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Protocol for Study M22-418

Chronic Migraine: Open-Label Atogepant When Added to BOTOX

VERSION:	6.0	DATE:	22 August 2024
SPONSOR:	AbbVie Inc*	PLANNED NUMBER OF SITES:	Approximately 30
ABBVIE INVESTIGATIONAL PRODUCT:	Atogepant	EudraCT:	Not applicable

FULL TITLE: A Phase 3 Multicenter 24-Week Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of Atogepant When Added to OnabotulinumtoxinA (BOTOX) for the Preventive Treatment of Chronic Migraine

Incorporating Versions 1.0, 2.0, 3.0, 4.0, 5.0, and 6.0

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1 SYNOPSIS

Title: A Phase 3 Multicenter 24-Week Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of Atogepant When Added to OnabotulinumtoxinA (BOTOX) for the Preventive Treatment of Chronic Migraine	
Background and Rationale:	Real-world evidence indicates that some individuals with chronic migraine (CM) have such severe disease that they respond to onabotulinumtoxinA (referred to hereinafter as BOTOX) but continue to have some headaches during BOTOX therapy. It is hypothesized that add-on treatment with atogepant in this population will provide clinically meaningful incremental efficacy and comprehensive migraine prevention beyond that achieved with BOTOX monotherapy and be well tolerated and have an acceptable safety profile.
Objectives and Endpoints:	**Objectives**: To evaluate the safety and tolerability of atogepant when added to BOTOX over 24 weeks in participants with CM. To prospectively evaluate the responder rates and change from baseline in monthly migraine days when atogepant is added to BOTOX monotherapy in participants with CM. **Efficacy Endpoints:** Efficacy Endpoints Collected via Daily Electronic Diary (eDiary): • Responder status (≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100%), reduction of monthly migraine days • Change from baseline in monthly migraine days, defined by International Headache Society (IHS) Guidelines 2018 • Change from baseline in monthly headache days, moderate or severe headache days, cumulative hours of headache, acute treatment medication use days, headache free days, and migraine symptom-free days, defined by IHS Guidelines 2018 • Change from baseline in monthly days with non-headache migraine symptoms such as photophobia, phonophobia, nausea and/or vomiting, dizziness, neck pain, tiredness, mood change, yawning, thirst, cravings, urinary frequency, cranial autonomic symptoms • Change from baseline in monthly Activity Impairment in Migraine - Diary (AIM-D) Health Outcome Measures: • Change from baseline in Migraine-Specific Quality of Life Questionnaire, version 2.1 (MSQ v2.1) • Change from baseline in Patient Health Questionnaire (PHQ-9) • Change from baseline in Work Productivity and Activity Impairment Questionnaire: Migraine v2.0 (WPAI:MIGRAINE) • Patient Satisfaction with Study Medications (PSSM) • Patient Global Impression of Change (PGIC) • Change from baseline in Generalized Anxiety Disorder-7 (GAD-7)

	• Change from baseline in PROMIS v2.0 Cognitive Function – Abilities Short-form 6a **Safety Endpoints:** Adverse event (AE) monitoring, serious adverse event (SAE) monitoring, AEs of special interest (AESI) monitoring, vital sign measurements, Columbia-Suicide Severity Rating Scale (C-SSRS) assessments, clinical laboratory testing (hematology, chemistry, and urinalysis), and electrocardiograms (ECGs).
Investigators:	Multicenter
Study Site(s):	Approximately 30
Study Population and Number of Participants to be Enrolled:	Chronic migraine; approximately 75 participants
Investigational Plan:	This is a 24-week, Phase 3, open-label, multicenter study to evaluate the safety and tolerability and explore efficacy of atogepant when added to BOTOX in participants with CM. The screening/baseline period is up to 12 weeks, which will include at least 28 days of eDiary collection of migraine days and headache days at the end of the screening/baseline period. The treatment period will include 7 visits and a safety follow-up period of 4-weeks that includes 1 remote visit at Week 28 (or 4-weeks post treatment for premature discontinuation). Eligible participants will receive once daily (QD) atogepant 60 mg from Day 1 to Week 24 along with their concomitant BOTOX (155 to 200 units, targeting approximately 50% of participants receiving 155 units). Concomitant BOTOX must be administered on Visits 2, 5, and 8. Final visit of the treatment period will be at Week 24 with a post-atogepant treatment follow-up at Week 28 or 4 weeks post-atogepant treatment for premature discontinuation.
Key Eligibility Criteria:	At least a 1-year history of chronic migraine, with or without aura, consistent with a diagnosis according to International Classification of Headache Disorders 3rd edition (ICHD-3 2018) and with or without acute medication overuse defined as follows: use of triptans on ≥ 10 days or use of ergots on ≥ 10 days or use of simple analgesics (i.e., aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], or acetaminophen) on ≥ 15 days, or use of any combination of triptans, ergots or simple analgesics on ≥ 10 days. Must be currently treated with BOTOX for CM: treated with ≥ 2 treatment cycles in the 8 months prior to Visit 2 (Day 1). Must have 8 to 23 (inclusive) migraine days in the eDiary screening/baseline period (eDiary data must have been collected for at least 20 days).
Study Drug and Duration of Treatment:	Atogepant 60 mg QD Approximately 24 weeks
Date of Protocol Synopsis:	22 August 2024

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] BOTOX is hypothesized to prevent migraine by blocking the release of neurotransmitters and neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P, and by inhibiting the insertion of ion channels like TRPV1 within the sensory neuron. BOTOX is approved for prophylaxis of headaches in adult patients with chronic migraine (CM). CGRP is a potent vasodilatory neurotransmitter that is believed to play a key role in the pathophysiology of migraine. Atogepant is an orally active CGRP receptor antagonist that is approved by the Food and Drug Administration (FDA) for the preventive treatment of migraine in adults.

Observations from recent real-world studies indicate that some individuals with CM responding to BOTOX benefit from add-on treatment inhibiting different groups of nociceptors.[3] Combination therapy with BOTOX and a CGRP monoclonal antibody (mAb) has been shown to be safe and tolerable and has been proposed to produce a synergistic effect through different pharmacologic mechanisms.[4]

Hence, there is a need to prospectively investigate the safety and efficacy of add-on treatment with atogepant in participants with CM receiving BOTOX. This open-label study will evaluate the safety and tolerability profile of concomitant treatment with atogepant and BOTOX in participants with CM. Additionally, the study will evaluate the incremental benefit of add-on treatment with atogepant in participants who are receiving BOTOX monotherapy for treatment of CM.

2.2 Benefits and Risks to Participants

BOTOX been approved since 2010 by the United States FDA for the prevention of headaches in adults with CM. Atogepant is approved by the FDA for the treatment of migraine (brand name QULIPTA™). While the mechanisms of action of BOTOX and atogepant suggest that there should be no interactions that would pose a safety risk to participants, the protocol is designed to ensure participant safety is assessed adequately throughout the study. The independent Data Monitoring Committee (DMC) and Hepatic Event Adjudication Committee (HEAC) will review safety data throughout the study and make recommendations to the sponsor, including modification or early termination of the study. Overall, the assessment of benefit/risk is favorable.

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.

For further details, please see findings from completed studies, including safety data in the current atogepant and BOTOX Investigator's Brochures.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

To evaluate the safety and tolerability of atogepant when added to BOTOX over 24 weeks in participants with CM.

To prospectively evaluate the responder rates and change from baseline in monthly migraine days when atogepant is added to BOTOX monotherapy in participants with CM.

3.2 Efficacy Endpoints

The primary objective of the study is to assess the safety endpoints (see Section 3.3).

Efficacy Endpoints Collected via Daily Electronic Diary (eDiary):

- Responder status (≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100%), reduction of monthly migraine days
- Change from baseline in monthly migraine days, defined by IHS Guidelines 2018
- Change from baseline in monthly headache days, moderate or severe headache days, cumulative hours of headache, acute treatment medication use days, headache free days, and migraine symptom-free days, defined by IHS Guidelines 2018
- Change from baseline in monthly days with non-headache migraine symptoms such as photophobia, phonophobia, nausea and/or vomiting, dizziness, neck pain, tiredness, mood change, yawning, thirst, cravings, urinary frequency, cranial autonomic symptoms
- Change from baseline in monthly Activity Impairment in Migraine - Diary (AIM-D)

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

A. Headache has at least 2 of the following 4 characteristics:
    - Unilateral location
    - Pulsating quality
    - Moderate or severe pain intensity
    - Aggravated by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
B. At least one of the following:
    - Nausea and/or vomiting

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

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

OR

D. Any headache which fulfills 1 criterion from (1) and at least 1 criterion from (2) OR fulfills at least 2 criteria from (1) and no criteria from (2).

1) Headache characteristics:

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

2) Symptoms:

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

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

Health Outcome Measures:

- Change from baseline in Migraine-Specific Quality-of-Life Questionnaire, version 2.1 (MSQ v2.1)
- Change from baseline in Patient Health Questionnaire (PHQ-9)
- Change from baseline in Work Productivity and Activity Impairment Questionnaire:Migraine v2.0 (WPAI:MIGRAINE)
- Patient Satisfaction with Study Medications (PSSM)
- Patient Global Impression of Change (PGIC)
- Change from baseline in Generalized Anxiety Disorder-7 (GAD-7)
- Change from baseline in PROMIS v2.0 Cognitive Function Abilities Short-Form 6a

All efficacy analyses will be performed using the modified intention-to-treat (mITT) population, consisting of participants who receive at least 1 dose of study intervention (atogepant), have an

evaluable baseline period of eDiary data and have at least 1 evaluable postbaseline 4-week period of eDiary data.

