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Protocol for Study M23-072

Migraine: Ubrogepant for the Acute Treatment of Migraine in Subjects Taking Atogepant for the Preventive Treatment of Episodic Migraine

VERSION:	2.0	DATE:	22 July 2022
SPONSOR:	AbbVie Inc.*	PLANNED NUMBER OF SITES:	Approximately 45
ABBVIE STUDY DRUG:	Atogepant and Ubrogepant	EudraCT:	Not applicable

FULL TITLE: A Phase 4, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of the Concomitant Use of Ubrogepant for the Acute Treatment of Migraine in Subjects Taking Atogepant for the Preventive Treatment of Episodic Migraine

Incorporating Versions 1.0 and 2.0 and Administrative Change 1

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: A Phase 4, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of the Concomitant Use of Ubrogepant for the Acute Treatment of Migraine in Subjects Taking Atogepant for the Preventive Treatment of Episodic Migraine	
Background and Rationale:	A proportion of individuals receiving preventive monotherapy for migraine may continue to experience migraine attacks and migraine-related disability. Atogepant has demonstrated efficacy in significantly reducing the number of migraine and headache days in patients with episodic migraine (EM). Ubrogepant has been approved by the FDA for the acute treatment of migraine with or without aura in adults. Both drugs have been shown to be safe and well tolerated. Ubrogepant is similar in structure and mechanism of action to atogepant and the additive effect of combination therapy is currently unknown. This open-label study is being conducted to evaluate the safety, tolerability, and efficacy of the concomitant use of ubrogepant for the acute treatment of breakthrough migraine headache in subjects taking atogepant once daily for the preventive treatment of EM.
Objectives and Endpoints:	**Primary Objective**: To evaluate the safety and tolerability of the concomitant use of ubrogepant 100 mg for the acute treatment of breakthrough migraine headache in subjects taking atogepant 60 mg once daily for preventive treatment of EM. **Safety Endpoints:** Safety evaluations include adverse event (AE) monitoring, vital sign measurements, electrocardiogram (ECG) variables, clinical laboratory testing (hematology, chemistry, and urinalysis), and Columbia Suicide Severity Rating Scale (C-SSRS) as measures of safety and tolerability for the entire study duration.
Investigators:	Investigator information on file at AbbVie.
Study Sites:	Approximately 45 sites in the United States.
Study Population and Number of Subjects to be Enrolled:	Subjects who have episodic migraine; approximately 235 subjects will be enrolled into the study.
Investigational Plan:	This is a multicenter, open-label, Phase 4 study conducted in the United States (US) to evaluate the safety, tolerability, and efficacy of the concomitant use of ubrogepant 100 mg for the acute treatment of breakthrough migraine headache in subjects taking atogepant 60 mg once daily for preventive treatment of EM. Subject participation will begin with up to a 1 week screening period. Subjects who continue to meet all entry criteria at Baseline/Visit 2 (Day 1) will be assigned atogepant 60 mg to take once daily for the preventive treatment of migraine. The open-label atogepant treatment period will last for 12 weeks (Visits 2-5). During this study period, subjects will use their usual medications for the acute treatment of breakthrough migraine

	headaches. At Visit 5, subjects who complete the open-label atogepant treatment period will continue into the open-label atogepant + ubrogepant concomitant use period which will last for an additional 12 weeks (Visits 5-8). During this study period, subjects will continue to take atogepant 60 mg once daily and will also be provided ubrogepant 100 mg to treat up to 8 breakthrough migraine headaches of any pain intensity per 4-week visit interval. For each breakthrough migraine, subjects will take a dose of ubrogepant 100 mg. If after 2 hours, the migraine attack has not resolved or the migraine headache returns within 24 hours, subjects can choose either to take a second dose of ubrogepant 100 mg or any of the acute medications listed in the Prior and Concomitant Therapy section of the protocol. There will be a total of 9 scheduled clinic visits: Screening/Visit 1 (Week -1), Baseline/Visit 2 (Day 1), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 6 (Week 16), Visit 7 (Week 20), Visit 8/Early Termination (Week 24), and Visit 9/Safety Follow-up (Week 28). Total duration of study participation is 29 weeks. Total treatment duration is 24 weeks. All subjects who take at least 1 dose of atogepant 60 mg will enter a safety follow-up period of 4 additional weeks after their last dose of study drug. All subjects, regardless of the number of doses of study drug taken, should complete Visit 8/Early Termination and Visit 9 (Safety Follow-up), unless the subject has withdrawn consent. An interim analysis that includes all safety and efficacy analyses is planned.
Key Eligibility Criteria:	At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders (ICHD)-3, 2018. Must have a history of 4 to 14 migraine days per month on average in the 3 months prior to Screening (Visit 1) in the investigator's judgment.
Study Drug and Duration of Treatment:	Atogepant (open label): atogepant 60 mg once daily for 24 weeks (Visits 2 to 8) Ubrogepant (open-label): ubrogepant 100 mg as needed to treat up to 8 breakthrough migraine headaches for every 4 weeks for 12 weeks (Visits 5-8)
Date of Protocol Synopsis:	22 July 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

A proportion of individuals receiving preventive monotherapy for migraine may continue to experience migraine attacks and migraine-related disability.[1,2] A large body of evidence suggests that calcitonin gene-related peptide (CGRP) plays a central role in the pathogenesis of migraine.[3,4,5] CGRP levels in the cranial circulation are increased during a migraine attack and CGRP itself has been shown to trigger migraine-like headache.

