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Study ID: 3101-302-002

Title: A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE

Protocol Date: April 24, 2020

ALLERGAN – [redacted]

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A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE

Protocol Number:	3101-302-002
EudraCT Number (if applicable):	
Phase:	3
Name of Study Intervention:	Atogepant
Sponsor:	Allergan Pharmaceuticals International Limited Marlow International The Parkway, Marlow SL7 1YL United Kingdom
US Agent	Allergan Sales, LLC 2525 DuPont Drive Irvine, California USA 92612
Emergency Telephone Number(s):	[redacted]
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Allergan Medical Safety Physician Contact Information:	Refer to the Study Contacts Page
Allergan Signatory:	[redacted]
Original Protocol Date:	22 August 2018
Amendment 1 Date:	14 March 2019
Amendment 2 Date:	April 2020

Refer to the final page of this protocol for electronic signature and date of approval.

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, GCPs and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an IRB, IEC or another group, it will be submitted with a designation that the material is [redacted]
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the study intervention(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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[redacted]

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2 Protocol Summary

Study Compound: Atogepant

Phase: 3

Study Objective:
To evaluate the safety and tolerability of treatment with atogepant 60 mg daily (QD) for the prevention of migraine in participants with episodic migraine (EM) over 52-week duration.

Clinical Hypotheses:
Atogepant 60 mg QD is safe and well tolerated when administered over 52 weeks for the prevention of migraine in participants with EM.

Study Design

Structure: Multicenter, randomized, open-label, 52-week long-term safety study conducted in the United States.
Duration: The study will consist of a 4-week screening and baseline period, a 52-week treatment period, and a safety follow-up period of an additional 4 weeks, for a total duration of 60 weeks.
Study Intervention: Atogepant 60 mg QD
Control: Oral standard of care (SOC) migraine prevention medication
Dosage/Dose Regimen: Atogepant 60 mg QD will be administered for 52 weeks.
Participants randomized to oral SOC migraine prevention medication will be treated with a medication recognized as safe and effective for the prevention of migraine (Evers 2009, Hoffmann 2014, Schürks 2008, Silberstein 2012, Steiner 2007). The selection of this initial migraine preventive medication will be based on investigator judgment in consultation with the participant.
Randomization: Participants will be randomized (5:2) to the following treatment groups: Atogepant 60 mg QD or oral SOC migraine prevention medication.
A minimum of 200 participants randomized to atogepant must be classified as *De Novo* Participants (see definition below under Study Population Characteristics).
Visit Schedule: After the screening and randomization visits, study visits will occur every 4 weeks for the duration of the 52-week study. For participants randomized to the atogepant arm, a safety follow-up visit will occur 4 weeks after the last dose of atogepant. For participants randomized to oral SOC migraine prevention medication a safety follow-up visit will occur 4 weeks after the last visit in the treatment period. There will be 16 scheduled clinic visits. For details, please see Table 1, the Schedule of Visits and Procedures.
This study will consist of 2 groups of participants: *De Novo* Participants and Study CGP-MD-01 Completers (see definition below under Study Population Characteristics).
De Novo Participants and Study CGP-MD-01 Completers will complete all 16 study visits, including the 28-day screening period.

Study Population Characteristics

Number of Participants/Sites: Approximately 700 participants will be randomized (500 participants in the atogepant arm and 200 participants in the oral SOC migraine prevention medication arm) from approximately 115 centers in the United States. Two groups of participants will be eligible to participate in this study.

- ***De Novo* Participants** - Participants who did not participate in any previous study with atogepant who meet the inclusion criteria and do not meet the exclusion criteria may be enrolled in this study (referred to as *De Novo* Participants).

- **Study CGP-MD-01 Completers** - Participants who completed Study CGP-MD-01 (Visit 8) without significant protocol deviations (eg, noncompliance to protocol-required procedures) and who meet the inclusion criteria and do not meet the exclusion criteria (referred to as CGP-MD-01 Completers).

    - For participants who completed Study CGP-MD-01, there will be a time gap from the time of completion of Study CGP-MD-01 to the start of this study. For this reason, participants from Study CGP-MD-01 will need to re-establish study eligibilty. In addition, these participants will have their baseline migraine days re-established during the screening period but this will not be used as an inclusion/exclusion criteria for randomization.

- *Condition/Disease*: Migraine with aura or migraine without aura (ICHD-3 Section 1.1 or Section 1.2; see Section 12.1.1)

Key Inclusion Criteria:

All participants:

- Participant is a candidate to be prescribed at least one of the protocol-defined acceptable oral SOC migraine prevention medications, and the participant is willing to accept SOC treatment.

For *De Novo* Participants only:

- Male or female participants age 18 to 80 years, inclusive, at Visit 1
- At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3 2018)
- Age of the participant at the time of migraine onset < 50 years
- History of 4 to 14 migraine days per month (see Section 6.1.1 for definition) in the 3 months prior to Visit 1 in the investigator's judgment

[redacted]

For CGP-MD-01 Completers only:

- Eligible participants who completed Study CGP-MD-01 (Visit 8) without significant protocol deviations (eg, noncompliance with protocol-required procedures) and who did not experience an AE that, in the investigator's opinion, may indicate an unacceptable safety risk

For *De Novo* Participants and CGP-MD-01 Completers:

- Completed at least 20 out of 28 days in the eDiary during baseline period and is able to read, understand, and complete the study questionnaires and eDiary per investigator's judgment

Key Exclusion Criteria (all participants except where noted otherwise):

- Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018

- Has a current diagnosis of chronic migraine (CM), new daily persistent headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018
- Has ≥ 15 headache days per month (see Section 6.1.2 for the definition of a headache day) on average across the 3 months prior to Visit 1 in the investigator's judgment **(for *De Novo* Participants only)**

[redacted]

- Participants with clinically significant hematologic, endocrine, cardiovascular, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease

Response Measures

Safety—AEs, physical examinations, clinical laboratory determinations, vital sign measurements, ECG parameters, and the Columbia-Suicide Severity Rating Scale (C-SSRS)

[redacted]

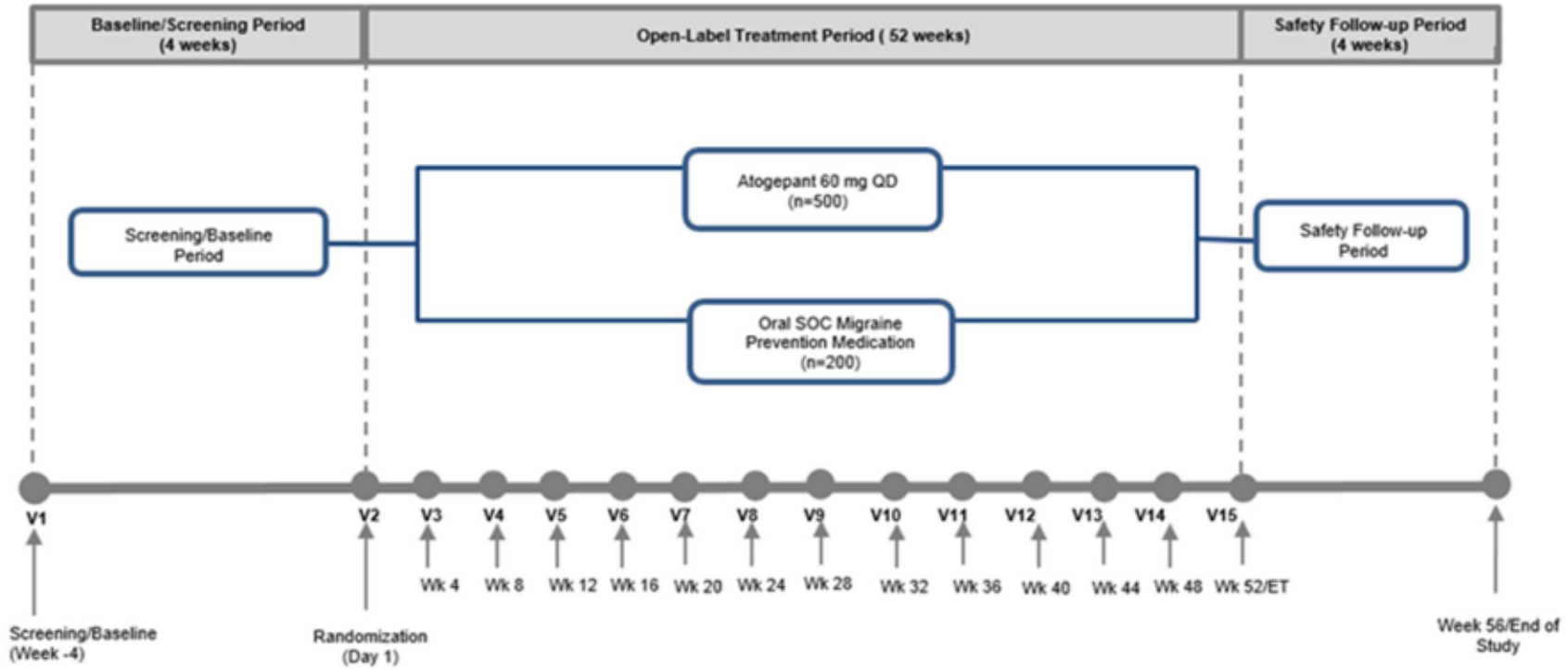
The safety parameters will include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, and the C-SSRS. For each of the clinical laboratory, vital sign, and ECG parameters, the last non-missing safety

assessment before the first dose of treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by the number of participants and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Sample Size Calculation:

This study plans to randomize a total of 700 participants. Participants will be randomized 5:2 to receive atogepant treatment 60 mg QD or oral SOC migraine prevention medication. Based on data from previous studies (Aurora, 2011; Rapoport, 2006), it is estimated that approximately 60% of those participants will complete 6 months of atogepant treatment, and of those, 65% will complete 12 months of atogepant treatment.