3.3 Safety Endpoints

Adverse event (AE) monitoring, serious adverse event (SAE) monitoring, AEs of special interest (AESI) monitoring, vital sign measurements, Columbia-Suicide Severity Rating Scale (C-SSRS) assessments, clinical laboratory testing (hematology, chemistry, and urinalysis), and electrocardiogram (ECG).

All safety analyses will be performed using the safety population, consisting of all participants who receive at least 1 dose of study intervention (atogepant).

3.4 Biomarker Research Endpoints

Optional fluid biomarker collection for genomics (single serum/plasma sample for DNA and RNA at Visit 2), and CGRP level (saliva and plasma sample at Visits 2, 5, and 8). An assessment of allodynia (via an allodynia symptom checklist, such as ASC-12)[5] will be completed at Baseline. Additionally, certain laboratory assessments at Visits 2 and 8 (Section 3.13 of Appendix F, footnote d) will be performed to provide information on the weight loss observed in previous trials with atogepant (see QULIPTA™ Package Insert).

Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual, Section 3.7.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

The schematic of the study is shown in Figure 1.

This is a 24-week, Phase 3, open-label, multicenter study to evaluate the safety and tolerability and explore efficacy of atogepant when added to BOTOX in participants with CM.

The screening/baseline period is up to 12 weeks, which will include at least 28 days of eDiary collection of migraine days and headache days at the end of the screening/baseline period. The treatment period will include 7 visits and a safety follow-up period of 4 weeks that includes 1 remote visit at Week 28 (or 4 weeks post-treatment for premature discontinuation).

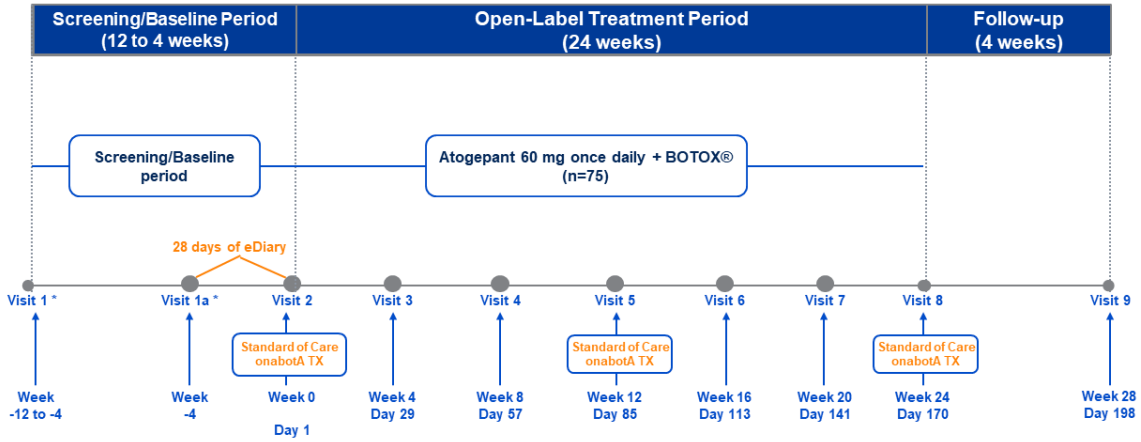
Rescreening of screen failures is permitted in certain situations with permission from the sponsor. Preapproval of rescreening from the Therapeutic Area Medical Director or Scientific Director is required.

Eligible participants will receive QD atogepant 60 mg from Day 1 to Week 24, along with their concomitant BOTOX (155 to 200 units, targeting approximately 50% of participants receiving 155 units). Concomitant BOTOX must be administered on Visits 2, 5, and 8. Final visit of the treatment period will be at Week 24 with a post-atogepant treatment follow-up at Week 28 or 4 weeks post-atogepant treatment for premature discontinuation.

Further details regarding study procedures are located in the Operations Manual (Appendix F).

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Design Schematic



Note: Visits 1 and 1a may be on the same day based on timing of the previous and next BOTOX administrations. Visit 1a should occur approximately 28 days prior to the next scheduled BOTOX administration. Screening assessments should be performed at the study visits specified in Appendix D.

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 participants with CM. All clinical and laboratory procedures in this study are standard and generally accepted.

Clinical Hypothesis

Add-on treatment of atogepant in participants with CM receiving BOTOX will be well tolerated and have an acceptable safety profile. The addition of atogepant to BOTOX will provide clinically meaningful incremental efficacy and comprehensive migraine prevention beyond that achieved with BOTOX monotherapy.

Selection of Doses in the Study

Results from Study 3101-301-002 (EM study) demonstrated atogepant 60 mg QD provided numerically greater improvement compared with the 10 mg and 30 mg QD doses. Results from Study 3101-303-002 (CM study) demonstrated that 60 mg QD is also efficacious in the CM patient population, providing evidence of the efficacy observed at 60 mg QD across the spectrum of migraine. As there was no marked difference in the safety profile across doses, the dose of 60 mg QD has been selected for this

study to evaluate the safety and tolerability of atogepant in combination with BOTOX for the preventive treatment of CM.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

- 1. Must voluntarily give consent, in a manner approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.
- 2. Adult male or female, between 18 and 75 years, inclusive.
- 3. Must be using a medically acceptable and effective method of birth control during the course of the entire study.
- 4. At least a 1-year history of CM, with or without aura, consistent with a diagnosis according to International Classification of Headache Disorders 3rd edition (ICHD-3) 2018 and with or without acute medication overuse defined as follows: use of triptans on ≥ 10 days ***or*** use of ergots on ≥ 10 days ***or*** use of simple analgesics (i.e., aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], or acetaminophen) on ≥ 15 days, ***or*** use of any combination of triptans, ergots or simple analgesics on ≥ 10 days.
- 5. Participants must be currently treated with BOTOX for CM: treated with ≥ 2 treatment cycles in the 8 months prior to Visit 2 (Day 1) with documentation of payer authorization or written attestation of self-pay to support continued use of BOTOX. Participants should have ability to coordinate standard-of-care BOTOX injections for Visits 2, 5, and 8 (± 7 days) through their primary care physician or another prescribing healthcare provider.
- 6. Previous administration of BOTOX prior to study entry was between 8 ± 1 week prior to scheduled Screening to ensure BOTOX administration at 12-week intervals and was between 155 U and 200 U divided between 31 to 39 sites across 7 specific head/neck muscle areas (frontalis, corrugator, procerus, occipitalis, temporalis, trapezius, and cervical paraspinal muscle groups), not to include the masseter. Participants must be able to have stability of dose and injection location paradigm during the study.
- 7. Must have completed at least 20 days of eDiary data collected during the eDiary screening/baseline period and have 8 to 23 (inclusive) migraine days in the eDiary screening/baseline period (refer to Section 4.1). To determine eligibility for participants who completed 20 to 27 days of eDiary data, use the following formula to calculate the prorated number of migraine days: (# Migraine Days / # Diary Days completed) * 28 = Prorated Migraine Days.
- 8. No use of opioid-containing products for more than 4 days per month for acute treatment of headache in the 3 months prior to Screening or during the screening/baseline period.
- 9. No treatment of study target muscles using acupuncture, transcutaneous electrical nerve stimulation (TENS), cranial traction, dental splints for headache, or head and/or neck injections of anesthetics/steroids within 4 weeks prior to Screening and throughout the study.

- 10. No anticipated need for botulinum toxin treatment for any reason during the study (other than study treatment).
- 11. No hypertension as defined by sitting systolic blood pressure (BP) > 160 mmHg or sitting diastolic BP > 100 mmHg at Screening. Vital sign measurements that exceed these limits may be repeated only once.
- 12. No known history of significant risk of self-harm based on clinical interview and responses on the C-SSRS, or of harm to others in the investigator's opinion; participants 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 6 months before Screening.
- 13. No known history prior to enrollment of clinically significant medical or surgical conditions or any other reason, including any physical, psychological, or psychiatric condition that in the investigator's opinion would compromise the safety or interfere with the participant's participation in this study, or would make the participant an unsuitable candidate to receive study drug, or would put the participant at risk by participating in the study, including history of or abnormal screening lab or imaging results that, in the investigator's opinion, are indicative of any irreparable cardiac, endocrinologic, hematologic, hepatic, immunologic, infectious, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurologic, and/or other major disease that would preclude administration of atogepant.
- 14. No known history of active varicella or herpes zoster virus infection or any severe viral infection requiring medical attention within 6 weeks before Screening, and no ongoing infection of any kind.
- 15. No active or suspected malignancy or known history of any malignancy within the last 5 years except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.
- 16. No known history of organ transplantation prior to enrollment or plans for transplantation during the trial.
- 17. No known history of clinically significant (per investigator's judgment) drug or alcohol abuse within past 2 years prior to enrollment that, in the investigator's opinion, may interfere with study procedures.
- 18. No known history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class prior to enrollment.
- 19. No known clinically relevant or significant ECG abnormalities (prior to current injury), including ECG with QT interval corrected for heart rate (QTc) using Fredericia's formula (QTcF) > 450 msec (males) or > 470 msec (females).
- 20. No known history of acute hepatitis within 6 months of Screening; or 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.
- 21. No clinically significant laboratory values ***or*** any of the following laboratory values at Screening: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1 × the upper limit of normal (ULN) ***or*** total bilirubin > 1 × ULN (except for participants with a diagnosis of Gilbert's disease) ***or*** serum albumin < 2.8 g/dL (4.06 µmol/L).