Atogepant is an orally active CGRP receptor antagonist. Atogepant has demonstrated efficacy in significantly reducing the number of migraine and headache days in patients with episodic migraine (EM) and was recently approved by the Food and Drug Administration (FDA) for the preventive treatment of EM in adults. Ubrogepant is another potent, selective, orally active, CGRP receptor antagonist that has been approved by the FDA for the acute treatment of migraine with or without aura in adults.

Both drugs have been shown to be safe and well tolerated. Ubrogepant is similar in structure and mechanism of action to atogepant and the additive effect of combination therapy is currently unknown. This open-label study is being conducted to evaluate the safety, tolerability, and efficacy of the concomitant use of ubrogepant for the acute treatment of breakthrough migraine headache in subjects taking atogepant once daily for the preventive treatment of EM.

2.2 Benefits and Risks to Subjects

Atogepant was approved in 2021[6] by the FDA for the preventive treatment of episodic migraine in adults and ubrogepant was approved in 2019[7] for the acute treatment of migraine in adults. Efficacy was demonstrated in the respective pivotal studies. Both drugs have shown to be safe and well tolerated. Atogepant and ubrogepant have very similar mechanisms of action; therefore, no additional safety risk is expected from concomitant use. An independent Data Monitoring Committee (DMC) will review safety data throughout the study and make recommendations to the sponsor including modification or early termination of the study. Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with atogepant and ubrogepant are justified by the anticipated benefits that may be afforded to subjects with migraine. Overall, the benefit risk assessment is favorable.

For further details, please see findings from completed studies, including safety data in the current atogepant and ubrogepant Investigator's Brochures (IBs).[4,5]

Considering the coronavirus – 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in migraine studies testing these compounds have been evaluated. Based on the limited information to date, no additional risk to study subjects is anticipated with the use of atogepant and ubrogepant. Currently, there is no data to suggest that these drugs interfere with the functioning of the immune system and, therefore, an increased risk is not expected.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

- To evaluate the safety and tolerability of the concomitant use of ubrogepant 100 mg for the acute treatment of breakthrough migraine headache in subjects taking atogepant 60 mg once daily for preventive treatment of EM.

Exploratory

- To evaluate the clinical benefit of the concomitant use of ubrogepant 100 mg, taken as needed, and atogepant 60 mg once daily in subjects with EM.
- To explore the efficacy of ubrogepant 100 mg, taken as needed, for the acute treatment of migraine in subjects taking atogepant 60 mg once daily for preventive treatment of EM.

3.2 Primary Endpoint

The endpoint is to assess the safety and tolerability (see Section 3.4) of atogepant and ubrogepant administered concomitantly.

3.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are as follows:

- Change from baseline in mean monthly migraine days, headache days, and acute medication use days across Weeks 1 to 12, Weeks 13 to 24), and at each 4-week interval.
- 25%, 50%, 75%, and 100% reduction in mean monthly migraine days across Weeks 1 to 12, Weeks 13 to 24, and at each 4-week interval.
- Percentage of migraine attacks treated with ubrogepant that result in pain freedom at 2 hours, pain relief at 2 hours, sustained pain freedom from 2 to 24 hours, and sustained pain relief from 2 to 24 hours across Weeks 13 to 24 and at each 4-week interval.
- Patient satisfaction with atogepant at Week 12 and Week 24.
- Patient satisfaction with ubrogepant, taken as needed, at Week 24.
- Patient satisfaction with the concomitant use of atogepant and ubrogepant (taken as needed) at Week 24.
- Change from baseline in the Headache Impact Test (HIT)-6 total score at Weeks 4, 8, 12, 16, 20, and 24.
- At least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, 12, 16, 20, and 24.

- Patient Global Impression of Change (PGIC) of "much better" or "very much better" at Week 12 (atogepant) and Week 24 (atogepant + ubrogepant).
- 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, 12, 16, 20, and 24) as assessed by the Work Productivity and Activity Impairment Questionnaire:Migraine (WPAI:MIGRAINE).
- Change from baseline in the Migraine-Specific Quality-of-Life Questionnaire (MSQ) v2.1 Role Function-Preventive domain score at Weeks 4, 8, 12, 16, 20, and 24.
- Change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Weeks 4, 8, 12, 16, 20, and 24.
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, 12, 16, 20, and 24.
- Change from baseline in the Patient Health Questionnaire (PHQ)-4 score at Weeks 4, 8, 12, 16, 20, and 24.
- Migraine Treatment Optimization Questionnaire (MTOQ)-6 score at Weeks 16, 20, and 24.

3.4 Safety Endpoints

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

3.5 Pharmacokinetic Endpoints

Plasma atogepant and ubrogepant concentrations will be obtained at the respective visits, as indicated in the Schedule of Activities (Appendix D). PK sample collection is optional. A nonlinear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of atogepant and ubrogepant oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data. The results of population PK analyses may not be included with the clinical study report.

3.6 Biomarker Research Endpoints

Biomarkers

Biospecimens (plasma and saliva) will be collected at specified time points (Appendix D) during the study to evaluate known and/or novel disease-related or drug-related biomarkers in circulation or at tissue sites. Sample collection is optional. The analyses may include but are not limited to: biomarkers associated with mechanisms of migraine, such as calcitonin gene-related peptide (CGRP) and its degradants. This research may be 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, Section 3.6 and Appendix F.

Pharmacogenetics

DNA isolated from whole blood (pharmacogenetic sample) will be collected at Screening (Visit 1). Sample collection is optional. DNA may be analyzed to determine specific genetic mutations in subjects with migraine and related conditions, as well as determine if any of these mutations are associated with response to treatment with atogepant or ubrogepant (or drugs of this class). Further details regarding the pharmacogenetic research rationale and collection time point are located in the Operations Manual, Section 3.6 and Appendix F.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicenter, open-label, Phase 4 study conducted in the United States (US) to evaluate the safety, tolerability, and efficacy of the concomitant use of ubrogepant 100 mg for the acute treatment of breakthrough migraine headache in subjects taking atogepant 60 mg once daily for preventive treatment of EM.

