, and at least one first- or second-degree relative has migraine aura including motor weakness.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*
B. At least one first- or second-degree relative has had attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*.

Comments: New genetic data have allowed a more precise definition of 1.2.3.1 *Familial hemiplegic migraine* than was previously possible. Specific genetic subforms have been identified: in FHM1 there are mutations in the *CACNA1A* gene (coding for a calcium channel) on chromosome 19; in FHM2 there are mutations in the *ATP1A2* gene (coding for a K/Na-ATPase) on chromosome 1; and in FHM3 there are mutations in the *SCN1A* gene (coding for a sodium channel) on chromosome 2. There may be other loci not yet identified. When genetic testing is done, the genetic subform (if discovered) should be specified at the fifth digit.

It has been shown that 1.2.3.1 *Familial hemiplegic migraine* very often presents with brainstem symptoms in addition to the typical aura symptoms, and that headache almost always occurs. Rarely, during FHM attacks, disturbances of consciousness (sometimes including coma), confusion, fever and cerebrospinal fluid (CSF) pleocytosis can occur.
1.2.3.1 *Familial hemiplegic migraine* may be mistaken for epilepsy and treated (unsuccessfully) as such. FHM attacks can be triggered by (mild) head trauma. In approximately 50% of FHM families, chronic progressive cerebellar ataxia occurs independently of the migraine attacks.

1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A mutation on the *CACNA1A* gene has been demonstrated.

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A mutation on the *ATP1A2* gene has been demonstrated.

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A mutation on the *SCN1A* gene has been demonstrated.

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. Genetic testing has demonstrated no mutation on the *CACNA1A, ATP1A2* or *SCN1A* genes.

1.2.3.2 Sporadic hemiplegic migraine (SHM)

Description: Migraine with aura including motor weakness, and no first- or second-degree relative has migraine aura including motor weakness.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*
B. No first- or second-degree relative fulfils criteria for 1.2.3 *Hemiplegic migraine.*

Comments: Epidemiological studies have shown that sporadic cases occur with approximately the same prevalence as familial cases.

The attacks in 1.2.3.2 *Sporadic hemiplegic migraine* have the same clinical characteristics as those in 1.2.3.1 *Familial hemiplegic migraine*. Some apparently sporadic cases have known FHM mutations and, in some, a first- or second-degree

relative later develops hemiplegic migraine, thus completing fulfilment of the criteria for 1.2.3.1 *Familial hemiplegic migraine* and requiring a change of diagnosis.

Sporadic cases usually require neuroimaging and other tests to rule out other causes. A lumbar puncture may be necessary to rule out 7.3.5 *Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)*.

1.2.4 Retinal migraine

Description: Repeated attacks of monocular visual disturbance, including scintillations, scotomata or blindness, associated with migraine headache.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below

B. Aura characterized by both of the following:
   1. fully reversible, monocular, positive and/or negative visual phenomena (e.g., scintillations, scotomata or blindness) confirmed during an attack by either or both of the following:
      a. clinical visual field examination
      b. the patient's drawing of a monocular field defect (made after clear instruction)
   2. at least two of the following:
      a. spreading gradually over ≥5 minutes
      b. symptoms last 5–60 minutes
      c. accompanied, or followed within 60 minutes, by headache

C. Not better accounted for by another ICHD-3 diagnosis, and other causes of amaurosis fugax have been excluded.

Comments: Some patients who complain of monocular visual disturbance in fact have hemianopia. Some cases without headache have been reported, but migraine as the underlying aetiology cannot be ascertained.

1.2.4 *Retinal migraine* is an extremely rare cause of transient monocular visual loss. Cases of permanent monocular visual loss associated with migraine have been described. Appropriate investigations are required to exclude other causes of transient monocular blindness.

1.3 Chronic migraine

Description: Headache occurring on 15 or more days/ month for more than three months, which, on at least eight days/month, has the features of migraine headache.