Contraception

- 22. No female who **is known to be pregnant, breastfeeding, or considering becoming pregnant** during the study or within 30 days after the last dose of study drug.

Concomitant Medications

- 23. Not known to have received any other investigational product within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.
- 24. No known history of prior use of atogepant prior to participation in this study.
- 25. No concurrent use of any migraine prevention treatment other than BOTOX (required concomitant medication) or topiramate ≤ 100 mg daily (including use of oral gepants [e.g., Nurtec™]) in the 4 weeks prior to screening nor during the screening/baseline period. Topiramate dose must have been stable for at least 3 months and expected to be stable for duration of this study. Participants on topiramate will be limited to 50% of total study enrollment.
- 26. No current use or use within the 6 months (24 weeks) prior to Screening, of mAbs blocking the CGRP pathway (erenumab [Aimovig™], eptinezumab [Vyepti™], fremanezumab [Ajovy™], or galcanezumab [Emgality™]).
- 27. No concurrent use of oral gepants for acute migraine treatment (e.g., Ubrelvy™, Nurtec™) in the 4 weeks prior to screening nor during the screening/baseline period.
- 28. 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 (refer to Section 5.3 of the study protocol and Section 7.1 of the Operations Manual [Appendix F]).
    - 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).

5.2 Contraception Recommendations

Contraception Requirements for Females

Participants must follow the following contraceptive guidelines as specified:

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

- Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 30 IU/L.

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

Females of childbearing potential must avoid pregnancy while taking study drug and for at least 30 days after the last dose of study drug.

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 1 month prior to Screening.
- Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to Screening.
- Bilateral tubal occlusion/ligation, i.e., Essure (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized sexual partner (provided the vasectomized partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial participant).
- Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the participant (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Contraception Requirements for Males

For males who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: postbilateral vasectomy, barrier contraception, or sexual abstinence. Contraception should be used while taking study drug and for at least 30 days after the last dose of study drug.

Male participants must also refrain from donating sperm during the course of the study for at least 30 days after the last dose of study drug.

5.3 Prohibited Medications and Therapy

- Strong/moderate CYP3A4 inducers, including but not limited to: barbiturates (e.g., phenobarbital and primidone), systemic (oral/intravenous [IV]) glucocorticoids (e.g., methylprednisolone, prednisolone, prednisone), nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, and St. John's Wort.
- Usage of opioids > 4 days/month in the 3 months prior to Screening, or during the screening/baseline period.

- Strong CYP3A4 inhibitors, including but not limited to: systemic (oral/IV) itraconazole, ketoconazole, clarithromycin, telithromycin, nefazodone, and HIV protease inhibitors.
- Oral medications with demonstrated efficacy for the prevention of migraine (e.g., amitriptyline, propranolol).
- Use of oral gepants (e.g., Ubrelvy™, Nurtec™) for acute or preventive migraine treatment.
- Injectable mAbs blocking the CGRP pathway (e.g., Aimovig™, Emgality™, Ajovy®, Vyepti™).
- New use of cannabinoids (i.e., marijuana), or cannabidiol (CBD) oil (systemically used) during study.
- Current use of ***any*** botulinum toxin (any serotype, therapeutic or cosmetic), regardless of location apart from BOTOX for migraine treatment.
- 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.
- A non-exhaustive list of prohibited medications can be found in the Operations Manual, Section 7.1 (Appendix F).

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded from 4 weeks prior to study drug administration through the post-treatment visit (Week 28).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with atogepant or with BOTOX can be located in the atogepant Investigator's Brochure and the BOTOX USPI.

Participants must be able to safely discontinue any prohibited medications 5 half-lives or 4 weeks prior to initial study drug administration. Participants must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

For the acute treatment of migraine, the following medications are allowed during the study:

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

5.5 Withdrawal of Participants and Discontinuation of Study

A participant 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 participant.
- The participant requests withdrawal from the study.
- Eligibility criteria violation was noted after the participant started study drug and continuation of the study drug would place the participant at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the participant at risk.
- The participant becomes pregnant while on study drug.
- Participant is significantly noncompliant with study procedures, which would put the participant at risk for continued participation in the trial.

A subject must be permanently discontinued from the study if any of the following criteria are met:

- The subject experiences any serious AE of hypersensitivity or anaphylactic reaction.
- The subject experiences a nonserious AE of hypersensitivity unless there is clear alternative etiology.

For participants to be considered lost to follow-up, reasonable attempts must be made to obtain information on the participant's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the participant'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 Participant Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, participants who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless participants have decided to discontinue the study participation entirely (withdrawal of informed consent). Participants should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a participant prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as

possible, preferably within 2 weeks. In addition, if participant is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

In the event a participant withdraws consent from the clinical study, biomarker research will continue unless the participant explicitly requests analysis to be stopped. When AbbVie is informed the participant has withdrawn and no longer wishes biomarker samples research to continue, samples will not be analyzed and no new biomarker analysis data will be collected for the withdrawn participant or added to the existing data or database(s). A participant 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 participant withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Atogepant manufactured by AbbVie will be taken orally with or without food once daily (QD) beginning on Day 1 and should be taken at approximately the same time each day. If participants 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.

Participant dosing will be recorded on the eCRF. The study site personnel will document compliance.

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

Atogepant will be packaged in bottles 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 participant via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the participant's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to participants. Study drug will only be used for the conduct of this study.

5.8 Randomization/Drug Assignment

Not applicable.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study participants. 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 Committees

An external DMC composed of clinicians and a statistician 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 participants, assessing the safety of the interventions during the trial, as well as for monitoring the integrity and interpretability of the trial. The DMC will provide recommendations to the sponsor regarding ongoing trial conduct or modifications to the trial as described in a separate DMC charter.

An external statistical data analysis center (SDAC) is responsible for performing the analyses described in the DMC charter as well as additional analyses requested by the DMC and facilitating interpretation and answering questions that arise before, during or after DMC review.

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

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 communications.

The atogepant HEAC will monitor events of post-treatment elevations of ALT and/or AST ≥ 3 × ULN 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 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 participant or clinical investigation participant 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, meets protocol-specific criteria, and/or if the investigator considers them to be AEs.

The investigators will monitor each participant 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)**	Major adverse cardiovascular events (MACE) eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE **A hepatic-related SAE** **ALT/AST ≥ 3 × ULN or** **ALT/AST ≥ 3 × ULN with a total bilirubin ≥ 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 Participant	An event that results in the death of a participant.
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 participant'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 participant. 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 participant and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of participant, 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 along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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 participant. In addition, study procedure-related serious and nonserious AEs will be collected from the time the participant signs the study-specific informed consent.

Adverse Events of Special Interest

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

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

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 participant.
Moderate	The AE causes the participant discomfort and interrupts the participant's usual activities.
Severe	The AE causes considerable interference with the participant'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 participant must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Participants who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study participant, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a participant'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 participant'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 & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on key 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 mITT population includes all participants who receive at least 1 dose of atogepant study drug, have an evaluable baseline period of eDiary data, and have at least 1 evaluable postbaseline 4-week period of eDiary data during the open-label treatment period. The mITT population will be used for all efficacy analyses.

The safety population consists of all participants who received at least 1 dose of atogepant study drug. The safety population will be used for all baseline and safety analyses.

7.3 Statistical Analyses for Efficacy

Unless stated otherwise, all analyses on efficacy variables will be performed with the mITT population. For analysis purposes, four weeks (28 days) will be considered as one month. For monthly endpoints, baseline is defined as assessments during the last 28 days of the screening/baseline period when the eDiary is collected. For efficacy endpoints that are assessed at clinical visits, baseline is defined as the last non-missing efficacy assessment before the first dose of atogepant.

The responders are defined as subjects with ≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, and 100% reduction compared to baseline in mean monthly migraine days across Weeks 1 to 12, Weeks 13 to 24, and for each 4-week interval. They will be summarized using descriptive statistics.

Unless stated otherwise, 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 the baseline value and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-participant repeated measurements. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. The analysis will be performed based on all post-baseline values using only the observed cases without imputation of missing values. Nominal p-values will be determined for the change from baseline efficacy endpoints.

Summary statistics will be provided for the proportion of responders for each monthly period.

7.4 Statistical Analyses for Safety

The 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 atogepant study drug will be used as the baseline for all analyses of that safety parameter.

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

7.5 Interim Analysis

No interim analysis will be performed.

7.6 Overall Type I Error Control

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

7.7 Sample Size Determination

The study was powered empirically to include approximately 75 participants. An estimated early termination rate of 20% will allow for 60 participants to complete the 6-month study. Seventy-five participants provide 95% probability to detect at least 1 occurrence of an AE with an incidence of ≥ 4%. The precision (half width of 95% confidence interval) of the estimate of change from baseline in monthly migraine days will be approximately 1.8 assuming an SD of 7.0 with an effective sample size of 60 participants.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant 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 participant 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 Participant Confidentiality

To protect participants' confidentiality, all participants 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 participants 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 participant 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 COMPLETION OF THE STUDY

The end-of-study is defined as the date of end of study participation by the last participant in the study.