Subject participation will begin with up to a 1 week screening period. Subjects who continue to meet all entry criteria at Baseline/Visit 2 (Day 1) will be assigned atogepant 60 mg once daily for the preventive treatment of migraine.

Screen failures are defined as subjects who consent to participate in the study, however, are not subsequently assigned to receive study drug. Rescreening of screen failures is permitted in certain situations, with permission from the Sponsor, however, subjects with exclusionary laboratory values at Visit 1 (including alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 1 x upper limit of normal [ULN], total bilirubin > 1 × ULN, or serum albumin < 2.8 g/dL) are not allowed to be rescreened (note that total bilirubin > 1 × ULN in subjects with Gilbert's disease is not exclusionary).

The open-label atogepant treatment period will last for 12 weeks (Visits 2-5). During this study period, subjects will use their usual medications for the acute treatment of breakthrough migraine headaches. At Visit 5, subjects who complete the open-label atogepant treatment period will continue into the open-label atogepant + ubrogepant concomitant use period which will last for an additional 12 weeks (Visits 5 to 8). During this study period, subjects will continue to take atogepant 60 mg once daily and will also be provided ubrogepant 100 mg to treat up to 8 breakthrough migraine headaches of any pain intensity per 4-week visit interval. During this time, subjects will take a dose of ubrogepant 100 mg to treat their breakthrough migraine headache. If after 2 hours, the migraine attack has not resolved or the migraine headache returns within 24 hours, subjects can choose either to take a second dose of ubrogepant 100 mg or any of the acute medications listed in Section 5.4.

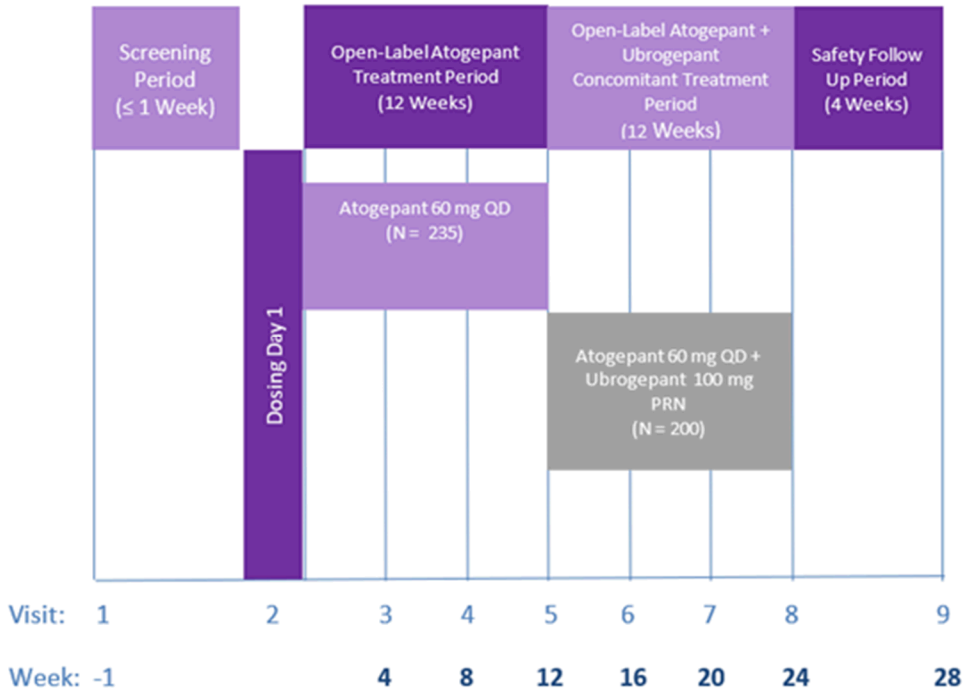
There will be a total of 9 scheduled clinic visits: Screening/Visit 1 (Week -1), Baseline/Visit 2 (Day 1), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 6 (Week 16), Visit 7 (Week 20), Visit 8/Early Termination (Week 24), and Visit 9/Safety Follow-up (Week 28).

The total duration of study participation is 29 weeks. Total treatment duration is 24 weeks. See Section 5 for information regarding eligibility criteria.

All subjects who take at least 1 dose of atogepant 60 mg will enter a safety follow-up period of 4 additional weeks after their last dose of study drug. All subjects, regardless of the number of doses of study drug which are self-administered, should complete Visit 8/Early Termination and Visit 9 (Safety Follow-up), unless the subject has withdrawn consent. An interim analysis that includes all safety and efficacy analyses is planned. Details are provided in Section 7.6.

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

Figure 1. Study Design



4.2 Discussion of Study Design

Choice of Control Group

Not applicable.

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.

Clinical Hypotheses

The concomitant use of ubrogepant for acute treatment and atogepant for preventive treatment of migraine will be well tolerated and have an acceptable safety profile.

The concomitant use of ubrogepant 100 mg taken as needed and atogepant 60 mg once daily provides substantial clinical benefit in subjects with EM.

Ubrogepant 100 mg taken as needed is effective for the acute treatment of migraine in subjects taking atogepant 60 mg once daily for preventive treatment of EM.

Suitability of Subject Population

Individuals receiving preventive monotherapy for migraine may continue to experience migraine attacks and migraine-related disability. Subjects taking the highest approved doses of atogepant (60 mg once daily) for the preventive treatment of EM are well suited to receive ubrogepant for the acute treatment of migraine headache of moderate/severe intensity when breakthrough migraine attacks occur while on atogepant.