Figure 1. Study Diagram



ET = early termination; QD = daily; V = visit.

Table 1. Schedule of Visits and Procedures

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1 Background and Clinical Rationale

1.1 Background

Migraine affects 18% of women and 6% of men in the United States with peak prevalence occurring between the ages of 25 and 55 years. Approximately one-third of patients with migraines have 3 or more migraine attacks per month, and over half report severe impairment or the need for bed rest (Lipton 2007). In the United States alone, work loss due to migraine is estimated to cost ~ $13 billion annually (Hu 1999). Prevalence is similar in Europe, with migraine headache affecting on average 17.6% of women and 8% of men (Stovner 2010). The Global Burden of Disease Survey 2010 (GBD 2010) estimated the global prevalence of migraine to be 14.7%, making it the third most common disease in the world in both males and females. Migraine was ranked seventh highest among specific causes of disability globally (Steiner 2013).

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

Because there are no biological markers for migraine, diagnosis is based on clinical history, examination, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnoses and subsequent treatment. EM is a syndrome diagnosis applied to patients with migraine (with or without aura) who have 1 to 14 headache days per month. CM is a specific ICHD-3 diagnosis applied to a subset of patients with ≥ 15 headache days per month (Katsarava 2012; Olesen 2004; ICHD-3 2018). [redacted]

1.2 Overview of Atogepant

Atogepant is a potent, selective oral CGRP receptor antagonist being developed for migraine prevention. Additional information on non-clinical pharmacology, toxicology, and PK properties of atogepant can be found in the investigator's brochure.

A Phase 2/3 clinical study was conducted, which compared atogepant 10 mg QD, atogepant 30 mg QD, atogepant 30 mg BID, atogepant 60 mg QD and atogepant 60 mg BID to placebo. Overall, all the atogepant doses tested were well tolerated. For the primary efficacy endpoint of change from baseline in mean monthly migraine days across the 12-week treatment period,

all atogepant doses demonstrated a statistically significant reduction compared with placebo in patients with EM.

1.3 Study Rationale

The purpose of this study is to evaluate the safety and tolerability of atogepant 60 mg QD, when taken for 52 weeks for the prevention of EM.

1.4 Rationale for Doses and Dose Regimens Selected

The Phase 3 pivotal studies to evaluate atogepant will test a maximum dose of 60 mg QD. For this reason, the same dose of 60 mg QD has been selected for this study to evaluate the long-term safety and tolerability of atogepant for the prevention of EM.

2 Study Objective and Clinical Hypotheses

2.1 Study Objective

To evaluate the safety and tolerability of treatment with atogepant 60 mg QD when administered over 52 weeks for the prevention of migraine in participants with EM.

2.2 Clinical Hypothesis

Atogepant 60 mg QD is safe and well tolerated when administered over 52 weeks for the prevention of migraine in participants with EM.

3 Study Design

3.1 Structure

This is a multicenter, randomized, open-label, 52-week, long-term safety study conducted in the United States and will enroll approximately 700 participants from approximately 115 sites. Participants will be randomized (5:2) to the following treatment groups: atogepant 60 mg QD or oral SOC migraine prevention medication.

All participants randomized to oral SOC migraine prevention medication will be treated with a medication recognized as safe and effective for the prevention of migraine. The selection of this initial migraine preventive medication is based on investigator judgment in consultation with the participant. For participants who do not tolerate this initial preventive medication or for whom the medication is not sufficiently effective (per investigator judgment), the investigator may choose to:

1. Prescribe an alternative medication from the medicines recognized as safe and effective for the prevention of migraine (Section 5.6.3), *OR*
2. Prescribe an alternative migraine preventive medication not listed in the medicines recognized as safe and effective for the prevention of migraine (eg, riboflavin, carbamazepine, gabapentin), *OR*
3. Not prescribe an alternative migraine preventive medication.

The purpose of the SOC arm is to collect comparative safety data for 52 weeks. Therefore, a participant who does not tolerate the initially selected migraine prevention medication, or for whom the medication is not sufficiently effective (per investigator judgment), may continue in the study regardless of which alternative option (1, 2, or 3) listed above the investigator selects. In addition, after the initial migraine prevention medication trial, participants who are prescribed an alternative medication (options 1 or 2), but do not tolerate the alternative migraine prevention medication, or for whom this medication is not sufficiently effective, may continue in the study regardless of which alternative option (1, 2, or 3) listed above the investigator selects. Furthermore, participants for whom investigators choose not to prescribe an alternative prevention medication may be prescribed an alternative medication (option 1 or 2) at any time during the study. This may be repeated as needed throughout participation in the study per investigator judgment.

The study will consist of a 4-week screening and baseline period, a 52-week treatment period, and a safety follow-up period of 4 weeks. *De Novo* Participants and Study CGP-MD-01 Completers will complete all 16 study visits, including the 28-day screening period.

For clarity, note that the participant must not be randomized until Visit 2 when eligibility has been confirmed.

After the randomization visit, the study visits will occur every 4 weeks for the duration of the 52-week treatment period. Participants will return to the clinic for safety assessments at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks relative to their randomization visit. A safety follow-up visit will occur 4 weeks after the last dose of atogepant 60 mg QD or after the last study visit for the SOC arm. For details, please see Table 1, Schedule of Visits and Procedures.

The primary objective of the study is to assess the safety and tolerability of long-term atogepant treatment. The planned safety assessments include collection of AEs, clinical

laboratory determinations, ECGs, vital sign measurements, physical examinations, and the C-SSRS.

3.2 Data Safety Monitoring Board

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

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

3.3 Adjudication Committee

An Adjudication Charter will be established and will describe the process for the surveillance, monitoring, and adjudication by the Clinical Adjudication Committee of events of post-treatment elevations of ALT and/or AST $\geq 3 \times$ ULN. The purpose of this charter will be to provide a standardized process for the adjudication of the events in order to determine whether the elevation was related to atogepant.

4 Study Population and Entry Criteria

4.1 Number of Participants

Approximately 700 participants will be randomized (5:2) to atogepant 60 mg QD (500 participants) or oral SOC migraine prevention medication (200 participants) at approximately 115 centers in the United States. A minimum of 200 participants randomized to atogepant must be classified as *De Novo* Participants (see definition below).

4.2 Study Population Characteristics

There will be 2 groups of participants eligible to participate in this study.

- *De Novo* Participants: participants with no previous exposure to atogepant and who meet the inclusion criteria and do not meet the exclusion criteria (referred to as *De Novo* Participants)
- Study CGP-MD-01 Completers: participants who completed Study CGP-MD-01 (Visit 8) without significant protocol deviations (eg, noncompliance to

protocol-required procedures) and who meet the inclusion criteria and do not meet the exclusion criteria (referred to as CGP-MD-01 Completers)

- For participants who completed Study CGP-MD-01, there will be a time gap from the time of completion of Study CGP-MD-01 to the start of this study. For this reason, participants from Study CGP-MD-01 will need need to re-establish study eligibilty. In addition, these participants will have their baseline migraine days re-established during the screening period but this will not be used as an inclusion/exclusion criteria for randomization.

4.3 Inclusion Criteria

The following are inclusion criteria for all participants:

1. Written informed consent and participant privacy information (eg, written authorization for use and release of health and research study information) obtained from the participant prior to initiation of any study-specific procedures
2. Participant is a candidate to be prescribed at least one of the protocol-defined acceptable oral SOC migraine prevention medications and the participant is willing to accept SOC treatment
3. Participants must be using a medically acceptable and effective method of birth control during the course of the entire study, as defined in Section 4.5.3

The following are inclusion criteria for De Novo Participants only:

4. Male or female participants aged 18 to 80 years, inclusive, at Visit 1
5. At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3, 2018
6. Age of the participant at the time of migraine onset < 50 years
7. History of 4 to 14 migraine days per month (see Section 6.1.1 for definition) on average in the 3 months prior to Visit 1 in the investigator's judgment

[redacted]

[redacted]

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study for De Novo Participants only:

1. Difficulty distinguishing migraine headaches from tension-type or other headaches
2. Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018
3. Has a current diagnosis of CM, new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018
4. ≥ 15 headache days per month (see Section 6.1.2 for definition of headache day) on average across the 3 months prior to Visit 1 in the investigator's judgment

[redacted]

6. Usage of opioids or barbiturates > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, NSAIDs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline period. For all participants, barbiturates are excluded 30 days prior to screening and during the baseline period. For participants randomized to atogepant, barbiturates are excluded through the duration of the study as well (see Section 4.5.2).