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. Melo-Carrillo A, Strassman AM, Schain AJ, Adams AM, Brin MF, Burstein R. Combined onabotulinumtoxinA/atogepant treatment blocks activation/sensitization of high-threshold and wide-dynamic range neurons. Cephalalgia. 2021;41(1):17-32.

4. Agostoni EC, Barbanti P, Calabresi P, Colombo B, Cortelli P, Frediani F, et al. Current and emerging evidence-based treatment options in chronic migraine: a narrative review. J Headache Pain. 2019;20(1):92.

5. Lipton RB, Bigal ME, Ashina S, Burstein R, Silberstein S, Reed ML, et al. Cutaneous allodynia in the migraine population. Ann Neurol. 2008;63(2):148-58.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
AIM-D	Activity Impairment in Migraine - Diary
ALT	alanine aminotransferase
ASC-12	Allodynia Symptom Checklist 12
AST	aspartate aminotransferase
BP	blood pressure
CBD	cannabidiol
CGRP	calcitonin gene-related peptide
CM	chronic migraine
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
FDA	Food and Drug Administration
FFA	free fatty acids
FSH	follicle-stimulating hormone
GAD-7	Generalized Anxiety Disorder-7
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide 1
HbA1c	Hemoglobin A1c
HDL	high-density lipoprotein
HEAC	Hepatic Event Adjudication Committee
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICHD-3	International Classification of Headache Disorders 3rd edition
IEC	Independent Ethics Committee

IHS	International Headache Society
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LDL	low-density lipoprotein
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
mITT	modified intention-to-treat
MMRM	mixed-effect model for repeated measures
mRNA	messenger ribonucleic acid
MSQ v2.1	Migraine-Specific Quality of Life Questionnaire, version 2.1
NEFA	non-esterified fatty acids
NMSC	non-melanoma skin cancer
NSAIDs	nonsteroidal anti-inflammatory drugs
PCR	polymerase chain reaction
PD	premature discontinuation
PGIC	Patient Global Impression of Change
PHQ-9	Patient Health Questionnaire
PROMIS	Patient-Reported Outcomes Measurement Information System
PSSM	Patient Satisfaction with Study Medications
QD	once a day
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SDAC	Statistical Data Analysis Center
TENS	transcutaneous electrical nerve stimulation
ULN	upper limit of normal
US	United States
USPI	United States package insert
VLDL	very low-density lipoprotein
WPAI:MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine v2.0

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M22-418: A Phase 3 Multicenter 24-Week Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of Atogepant When Added to OnabotulinumtoxinA (BOTOX) for the Preventive Treatment of Chronic Migraine

Protocol Date: 22 August 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 participant from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all participants, 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, all changes in the research activity and all unanticipated problems involving risks to human participants or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
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
PPD		Statistics Clinical Development - CNS

APPENDIX D. ACTIVITY SCHEDULE

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

Study Activities Table

	Screening		BL	Treatment Period						Follow Up
	Visit 1	Visit 1a	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 or 4-Week Post Early Termination Visit
Activity	Week -12 to Week -4	Day -28/ Week -4	Day 1/ Week 0	Day 29/ Week 4	Day 57/ Week 8	Day 85/ Week 12	Day 113/ Week 16	Day 141/ Week 20	Day 169/ Week 24	Day 197/ Week 28
Visit Windows	N/A	Day -35 to Day -28	N/A	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
INTERVIEWS, ASSESSMENTS, & QUESTIONNAIRES										
Informed consent	✓									
Assess inclusion/exclusion criteria	✓	✓	✓							
Collect demographic information	✓									
Collect medical history	✓									
Collect migraine headache history	✓									
Review prior medications (including migraine medication use)	✓	✓	✓							
Review concomitant medications and procedures	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Provide eDiary instructions and training		✓	✓							
Review eDiary data and compliance			✓	✓	✓	✓	✓	✓	✓	
C SSRS	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Allodynia symptom checklist (ASC 12)			✓							
PROMIS v2.0 Cognitive Function Abilities Short Form 6a			✓	✓	✓	✓	✓	✓	✓	

	Screening		BL	Treatment Period						Follow Up
	Visit 1	Visit 1a	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 or 4-Week Post Early Termination Visit
Activity	Week -12 to Week -4	Day -28/ Week -4	Day 1/ Week 0	Day 29/ Week 4	Day 57/ Week 8	Day 85/ Week 12	Day 113/ Week 16	Day 141/ Week 20	Day 169/ Week 24	Day 197/ Week 28
Visit Windows	N/A	Day -35 to Day -28	N/A	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
MSQ v2.1 (Migraine Specific QoL questionnaire, version 2.1)			✓	✓	✓	✓	✓	✓	✓	
PHQ 9 (Patient Health Questionnaire 9)			✓	✓	✓	✓	✓	✓	✓	
GAD 7 (Generalized Anxiety Disorder 7)			✓	✓	✓	✓	✓	✓	✓	
WPAI:MIGRAINE (Work Productivity and Activity Impairment:Migraine v2.0)			✓	✓	✓	✓	✓	✓	✓	
PSSM (Patient Satisfaction with Study Medications)				✓	✓	✓	✓	✓	✓	
PGIC (Patient Global Impression of Change)				✓	✓	✓	✓	✓	✓	
Complete headache assessments via eDiary daily		✓	✓							
AIM D (Activity Impairment in Migraine Diary)		✓	✓							
eDiary return visit									✓	
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
LOCAL LABS & EXAMS										
ECG			✓						✓	
Collect vital sign measurements (see Operations Manual for details)	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Perform physical examination		✓							✓	
Urine pregnancy test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	Screening		BL	Treatment Period						Follow Up
	Visit 1	Visit 1a	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 or 4-Week Post Early Termination Visit
Activity	Week -12 to Week -4	Day -28/ Week -4	Day 1/ Week 0	Day 29/ Week 4	Day 57/ Week 8	Day 85/ Week 12	Day 113/ Week 16	Day 141/ Week 20	Day 169/ Week 24	Day 197/ Week 28
Visit Windows	N/A	Day -35 to Day -28	N/A	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
CENTRAL LABS										
Collect clinical laboratory samples		✓	✓	✓	✓	✓	✓	✓	✓	
Lipid profile, marker of inflammation, adipokine hormones, HbA1c			✓						✓	
Optional blood samples for genomics			✓							
Optional biomarker collection for CGRP (saliva and plasma)			✓			✓			✓	
Urine drug and alcohol screen		✓								
TREATMENT										
Atogepant dosing (daily until Visit 8)			✓							
Dispense study drug			✓	✓	✓	✓	✓	✓		
Administer BOTOX injection (concomitant medication), ± 7 days from Visits 2, 5 and 8 dates			✓ (±7 days)			✓ (±7 days)			✓ (±7 days)	

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	22 November 2021
Version 2.0	10 March 2022
Version 3.0	12 May 2022
Version 4.0	14 December 2022
Version 5.0	12 December 2023

The purpose of this amendment is to add information on a newly identified risk of hypersensitivity and anaphylactic reactions with the use of atogepant and update and/or correct verbiage for study conduct:

- Section 2.2 Added description of hypersensitivity reactions and anaphylaxis to the discussion of benefits and risks to subjects.
- Section 5.5 Added study discontinuation criteria for nonserious hypersensitivity and serious hypersensitivity.

APPENDIX F. OPERATIONS MANUAL

abbvie

Operations Manual for Clinical Study Protocol M22-418

Chronic Migraine: Open-Label Atogepant When Added to BOTOX

SPONSOR:	AbbVie Inc	ABBVIE INVESTIGATIONAL PRODUCT:	Atogepant

FULL TITLE: A Phase 3 Multicenter 24-Week Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of Atogepant When Added to OnabotulinumtoxinA (BOTOX) for the Preventive Treatment of Chronic Migraine

1 CONTACTS

Sponsor/ Emergency Medical Contact	Jonathan Smith, MD AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064 **EMERGENCY 24-hour Number:** **+1 (973) 784-6402**	Office: +1 (847) 935-2938 Mobile: +1 (224) 423-3001 Fax: +1 (847) 937-0745 Email: jonathan.h.smith@abbvie.com
Sponsor Primary Contact	Kimberly Pfleeger, PhD AbbVie Dept. R48S, Bldg. AP32-1 1 North Waukegan Road North Chicago, IL 60064	Office: +1 (847) 937-9205 Mobile: +1 (224) 430-2497 Email: kimberly.pfleeger@abbvie.com **EMERGENCY 24-hour Number:** **+1 (973)-784-6402**
Safety Concerns	Neuroscience Safety Team 1 North Waukegan Road North Chicago, IL 60064	Toll Free: +1 (833) 942-2226 Email: SafetyManagement_Neuroscience@abbvie.com
SAE Reporting outside of EDC	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 806-2062 Backup +1 (847) 935-2844
Certified Clinical Lab	Labcorp Central Laboratory Services 8211 SciCor Drive Indianapolis, IN 46214	Phone: +1 (248) 727-1118 +1 (800) 462-8885 (toll free) Fax: +1 (317) 616-2362
Biomarker Sample Lab	AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064	Email: bpm@abbvie.com
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abbvie

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2 PROTOCOL ACTIVITIES BY VISIT

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

VISIT 1 (Week -12 to Week -4) – SCREENING:

INTERVIEW	• Informed consent • Assess inclusion/exclusion criteria • Collect demographic information • Collect medical history • Collect migraine headache history	• Review prior medications (including migraine medication use) • Review concomitant medications and procedures • Adverse events
PRO	• Columbia-Suicide Severity Rating Scale (C-SSRS)	
EXAM	• Collect vital sign measurements (vital sign measurements: sitting blood pressure [BP] and pulse rate, respiratory rate, temperature, weight, and at Screening only, height)	
LOCAL LAB	• Urine pregnancy test	

NOTES: All screening procedures must be performed on site.