Selection of Doses in the Study

The approved doses for ubrogepant are 50 or 100 mg taken once or twice for the acute treatment of migraine within a 24-hour period. The approved doses for atogepant are 10, 30, or 60 mg once daily for the preventive treatment of EM. For this study, the highest approved doses (60 and 100 mg, respectively) were selected to evaluate the safety and tolerability of the concomitant use of atogepant and ubrogepant.

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 must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (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. Must not have clinically significant **laboratory values** OR any of the following criteria at Visit 1:
  - ALT or AST > 1 × ULN;
  - total bilirubin > 1 × ULN (except for subjects with a diagnosis of Gilbert's disease); OR

- serum albumin < 2.8 g/dL.

- 4. Are willing and able to comply with procedures required in this protocol.

Disease/Condition Activity

- 5. At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders (ICHD)-3, 2018. (See Section 7.1 of the Operations Manual).
- 6. Age of the subject at the time of migraine onset < 50 years.
- 7. History of 4 to 14 **migraine** days per month (see Section 3.4 of the Operations Manual for definition of migraine day) on average in the 3 months prior to Screening/Visit 1 in the investigator's judgment.
- 8. History of less than 15 **headache** days per month (see Section 3.4 of the Operations Manual for definition of headache day) on average across the 3 months prior to Screening/Visit 1 in the investigator's judgment.
- 9. Able to distinguish migraine headaches from tension-type or other headaches.

Subject History

- 10. No history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018. (See Section 7.1 of the Operations Manual)
- 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. For subjects who have taken 5 or more preventive medications for migraine with proven efficacy in the past, no history of an inadequate response to 5 or more prescription prevention medications in 2 or more different mechanisms of action (see Section 7.3 of the Operations Manual for list of preventive treatments for migraine with proven efficacy and failure/inadequate response definitions).
- 13. No ECG with clinically significant abnormalities at Screening/Visit 1 as determined by the investigator.
- 14. No clinically significant cardiovascular or cerebrovascular disease per the investigator's judgment 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 Screening/Visit 1

- Heart failure defined as Class III or IV by the New York Heart Association functional classification system

15. No hypertension as defined by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Screening/Visit 1 or Baseline/Visit 2. Vital sign measurements that exceed these limits may be repeated only once at each visit.

16. No clinically significant hematologic, endocrine, pulmonary, renal, hepatic, neurologic, or gastrointestinal disease:

- If there is a history of such a disease, but the condition has been stable for more than 1 year prior to Screening/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 are not eligible to participate

17. No known history of 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 at Screening/Visit 1; no history of acute hepatitis within 6 months of Screening/Visit 1.

18. No known active SARS-CoV-2 infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., polymerase chain reaction [PCR]) test result. Note: SARS CoV-2 diagnostic tests should be applied following local requirements/recommendations.

19. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:

- At least 14 days since the first PCR test result has passed in asymptomatic subjects or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

20. No unremitting symptoms of "long COVID" due to prior SARS-CoV-2 infection or any other lasting symptoms that, in the investigator's judgment, may put the participant at significant risk or, may confound the study results.

21. In the judgment of the investigator, no **confounding** psychiatric conditions, dementia, epilepsy, or significant neurological disorders other than migraine.

22. No other concurrent pain condition that, in the judgment 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 judgment 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 Screening/Visit 1 or at Baseline/Visit 2 assessments.

24. No **history** of malignancy in the 5 years prior to Screening/Visit 1, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer.

- 25. No **history** of any gastrointestinal (GI) prior procedures or GI conditions (e.g., diarrhea syndromes, inflammatory bowel disease) that may affect the absorption or metabolism of study intervention; subjects with prior gastric bariatric interventions (e.g., Lap Band) which have been reversed are not excluded.
- 26. At Screening/Visit 1, subject is **not** a user of illegal drugs and has no history within the past year of drug or alcohol abuse or dependence per investigator judgment.
- 27. No **history** of hypersensitivity or clinically significant adverse reaction to a CGRP receptor antagonist.
- 28. Not **employed** by or is an immediate family member (parents, spouses, siblings, or children) of one of the investigators, study staff, or AbbVie.
- 29. No **conditions or current situations** which in the investigator's judgment may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
- 30. 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 judgment, might indicate that the subject is unsuitable for the study.

Contraception (See also Section 5.2 Contraception Requirements)

- 31. For all females of childbearing potential; a **negative urine pregnancy test** at the Screening/Visit 1 and a negative urine pregnancy test at Baseline/Visit 2 prior to the first dose of study drug.
- 32. Female subjects of childbearing potential must agree to practice at least 1 protocol-specified **method of birth control**, that is effective from Baseline/Visit 2 (Day 1) through at least 30 days after the last dose of study drug. Female subjects of nonchildbearing potential do not need to use birth control.
- 33. Female who is not **pregnant or breastfeeding and is** not **considering becoming pregnant** or donating eggs during the study or for approximately 30 days after the last dose of the study drug.
- 34. For **male** subjects with **sexually active female partner(s) of childbearing potential**, he must agree, from Baseline/Visit 2 (Day 1) through 30 days after the last dose of study drug, to practice the protocol-specified contraception.
- 35. Male who is not considering **fathering a child or donating sperm** during the study or for approximately 30 days after the last dose of study drug.

Concomitant Medications

- 36. No requirement for any medication, diet (i.e., grapefruit juice), or nonpharmacological treatment 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 Protocol Section 5.3 Prohibited Medications and Therapy and Section 7.2 of Operations Manual).

- This includes no requirement for the use of concomitant medications with demonstrated efficacy for the prevention of migraine (e.g., amitriptyline, topiramate, propranolol) for any reason (e.g., hypertension).