The following are criteria for exclusion from participating in the study for all participants unless noted otherwise:

[redacted]

8. Female participant is pregnant, planning to become pregnant during the course of the study, or currently lactating. Women of childbearing potential must have a negative urine pregnancy test at Visit 1 and Visit 2

[redacted]

12. Hypertension as defined by sitting systolic BP > 160 mm Hg or sitting diastolic BP > 100 mm Hg at Visits 1 or Visit 2. Vital sign measurements that exceed these limits may be repeated only once

[redacted]

14. Any clinically significant hematologic, endocrine, pulmonary, renal, hepatic, GI, or neurologic disease

[redacted]

20. History of any GI prior procedures or GI conditions (eg, diarrhea syndromes, inflammatory bowel disease) that may affect the absorption or metabolism of

atogepant; participants with prior gastric bariatric interventions (eg, Lap Band) which have been reversed are not excluded

21. At Visit 1, a user of recreational or illicit drugs or has had a history within the past year of drug or alcohol abuse or dependence

[redacted]

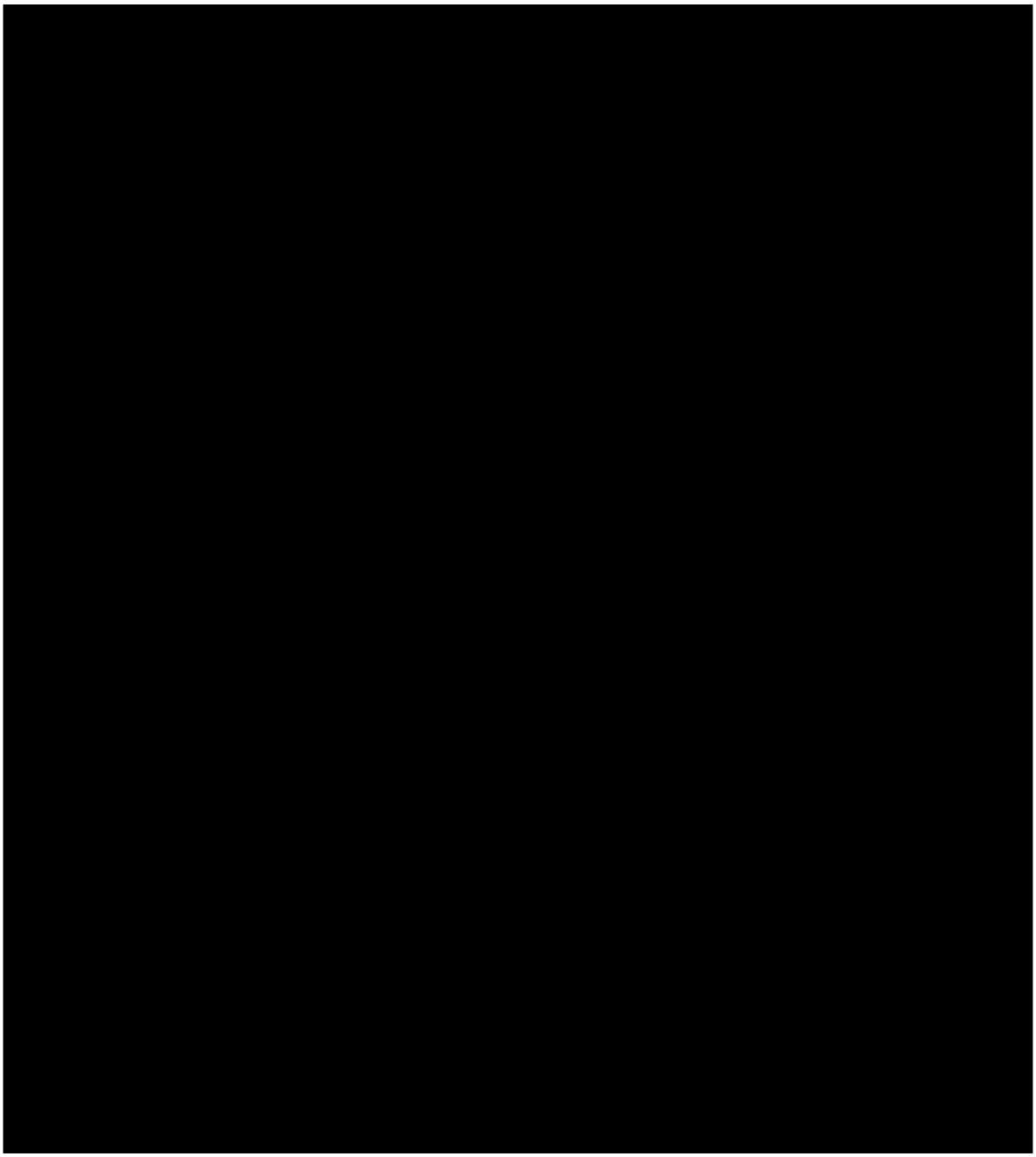
4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

[redacted]

4.5.2 Prohibited Medications/Treatments

[redacted]



4.5.3 Definition of Women of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

For purposes of this study, women will be considered of childbearing potential unless they are naturally postmenopausal (ie, no menses for 2 years) or permanently sterilized (ie, bilateral tubal ligation, bilateral tubal occlusion [eg, Essure® placement with HSG confirmation], bilateral salpingectomy, bilateral oophorectomy, or hysterectomy). For women

of child-bearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered highly effective:

- Combined (estrogen and progestogen containing) hormonal contraception such as oral, intravaginal, or transdermal (ie, pill, vaginal ring, patch)
- Progestogen-only hormonal contraception (with inhibition of ovulation) that are oral, injectable, or implantable
- IUD or IUS
- Vasectomized partner (provided that the partner is the sole sexual partner of study participant and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse for the duration of the study)

Acceptable birth control methods which may not be considered as highly effective:

- Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action)
- Male or female condom with or without spermicide (female and male condoms should not be used together)
- Cap, diaphragm or sponge with spermicide
- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

For males who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: post-bilateral vasectomy, barrier contraception or sexual abstinence. Male participants must also refrain from donating sperm during the course of the study.

The investigator and each participant will determine the appropriate method of contraception for the participant during participation in the study.

If a woman becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the participant will be discontinued from the study after appropriate safety follow-up. The investigator will (1) notify the participant's physician that the participant was being treated with atogepant or the SOC migraine prevention medication and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

4.5.4 Special Diet or Activities

Participants should refrain from consuming grapefruit or grapefruit juice from the time the ICF is signed until completion of the study. Participants should also refrain from making significant changes to their diet or caffeine intake during the study.

Alcohol intake should be limited to no more than 1 drink per day throughout the study. A drink is defined as a 12-ounce can/bottle of beer, a 4-ounce glass of wine, or 1 ounce of liquor.

4.6 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized to treatment. Rescreening of screen failures is permitted in certain situations. However, participants with clinically significant laboratory values at Visit 1 (including ALT or AST > 1 × ULN, total bilirubin > 1 x ULN or serum albumin < 2.8 g/dL), or those with a positive result on the Visit 1 urine drug screen for recreational (including marijuana regardless of legality) or illicit drugs or non-disclosed concomitant medications, are not allowed to be rescreened.

5 Study Intervention

5.1 Study Intervention and Formulations

Tablets containing atogepant 60 mg (Formulation Numbe[redacted])

5.2 Control Intervention

Allergan will not be providing oral SOC migraine prevention medications. See Section 5.6.2 for details on acceptable oral SOC migraine prevention medications.

5.3 Methods for Masking/Blinding

This is an open-label study.

5.4 Treatment Allocation Ratio

Participants will be randomized to the following 2 arms in a 5:2 ratio:

- Atogepant 60 mg QD (n = 500)
    - Note: A minimum of 200 participants randomized to atogepant must be classified as *De Novo* Participants
- Oral SOC migraine prevention medication (n = 200)

No stratification will be performed.

5.5 Method for Assignment to Treatment Groups/Randomization

Prior to initiation of atogepant or oral SOC migraine prevention medication, each participant who provides informed consent will be assigned a participant number that will serve as the participant identification number on all study documents. CGP-MD-01 Completers will maintain their lead-in study participant identification number.

At randomization (Visit 2), eligible participants will be randomly assigned to 1 of 2 treatment arms in a 5:2 ratio to receive atogepant 60 mg QD or oral SOC migraine prevention medication.