Screening may be split into two Visits (Visit 1 and Visit 1a). Visit 1 may occur prior to Visit 1a based on cycle time of concomitant BOTOX injection.

If screening Visits 1 and 1a are performed separately, then screening assessments should be performed at the study visits specified in Appendix D of the study protocol.

If screening Visits 1 and 1a are performed on the same day, then the duplicate screening assessments should only be performed once.

Visit 1a (Day -35 to Day -28) – SCREENING:

INTERVIEW	• Assess inclusion/exclusion criteria • Review prior medications (including migraine medication use)	• Review concomitant medications and procedures • Adverse events
PRO	• Provide eDiary instructions and training • C-SSRS	• Complete headache assessments via eDiary (daily) • Activity Impairment in Migraine-Diary (AIM-D)
EXAM	• Collect vital sign measurements (vital sign measurements: sitting blood pressure [BP] and pulse rate, respiratory rate, temperature, weight, and at Screening only, height)	• Physical examination
LOCAL LAB	• Urine pregnancy test	
CENTRAL LAB	• Collect clinical laboratory samples	• Urine drug and alcohol screening

NOTES: All screening procedures must be performed on site.

Screening may be split into two Visits (Visit 1 and Visit 1a). Visit 1 may occur prior to Visit 1a based on cycle time of concomitant BOTOX injection.

If screening Visits 1 and 1a are performed separately, then screening assessments should be performed at the study visits specified in Appendix D of the study protocol.

If screening Visits 1 and 1a are performed on the same day, then the duplicate screening assessments should only be performed once.

The participant should begin using the handheld e-Diary as soon as they receive it. The participant will take the eDiary home and use it as instructed. If it is subsequently determined that the participant has failed entry criteria, the eDiary should be returned to the site.

VISIT 2 - DAY 1:

INTERVIEW	• Assess inclusion/exclusion criteria • Review prior medications (including migraine medication use)	• Review concomitant medications and procedures • Adverse events
PRO	• Provide eDiary instructions and training • Review eDiary data and compliance • C-SSRS • Allodynia symptom checklist (ASC-12) • PROMIS v2.0 Cognitive Function Abilities Short-Form 6a • Migraine-specific QoL Questionnaire, version 2.1 (MSQ v2.1)	• Patient Health Questionnaire (PHQ-9) • Generalized Anxiety Disorder-7 (GAD-7) • Work Productivity and Activity Impairment: Migraine v2.0 (WPAI:MIGRAINE) • Complete headache assessments via eDiary (daily) • AIM-D
EXAM	• Electrocardiogram (ECG)	• Collect vital sign measurements (vital sign measurements: sitting BP and pulse rate, respiratory rate, temperature, weight)
LAB	• Urine pregnancy test	
CENTRAL LAB	• Collect clinical laboratory samples • Optional blood samples for genomics	• Lipid profile, marker of inflammation, adipokine hormones, HbA1c • Optional biomarker collection for CGRP (saliva and plasma)
TREATMENT	• Dispense study drug	• Atogepant dosing (daily until Visit 8) • Administer BOTOX injection (concomitant medication), ± 7 days

NOTES: All Day 1 procedures must be performed on site.

VISIT 3 - WEEK 4:

INTERVIEW	• Review concomitant medications and procedures	• Adverse events
PRO	• Review eDiary data and compliance • C-SSRS • PROMIS v2.0 Cognitive Function Abilities Short-Form 6a • MSQ v2.1 • PHQ-9	• GAD-7 • WPAI:MIGRAINE • Patient Satisfaction with Study Medications (PSSM) • Patient Global Impression of Change (PGIC) • Complete headache assessments via eDiary (daily) • AIM-D
EXAM	• Collect vital sign measurements (vital sign measurements: sitting BP and pulse rate, respiratory rate, temperature, weight)	
LAB	• Urine pregnancy test	
CENTRAL LAB	• Collect clinical laboratory samples	
TREATMENT	• Dispense study drug	• Atogepant dosing (daily until Visit 8)

VISIT 4 - WEEK 8:

INTERVIEW	• Review concomitant medications and procedures	• Adverse events
PRO	• Review eDiary data and compliance • C-SSRS • PROMIS v2.0 Cognitive Function Abilities Short-Form 6a • MSQ v2.1 • PHQ-9	• GAD-7 • WPAI:MIGRAINE • PSSM • PGIC • Complete headache assessments via eDiary (daily) • AIM-D
EXAM	• Collect vital sign measurements (vital sign measurements: sitting BP and pulse rate, respiratory rate, temperature, weight)	
LAB	• Urine pregnancy test	
CENTRAL LAB	• Collect clinical laboratory samples	
TREATMENT	• Dispense study drug	• Atogepant dosing (daily until Visit 8)

VISIT 5 - WEEK 12:

INTERVIEW	• Review concomitant medications and procedures	• Adverse events
PRO	• Review eDiary data and compliance • C-SSRS • PROMIS v2.0 Cognitive Function Abilities Short-Form 6a • MSQ v2.1 • PHQ-9	• GAD-7 • WPAI:MIGRAINE • PSSM • PGIC • Complete headache assessments via eDiary (daily) • AIM-D
EXAM	• Collect vital sign measurements (vital sign measurements: sitting BP and pulse rate, respiratory rate, temperature, weight)	
LAB	• Urine pregnancy test	
CENTRAL LAB	• Collect clinical laboratory samples	• Optional biomarker collection for CGRP (saliva and plasma)
TREATMENT	• Dispense study drug	• Atogepant dosing (daily until Visit 8) • Administer BOTOX injection (concomitant medication), ± 7 days

VISIT 6 - WEEK 16:

INTERVIEW	• Review concomitant medications and procedures	• Adverse events
PRO	• Review eDiary data and compliance • C-SSRS • PROMIS v2.0 Cognitive Function Abilities Short-Form 6a • MSQ v2.1 • PHQ-9	• GAD-7 • WPAI:MIGRAINE • PSSM • PGIC • Complete headache assessments via eDiary (daily) • AIM-D
EXAM	• Collect vital sign measurements (vital sign measurements: sitting BP and pulse rate, respiratory rate, temperature, weight)	
LAB	• Urine pregnancy test	
CENTRAL LAB	• Collect clinical laboratory samples	
TREATMENT	• Dispense study drug	• Atogepant dosing (daily until Visit 8)

VISIT 7 - WEEK 20:

INTERVIEW	• Review concomitant medications and procedures	• Adverse events
PRO	• Review eDiary data and compliance • C-SSRS • PROMIS v2.0 Cognitive Function Abilities Short-Form 6a • MSQ v2.1 • PHQ-9	• GAD-7 • WPAI:MIGRAINE • PSSM • PGIC • Complete headache assessments via eDiary (daily) • AIM-D
EXAM	• Collect vital sign measurements (vital sign measurements: sitting BP and pulse rate, respiratory rate, temperature, weight)	
LAB	• Urine pregnancy test	
CENTRAL LAB	• Collect clinical laboratory samples	
TREATMENT	• Dispense study drug	• Atogepant dosing (daily until Visit 8)

VISIT 8 - WEEK 24:

INTERVIEW	• Review concomitant medications and procedures	• Adverse events • eDiary return visit
PRO	• Review eDiary data and compliance • C-SSRS • PROMIS v2.0 Cognitive Function Abilities Short-Form 6a • MSQ v2.1 • PHQ-9	• GAD-7 • WPAI:MIGRAINE • PSSM • PGIC • Complete headache assessments via eDiary (daily) • AIM-D • eDiary return
EXAM	• ECG • Physical examination	• Collect vital sign measurements (vital sign measurements: sitting BP and pulse rate, respiratory rate, temperature, weight)
LAB	• Urine pregnancy test	
CENTRAL LAB	• Collect clinical laboratory samples • Optional biomarker collection for CGRP (saliva and plasma)	• Lipid profile, marker of inflammation, adipokine hormones, HbA1c
TREATMENT	• Completion of atogepant dosing	• Administer BOTOX injection (concomitant medication), ± 7 days

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

Visit 9 or 4-Week Post Early Termination Visit:

INTERVIEW	• Review concomitant medications and procedures	• Adverse events
LAB	• Urine pregnancy test	

NOTES: For remote visits such as Visit 9 (Follow-up or End of Study) and for women of childbearing potential only, a urine pregnancy test must be performed within 48 hours prior to the remote visits. Investigators/site staff will provide participants with FDA-approved urine pregnancy tests and corresponding written instructions to be used at home by participants for the remote study visits. Sites are required to verbally review testing instructions with all participants.