37. No **previous exposure** to atogepant; no exposure to injectable monoclonal antibodies blocking the CGRP pathway within the last 6 months; no exposure to rimegepant for preventive treatment of migraine within the last 1 month.

38. Not **currently participating** in or has not participated in a study with an investigational compound or device within 30 days prior to Screening/Visit 1 (this includes studies using marketed compounds or devices).

39. No usage of opioids > 4 days/month in the 3 months prior to Screening/Visit 1 per investigator's judgment.

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 follicle-stimulating hormone level ≥ 30 IU/L.

- Females, of Childbearing Potential
  - Combined (estrogen- and progestogen-containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation-initiated at study Baseline/Visit 2 (Day 1).
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at study Baseline/Visit 2 (Day 1).

- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the study 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, postovulation methods] and withdrawal are not acceptable).

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

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 Baseline/Visit 2 (Day 1) through at least 30 days after the last dose of study drug.

5.3 Prohibited Medications and Therapy

The following medications/treatments/therapies/lifestyle activities are prohibited 30 days prior to Screening/Visit 1 (unless otherwise indicated) and throughout the study. An extended list of examples of prohibited medications are displayed in Section 7.2 in the Operations Manual.

- Medications with demonstrated efficacy for the prevention of migraine (e.g., amitriptyline, topiramate, propranolol) used to prevent migraine or for any indication (e.g., propranolol for hypertension is not allowable). If the subject is on a routine prescription medication for migraine prevention and if the permissibility of a specific medication/treatment is in question, please contact the Therapeutic Area Medical Director.
- Commercially available rimegepant (Nurtec™) is prohibited from Visits 1 to 9. Commercially available ubrogepant (Ubrelvy™) is prohibited from Visits 1-9 (ubrogepant provided as study drug is allowed from Visits 5-8).
- Injectable monoclonal antibodies blocking the CGRP pathway (e.g., Aimovig™, Emgality™, Ajovy®, Vyepti™) within 6 months prior to Screening/Visit 1 and throughout 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 Screening/Visit 1 and throughout the study period.
- Acupuncture, noninvasive 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.

- Strong and moderate CYP3A4 inhibitors, including, but not limited to: systemic (oral/intravenous [IV]) boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole, clarithromycin, idelalisib, nefazodone, nelfinavir, aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, and verapamil.
- Strong and moderate CYP3A4 inducers, including but not limited to: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, phenobarbital, primidone.
- Strong OATP1B1 inhibitors (e.g., gemfibrozil).
- Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions (e.g., warfarin).
- Cannabinoids (e.g., marijuana, tetrahydrocannabinol [THC] containing products) or ingested cannabidiol (CBD) containing products.
- Subjects should refrain from consuming grapefruit or grapefruit juice from the time the consent form is signed until completion of the study. Participants 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/day throughout the study. A drink is defined as a 12-ounce can/bottle of beer, a 4-ounce glass of wine or 1 ounce of liquor.

The decision to administer a prohibited medication/treatment is done with the safety of the study subject as the primary consideration. Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. When possible, AbbVie should be notified before the prohibited medication/treatment is administered. If the permissibility of a specific medication/treatment is in question, please contact AbbVie.

Medications/vaccines that are not specifically prohibited are allowed, with the following clarifications and restrictions:

- Aspirin up to 325 mg/day is allowed for cardiac prophylaxis (see Section 5.4 for non-steroidal anti-inflammatory drugs [NSAIDs] use for migraine).
- Selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs), except venlafaxine and desvenlafaxine, are 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, and is not indicated for the treatment of migraine or headaches.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study

must be recorded from 6 months prior to Screening/Visit 1 (Day 1) through the Safety Follow-up/Visit 9 (Week 28). All prior and concomitant headache/migraine medications including migraine prevention medications must be recorded.

Any questions regarding concomitant or prior therapy should be raised to the sponsor contact. Information regarding potential drug interactions with atogepant or ubrogepant can be located in the current atogepant or ubrogepant Investigator's Brochure.[4,5]

During the study, the following medications are allowed for the acute treatment of migraines as needed with no restrictions with the exception of opioid use.

- Any triptan
- Any ditan
- Any ergot derivative
- Any opioid (≤ 4 days/month)
- Any other form of analgesic (including acetaminophen)
- Any NSAID agent
- Any antiemetic agent

During the open-label atogepant period (Visits 2-5 [Day 1 to Week 12]), any of the acute medications listed above may be taken for breakthrough migraine attacks.

During the open-label atogepant and ubrogepant concomitant use period (Visits 5-8 [Weeks 12 to 24]), ubrogepant 100 mg (provided as study drug by AbbVie) should be used as the acute treatment for all breakthrough migraine attacks. If after 2 hours, the migraine attack has not resolved or the migraine headache returns within 24 hours, subjects can choose either to take a second dose of ubrogepant 100 mg or any of the acute medications listed above.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during the study, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of atogepant and ubrogepant on SARS-CoV-2 vaccination is unknown. Therefore, study drug should be administered as follows:

- The first dose of atogepant and ubrogepant, when possible, is preferred to be given at least ± 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine electronic case report form (eCRF). Refer to the Operations Manual in Appendix F for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of 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 during the study.
- The investigator determines the subject is significantly noncompliant with study procedures.
- Subject meets one of the following criteria for ALT/AST elevations, and is advised not to be rechallenged:
    - 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 international normalized ratio (INR) > 1.5
    - ALT or AST ≥ 5 × ULN for more than 2 weeks
    - ALT or AST ≥ 8 × ULN
- Subjects who reply with "yes" to Questions 4 or 5 in the suicidal ideation section or "yes" to any question in the suicidal behavior section for the C-SSRS at Visits 2 through 9 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including Early Termination Visit and Safety Follow-up (Visit 9).