All participants will be centrally assigned to randomized atogepant or oral SOC migraine prevention medication [redacted]

5.6 Treatment Regimen and Dosing

Participants who meet all of the study entry criteria at Visit 2 will be randomized.

5.6.1 Participants Randomized to Atogepant

Only participants randomized to atogepant will be provided with atogepant to be taken on an outpatient basis. Atogepant to be used in this trial is listed in (Table 5–1). Participants will take their first dose of atogepant at the clinic at Visit 2.

Participants will be instructed to take their atogepant at approximately the same time each day. Atogepant will be administered orally for 52 weeks, and participants will be followed for 4 weeks following completion or discontinuation of the atogepant.

Table 5–1. Study Intervention

Drug/Dose	Study Intervention Frequency	Route of Administration
Atogepant 60 mg	QD	Oral

QD = daily.

5.6.2 Participants Randomized to Oral SOC Migraine Prevention Medication

All participants randomized to oral SOC migraine prevention medication will be treated with a medication recognized as safe and effective for the prevention of migraine. The selection of this initial migraine prevention medication is based on investigator judgment in consultation with the participant. [redacted]

[redacted]

At the end of the open-label treatment period, participants do not need to discontinue oral SOC medication. Oral SOC medication may be continued during the safety follow-up period. Alternatively, the investigator may choose to discontinue oral SOC medication.

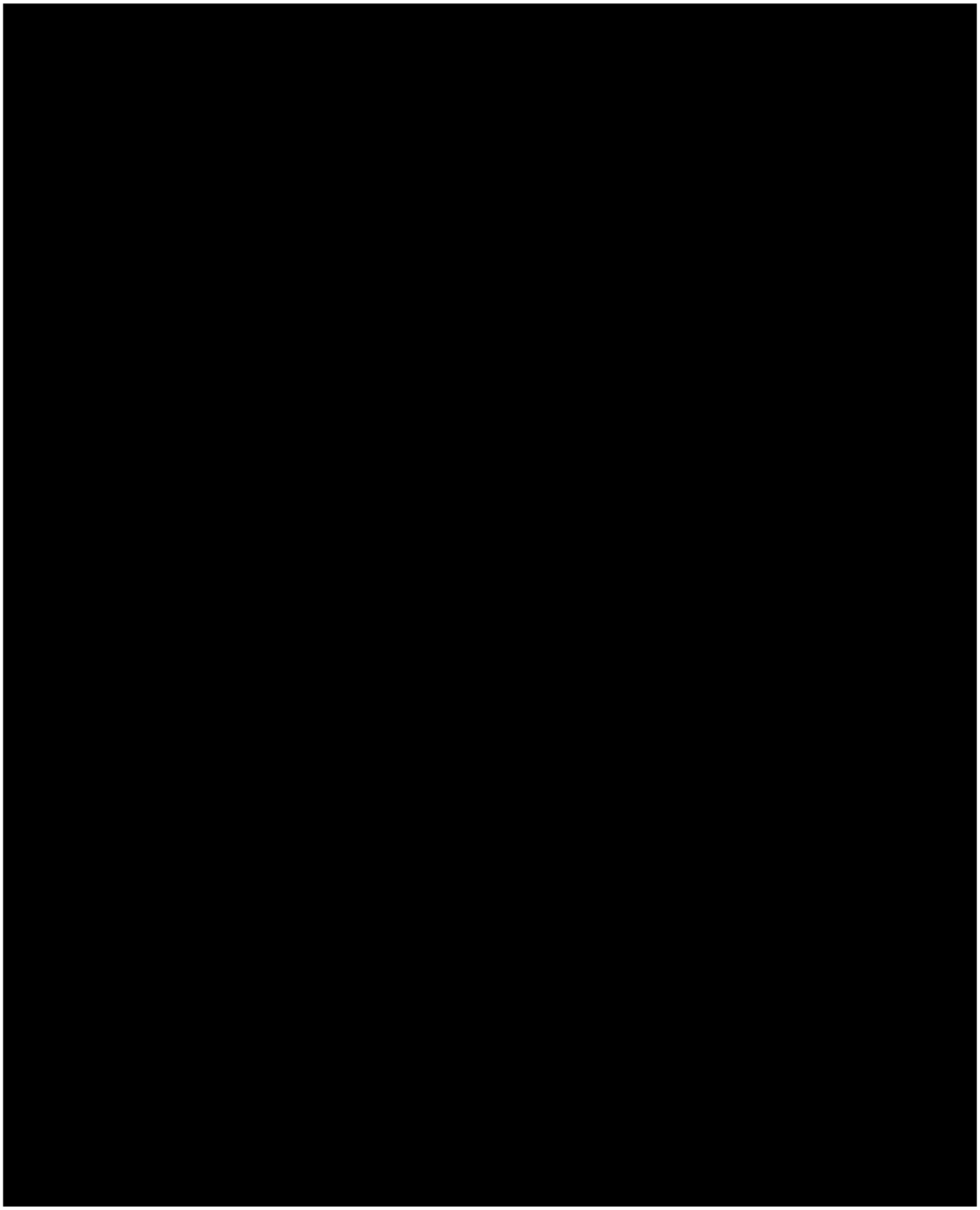
[redacted]

5.7 Storage of Study Intervention

[redacted]

6 Response Measures and Summary of Data Collection Methods

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

6.4 Safety Measures

6.4.1 Adverse Events

Adverse events will be collected from the time of consent through the last visit. For all AEs, the investigator must provide an assessment of the severity, causal relationship to the investigational product, start and stop date, and seriousness of the event (eg, SAE), document all actions taken with regard to the study or control intervention, and detail any other treatment measures taken for the AE. For events noted as SAEs, Allergan must be notified immediately to meet their reporting obligations to appropriate regulatory authorities.

6.4.2 Adverse Events of Special Interest

Selected non-serious and serious adverse events are of special interest and will require immediate reporting, recording and follow-up. The following events will be closely monitored:

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

Reporting requirements for ALT or AST elevations and potential Hy's law cases are outlined in Sections 9.5 and 9.5.1. Responses to the C-SSRS that meet the above criterion will be captured in the eTablet and monitored by Allergan. These AEs or events determined to be SAEs must be reported appropriately via the designated eCRFs and safety forms.

6.4.3 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the visits outlined in Table 1. Hematology, chemistry, INR, and urinalysis will be conducted at these visits.

Serology and the urine drug screen will only be conducted at screening (Visit 1). The investigator will assess the clinical significance of any values outside the reference ranges provided by the central laboratory. Participants with abnormalities judged to be clinically significant, laboratory values that meet exclusionary criteria, or positive results on the urine drug screen at screening (Visit 1) will be excluded from the study. Women of childbearing potential will be required to have a urine pregnancy test at all visits. A positive pregnancy test at Visit 1 or Visit 2 will exclude the participant from the study.

Investigators may also perform unscheduled clinical laboratory determinations at any time for the purpose of participant safety.

Participants are not required to fast overnight before coming in for their appointments.

The clinical laboratory parameters to be measured are shown in Table 6–1.

Table 6–1. Clinical Laboratory Parameters

Category	Parameter
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol. The estimated glomerular filtration rate will be calculated by the central laboratory
Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count
Urinalysis	Urine dipstick for specific gravity, pH, protein, glucose, ketones, bilirubin, and blood; microscopic examination including red blood cells/high-power field, white blood cells/high-power field, and casts/low-power field
Coagulation	INR
Serology	At Visit 1 only: anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti-hepatitis C antibody, anti-hepatitis E IgM antibody
Urine Drug Screen	Screening for drugs of abuse (eg, marijuana, cocaine, phencyclidine, amphetamines, benzodiazepines, barbiturates, opiates) will be conducted using a urine drug screen at Visit 1. Those with a positive result on the Visit 1 urine drug screen for recreational (including marijuana regardless of legality) or illicit drugs or non-disclosed concomitant medications are not allowed to be repeated. For all other positive results, the urine drug screen may be repeated with permission from Allergan; a negative result or an explanation of a positive result due to concomitant medication use (eg, opioids prescribed for migraine pain) will be required for randomization.

IgM = immunoglobulin M; INR = International Normalized Ratio

A central laboratory will be used to evaluate all urine and blood samples, which will be collected, processed, and stored according to the instructions provided by the laboratory.

6.4.4 Vital Signs

Vital sign measurements, including sitting and standing BP, sitting and standing pulse rate, respiratory rate, temperature, weight, and height (at Visit 1 only), will be performed at every visit. Sitting and standing BP and pulse rate will be determined as follows: BP and pulse measurements will be performed after the participant sits quietly for 5 minutes, followed by a second set of measurements taken after the participant stands for at least 3 minutes (but no longer than 10 minutes).