Diagnostic criteria:

A. Headache (migraine-like or tension-type-like[1]) on ≥15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*

C. On ≥8 days/month for >3 months, fulfilling any of the following[2]:
   1. criteria C and D for 1.1 *Migraine without aura*
   2. criteria B and C for 1.2 *Migraine with aura*
   3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.[3] [5]

Notes:

1. The reason for singling out 1.3 *Chronic migraine* from types of episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. Such patients are extremely difficult to keep medication-free in order to observe the natural history of the headache. In this situation, attacks with and those without aura are both counted, as are both migraine-like and tension-type-like headaches (but not secondary headaches).
2. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day by day for at least one month.
3. Because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*, this diagnosis excludes the diagnosis of 2. *Tension-type headache* or its types.
4. 4.10 *New daily persistent headache* may have features suggestive of 1.3 *Chronic migraine*. The latter disorder evolves over time from 1.1 *Migraine without aura* and/ or 1.2 *Migraine with aura*; therefore, when these criteria A–C are fulfilled by headache that, unambiguously, is daily and

unremitting from <24 hours after its first onset, code as 4.10 *New daily persistent headache*. When the manner of onset is not remembered or is otherwise uncertain, code as 1.3 *Chronic migraine*.

5. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 *Medication-overuse headache*. Around 50% of patients apparently with 1.3 *Chronic migraine* revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 *Chronic migraine*. Equally, many patients apparently overusing medication do not improve after drug withdrawal; the diagnosis of 8.2 *Medication-overuse headache* may be inappropriate for these (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule to apply all relevant diagnoses, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be coded for both. After drug withdrawal, migraine will either revert to an episodic type or remain chronic and should be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse headache* may be rescinded.

1.4 Complications of migraine

Comment: Code separately for both the migraine type, subtype or subform and for the complication.

1.4.1 Status migrainosus

Description: A debilitating migraine attack lasting for more than 72 hours.

Diagnostic criteria:

A. A headache attack fulfilling criteria B and C
B. Occurring in a patient with 1.1 *Migraine without aura* and/or 1.2 *Migraine with aura*, and typical of previous attacks except for its duration and severity
C. Both of the following characteristics:
   1. unremitting for >72 hours[1]
   2. pain and/or associated symptoms are debilitating[2]
D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

1. Remissions of up to 12 hours due to medication or sleep are accepted.
2. Milder cases, not meeting criterion C2, are coded 1.5.1 *Probable migraine without aura*.

Comment: Headache with the features of 1.4.1 *Status migrainosus* may often be caused by medication overuse. When headache in these circumstances meets the criteria for 8.2 *Medication-overuse headache*, code for this disorder and the relevant type or subtype of migraine but not for 1.4.1 *Status migrainosus*. When overuse of medication is of shorter duration than three months, code for the appropriate migraine type or subtype(s) only.

1.4.2 Persistent aura without infarction

Description: Aura symptoms persisting for one week or more without evidence of infarction on neuroimaging.

Diagnostic criteria:

A. Aura fulfilling criterion B
B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous auras except that one or more aura symptoms persists for ≥1 week
C. Neuroimaging shows no evidence of infarction
D. Not better accounted for by another ICHD-3 diagnosis.

Comments: Persistent aura symptoms are rare but well documented. They are often bilateral and may last for months or years. The one-week minimum in criterion B is based on the opinion of experts and should be formally studied.
Diagnostic work-up must distinguish 1.4.2 *Persistent aura without infarction* from 1.4.3 *Migrainous infarction* and exclude symptomatic aura due to cerebral infarction of other causes. Attacks with prolonged aura lasting less than one week and not fulfilling criteria for 1.2.1 *Migraine with typical aura* are coded 1.5.2 *Probable migraine with aura.*

1.4.3 Migrainous infarction

Description: One or more migraine aura symptoms occurring in association with an ischaemic brain lesion in the appropriate territory demonstrated by neuroimaging, with onset during the course of a typical migraine with aura attack.