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.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has 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

If a subject early terminates study participation after taking at least one dose of study drug, the procedures outlined for the Early Termination Visit should be completed as soon as possible, preferably within 2 weeks. In addition, the Safety Follow-up (Visit 9) should be completed 4 weeks after the Early Termination Visit to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been resolved.

In the event a subject withdraws consent from the clinical study, PK and/or 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 PK and/or biomarker samples research to continue, previous unanalyzed samples will not be analyzed and no new PK and/or biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). A subject may withdraw consent for optional PK and/or biomarker research at any time and remain in the clinical study. Data generated from the clinical study and/or optional PK and/or biomarker research, before the subject withdrawal of consent, will remain part of the study results.

5.7 Study Drugs

Atogepant tablets, manufactured by AbbVie, will be taken orally with or without food once daily beginning on Day 1 in the clinic and should be taken at approximately the same time each day. If subjects should forget to take their atogepant dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember, and then take their next dose at the regularly scheduled dosing time.

Ubrogepant tablets, manufactured by AbbVie, will be taken orally with or without food as needed to treat up to 8 breakthrough migraine headaches for the 4 weeks between each visit for Visits 5 to 8. During this time, subjects will take a dose of ubrogepant 100 mg to treat their breakthrough migraine headache. If after 2 hours the migraine attack has not resolved or the migraine headache returns within 24 hours, subjects can choose either to take a second dose of ubrogepant 100 mg or any of the acute medications listed in Section 5.4.

All subject dosing will be recorded. The study site personnel will document compliance.

AbbVie will provide atogepant tablets and ubrogepant tablets. AbbVie-provided study drugs should not be substituted or alternately sourced, unless otherwise directed by AbbVie.

Atogepant tablets will be packaged in bottles with quantities sufficient to accommodate study design. Ubrogepant tablets will be packaged in blisters or packets 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 at

the site. Each kit will contain a unique kit number. This kit number is assigned to a subject via the interactive response technology (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.

Study drugs are described in Table 1.

Table 1. Study Drugs

Study drug	Manufacturer	Mode of Administration	Dosage Form	Strength
Atogepant	AbbVie	Oral	Tablet	60 mg
Ubrogepant	AbbVie	Oral	Tablet	100 mg

5.8 Randomization/Drug Assignment

No randomization or stratification is required as this will be an open-label study.

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.

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 Data Monitoring Committee and Hepatic Event Adjudication Committee

An external data monitoring committee (DMC) composed of clinicians and statisticians independent of AbbVie and with relevant expertise in their field will review data from the ongoing study. The DMC is responsible for safeguarding the interests of trial subjects, assessing the safety of the interventions during the study, as well as for monitoring the integrity and interpretability of the study. The DMC will provide recommendations to the sponsor regarding ongoing trial conduct or modifications to the trial as described in a separate DMC charter and identify any safety issues and trends.

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

An external Hepatic Event Adjudication Committee (HEAC) will review and adjudicate events of post-treatment elevations of ALT and/or AST ≥ 3 x ULN. An Adjudication Charter will be established and will describe the standardized process for the adjudication of the events to determine whether the elevation was related to study drug(s). The charter will describe the process for the adjudication of ALT and/or AST levels meeting the thresholds provided above, by the HEAC. The purpose of the charter will be to provide a standardized process for the adjudication of data associated with these events in order to determine whether the elevation(s) are related to study drug.

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 study drug 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 study drug 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 electronic data capture (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

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. Worsening 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 Arrythmias **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** **ALT/AST $\geq$ 3 × ULN with a total bilirubin $\geq$ 2 × ULN**	Hepatic AE 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 an SAE 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):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the judgment 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 or 5 half-lives, whichever is longer, after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

Adverse events 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

All AEs of special interest must be reported within 24 hours of the time the investigator becomes aware of the event using the AE eCRF and the hepatic eCRF.

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

- 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 an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS and DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

7.2 Definition for Analysis Populations

The modified intent-to-treat 1 (mITT1) population includes all enrolled subjects who receive at least 1 dose of study drug, have a baseline assessment, and have at least 1 postbaseline assessment during the open-label atogepant treatment period. The modified intent-to-treat 2 (mITT2) population includes all enrolled subjects who receive at least 1 dose of study drug, have a baseline assessment, and have at least 1 postbaseline assessment during the open-label atogepant+ubrogepant treatment period. The mITT1 or mITT2 populations will be used for efficacy analyses.

The safety population 1 consists of all subjects who received at least 1 dose of study drug during the open-label atogepant treatment period. The safety population 2 consists of all subjects who received at least 1 dose of study drug during the open-label atogepant + ubrogepant treatment period. The safety population 1 will be used for all baseline analysis, and the safety population 1 or safety population 2 will be used for safety analyses.

7.3 Handling Potential Intercurrent Events for the Primary and Exploratory Endpoints

The efficacy endpoints are exploratory in this study; therefore, no estimand attributes for efficacy endpoints will be provided.

7.4 Statistical Analyses for Efficacy

All analyses on the exploratory efficacy endpoints will be performed with the mITT1 or mITT2 population.

Unless otherwise specified, change from baseline of continuous endpoints will be analyzed using a mixed-effect model for repeated measures (MMRM), including visit as a categorical fixed effect, and baseline value 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

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. Nominal p-values and 95% confidence intervals (CIs) will be reported.

The MTOQ-6 score and percentages of migraine attacks treated with ubrogepant that result in pain freedom or pain relief will be summarized using descriptive statistics.