6.4.5 Physical Examination

A complete physical examination will be performed at the visits outlined in Table 1. A professionally trained physician or healthcare professional licensed to perform physical examinations will examine the participant for any detectable abnormalities of the following body systems: general appearance; neck (including thyroid); head, eyes, ears, nose, and throat; lungs; heart/cardiovascular; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; skin; and other. The neurologic examination should be conducted to detect the presence of any significant sensory/motor abnormalities.

6.4.6 Electrocardiograms

A 12-lead ECG will be performed at the visits outlined in Table 1. All ECGs should be performed after the participant has been supine for at least 5 minutes. All ECGs performed will be saved as a source document. ECGs will be transmitted electronically to the central ECG laboratory for analysis according to the instructions provided by the laboratory to be centrally read by a cardiologist. The overall interpretation of the clinical significance of the ECG will be determined by the investigator and recorded in the participant's eCRF.

6.4.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual

or potential lethality is classified for the initial, most lethal, and most recent attempts. The C-SSRS will be completed at all study visits. At screening (Visit 1) for *De Novo* Participants and CGP-MD-01 Completers the C-SSRS will be completed for the participant's lifetime history of suicidal ideation and behavior. At all other visits the C-SSRS will be completed for ideation and behavior since last visit for all participants. The C-SSRS will be completed on the eTablet by the investigator or designee with current and valid training in administering the assessment. A participant should not be released from the study center until the results of C-SSRS are reviewed and it is confirmed that the participant is not considered to be at risk. Participants who reply with "yes" to questions 4 or 5 in the suicidal ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS at Visits 3 through 14 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the ET (Visit 15) and the safety follow-up (Visit 16).

6.5 Other Study Supplies

[redacted]

6.6 Summary of Methods of Data Collection

[redacted]

[redacted]

7 Statistical Procedures

[redacted]

[redacted]

[redacted]

[redacted]

7.3.2 Safety Analyses

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 treatment 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, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

[redacted]

[redacted]

7.5 Sample Size Calculation

This study plans to randomize a total of 700 participants. Participants will be randomized 5:2 to receive atogepant 60 mg QD or oral SOC migraine prevention medication. Based on data from previous studies (Aurora 2011; Rapoport 2006), it is estimated that approximately 60% of those participants will complete 6 months of treatment, and of those, 65% will complete 12 months of treatment.

7.6 Interim Analyses

None.

8 Study Visit Schedule and Procedures

Please see Table 1 for a schematic of the Schedule of Visits and Procedures and Figure 1 for a study visit flowchart.

8.1 Participant Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective participants as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Participant Privacy

The study will be discussed with the participant, and a participant wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The participant must also give authorization, and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each participant that provides informed consent will be assigned a participant identification number that will be used on participant documentation throughout the study. CGP-MD-01 Completers will maintain their lead-in study participant identification number.

The investigator or qualified designee will explain the future biomedical research sub-study consent (*De Novo* Participants only) to the participant and answer all of his/her questions. Participants will sign a separate consent form to participate in the future biomedical research sub-study before performing any procedure related to the sub-study.

8.1.3 Procedure for Duplicate Participant Identification – Verified Clinical Trials

A central vendor will be used to verify participants current and past research study status in order to mitigate safety concerns associated with duplicate enrollment and protocol deviations associated with multiple trial enrollment. The use of this central vendor will be mandatory for US sites. Following proper informed consent and after issuing a participant number, each participant will be checked in the VCT database, indicated in the Schedule of Visits and Procedures (Table 1). Partial identifiers will be utilized. Participants who are identified as verification failures by VCT should not be enrolled without documented approval from Allergan.

8.2 Washout Intervals/Run-in

This study will not include a washout period.

8.3 Procedures for Final Study Entry

At the screening and randomization visits (Visits 1 and 2) participants must meet all of the inclusion criteria and must not meet any of the exclusion criteria. Rescreening of participants may be considered with permission from Allergan. Also, all females of childbearing potential must have negative results on the urine pregnancy test at the screening and randomization visits (Visits 1 and 2, prior to the first administration of atogepant or oral SOC migraine prevention medication).

Prior to randomization, it must be confirmed that the participant had 4 to 14 migraine days per month in the 3 months prior to Visit 1 in the opinion of the investigator (for *De Novo* Participants only), and 4 to 14 migraine days during the 4-week screening/baseline period per the eDiary (for *De Novo* Participants only [see Section 6.1.1 for definition]), and completed the eDiary for at least 20 of the 28 days (for *De Novo* Participants and CGP-MD-01 Completers only).

See Section 5.5 for the method for assignment to treatment groups/randomization.

8.4 Visits and Associated Procedures

There will be 16 scheduled clinic visits: Visit 1 (screening/baseline), Visit 2 (randomization), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 6 (Week 16), Visit 7 (Week 20), Visit 8 (Week 24), Visit 9 (Week 28), Visit 10 (Week 32), Visit 11 (Week 36), Visit 12 (Week 40), Visit 13 (Week 44), Visit 14 (Week 48), Visit 15/ET (Week 52), and Visit 16 (safety follow-up). For details, please see Table 1, Schedule of Visit and Procedures.

8.4.1 Visit 1 (Screening/Baseline) Day -35 to Day -28

[redacted]

8.4.2 Open-label Treatment Period (52 Weeks)

8.4.2.1 Visit 2 (Randomization) Day 1

[redacted]

[redacted]

8.4.2.2 Visits 3 to 14 (Week 4 to 48)

[redacted]

[redacted]

8.4.2.3 Visit 15/Early Termination (Week 52)

[redacted]

[redacted]

8.4.3 Safety Follow-up Period (4 Weeks)

Refer to Section 8.4.3.1.1 and Table 1 for assessments to be conducted remotely due to the COVID-19 pandemic.

8.4.3.1 Visit 16/End of Study (Week 56) Conducted During In-Person Visit (Prior to the COVID-19 Pandemic)

[redacted]

[redacted]

8.4.3.1.1 Visit 16/End of Study (Week 56) Conducted Remotely (Due to the COVID-19 Pandemic)

[redacted]

8.5 Instructions for the Participants

Section 4.5.4 provides diet and activity instructions for participants enrolled in the study.

Participants will be provided with instructions on daily completion of the eDiary. A practice session with a hypothetical scenario should be administered to ensure the participant's comprehension of the questions and the information to be entered. In addition, prohibited medications should be reviewed with the participants. Participants will be instructed to bring their eDiary to each clinic visit and return their atogepant bottle(s), both used and unused.

Participants should be instructed to take atogepant 60 mg QD at approximately the same time each day (approximately 24 hours between doses). For dosing on Day 1 (Visit 2), the first dose is to be taken at the study site. For participants randomized to oral SOC migraine prevention medication, the first dose should be taken on Day 1.

[redacted]

8.6 Unscheduled Visits

Additional examinations and laboratory assessments may be performed as necessary to ensure the safety and well-being of the participants during the study period. Unscheduled visit eCRFs should be completed for each unscheduled visit.

8.7 Compliance with Protocol

All assessments will be conducted at the appropriate visits as outlined in Table 1, and the timing of the visits should occur as close as possible to the day specified. At each visit, the participant will be asked if the participant changed the dose/regimen of any existing concomitant medications or initiated the use of any new concomitant medications since the last visit, to ensure compliance with the protocol.

Atogepant compliance during any period will be closely monitored by counting the number of tablets dispensed and returned. Every effort will be made to collect all unused atogepant.

8.8 Early Discontinuation of Participants

A premature discontinuation will occur when a participant who signed the ICF and has been randomized ceases participation in the study, regardless of circumstances, before completion of the study. Participants can be prematurely discontinued from the study for one of the following reasons:

- AE
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study intervention (ie, atogepant)
- Pregnancy
- Protocol deviation
- Site terminated by Allergan
- Study terminated by Allergan
- Withdrawal by participant

Participants may voluntarily withdraw from the study at any time.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF. All randomized participants who prematurely discontinue from the study, regardless of cause, should be seen for final study assessments. The final assessments will be defined as completion of the evaluations scheduled for Visit 15/ET and Visit 16 (safety follow-up), 4 weeks post the last dose of atogepant or after the last study visit for oral SOC migraine prevention arm.

8.9 Withdrawal Criteria

Women who become pregnant (Section 9.4) and participants who meet atogepant or oral SOC migraine prevention medication discontinuation criteria related to abnormal liver function tests (Section 9.5), and advised not to be rechallenged, will be withdrawn from the study and should refrain from taking atogepant or oral SOC migraine prevention medication. The participant should return to the clinic for ET procedures (Visit 15) and the safety follow-up (Visit 16). Participants who reply with "yes" to questions 4 or 5 in the suicidal ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS at Visits 3 through 14 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the ET (Visit 15) and the safety follow-up (Visit 16).

A participant with a condition and/or a situation that, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study may be withdrawn from treatment.