Diagnostic criteria:

A. A migraine attack fulfilling criteria B and C
B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous attacks except that one or more aura symptoms persists for >60 minutes[1]

C. Neuroimaging demonstrates ischaemic infarction in a relevant area
D. Not better accounted for by another ICHD-3 diagnosis.

Note:

1. There may be additional symptoms attributable to the infarction.

Comments: Ischaemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with 1. *Migraine*, cerebral infarction of other cause presenting with symptoms resembling 1.2 *Migraine with aura*, or cerebral infarction occurring during the course of a typical attack of 1.2 *Migraine with aura.* Only the last fulfils criteria for 1.4.3 *Migrainous infarction*.
1.4.3 Migrainous infarction mostly occurs in the posterior circulation and in younger women. A twofold increased risk of ischaemic stroke in patients with 1.2 *Migraine with aura* has been demonstrated in several population-based studies. However, it should be noted that these infarctions are not migrainous infarctions. The mechanisms of the increased risk of ischaemic stroke in migraine sufferers remain unclear; likewise, the relationship between increased risk and frequency of aura and the nature of aura symptoms denoting the increase in risk are unknown. Most studies have shown a lack of association between 1.1 *Migraine without aura* and ischaemic stroke.

1.4.4 Migraine aura-triggered seizure

Description: A seizure triggered by an attack of migraine with aura.

Diagnostic criteria:

A. A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below
B. Occurring in a patient with 1.2 *Migraine with aura*, and during or within one hour after an attack of migraine with aura
C. Not better accounted for by another ICHD-3 diagnosis.

Comment: Migraine and epilepsy are prototypical examples of paroxysmal brain disorders. While migraine-like headaches are quite frequently seen in the epileptic post-ictal period, sometimes a seizure occurs during or following a migraine attack. This phenomenon, sometimes referred to as *migralepsy*, is a rare event, originally described in patients with 1.2 *Migraine with aura*. Evidence of an association with 1.1 *Migraine without aura* is lacking.

1.5 Probable migraine

Previously used term: Migrainous disorder.

Coded elsewhere: Migraine-like headache secondary to another disorder (*symptomatic migraine*) is coded according to that disorder.

Description: Migraine-like attacks missing one of the features required to fulfil all criteria for a type or subtype of migraine coded above, and not fulfilling criteria for another headache disorder.

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A-D for 1.1 *Migraine without aura*, or all but one of criteria A–C for 1.2 *Migraine with aura*
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

Comment: In making a headache diagnosis, attacks that fulfil criteria for both 2. *Tension-type headache* and 1.5 *Probable migraine* are coded as the former in accordance with the general rule that a definite diagnosis always trumps a probable diagnosis. However, in patients who already have a migraine diagnosis, and where the issue is to count the number of attacks they are having (e.g., as an outcome measure in a drug trial), attacks fulfilling criteria for 1.5 *Probable migraine* should be counted as migraine. The reason for this is that mild migraine attacks, or attacks treated early, often do not achieve all characteristics necessary for a migraine attack diagnosis but nevertheless respond to specific migraine treatments.

1.5.1 Probable migraine without aura Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A-D for 1.1 *Migraine without aura*
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

1.5.2 Probable migraine with aura

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A–C for 1.2 *Migraine with aura* or any of its subtypes
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

1.6 Episodic syndromes that may be associated with migraine

Previously used terms: Childhood periodic syndromes; periodic syndromes of childhood.

Comments: This group of disorders occurs in patients who also have 1.1 *Migraine without aura* or 1.2 *Migraine with aura*, or who have an increased likelihood to develop either of these disorders. Although historically noted to occur in childhood, they may also occur in adults.

Additional conditions that may also occur in these patients include episodes of motion sickness and periodic sleep disorders including sleep walking, sleep talking, night terrors and bruxism.