If the endpoints are binary or categorical, they will be summarized using descriptive statistics.

7.5 Statistical Analyses for Safety

The safety analyses will be performed using the safety population 1 or safety population 2. The safety endpoints include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, the C-SSRS, and pregnancy test. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety assessment before the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

Continuous variables will be summarized by the number of subjects, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of subjects. The Kaplan-Meier Curve will provide the time to the occurrence of certain AEs, if needed.

7.6 Interim Analysis

An interim analysis that includes all safety and efficacy analyses is planned when at least 30 subjects have completed Visit 8 to support access/reimbursement negotiations.

7.7 Overall Type I Error Control

No multiplicity adjustment for overall Type I Error Control is planned for this study.

7.8 Sample Size Determination

Approximately 235 subjects will be assigned to receive open-label atogepant 60 mg once daily for the preventive treatment of episodic migraine at Baseline/Visit 2 (Day 1). Based on historical data from previously completed clinical studies, it is assumed that 15% of subjects will discontinue from the study during the atogepant treatment period (Day 1 to Week 12). Therefore, approximately 200 subjects will be assigned to also receive ubrogepant 100 mg for the acute treatment of migraine starting at Visit 5 (Week 12).

This sample size will provide estimation for AEs of interest occurring in either the open-label atogepant treatment period (Day 1 to Week 12) or the open-label atogepant and ubrogepant concomitant use treatment period (Weeks 12 to 24) with a precision (defined as the half width of 95% confidence interval) of approximately ± 3% to 5%.

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, International Council for Harmonisation (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 Good Clinical Practice (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 the last subject's last visit or date of the last follow-up contact, whichever is later.

12 REFERENCES

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2. D'Antona L, Matharu M. Identifying and managing refractory migraine: barriers and opportunities? J Headache Pain. 2019;20(1):89.

3. Fischer MJ. The role of calcitonin gene-related peptide (CGRP) in the pathogenesis of primary headache. Drugs Fut. 2006;31(2):175-81.

4. Atogepant Investigator's Brochure. Current Version.

5. Ubrogepant Investigator's Brochure. Current Version.

6. Qulipta USPI. 2021.

7. Ubrelvy USPI. 2019.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CL/F	Apparent clearance
CBD	Cannabidiol
CGRP	Calcitonin gene-related peptide
COVID-19	Coronavirus Disease – 2019
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
EM	Episodic Migraine
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEAC	Hepatic Event Adjudication Committee
HIT-6	Headache Impact Test-6
ICHD	International Classification of Headache Disorders
INR	International normalized ratio
IRT	Interactive response technology
IV	Intravenous
mITT	Modified intent-to-treat
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire version 2.1
MTOQ-6	Migraine Treatment Optimization Questionnaire-6
NSAID	Non-steroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PGIC	Patient Global Impression of Change
PHQ-4	Patient Health Questionnaire-4
PK	Pharmacokinetic(s)

QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SNRI	Serotonin-norepinephrine reuptake Inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reactions
THC	Tetrahydrocannabinol
ULN	Upper limit of normal
US	United States
V/F	Apparent volume of distribution
WPAI:MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M23-072: A Phase 4, Multicenter, Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of the Concomitant Use of Ubrogepant for the Acute Treatment of Migraine in Subjects Taking Atogepant for the Preventive Treatment of Episodic Migraine.

Protocol Date: 22 July 2022

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 study drug(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]	Program Lead	Clinical Study Leadership
[redacted]	Associate Director	Medical Writing
[redacted]	Therapeutic Area MD	Neuroscience Development
[redacted]	Senior Director and Therapeutic Area Head, Neuroscience	Statistics
[redacted]	Senior Manager	Statistics
[redacted]	Executive Director, Clinical Pharmacology	Clinical Pharmacology and Pharmacometrics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities. The individual activities are described in detail in the **Operations Manual** (Appendix F).

Study Activities Table

	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 OR Early Termination	Visit 9 Safety Follow-Up Visit
Activity	**Week -1**	**Day 1 +3days**	**Week 4 ±3days**	**Week 8 ±3days**	**Week 12 ±3days**	**Week 16 ±3days**	**Week 20 ±3days**	**Week 24 +3days**	**Week 28 ±3days**
INTERVIEWS & QUESTIONNAIRES									
Informed consent	✓								
Eligibility criteria	✓	✓							
Medical/surgical history	✓								
Migraine history	✓								
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient-reported outcomes: HIT-6		✓	✓	✓	✓	✓	✓	✓	
Patient-reported outcomes: MSQ v2.1	✓	✓	✓	✓	✓	✓	✓	✓	
Patient-reported outcomes: WPAI:MIGRAINE		✓	✓	✓	✓	✓	✓	✓	
Patient-reported outcomes: PGIC (atogepant)					✓				
Patient-reported outcomes: PGIC (atogepant + ubrogepant)								✓	
Patient-reported outcomes: PHQ-4		✓	✓	✓	✓	✓	✓	✓	
Patient-reported outcomes: MTOQ-6						✓	✓	✓	
Patient-reported outcomes: Subject satisfaction with atogepant					✓			✓	
Patient-reported outcomes: subject satisfaction with ubrogepant								✓	