8.10 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

9 Adverse Events

AEs occurring during the study will be recorded on an AE eCRF. If AEs occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical study participant associated with the use of atogepant or oral SOC migraine prevention medication, whether or not considered

related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of atogepant or oral SOC migraine prevention medication. In addition, during the screening period, AEs will be assessed regardless of the administration of a pharmaceutical product.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to atogepant or study procedures, or that caused the participant to discontinue atogepant or oral SOC migraine prevention medication or study (see Section 8.8).

All AEs from the signing of the ICF until the safety follow-up visit (Visit 16), or 30 days after the last dose of atogepant (or 30 days after the last study visit for the oral SOC migraine prevention medication arm) if the safety follow-up visit is not done, will be collected at the timepoints specified in the Schedule of Visits and Procedures (Table 1), and as observed or reported spontaneously by study participants.

Investigators are not obligated to actively seek AE information after conclusion of the study participation.

AEs will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent has been obtained). At each visit, the investigator will begin by querying for AEs by asking each participant a general, non-directed question such as "How have you been feeling since the last visit?" Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Care will be taken not to introduce bias when detecting AEs and/or SAEs. All reported AEs will be documented on the appropriate eCRF.

9.1.2 Serious Adverse Event

An SAE is any AE occurring at any dose that results in any of the following outcomes:

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Allergan considers all cancer AEs as SAEs. In addition, Allergan considers any abortion (spontaneous or elective) as an SAE.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a participant requires hospitalization is not reportable as an SAE.

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the participant's entry into

the study. If it has not been documented at the time of the participant's entry into the study, then it should be documented as a SAE and reported to Allergan.

9.1.3 Intensity

The intensity assessment for a clinical AE must be completed using the following definitions as guidelines:

Assessment of Intensity	
MILD	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

9.1.4 Assessment of Causality

Assessment of Causality

- The investigator is obligated to assess the relationship between atogepant or oral SOC migraine prevention medication and each occurrence of each AE or SAE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to atogepant administration or oral SOC migraine prevention medication will be considered and investigated.
- The investigator will also consult the investigator's brochure in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Allergan. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Allergan.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.1.5 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs and non-serious AEs of special interest (as defined in Section 6.4.2) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.8).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Allergan to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Prior to database lock, new or updated information will be recorded in the originally completed eCRF. If the event is an SAE, it will also need to be reported on the SAE reporting form. Post database lock, new or updated SAE information will only be reported on the SAE reporting form.

The investigator will submit any updated SAE data to Allergan within 24 hours of receipt of the information.

9.2 Procedures for Reporting Adverse Events

All AEs must be recorded on the appropriate eCRF.

All AEs that are atogepant-related and unexpected (not listed as treatment-related in the current investigator's brochure) must be reported to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities. Any AE that is marked 'ongoing' at the exit visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any SAE occurring during the study period (beginning with informed consent) until the safety follow-up visit (Visit 16) or 30 days after the last dose of atogepant (or 30 days after the last study visit for the SOC arm) if the safety follow-up visit is not done must be immediately reported but no later than 24 hours after learning of an SAE. SAEs must be reported to Allergan as listed on the Allergan Study Contacts Page and recorded on the SAE form. All participants with an SAE must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

9.3.1 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to Allergan of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention (ie, atogepant) under clinical investigation are met.

- Allergan has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention (ie, atogepant) under clinical investigation. Allergan will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and investigators

- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Allergan policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs from Allergan) will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.4 Exposure to Study Intervention During Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of atogepant and oral SOC migraine prevention medication and until the safety follow-up visit (Visit 16) or 30 days after the last dose of atogepant (or 30 days after the last study visit for the oral SOC migraine prevention medication arm) if the safety follow-up visit is not done. Study center personnel must report every pregnancy on the Pregnancy Form (within 24 hours of learning of the pregnancy to the Serious Adverse Event Reporting Fax Numbe[redacted], even if no AE has occurred. The pregnancy must be

followed to term and the outcome reported by completing a follow-up Pregnancy Form. Abnormal pregnancy outcomes (eg, spontaneous or elective abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. For pregnancy related SAEs, in addition to the Pregnancy Form, a separate SAE Form must be filed as described in Section 9.3 with the appropriate serious criterion (eg, hospitalization) indicated.

9.5 ALT or AST Elevations

A treatment-emergent ALT ≥ 3 × ULN and/or AST ≥ 3 × ULN is considered an AESI. [redacted]

All AESIs must be reported to Allergan within 24 hours of the time the investigator becomes aware of the event using the abnormal liver function reporting form and the AE eCRF. All new elements of history, physical examination, diagnostic testing results, and other relevant medical reports are to be reported for each AESI.

If an ALT or AST ≥ 3 × ULN is confirmed, close medical follow-up is required:

[redacted]

Atogepant and oral SOC migraine prevention medication must be discontinued if any of the following criteria are met:

- ALT or AST ≥ 3 × ULN and the participant is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)

- ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN
- ALT or AST ≥ 3 × ULN and INR > 1.5
- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

The participant may be rechallenged with atogepant or oral SOC migraine prevention medication only after consultation with the Allergan Medical Monitor. For participants who are not rechallenged with oral SOC migraine prevention medication, the participant should be discontinued from the study and complete an ET visit and 4-week safety follow-up visit. Participants should receive appropriate follow-up as per standard of care.

The investigator must contact the Allergan Medical Monitor to discuss all cases of confirmed ALT/AST elevation ≥ 3 x ULN. All ALT/AST elevations must be followed until ALT and AST return to < 1.5 x ULN and there is full clinical resolution.

9.5.1 Potential Hy's Law Cases

Sites must report every participant who meets the following potential Hy's law criteria if this occurs within the time the participant signs the ICF until 30 days after the last dose of atogepant or oral SOC migraine prevention medication:

- ALT or AST ≥ 3 x ULN **AND**
- Total bilirubin ≥ 2 x ULN **AND**
- Alkaline phosphatase < 2 x ULN

Study site personnel must report every participant who meets these criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until 30 days after the final protocol-defined study visit or the last known dose of atogepant or oral SOC migraine prevention medication (if the final visit does not occur).

A laboratory alert for possible Hy's law cases will be in place and must notify investigators and Allergan immediately when the above criteria have been met. A possible Hy's law case must be faxed to Allergan on an abnormal liver function reporting form as soon as possible (within 24 hours of learning of the possible Hy's law case) to the SAE/Pregnancy fax number, even if no AE has occurred. If the event is serious, please complete the AESI/SAE

form. The eCRF for possible Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the medical monitor and medical safety physician and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. The participant should return to the study site and be evaluated as soon as possible, preferably within 48 hours from the time the investigator becomes aware of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

10 Administrative Items

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines (eg, the ICH Guideline on GCP).

10.1 Protection of Human Participants

10.1.1 Compliance With Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent is to be obtained from each participant prior to any study-related activities or procedures in the study, and/or from the participant's legally authorized representative.

The following process will be followed:

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study if required by the IRB.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.2 Compliance With IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signatures.

10.2 Financial Disclosure

Investigators and subinvestigators will provide Allergan with sufficient, accurate financial information as requested to allow Allergan to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.3 Changes to the Protocol

The investigator must not implement any deviation from or changes to the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study participants, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.4 Data Protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to Allergan will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Allergan in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Allergan, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.5 Participant Privacy

Written authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each participant prior to enrollment into the study, and/or from the participant's legally authorized representative in accordance with the applicable privacy requirements (eg, HIPAA).

In accordance with HIPAA requirements, additional purposes of this study may include publishing of anonymous participant data from the study.

10.6 Documentation

10.6.1 Source Documents

[redacted]

[redacted]

10.6.2 Case Report Form Completion

[redacted]

10.6.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.6.4 Retention of Documentation

All study related correspondence, participant records, consent forms, participant privacy documentation, records of the distribution and use of all atogepant, and copies of eCRFs should be maintained on file.

[redacted]

10.7 Labeling, Packaging, and Return or Disposal of Study Intervention

[redacted]

10.7.2 Clinical Supply Inventory

[redacted] Atogepant must be dispensed or administered only by an appropriately qualified person to participants in the study. Atogepant is to be used in accordance with the protocol for participants who are under the direct supervision of an investigator.

10.7.3 Return or Disposal of Study Intervention and/or Supplies

[redacted]

10.8 Monitoring by the Sponsor

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit, and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.9 Handling of Biological Specimens

[redacted]

10.10 Publications

Allergan as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.11 Coordinating Investigator

A signatory Coordinating Investigator will be designated prior to the writing of the clinical study report.