1.6.1 Recurrent gastrointestinal disturbance

Previously used terms: Chronic abdominal pain; functional abdominal pain; functional dyspepsia; irritable bowel syndrome; functional abdominal pain syndrome.

Description: Recurrent episodic attacks of abdominal pain and/or discomfort, nausea and/or vomiting, occurring infrequently, chronically or at predictable intervals, that may be associated with migraine.

Diagnostic criteria:

A. At least five attacks with distinct episodes of abdominal pain and/or discomfort and/or nausea and/or vomiting
B. Normal gastrointestinal examination and evaluation
C. Not attributed to another disorder.

1.6.1.1 Cyclic vomiting syndrome

Description: Recurrent episodic attacks of intense nausea and vomiting, usually stereotypical in the individual and with predictable timing of episodes. Attacks may be associated with pallor and lethargy. There is complete resolution of symptoms between attacks.

Diagnostic criteria:

A. At least five attacks of intense nausea and vomiting, fulfilling criteria B and C
B. Stereotypical in the individual patient and recurring with predictable periodicity
C. All of the following:
    1. nausea and vomiting occur at least four times per hour
    2. attacks last for ≥1 hour, up to 10 days
    3. attacks occur ≥1 week apart
D. Complete freedom from symptoms between attacks
E. Not attributed to another disorder.[1]

Note:

1. In particular, history and physical examination do not show signs of gastrointestinal disease.

*Comments:*1.6.1.1 *Cyclic vomiting syndrome* is typically a self-limiting episodic condition occurring in childhood, with periods of complete normality between episodes. The cyclic nature is the hallmark, and attacks are predictable.

This disorder was first included as a childhood periodic syndrome in ICHD-II. The clinical features of this syndrome resemble those found in association with migraine headaches, and multiple threads of research over the last years have suggested that 1.6.1.1 *Cyclic vomiting syndrome* is a condition related to migraine.

1.6.1.2 Abdominal migraine

Description: An idiopathic disorder seen mainly in children as recurrent attacks of moderate to severe midline abdominal pain, associated with vasomotor symptoms, nausea and vomiting, lasting 2–72 hours and with normality between episodes. Headache does not occur during these episodes.

Diagnostic criteria:

A. At least five attacks of abdominal pain, fulfilling criteria B–D
B. Pain has at least two of the following three characteristics:
    1. midline location, periumbilical or poorly localized
    2. dull or 'just sore' quality
    3. moderate or severe intensity
C. At least two of the following four associated symptoms or signs:
    1. anorexia
    2. nausea
    3. vomiting
    4. pallor
D. Attacks last 2–72 hours when untreated or unsuccessfully treated
E. Complete freedom from symptoms between attacks

F. Not attributed to another disorder.[1]

Note:

1. In particular, history and physical examination do not show signs of gastrointestinal or renal disease, or such disease has been ruled out by appropriate investigations.

Comments: Pain of 1.6.1.2 *Abdominal migraine* is severe enough to interfere with normal daily activities.
In young children, the presence of headache is often overlooked. A careful history of presence or absence of headache must be taken and, when headache or head pain during attacks is identified, a diagnosis of 1.1 *Migraine without aura* should be considered.
Children may find it difficult to distinguish anorexia from nausea. Pallor is often accompanied by dark shadows under the eyes. In a few patients, flushing is the predominant vasomotor phenomenon.
Most children with abdominal migraine will develop migraine headache later in life.

1.6.2 Benign paroxysmal vertigo

Description: A disorder characterized by recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously, in otherwise healthy children.