	Visit 1 Screening	Visit 2 Baseline	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 OR Early Termination	Visit 9 Safety Follow-Up Visit
Activity	Week -1	Day 1 +3days	Week 4 ±3days	Week 8 ±3days	Week 12 ±3days	Week 16 ±3days	Week 20 ±3days	Week 24 +3days	Week 28 ±3days
Patient-reported outcomes: subject satisfaction with atogepant & ubrogepant								✓	
Investigator interviewer questionnaire migraine - screening	✓								
Investigator interviewer questionnaire migraine - Visit 2-5		✓	✓	✓	✓				
Investigator interviewer questionnaire migraine - Visit 6-8						✓	✓	✓	
C-SSRS	✓	✓	✓	✓	✓	✓	✓	✓	✓
LABORATORY & SITE EXAMINATIONS									
12-lead ECG	✓				✓			✓	
Height (screening only) and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓							✓	✓
Urine pregnancy test	✓	✓	✓	✓	✓	✓	✓	✓	✓
CENTRAL LABORATORY									
Clinical laboratory tests	✓	✓	✓	✓	✓	✓	✓	✓	✓
PK (optional): predose at Visit 2		✓		✓				✓	
Biomarker samples (optional): predose at Visit 2		✓		✓				✓	✓
Pharmacogenetic sample – blood (optional)	✓								
TREATMENT									
IRT entry	✓	✓	✓	✓	✓	✓	✓	✓	
Dispense study drug (atogepant)		✓	✓	✓	✓	✓	✓		
Dispense study drug (ubrogepant)					✓	✓	✓		
Perform drug reconciliation			✓	✓	✓	✓	✓	✓	
Atogepant administration		Once daily							
Ubrogepant administration					As needed				

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	10 January 2022
Administrative Change 1	18 May 2022

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

- Incorporated changes from Protocol Administrative Change 1, including the name and contact information for the Therapeutical Area Medical Director and correction of typographical and formatting errors.
  - Title page - added atogepant and ubrogepant to AbbVie Study Drug.
  - Updated the name and contact information of the Sponsor/Emergency Medical Contact globally.
  - Section 6.1 - referenced Section 4.2 of the Operations Manual for SAE reporting details and contact info to correct numerical typographical error.
- Global - modified wording regarding use of ubrogepant for breakthrough migraine headaches and criteria for optional second dose of ubrogepant 100 mg or acute medications listed in Section 5.4, for clarity and consistency.
- Synopsis and Section 4.1 - clarified which visits subjects should complete in the study.
- Section 3.3 - modified language of exploratory efficacy endpoints for clarity and consistency.
- Section 4.1 - modified language to clarify that subjects with exclusionary laboratory values at Visit 1 are not allowed to be rescreened, but clarified that total bilirubin > 1 × ULN in subjects with Gilbert's disease is not exclusionary.
- Section 5.1 - modified eligibility Criterion 3 to clarify that to be eligible for the study, subjects must not have clinically significant laboratory values OR any of the specified ALT/AST, total bilirubin, or serum albumin criteria at Visit 1.
- Section 5.1 - modified eligibility Criterion 8 to correct a typographical error and clarify that the number of headache days per month allowed for entry to the study is less than 15 headache days per month on average across the 3 months prior to Screening/Visit 1.
- Section 5.1 and Section 5.2 - modified eligibility Criteria 34 and 35 and contraception requirements for males to align with safety profile of study drug.
- Section 5.1 - modified eligibility Criterion 37 for clarity.
- Section 5.3 - modified language of prohibited medications for clarity.
- Section 5.3 - added reference to Section 5.4 for NSAID use for migraine and added/modified wording regarding restrictions of concomitant SSRIs and SNRIs.

- Section 5.5 - modified language regarding noncompliance to highlight determination of investigator.
- Section 5.5 - added language regarding which responses on C-SSRS require withdrawal from study and appropriate follow-up to minimize risk to subjects.
- Section 5.6 - modified wording regarding follow-up after subject discontinuation of study drug or from study for clarity.
- Section 5.7 - added wording regarding study drug return or destruction to align with sponsor instructions and local regulations.
- Section 6.1 - modified wording to clarify that 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 to be consistent with male contraception.
- Section 7.2 and Section 7.4 - wording modified to clarify the definition of analysis populations and efficacy analyses.
- Section 11 - renamed section to reflect that start-of-study definition was added.
- Appendix A - added definitions for clarity.
- Appendix B - modified language regarding responsibilities of the investigator to detail criteria that would meet prompt reporting.
- Appendix C - updated the list of protocol signatories.
- Appendix D - PROs formatted for consistency.
- Appendix E - added protocol summary of changes appendix.
- Appendix F - Operations Manual modified to correct formatting errors and incorporate the following changes:
    - Incorporated changes from Protocol Administrative Change 1 - added atogepant and ubrogepant to AbbVie Study Drug; update the name and contact information of the Sponsor/Emergency Medical Contact globally; and reformatted the PRO and Clinician-Reported Outcomes, Definition of Migraine Day subsection of the Operations Manual for clarity.
    - Global - Added/modified wording regarding use of ubrogepant for breakthrough migraine headaches for clarity and consistency.
    - Added PRO assessment MSQ v2.1 at Screening (Visit 1) for consistency with Appendix D of the protocol, and added version of MSQ globally.
    - Clarified which visits subjects should complete if they take at least 1 dose of atogepant and discontinue.
    - Modified name of Subject Withdrawal section of the Operations Manual to reflect that section describes discontinuation of study drug or study participation.
    - Modified language of Methods and Timing of Safety Assessment section of the Operations Manual to clarify that after 30 days following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected.

- Added wording regarding RAVE system to the Reporting AEs and Intercurrent Illnesses section of the Operations Manual for clarity.
- Global - Added/modified wording regarding use of ubrogepant for breakthrough migraine headaches for clarity and consistency.
- Added additional medications as examples of prohibited medications to minimize risk to subjects.
- Modified the list of migraine-preventive medications with proven efficacy for clarity; specified flunarizine is not available in the United States, added verapamil as an example of a calcium channel blocker, and added a reference source.
- Added a reference section for the Operations Manual.