3 STUDY PROCEDURES

3.1 Study Participant Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the participant, the benefits and risks anticipated from participation in the study and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the participant or any medications being discontinued by the participant in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the participant or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the participant and the original will be placed in the participant's medical record. An entry must also be made in the participant's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the participant received a signed copy.

Information regarding benefits for participants and information regarding provisions for treating and/or compensating participants who are harmed because of participation in the study can be found in the informed consent form.

Samples for optional pharmacogenetic analyses or other exploratory analyses will only be collected if the participant has voluntarily signed and dated a separate written consent form for this testing that has been approved by an IRB/IEC, after the nature of the testing has been explained and the participant has had an opportunity to ask questions. The separate written consent may be part of the main consent form. If the participant does not consent to the testing, it will not impact the participant's participation in the study.

3.2 Medical History

A complete medical history including demographics, history of tobacco, alcohol, and drug use will be taken at screening.

3.3 Drug and Alcohol Screen

Participants should have no history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.

Urine specimens will be tested at the screening visit for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed below. Any positive result must be assessed for clinical significance. These analyses will be performed by the certified central laboratory chosen for the study.

- Opiates
- Barbiturates
- Amphetamines
- Cocaine
- Benzodiazepines
- Alcohol
- Phencyclidine
- Methadone

3.4 Adverse Event Assessment

Please refer to Section 4.1.

3.5 Patient-Reported Outcomes

Participants may be asked to complete the self-administered patient-reported outcome (PRO) instrument (when allowed per local regulatory guidelines). Participants should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to participants other than encouragement to complete the tasks. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items. PRO assessments will include:

- Allodynia symptom checklist (ASC-12)
    - Allodynia is characterized by pain provoked by stimulation of the skin that would ordinarily not produce pain. Allodynia is associated with frequency, severity, disability and associated symptoms of migraine and maps to migraine biology. The ASC-12 measures overall allodynia and subtypes. Cutaneous allodynia affects patients with migraine and is associated with frequency, severity, disability and associated symptoms of migraine. ASC-12 includes 12 questions about the frequency of various allodynic symptoms in association with headache attacks. Each item is scored as "0" (i.e., very rarely or does not apply to me), "1" (less than half the time), or "2" (half the time or more).

- Columbia-Suicide Severity Rating Scale (C-SSRS)
  - The C-SSRS is a questionnaire used to assess suicide risk based on responses to series of questions on suicidal ideation and behavior.
- Headache assessments
  - The daily headache diary will collect data on presence of headache, headache duration, headache severity, headache characteristics and symptoms, acute medication use, and non-headache migraine symptoms.
- Activity Impairment in Migraine-Diary (AIM-D)
  - The AIM-D is an 11-item daily diary measure that assesses the impact of migraine and is comprised of two domains that evaluate performance of daily activities (7 items) and physical impairment (4 items). Participants are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities (ie, difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and physical impairment (i.e., difficulty walking, moving body, bending forward, moving head) using the 6-point rating scale: "Not difficult at all," "A little difficult," "Somewhat difficult," "Very difficult," "Extremely difficult," and "I could not do it at all." Three items include a response of "I did not…," for example, "I did not have errands planned." In addition to the 2 domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (i.e., higher disease burden).
- MSQ v2.1 (Migraine-Specific Quality-of-Life Questionnaire [QOL])
  - The MSQ v2.1 is a 14-item questionnaire designed to measure health-related quality of life impairments attributed to migraine over the past 4 weeks. It is divided into 3 domains: Role Function Restrictive (RFR) assesses how migraines limit one's daily social and work-related activities; Role Function Preventive (RFP) assesses how migraines prevent these activities; and the Emotional Function (EF) domain assesses the emotions associated with migraines. Participants respond to items using a 6-point scale ranging from "none of the time" to "all of the time." Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life.
- PHQ-9 (Patient Health Questionnaire-9)
  - The PHQ-9 is a concise, self-administered, validated, screening and diagnostic tool for mental health disorder, which has been field-tested in office practice. The PHQ-9 consists of the 9 diagnostic criteria for depressive disorders in the past 2 weeks from the DSM-IV. Participants are asked to indicate the frequency with which they have been bothered by 9 symptoms of depressive disorders over the previous 2 weeks, on a 4-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 27 (from best to worst). A score of 15 to 19 is considered as moderately severe depression and 20 to 27 as severe depression.

- Work Productivity and Activity Impairment:Migraine (WPAI:MIGRAINE)
    - The WPAI:MIGRAINE will be used to assess work productivity specific to migraine. The measure uses a 1-week recall and contains 6 questions related to work productivity. The WPAI measures both presenteeism and absenteeism. The measure yields 4 scores, expressed as percentage of impairment, each ranging from 0% to 100%: percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to migraine.
- Patient Satisfaction with Study Medication (PSSM)
    - The PSSM is a survey that assesses participants satisfaction with their study medication, using a single item and a 7-point rating scale ranging from extremely satisfied (0) to extremely dissatisfied (6). For this study, it will be worded to assess participant satisfaction with atogepant as addition to BOTOX.
- Patient Global Impression of Change (PGIC)
    - The PGIC is a single-item measure used to measure the participant's impression of overall change in migraine since the first dose of study intervention (atogepant). The measure uses a 7-point rating scale with responses ranging from "very much better" to "very much worse."
- Generalized Anxiety Disorder-7 (GAD-7)
    - GAD-7 is a self-reported 7-item questionnaire for screening and severity measuring of generalized anxiety disorder (GAD) in the past 2 weeks. GAD-7 measures severity of various signs of GAD according to reported response categories with assigned points. The GAD-7 items are: 1) nervousness, 2) inability to stop worrying, 3) excessive worry, 4) restlessness, 5) difficulty in relaxing, 6) easy irritation, and 7) fear of something awful happening. The GAD-7 is scored on a 4-point (0 - 3) scale where 'Not at all'=0, 'Several days'= 1, 'More than half the days'= 2, and 'Nearly every day'= 3. The total GAD-7 score range is 0 - 21 (from 'best to worst'), and a score of 10 or greater indicates a reasonable cut point for identifying cases of GAD. Cut points of 5, 10, and 15 might be interpreted as representing mild, moderate, and severe levels of anxiety on the GAD-7.
- Patient-Reported Outcomes Measurement Information System (PROMIS) v2.0 Cognitive Function Abilities Short-Form 6a
    - The PROMIS Cognitive Function and Cognitive Function Abilities Subset item banks assess patient-perceived cognitive deficits. Facets include mental acuity, concentration, verbal and nonverbal memory, verbal fluency, and perceived changes in these cognitive functions. Extent to which cognitive impairments interfere with daily functioning, whether other people observe cognitive impairments, and the impact of cognitive dysfunction on quality of life are also assessed.

On Day 1, the PRO instrument should be completed prior to drug administration and prior to any discussion of adverse event (AE) or any review of laboratory findings.

The participant should complete the questionnaire before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the participant's response.

3.6 Pharmacokinetic Sampling

Not applicable.

3.7 Biomarker Research Sampling

Biospecimens (whole blood and saliva) will be collected to support the biomarker research objectives of the study. Please refer to the Study Activities Schedule in Appendix D for the schedule of biomarker research sample collections. 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(s) being studied. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to chronic migraine, and/or in the development of new therapies and diagnostic tests.

DNA/RNA isolated from whole blood may be analyzed to determine specific genetic mutations in patients with migraine and related conditions as well as determine if any of these mutations are associated with response to treatment with BOTOX and/or atogepant (or drugs of this class). In addition, plasma and saliva may be analyzed to determine concentrations of calcitonin gene-related peptide (CGRP) or related neuropeptides to determine if changes in these peptides are related to migraine or associated with response to treatment with BOTOX and/or atogepant (or drugs of this class).

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with measures to protect confidentiality. The samples may be retained while research on atogepant and/or onabotulinumtoxinA (BOTOX) (or drugs of this class) or migraine and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

3.8 12-Lead Electrocardiogram

12 Lead Electrocardiogram (Single Only)

Resting 12-lead electrocardiogram (ECG) will be obtained singly as specified in Appendix D of the study protocol.

The ECG acquired prior to atogepant dosing will serve as the baseline measurements for clinical assessment.

When an ECG is scheduled at the same time as a blood collection, the ECG will be obtained prior to the blood collection. ECGs occurring near meals will take place prior to meals.

ECGs will be acquired after the participant has been in the supine position for at least 5 minutes. Participants will be instructed to remain completely stationary (no talking, laughing, deep breathing,

sleeping, or swallowing) for approximately 10 seconds during the ECG recording. While ECGs are being acquired, participants and staff are prohibited from having devices (e.g., cellular telephones, fans, heaters, etc.) that emit electrical interference in the room.

ECG Safety Review

Each ECG will be evaluated by an appropriately trained investigator at the study site (the "local reader"). The local reading of the ECG will be used by the investigator to determine participant eligibility and safety assessments, including AE determination and management, and decision on whether a participant will be discontinued from the study.