Diagnostic criteria:

A. At least five attacks fulfilling criteria B and C
B. Vertigo[1] occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness
C. At least one of the following five associated symptoms or signs:
    1. nystagmus
    2. ataxia
    3. vomiting
    4. pallor
    5. fearfulness
D. Normal neurological examination and audiometric and vestibular functions between attacks
E. Not attributed to another disorder.[2]

Notes:

1. Young children with vertigo may not be able to describe vertiginous symptoms. Parental observation of episodic periods of unsteadiness may be interpreted as vertigo in young children.
2. In particular, posterior fossa tumours, seizures and vestibular disorders have been excluded.

Comment: The relationship between 1.6.2 *Benign paroxysmal vertigo* and A1.6.6 *Vestibular migraine* (see Appendix) needs to be further examined.

1.6.3 Benign paroxysmal torticollis

Description: Recurrent episodes of head tilt to one side, perhaps with slight rotation, which remit spontaneously. The condition occurs in infants and small children, with onset in the first year.

Diagnostic criteria:

A. Recurrent attacks[1] in a young child, fulfilling criteria B and C
B. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
C. At least one of the following five associated symptoms or signs:
    1. pallor
    2. irritability
    3. malaise
    4. vomiting
    5. ataxia[2]
D. Normal neurological examination between attacks
E. Not attributed to another disorder.[3]

Notes:

1. Attacks tend to recur monthly.
2. Ataxia is more likely in older children within the affected age group.
3. The differential diagnosis includes gastro-oesophageal reflux, idiopathic torsional dystonia and complex partial seizure, but particular attention must be paid to the posterior fossa and craniocervical junction where congenital or acquired lesions may produce torticollis.

Comments: The child's head can be returned to the neutral position during attacks: some resistance may be encountered but can be overcome.
These observations need further validation by patient diaries, structured interviews and longitudinal data collection.
1.6.3 *Benign paroxysmal torticollis* may evolve into 1.6.2 *Benign paroxysmal vertigo* or 1.2 *Migraine with aura* (particularly 1.2.2 *Migraine with brainstem aura*) or cease without further

symptoms.

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1.6.2 Benign paroxysmal vertigo

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1.6.3 Benign paroxysmal torticollis

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APPENDIX E. EXAMPLES OF PROHIBITED MEDICATIONS

The following medications are prohibited 30 days prior to screening and throughout the study period:

- CBD oil, cannabis

	Strong/moderate CYP3A4 inducers	**Strong CYP3A4 inhibitors**
Anti-depressants/ Anti-anxiety	Barbiturates Amobarbital Aprobarbital[a] Butalbital[a] Butabarbital[a] Mephobarbital[a] Pentobarbital Phenobarbital Secobarbital	Nefazodone[a]
Anti-seizure	Carbamazepine Oxcarbazepine[a] Phenytoin Primidone	
Diabetes	Troglitazone[a]	
Glucocorticoid (Systemic)	Dexamethasone	
Antibiotics	Rifabutin Rifampicin/ Rifampin[a]	Clarithromycin Telithromycin[a]
Anti-fungal		Itraconazole Ketoconazole
Anti-HIV	Efavirenz	Indinavir Nelfinavir Ritonavir Saquinavir
Others	St. John's Wort Enzalutamide Modafinil Armodafinil[a]	Buprenorphine

a. Not approved in Japan.

Strong OATP1B1 and OATP1B3 inhibitors	Atazanavir Atorvastatin Cyclosporine Dipyridamole Indocyanine green Gemfibrozil[a] Glibenclamide Glycyrrhizic acid PSC833 (Valspodar)[a] Pitavastatin Rifampicin Rifamycin SV[a] Salazosulfapyridine Silymarin[a,b] Telmisartan Tipranavir[a]
Drugs with narrow therapeutic margins with potential for CYP drug interactions	Warfarin Digoxin Cisapride[a] Pimozide
Drugs with demonstrated efficacy for the prevention of migraine	Topiramate Valproic acid, sodium valproate, divalproex sodium[a] Amitriptyline Nortriptyline Metoprolol Bisoprolol Atenolol Nadolol Propranolol Timolol[a] Flunarizine[a] Lomerizine Verapamil Candesartan Lisinopril Desvenlafaxine[a] Venlafaxine Pizotifena[a]
Non-pharmacologic headache interventions	Acupuncture Non-invasive neuromodulation devices (e.g., transcutaneous supraorbital neurostimulator, single-pulse transcranial magnetic stimulator, vagus nerve stimulator). Cranial traction Nociceptive trigeminal inhibition Occipital nerve block treatments Dental splints for headache

a. Not approved in Japan.

b. May be included in dietary supplements.