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12 Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques

12.1.1 International Classification of Headache Disorders, 3rd Edition

1. Migraine
1.1 Migraine without aura
1.2 Migraine with aura
1.2.1 Migraine with typical aura
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1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
1.2.3.1.4 Familial hemiplegic migraine, other loci
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1.6.1.1 Cyclical vomiting syndrome
1.6.1.2 Abdominal migraine
1.6.2 Benign paroxysmal vertigo
1.6.3 Benign paroxysmal torticollis

Coded elsewhere:

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

General comment

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

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

Introduction

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

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

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

1.1 Migraine without aura

Previously used terms: Common migraine; hemicrania simplex
Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity

and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

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

Notes:

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

Comments: Migraine headache in children and adolescents (aged under 18 years) is more often bilateral than is the case in adults; unilateral pain usually emerges in late adolescence or early adult life. Migraine headache is usually frontotemporal. Occipital headache in *children* is rare and calls for diagnostic caution. A subset of otherwise typical patients have facial location of pain, which is called 'facial migraine' in the literature; there is no evidence that these patients form a separate subgroup of migraine patients. Prodromal symptoms may begin hours or a day or two before the other symptoms of a migraine attack with- out aura. They include various combinations of fatigue, di□culty in concentrating, neck sti□ness, sensitivity to light and/or sound, nausea, blurred vision, yawning and pallor. Postdromal symptoms, most commonly feeling tired or weary, difficulty with concentration and neck stiffness, may follow resolution of the headache, persisting for up to 48 hours; these are less well studied.

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

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

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

Very frequent migraine attacks are distinguished as 1.3 *Chronic migraine*. When there is associated medication overuse, both of the diagnoses 1.3 *Chronic migraine* and 8.2 *Medication-overuse headache* should be applied. 1.1 *Migraine without aura* is the disease most prone to accelerate with frequent use of symptomatic medication. Regional cerebral blood flow imaging shows no changes suggestive of cortical spreading depression (CSD) during attacks of 1.1 *Migraine without aura*, although blood flow changes in the brainstem may occur, as may cortical changes secondary to pain activation. This contrasts with the pathognomonic spreading oligaemia of 1.2 *Migraine with aura*. While the bulk of the literature suggests that CSD does not occur in 1.1 *Migraine without aura*, some recent studies disagree. Furthermore, it has been suggested that glial waves or other cortical phenomena may be involved in 1.1 *Migraine without aura*. The messenger molecules nitric oxide (NO), serotonin (5-hydroxytryptamine; 5-HT) and calcitonin gene-related peptide (CGRP) are involved. While the disease was previously regarded as primarily vascular, the importance of sensitization of pain path- ways, and the possibility that attacks may originate in the

central nervous system, have gained increasing attention over the last decades.

At the same time, the circuitry of migraine pain, the trigeminovascular system, and several aspects of its neurotransmission peripherally and in the trigeminal nucleus caudalis, central mesencephalic grey and thalamus, have been recognized. Highly receptor- specific acute medications including 5-HT1B/D receptor agonists (triptans), 5-HT1F receptor agonists and CGRP receptor antagonists have demonstrated efficacy in the acute treatment of migraine attacks. Because of their high receptor-specificity, their mechanisms of action pro- vide new insight into migraine mechanisms. It is now clear that 1.1 *Migraine without aura* is a neurobiological disorder, while clinical as well as basic neuroscience stu- dies continue to advance our knowledge of migraine mechanisms.

1.2 *Migraine with aura*

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

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

Diagnostic criteria:

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

Notes:

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

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

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

The aura is the complex of neurological symptoms that occurs usually before the headache of 1.2 *Migraine with aura*, but it may begin after the headache phase has commenced or continue into the headache phase.

Visual aura is the most common type of aura, occur- ring in over 90% of patients with 1.2 *Migraine with aura*, at least in some attacks. It often presents as a fortification spectrum: a zigzag figure near the point of fixation that may gradually spread right or left and assume a laterally convex shape with an angulated scintillating edge, leaving absolute or variable degrees of relative scotoma in its wake. In other cases, scotoma without positive phenomena may occur; this is often perceived as being of acute onset but, on scrutiny, usually enlarges gradually. In children and adolescents, less typical bilateral visual symptoms occur that may represent an aura. A visual aura rating scale with high specificity and sensitivity has been developed and validated.

Next in frequency are sensory disturbances, in the form of pins and needles moving slowly from the point of origin and a□ecting a greater or smaller part of one side of the body, face and/or tongue. Numbness may occur in its wake, but numbness may also be the only symptom.

Less frequent are speech disturbances, usually aphasic but often hard to categorize.

Systematic studies have demonstrated that many patients with visual aura occasionally have

symptoms in the extremities and/or speech symptoms. Conversely, patients with symptoms in the extremities and/or speech or language symptoms almost always also experience visual aura symptoms at least during some attacks. A distinction between migraine with visual aura, migraine with hemiparaesthetic aura and migraine with speech and/or language aura is probably artificial, and therefore not recognized in this classification: they are all coded as 1.2.1 *Migraine with typical aura*.

When aura symptoms are multiple, they usually follow one another in succession, beginning with visual, then sensory, then aphasic; but the reverse and other orders have been noted. The accepted duration for most aura symptoms is one hour, but motor symptoms are often longer lasting.

Patients with aura symptoms arising from the brain- stem are coded as 1.2.2 *Migraine with brainstem aura*, but they almost always have additional typical aura symptoms. When the aura includes motor weakness, the dis- order should be coded as 1.2.3 *Hemiplegic migraine* or one of its subforms. 1.2.3 *Hemiplegic migraine* is classified as a separate subtype because of genetic and pathophysiological differences from 1.2.1 *Migraine with typical aura*. Patients with 1.2.3 *Hemiplegic migraine* often have brainstem symptoms in addition.

Patients often find it hard to describe their aura symptoms, in which case they should be instructed to time and record them prospectively. The clinical picture then becomes clearer. Common mistakes are incorrect reports of lateralization, of sudden rather than gradual onset and of monocular rather than homonymous visual disturbances, as well as of duration of aura and mistaking sensory loss for weakness. After an initial consultation, use of an aura diary may clarify the diagnosis.

Migraine aura is sometimes associated with a head- ache that does not fulfill criteria for 1.1 *Migraine without aura*, but this is still regarded as a migraine headache because of its relation to the aura. In other cases, migraine aura may occur without headache.

Before or simultaneously with the onset of aura symptoms, regional cerebral blood flow is decreased in the cortex corresponding to the clinically affected area and often over a wider area. Blood flow reduction usually starts posteriorly and spreads anteriorly, and is usually above the ischaemic threshold. After one to several hours, gradual transition into hyperaemia occurs in the same region. Cortical spreading depression of Lea˜ o is the likely underlying mechanism.

The previously defined syndromes, *migraine with prolonged aura* and *migraine with acute-onset aura*, have been abandoned. It is not rare for aura to last more than one hour but, in most such cases, patients have at least two of the other characteristics of criterion
C. Even when most of a patient's attacks do not fulfil criterion C, it is usual that other attacks fulfil criteria for one of the recognized subtypes or subforms of 1.2 *Migraine with aura*, and this should be the diagnosis. The few other cases should be coded to 1.5.2 *Probable migraine with aura*, specifying the atypical feature (pro- longed aura or acute-onset aura) in parenthesis. The diagnosis is usually evident after a careful history alone, although there are rare secondary mimics including carotid dissection, arteriovenous malformation and seizure.

Prodromal symptoms may begin hours or a day or two before the other symptoms of a migraine attack with aura. They include various combinations of fatigue, difficulty in concentrating, neck sti□ness, sensitivity to light and/or sound, nausea, blurred vision, yawning and pallor. The term 'prodrome', which has replaced 'pre- monitory phase' or 'premonitory symptoms', does not include aura. Postdromal symptoms, most commonly feeling tired or weary, difficulty with concentration and neck stiffness, may follow resolution of the headache, persisting for up to 48 hours; these are less well studied.

1.2.1 Migraine with typical aura

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

Diagnostic criteria:

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

1.2.1.1 Typical aura with headache

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

Diagnostic criteria:

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

1.2.1.2 Typical aura without headache

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

Diagnostic criteria:

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

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

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

1.2.2 Migraine with brainstem aura

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

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

Diagnostic criteria:

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

Notes:

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

Comments: Originally the terms *basilar artery migraine* or *basilar migraine* were used but, since

involvement of the basilar artery is unlikely, the term *migraine with brainstem aura* is preferred.

There are typical aura symptoms in addition to the brainstem symptoms during most attacks. Many patients who have attacks with brainstem aura also report other attacks with typical aura and should be coded for both 1.2.1 *Migraine with typical aura* and 1.2.2 *Migraine with brainstem aura*.

Many of the symptoms listed under criterion B1 may occur with anxiety and hyperventilation, and are therefore subject to misinterpretation.

1.2.3 Hemiplegic[1] migraine

Description: Migraine with aura including motor weakness.

Diagnostic criteria:

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

Notes:

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

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

1.2.3.1 Familial hemiplegic migraine (FHM)

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

Diagnostic criteria:

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

Comments: New genetic data have allowed a more precise definition of 1.2.3.1 *Familial hemiplegic migraine* than was previously possible. Specific genetic subforms have been identified: in FHM1 there are mutations in the

CACNA1A gene (coding for a calcium channel) on chromosome 19; in FHM2 there are mutations in the *ATP1A2* gene (coding for a K/Na-ATPase) on chromo- some 1; and in FHM3 there are mutations in the *SCN1A* gene (coding for a sodium channel) on chromosome 2. There may be other loci not yet identified. When genetic testing is done, the genetic subform (if discovered) should be specified at the fifth digit.