The local reader will sign and date all the ECGs collected in this study and provide a global interpretation for each ECG using the following categories:

- Normal ECG
- Abnormal ECG Not clinically significant (NCS)
- Abnormal ECG Clinically significant (CS)
- Unable to evaluate

All local reader evaluations of ECGs will be entered into the source documents. If the global interpretation (i.e., central reader interpretation) is abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia). The QT interval corrected for heart rate (QTc) using Fridericia's formula (QTcF) will be calculated and documented for all ECGs.

All ECGs will be transmitted to the central ECG reading center regardless of readability. All ECG source documentation will be retained at the study site. The automatic cardiograph reading (i.e., cardiograph-generated measurements and interpretations) will not be collected for analysis.

3.9 Height and Weight

Height will be measured at Screening only. Body weight will be measured at scheduled visits as specified in Section 2.1. The participant will wear lightweight clothing and no shoes during weighing.

3.10 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Section 2.1. Blood pressure and pulse rate should be measured after the participant has been sitting for at least 3 minutes.

Measurements should be assessed consistently throughout the study. Vital sign measurements determined prior to dosing on Day 1 or specify timing will serve as baseline.

3.11 Physical Examination

A complete physical examination, including height (at Screening only) and weight, will be performed at the designated study visits as specified in Section 2.1. The physical examination performed at Screening will serve as the baseline physical examination for the entire study. Physical examination abnormalities noted at screening, prior to the first dose of study drug, should be recorded in the participant's medical history. Any significant physical examination findings after the first dose will be recorded as AEs. All findings, whether related to an AE or part of each participant's medical history, will be captured on the appropriate electronic case report form (eCRF) page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

3.12 Dispense Study Drug

Study drug (atogepant) will be dispensed to participants beginning at Baseline (Day 1) and as specified in Section 2.1. The first dose of atogepant study drug will be administered after all other baseline (Day 1) procedures are completed. At the visits specified in Section 2.1, the site personnel will review and retain a copy of the dosing diary, review returned study drug kits, and empty study drug packaging to verify compliance.

Each site will be responsible for maintaining drug accountability records including product description, manufacturer, and lot numbers for all non-investigational products dispensed by the site.

Study drug (i.e., atogepant tablets) can be taken with or without food.

3.13 Clinical Laboratory Tests

The blood samples for serum chemistry tests will be collected prior to study drug intake (except for the Screening Visit). An 8-hour fast is preferred but not required prior to blood sample collection. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or

- discontinue the participant from the study or require the participant to receive treatment; in this case, the laboratory result will be recorded as an AE.

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry[a]</th><th>Urinalysis</th></tr>
<tr><td>Hematocrit
Hemoglobin
Red blood cell (RBC) count
Red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration)
White blood cell (WBC) count
Neutrophils
Bands
Lymphocytes
Monocytes
Basophils
Eosinophils
Platelet count (estimate not acceptable)</td><td rowspan="4">Blood urea nitrogen (BUN)
Creatinine
Creatine kinase
Total bilirubin
Direct and indirect bilirubin
Gamma-glutamyl transferase (GGT)
Lactate dehydrogenase (LDH)
Alanine aminotransferase (SGPT/ALT)
Aspartate aminotransferase (SGOT/AST)
Alkaline phosphatase
Sodium
Potassium
Calcium
Inorganic phosphorus
Total protein
Glucose
Albumin
Chloride
Bicarbonate/CO_2
Uric acid
Cholesterol
Triglycerides
Estimated glomerular filtration rate (GFR) Calculation</td><td>Specific gravity
Ketones
pH
Protein
Blood
Microscopic examination including red blood cells/high-power field, white blood cells/high-power field, and casts/low-power field[b]
Glucose</td></tr>
<tr><td>Coagulation</td><td rowspan="3">Other Tests</td></tr>
<tr><td>Prothrombin time (PT)/INR</td></tr>
<tr><td>Serology[b]</td></tr>
<tr><td>Hepatitis B surface antigen[b]
Anti-hepatitis C antibody[b]</td><td>Urine human chorionic gonadotropin[c]
Follicle-stimulating hormone[d]
Marker of Inflammation: TNFα – Serum[e]
Marker of Inflammation: C- Reactive Protein (CRP)[e]
Adipokine Hormones: Adiponectin - serum or plasma[e]
Adipokine Hormones: leptin - serum or plasma[e]
Hormones: GLP-1[e]
Glucose metabolism: HbA1c - separate collection[e]
Lipid profile: LDL[e]
Lipid profile: HDL[e]
Lipid profile: VLDL[e]
Lipid profile: NEFAs (FFAs)[e]
Urine drug screen: alcohol, opiates, barbiturates, amphetamines, cocaine, benzodiazepines, alcohol, phencyclidine, methadone</td></tr>
</table>

FFA = free fatty acids; GLP-1 = glucagon-like peptide 1; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; NEFA = non-esterified fatty acids; TNFα = TNF alpha; VLDL = very low-density lipoprotein

a. All chemistries should be performed at all visits.

b. Performed only at screening.

c. Pregnancy testing is not required for females of nonchildbearing potential. Test materials are provided by central lab, but testing is performed locally.

d. Performed only at screening for females aged ≤ 55 years with no menses for 12 months without an alternative medical cause for menopause.

e. Performed only at Visit 2 and Visit 8.

Clinical Laboratory Kits for Incidences of Elevated ALT or AST		
ALT/AST Confirmation	**ALT/AST Investigation**	**ALT/AST Follow-up**
Chemistry Blood urea nitrogen (BUN) Creatinine Creatine kinase Total bilirubin Direct and indirect bilirubin Gamma-glutamyl transferase (GGT) Lactate dehydrogenase (LDH) Alanine aminotransferase (SGPT/ALT) Aspartate aminotransferase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Total protein Glucose Albumin Chloride Bicarbonate/CO_2 Uric acid Cholesterol Triglycerides Estimated glomerular filtration rate (GFR) Calculation **Hematology** Hematocrit Hemoglobin Red blood cell (RBC) count Red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration) White blood cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	**Chemistry**[a] Blood urea nitrogen (BUN) [a] Creatinine[a] Creatine kinase[a] Total bilirubin[a] Direct and indirect bilirubin[a] Gamma-glutamyl transferase (GGT)[a] Lactate dehydrogenase (LDH)[a] Alanine aminotransferase (SGPT/ALT)[a] Aspartate aminotransferase (SGOT/AST)[a] Alkaline phosphatase[a] Sodium[a] Potassium[a] Calcium[a] Inorganic phosphorus[a] Total protein[a] Glucose[a] Albumin[a] Chloride Bicarbonate/CO_2[a] Uric acid[a] Cholesterol[a] Triglycerides[a] Estimated glomerular filtration rate (GFR) Calculation[a] **Serology**[a] Hepatitis B surface antigen[a] **Other Tests** Anti-hepatitis A IgM[a] Anti-hepatitis B Core IgM[a] Hepatitis C antibody[a] Hepatitis C quantitative RNA by PCR[a] Anti-hepatitis E IgM [a] Cytomegalovirus, IgM antibody[a] Epstein-Barr Virus, IgM antibody[a] Ceruloplasmin[b] Serum Iron[b] Alpha-Fetoprotein[b] Serum Electrophoresis[b] Antinuclear antibody (ANA) [b] Anti-liver – Kidney microsomal antibody[b] Anti-Soluble liver antigen[b] Anti-Mitochondrial antibody[b] Mitochondrial antibodies[b] Serum alpha-I anti trypsin[b] IgG-1[b]	**Chemistry** Blood urea nitrogen (BUN) Creatinine Creatine kinase Total bilirubin Direct and indirect bilirubin Gamma-glutamyl transferase (GGT) Lactate dehydrogenase (LDH) Alanine aminotransferase (SGPT/ALT) Aspartate aminotransferase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Total protein Glucose Albumin Chloride Bicarbonate/CO_2 Uric acid Cholesterol Triglycerides Estimated glomerular filtration rate (GFR) Calculation

Clinical Laboratory Kits for Incidences of Elevated ALT or AST		
ALT/AST Confirmation	**ALT/AST Investigation**	**ALT/AST Follow-up**
Coagulation Prothrombin time (PT)/INR **Other Tests** Serum Ethanol Serum Acetaminophen Urine Drugs of Abuse (not including tramadol) Oxycodone Screen Banked Serum Future Testing	Anti-smooth muscle antibody[b] Anti- LC1[b]	

a. Mandatory test.

b. Optional test.

Pregnancy Tests (Urine)

Pregnancy testing should not be performed for postmenopausal women.

A urine pregnancy test will be performed at each visit for all female participants of childbearing potential.

More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

- If the urine pregnancy test at Screening is negative, then dosing with study drug may begin.
- If the Day 1 or post-baseline urine pregnancy test is positive, dosing with study drug must be withheld.
- For remote visits such as Visit 9 (Follow-up or End of Study) and for women of childbearing potential only, a urine pregnancy test must be performed within 48 hours prior to the remote visits. Investigators/site staff will provide participants with FDA-approved urine pregnancy tests and corresponding written instructions to be used at home by participants for the remote study visits. Sites are required to verbally review testing instructions with all participants.