The following treatments are prohibited 6 months prior to screening and throughout the study period:

- Therapeutic or cosmetic botulinum toxin injections into areas of the head, face, or neck (e.g., Dysport®, Botox®, Xeomin®, Myobloc®, JeuveauTM).
- Injectable monoclonal antibodies blocking the CGRP pathway (e.g., erenumab, galcanezumab, fremanezumab, eptinezumab).

APPENDIX F. LIST OF MIGRAINE-PREVENTIVE MEDICATIONS WITH PROVEN EFFICACY AND CRITERIA FOR DETERMINING INADEQUATE RESPONSE TO A PRIOR MIGRAINE-PREVENTIVE MEDICATION

List of Migraine preventive Medications with Proven Efficacy

Below is a list of migraine-preventive medications considered effective or probably effective sorted by mechanism of action. Of note, topiramate and valproic acid derivatives are considered separate categories. A history of inadequate response to greater than 4 of these medications (2 of which have different mechanisms of action) will exclude the subject from the study.

Pharmacologic Category	**Drug Name**
Antiepileptic	Divalproex sodium[a], valproic acid, sodium valproate Topiramate
Tricyclic antidepressant	Amitriptyline Nortriptyline
Beta-blockers	Metoprolol Bisoprolol Atenolol Nadolol Propranolol Timolol[a]
Calcium channel blocker	Flunarizine[a] Lomerizine Verapamil
Angiotensin receptor blocker (ARB)	Candesartan
Angiotensin converting enzyme (ACE) inhibitor	Lisinopril
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine[a] Venlafaxine
Miscellaneous	Pizotifen[a]

Source: Evers 2009, Hoffmann 2014, Schürks 2008, Silberstein 2012, Steiner 2007[18-22]

a. Not approved in Japan

Criteria for Determining Inadequate Response to a Prior Migraine Preventive Medication

Failure of a migraine-preventive medication can be assessed on the basis of efficacy or tolerability and is based on investigator judgment. The criteria below should be used to determine eligibility related to the number of prior failed migraine-preventive medications with unique mechanisms of action.

For efficacy:

- Failure is defined as no meaningful reduction in frequency of migraine days after an adequate trial of at least 2 months at generally accepted therapeutic doses, per investigator judgment and subject interview.
- Medications should have been taken within the past 7 years.

For tolerability:

- Failure is defined as discontinuation of a drug treatment due to adverse effects.
- In assessing failure of a migraine preventive drug on the basis of inadequate tolerability, the entire medical history can be considered. For example, a subject who tried and discontinued topiramate 10 years ago for cognitive clouding should be considered to have failed this treatment.

APPENDIX G. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

The table below describes the New York Heart Association Functional Classification system (adapted from Criteria Committee NY Heart Association 1994). It places patients in 1 of 4 categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

APPENDIX H. ACTIVITY SCHEDULE

The following tables show the required activities. The individual activities are described in detail in the **Operations Manual (Appendix J)**.

Table 3. Schedule of Activities

Activity	Screening period (4 weeks)	Double Blind Treatment Period (12 weeks)				Active Treatment Extension Period (dose blinded, 12 weeks)			Follow up Period (30 days)
	Visit 1/ Screening/ Baseline	Visit 2	Visit 3	Visit 4	Visit 5/ ET DB	Visit 6	Visit 7	Visit 8/ ET EX	Visit 9/EOS
	Week 4 (Day 35 to Day 28)	Day 1	Week 4 (Day 28) ± 3 days	Week 8 (Day 56) ± 3 days	Week 12 (Day 84) + 3 days	Week 16 (Day 112) ± 3 days	Week 20 (Day 140) ± 3 days	Week 24 (Day 168) + 3 days	Week 28 (Day 198/ 30 days after the last dose of study drug) + 3 days
INTERVIEWS & QUESTIONNAIRES									
Informed consent	✓								
Informed consent for biomarker research (optional)	✓								
Eligibility criteria	✓	✓							
Demographics	✓								
Medical history	✓								
Migraine headache history	✓								
Review prior medications including all migraine prophylactic medication use	✓								
Menstrual cycle assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medications/concurrent procedures	✓	✓	✓	✓	✓	✓	✓	✓	✓
Provide eDiary, instructions and training	✓								
eDiary data collection	✓	✓	✓	✓	✓				
Collect eDiary device		✓			✓				
Review of eDiary data and compliance		✓	✓	✓	✓				

Activity	Screening period (4 weeks)	Double Blind Treatment Period (12 weeks)				Active Treatment Extension Period (dose blinded, 12 weeks)			Follow up Period (30 days)
	Visit 1/ Screening/ Baseline	Visit 2	Visit 3	Visit 4	Visit 5/ ET DB	Visit 6	Visit 7	Visit 8/ ET EX	Visit 9/EOS
	Week 4 (Day 35 to Day 28)	Day 1	Week 4 (Day 28) ± 3 days	Week 8 (Day 56) ± 3 days	Week 12 (Day 84) + 3 days	Week 16 (Day 112) ± 3 days	Week 20 (Day 140) ± 3 days	Week 24 (Day 168) + 3 days	Week 28 (Day 198/ 30 days after the last dose of study drug) + 3 days
C SSRS (eTablet)	✓	✓	✓	✓	✓	✓	✓	✓	✓
ASC 12 (eTablet)	✓								
HIT 6 (eTablet)		✓	✓	✓	✓				
PGIC (eTablet)					✓				
PGI S (eTablet)		✓	✓	✓	✓				
WPAI:MIGRAINE (eTablet)		✓	✓	✓	✓				
PSSM (eTablet)			✓	✓	✓				
EQ 5D 5L (eDiary)	✓	✓	✓	✓	✓				
MIDAS (eTablet)		✓			✓				
MSQ v2.1 (eTablet)		✓	✓	✓	✓				
PROMIS PI (eTablet)		✓	✓	✓	✓				
PHQ 9 (eTablet)		✓			✓				
LOCAL LABS & EXAMS									
Physical examination	✓				✓			✓	✓
Height (Visit 1 only) and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital sign measurements	✓	✓	✓	✓	✓	✓	✓	✓	✓
12 lead ECG	✓				✓			✓	

Activity	Screening period (4 weeks)	Double Blind Treatment Period (12 weeks)				Active Treatment Extension Period (dose blinded, 12 weeks)			Follow up Period (30 days)
	Visit 1/ Screening/ Baseline	Visit 2	Visit 3	Visit 4	Visit 5/ ET DB	Visit 6	Visit 7	Visit 8/ ET EX	Visit 9/EOS
	Week 4 (Day 35 to Day 28)	Day 1	Week 4 (Day 28) ± 3 days	Week 8 (Day 56) ± 3 days	Week 12 (Day 84) + 3 days	Week 16 (Day 112) ± 3 days	Week 20 (Day 140) ± 3 days	Week 24 (Day 168) + 3 days	Week 28 (Day 198/ 30 days after the last dose of study drug) + 3 days
Urine pregnancy test		✓	✓	✓	✓	✓	✓	✓	✓
CENTRAL LABS									
Serum pregnancy test	✓								
Clinical laboratory test	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urine drug screen	✓								
PK plasma sample		✓	✓	✓	✓				
Optional biomarker sample: whole blood DNA		✓							
Optional biomarker sample: saliva and plasma		✓			✓			✓	
TREATMENT									
Access IRT	✓	✓	✓	✓	✓	✓	✓	✓	
Randomization		✓							
Dispense study drug		✓	✓	✓	✓	✓	✓		
Review of study drug compliance and accountability			✓	✓	✓	✓	✓	✓	