Clinical Chemistry

A minimum 8-hour fast prior to study drug intake is preferred but not required for blood samples to be drawn for chemistry. If a participant does not fast, the nonfasting status will be recorded in study source documentation.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

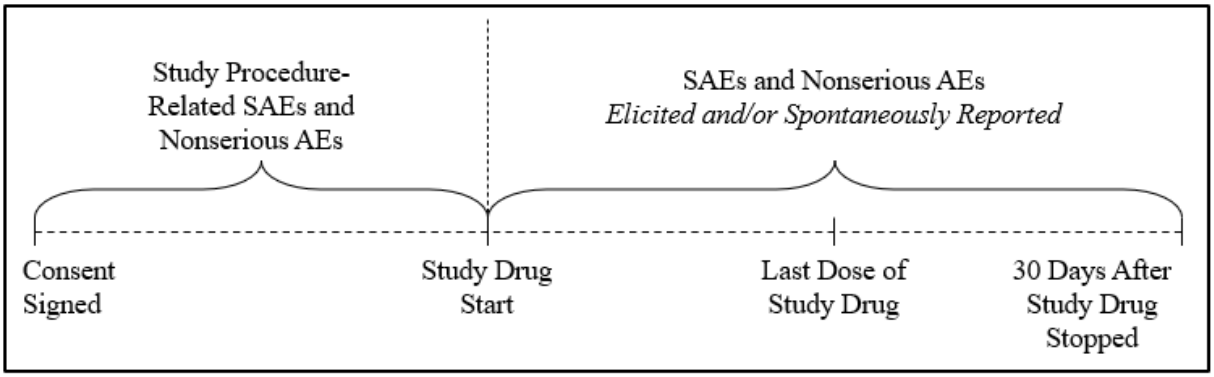
3.14 Participant Withdrawal from Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the participant's condition. Following discontinuation of study drug, the participant will be treated in accordance with the investigator's best clinical judgment, irrespective of whether the participant decides to continue participation in the study.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious and nonserious AEs which could be related to study procedures (e.g., infection at liver biopsy site, done during screening) will be collected from the time the participant signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days or 5 half-lives after the last dose of study drug or study treatment, all nonserious and serious adverse event (SAE) will be collected whether solicited or spontaneously reported by the participant. After 30 days or 5 half-lives 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).



AE = adverse event; SAE = serious adverse event

4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system, RAVE®. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1-(847) 806-2062 Backup: +1-(847) 935-2844

For safety concerns, contact the Neuroscience Safety Team at:

Neuroscience Safety Team
1 North Waukegan Road
North Chicago, Illinois 60064
Toll Free: +1 (833) 942-2226
Email: SafetyManagement_Neuroscience@abbvie.com

For any participant safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
Jonathan Smith, MD
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: +1 (847) 935-2938
Mobile: +1 (224) 423-3001
Fax: +1 (847) 937-0745
Email: jonathan.h.smith@abbvie.com

In emergency situations involving study participants when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the IMP in accordance with global and local guidelines and Appendix A of the Investigator Brochure will

serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

6 STUDY DRUG

6.1 Treatments Administered

The study drug (atogepant) will be dispensed in the form of tablets at the visits listed in Section 2.1. Participants will be instructed to take study drug at the same time every day with or without food.

Study drug must not be dispensed without contacting the interactive response technology (IRT) system. Study drug may only be dispensed to participants enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature Discontinuation visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.2 Packaging and Labeling

Study drug will be supplied in bottles (atogepant).

Each bottle will be labeled as required per country requirements.

The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to participant.

6.3 Storage and Disposition of Study Drug

Atogepant must be stored at room temperature. If the temperature goes out of the specified range of 2°C to 30°C (36°F to 86°F), the excursion should be reported.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for participant use or destroyed on site as appropriate.

Sites are responsible for maintaining the investigational study drug according to the storage conditions specified on the clinical label and monitoring for temperature excursions with the use of a calibrated continuous temperature monitoring device (for example, chart recorders and/or acceptable calibrated min/max thermometers) or continuous monitoring systems. Specific guidance on appropriate temperature monitoring and temperature excursions reporting requirements will be provided separately.

6.4 Method of Assigning Participants to Treatment Groups

This is a nonrandomized, open-label, single-arm study. All eligible participants will receive the same dosage of study drug for the duration of the study.

At the Screening visit, all participants will be assigned a unique participant number using the IRT. For participants who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the participant as a screen failure.

Participants who are enrolled will retain their participant number assigned at the screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.5 Selection and Timing of Dose for Each Participant

All tablets of atogepant will be dosed once daily. All participants should take all doses of atogepant with or without food around the same time each day.

7 APPENDICES

7.1 EXAMPLES OF PROHIBITED MEDICATIONS

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

- Strong OATP1B1 inhibitors e.g., Gemfibrozil (Lopid™)

	Strong/Moderate CYP3A4 Inducers	Strong/Moderate CYP3A4 Inhibitors
Anti-depressants/ Anti-anxiety	Barbiturates: Amobarbital (Amytal™) Aprobarbital (Alurate™) Butalbital (Fiorinal™, Fioricet™) Butabarbital (Busodium™, Butisol™) Mephobarbital (Mebaral™) Pentobarbital (Nembutal™) Phenobarbital (Luminal™, Solfoton™) Secobarbital (Seconal™)	Nefazodone (Serzone™)
Anti-seizure	Carbamazepine (Atretol™, Carbatrol™, Epitol™, Equetro™, Tegretol™) Oxcarbazepine (Trileptal™) Phenytoin (Dilantin™, Phenytek™) Primidone (Myidone™, Mysoline™)	
Diabetes	Pioglitazone (Actos™) Troglitazone (Rezulin™, Resulin™)	
Antiemetic		Aprepitant (Emend™)
Anti-hypertension		Diltiazem (Cardizem™) Verapamil (Calan™, Calan SR™)
Glucocorticoid (systemic)	Betamethasone (Celestone™) Dexamethasone (Baycadron™, DexPak™) Hydrocortisone (Cortef™) Methylprednisolone (Medrol™) Prednisolone (Prelone™) Prednisone (Deltasone™) Triamcinolone (Kenalog™)	
Antibiotics	Rifabutin (Mycobutin™) Rifampicin/Rifampin (Rifadin™, Rifater™, Rimactane™)	Erythromycin (Benzamycin™, EryTab™) Clarithromycin (Biaxin™) Telithromycin (Ketek™)
Anti-fungal		Fluconazole (Diflucan™, Trican™) Itraconazole (Sporanox™) Ketoconazole (Nizoral™)

	Strong/Moderate CYP3A4 Inducers	Strong/Moderate CYP3A4 Inhibitors
Anti-HIV	Efavirenz (Stocrin™, Sustiva™) Nevirapine (Viramune™)	Indinavir (Crixivan™) Nelfinavir (Viracept™) Ritonavir (Norvir™) Saquinavir (Fortovase™, Invirase™)
Immune Suppressant		Cyclosporine - Oral/IV only (Neoral™, Sandimmune™)
Others	St. John's wort Enzalutamide (Xtandi™) Modafinil (Provigil™) Armodafinil (Nuvigil™)	Buprenorphine (Cizol™, Subutex™, Suboxone™) Quinine

Drugs with narrow therapeutic margins with potential for CYP drug interactions	Warfarin (Coumadin™) Digoxin (Digitek™, Lanoxin™, Digox™) Cisapride (Prepulsid™, Propulsid™) Pimozide (Orap™)
Drugs with demonstrated efficacy for the prevention of migraine	Valproic acid, sodium valproate, divalproex sodium (Depakote™) Amitriptyline (Elavil™) Nortriptyline (Pamelor™) Metoprolol (Lopressor™, Toprol™) Atenolol (Tenormin™) Nadolol (Corgard™) Propranolol (Inderal™) Timolol (Apo-Timol™) Flunarizine (Sibelium™) Candesartan (Atacand™) Lisinopril (Zestril™, Prinivil™) Desvenlafaxine (Pristiq™) Venlafaxine (Effexor™)

The following medications or treatments are prohibited 6 months prior to Screening and throughout the study:

- Therapeutic or cosmetic botulinum toxin injections (e.g., Dysport®, BOTOX®, Xeomin®, Myobloc®, JeuveauTM) into areas of the head, face, or neck.
- Injectable monoclonal antibodies blocking the CGRP pathway (e.g., Aimovig™, Emgality™, Ajovy®).

Document Approval

Study M22418 - A Phase 3 Multicenter 24-Week Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of Atogepant When Added to OnabotulinumtoxinA (BOTOX) for the Preventive Treatment of Chronic Migraine - Operations Manual for Protocol Version 6-0 - 22Aug2024

Version: 2.0 **Date:** 22-Aug-2024 **Company ID:** 20240822-0900f9f688229f10-2.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	22-Aug-2024 21:15 UTC	Approver - Statistics
	22-Aug-2024 20:11 UTC	Approver

Document Approval

Study M22418 - A Phase 3 Multicenter 24-Week Open-Label Study to Evaluate the Safety, Tolerability, and Efficacy of Atogepant When Added to OnabotulinumtoxinA (BOTOX) for the Preventive Treatment of Chronic Migraine - Protocol Version 6-0 - 22Aug2024

Version: 2.0 **Date:** 22-Aug-2024 **Company ID:** 20240822-0900f9f688229ef4-2.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	22-Aug-2024 21:16 UTC	Approver - Statistics
	22-Aug-2024 20:11 UTC	Approver