Table 4. Schedule of Activities for Remote Visits (only after completion of Visit 3)

Activity	Double blind Treatment Period (12 weeks)		Active Treatment Extension Period (dose blinded, 12 weeks)			Follow up Period (30 days)
	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/ ET EX	Visit 9/ EOS
	Week 8 (Day 56) ± 3 days	Week 12 (Day 84) + 3 days	Week 16 (Day 112) ± 3 days	Week 20 (Day 140) ± 3 days	Week 24 (Day 168) + 3 days	Week 28 (Day 198/30 days after the last dose of study drug) + 3 days
INTERVIEWS & QUESTIONNAIRES						
Adverse events	✓	✓	✓	✓	✓	✓
Concomitant medications/concurrent procedures	✓	✓	✓	✓	✓	✓
eDiary data collection	✓	✓				
Review of eDiary data and compliance	✓	✓				
C SSRS (eTablet)	✓	✓	✓	✓	✓	✓
HIT 6 (eTablet)	✓	✓				
PGIC (eTablet)		✓				
PGI S (eTablet)	✓	✓				
WPAI:MIGRAINE (eTablet)	✓	✓				
PSSM (eTablet)	✓	✓				
EQ 5D 5L (eDiary)	✓	✓				
MIDAS (eTablet)		✓				
MSQ v2.1 (eTablet)	✓	✓				
PROMIS PI (eTablet)	✓	✓				
PHQ 9 (eTablet)		✓				

Activity	Double blind Treatment Period (12 weeks)		Active Treatment Extension Period (dose blinded, 12 weeks)			Follow up Period (30 days)
	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8/ ET EX	Visit 9/ EOS
	Week 8 (Day 56) ± 3 days	Week 12 (Day 84) + 3 days	Week 16 (Day 112) ± 3 days	Week 20 (Day 140) ± 3 days	Week 24 (Day 168) + 3 days	Week 28 (Day 198/30 days after the last dose of study drug) + 3 days
LOCAL LABS & EXAMS						
Urine pregnancy test	✓	✓	✓	✓	✓	✓
TREATMENT						
Dispense study drug	✓	✓	✓	✓		
Review of study drug compliance and accountability	✓	✓	✓	✓	✓	

APPENDIX I. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	27 Mar 2020
Version 2.0 (Amendment #1)	11 Jan 2022
Version 3.0 (Amendment #2)	29 Apr 2022
Administrative Change 1	02 Jun 2022
Version 4.0 (Amendment #3)	08 Dec 2022
Version 5.0 (Amendment #4)	20 Feb 2023
Version 6.0 (Amendment # 5)	30 Oct 2023

The purpose of this version is to update the protocol to add information on a newly identified risk of hypersensitivity and anaphylactic reactions with the use of atogepant. Additionally, some minor editorial changes were made during this amendment:

- Section 2.2 Added description of hypersensitivity reactions and anaphylaxis to the discussion of benefits and risks to subjects.
- Section 5.3 Updated with strong OATP1B1 and OATP1B3 inhibitors to align with the clarification letters.
- Section 5.5 Added withdrawal criteria for nonserious hypersensitivity and serious hypersensitivity or anaphylactic reactions.
- Appendix C Updated signatories based on new SOP.
- Appendix E
  - Updated with strong OATP1B1 and OATP1B3 inhibitors to align with the clarification letters.
  - Updated with strong/moderate CYP3A4 inducers for diabetes and glucocorticoids.