It has been shown that 1.2.3.1 *Familial hemiplegic migraine* very often presents with brainstem symptoms in addition to the typical aura symptoms, and that headache almost always occurs. Rarely, during FHM attacks, disturbances of consciousness (sometimes including coma), confusion, fever and cerebrospinal fluid (CSF) pleocytosis can occur.

1.2.3.1 *Familial hemiplegic migraine* may be mistaken for epilepsy and treated (unsuccessfully) as such. FHM attacks can be triggered by (mild) head trauma. In approximately 50% of FHM families, chronic progressive cerebellar ataxia occurs independently of the migraine attacks.

1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)

Diagnostic criteria:

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

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

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

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

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

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*

B. Genetic testing has demonstrated no mutation on the *CACNA1A*, *ATP1A2* or *SCN1A* genes.

1.2.3.2 Sporadic hemiplegic migraine (SHM)

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

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*

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

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

The attacks in 1.2.3.2 *Sporadic hemiplegic migraine* have the same clinical characteristics as those in 1.2.3.1 *Familial hemiplegic migraine*. Some apparently sporadic cases have known FHM mutations and, in some, a first- or second-degree relative later develops hemiplegic migraine, thus completing fulfilment of the criteria for

1.2.3.1 *Familial hemiplegic migraine* and requiring a change of diagnosis.

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

1.2.4 Retinal migraine

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

Diagnostic criteria:

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

B. Aura characterized by both of the following:

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

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

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

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

1.3 Chronic migraine

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

Diagnostic criteria:

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

B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 *Migraine with- out aura* and/or criteria B and C for 1.2 *Migraine with aura*

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

D. Not better accounted for by another ICHD-3

diagnosis.[3–5]

Notes:

1. The reason for singling out 1.3 *Chronic migraine* from types of episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. Such patients are extremely di□cult to keep medication-free in order to observe the natural history of the headache. In this situation, attacks with and those without aura are both counted, as are both migraine-like and tension-type-like headaches (but not secondary headaches).
2. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day by day for at least one month.
3. Because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*, this diagnosis excludes the diagnosis of 2. *Tension-type headache* or its types.
4. 4.10 *New daily persistent headache* may have features suggestive of 1.3 *Chronic migraine*. The latter disorder evolves over time from 1.1 *Migraine without aura* and/ or 1.2 *Migraine with aura*; therefore, when these criteria A–C are fulfilled by headache that, unambiguously, is daily and unremitting from <24 hours after its first onset, code as 4.10 *New daily persistent head- ache*. When the manner of onset is not remembered or is otherwise uncertain, code as 1.3 *Chronic migraine*.
5. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under 8.2 *Medication-overuse headache*. Around 50% of patients apparently with 1.3 *Chronic migraine* revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed as 1.3 *Chronic migraine*. Equally, many patients apparently overusing medication do not improve after drug withdrawal; the diagnosis of 8.2 *Medication-overuse headache* may be inappropriate for these (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule to apply all relevant diagnoses, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be coded for both. After drug withdrawal, migraine will either revert to an episodic type or remain chronic and should be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse headache* may be rescinded.

1.4 Complications of migraine

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

1.4.1 Status migrainosus

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

Diagnostic criteria:

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

Notes:

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

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

1.4.2 Persistent aura without infarction

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

Diagnostic criteria:

A. Aura fulfilling criterion B
B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous auras except that one or more aura symptoms

persists for 1 week

C. Neuroimaging shows no evidence of infarction

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

Comments: Persistent aura symptoms are rare but well documented. They are often bilateral and may last for months or years. The one-week minimum in criterion B is based on the opinion of experts and should be formally studied.

Diagnostic work-up must distinguish 1.4.2 *Persistent aura without infarction* from 1.4.3 *Migrainous infarction* and exclude symptomatic aura due to cerebral infarction of other causes. Attacks with prolonged aura lasting less than one week and not fulfilling criteria for 1.2.1 *Migraine with typical aura* are coded 1.5.2 *Probable migraine with aura.*

1.4.3 Migrainous infarction

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

Diagnostic criteria:

A. A migraine attack fulfilling criteria B and C

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

C. Neuroimaging demonstrates ischaemic infarction in a relevant area

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

Note:

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

Comments: Ischaemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with 1. *Migraine*, cerebral infarction of other cause presenting with symptoms resembling 1.2 *Migraine with aura*, or cerebral infarction occurring during the course of a typical attack of 1.2 *Migraine with aura.* Only the last fulfils criteria for 1.4.3 *Migrainous infarction.*

1.4.3 Migrainous infarction mostly occurs in theposterior circulation and in younger women.

A twofold increased risk of ischaemic stroke in patients with 1.2 *Migraine with aura* has been demonstrated in several population-based studies. However, it should be noted that these infarctions are not migrainous infarctions. The mechanisms of the increased risk of ischaemic stroke in migraine sufferers remain unclear; likewise, the relationship between increased risk and frequency of aura and the nature of aura symptoms denoting the increase in risk are unknown. Most studies have shown a lack of association between 1.1 *Migraine without aura* and ischaemic stroke.

1.4.4 Migraine aura-triggered seizure

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

Diagnostic criteria:

A. A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below

B. Occurring in a patient with 1.2 *Migraine with aura*, and during or within one hour after an attack of migraine with aura

C. Not better accounted for by another ICHD-3 diagnosis.

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

1.5 Probable migraine

Previously used term: Migrainous disorder.

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

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

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A–D for

1.1 *Migraine without aura*, or all but one of criteria A–C for 1.2 *Migraine with aura*

B. Not fulfilling ICHD-3 criteria for any other head- ache disorder

C. Not better accounted for by another ICHD-3 diagnosis.

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

1.5.1 Probable migraine without aura Diagnostic criteria:

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

1.5.2 Probable migraine with aura

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A–C for 1.2 *Migraine with aura* or any of its subtypes

B. Not fulfilling ICHD-3 criteria for any other head- ache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

1.6 Episodic syndromes that may be associated with migraine

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

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

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

1.6.1 Recurrent gastrointestinal disturbance

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

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

Diagnostic criteria:

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

1.6.1.1 Cyclic vomiting syndrome

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

Diagnostic criteria:

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

Note:

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

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

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

1.6.1.2 Abdominal migraine

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

Diagnostic criteria:

A. At least five attacks of abdominal pain, fulfilling criteria B–D
B. Pain has at least two of the following three characteristics:
   1. midline location, periumbilical or poorly localized
   2. dull or 'just sore' quality
   3. moderate or severe intensity
C. At least two of the following four associated symptoms or signs:
   1. anorexia
   2. nausea
   3. vomiting
   4. pallor
D. Attacks last 2–72 hours when untreated or unsuccessfully treated
E. Complete freedom from symptoms between attacks
F. Not attributed to another disorder.[1]

Note:

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

Comments: Pain of 1.6.1.2 *Abdominal migraine* is severe enough to interfere with normal daily activities.

In young children, the presence of headache is often overlooked. A careful history of presence or absence of headache must be taken and, when headache or head pain during attacks is identified, a diagnosis of 1.1 *Migraine without aura* should be considered.

Children may find it difficult to distinguish anorexia from nausea. Pallor is often accompanied by dark shadows under the eyes. In a few patients, flushing is the predominant vasomotor phenomenon.

Most children with abdominal migraine will develop migraine headache later in life.

1.6.2 Benign paroxysmal vertigo

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

Diagnostic criteria:

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

Notes:

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

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

1.6.3 Benign paroxysmal torticollis

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

Diagnostic criteria:

A. Recurrent attacks[1] in a young child, fulfilling criteria B and C
B. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after

minutes to days

C. At least one of the following five associated symptoms or signs:
   1. pallor
   2. irritability
   3. malaise
   4. vomiting
   5. ataxia[2]

D. Normal neurological examination between attacks

E. Not attributed to another disorder.[3]

Notes:

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

Comments: The child's head can be returned to the neutral position during attacks: some resistance may be encountered but can be overcome.
These observations need further validation by patient diaries, structured interviews and longitudinal data collection.

1.6.3 *Benign paroxysmal torticollis* may evolve into

1.6.2 *Benign paroxysmal vertigo* or 1.2 *Migraine with aura* (particularly 1.2.2 *Migraine with brainstem aura*) or cease without further symptoms.

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12.2 Examples of Prohibited Medications

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.4 Glossary of Abbreviations

Term/Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
[redacted]	
ALT	alanine aminotransferase
ASC-12	allodynia symptom checklist
AST	aspartate aminotransferase
BID	twice daily
BP	blood pressure
CGRP	calcitonin gene-related peptide
COVID-19	coronavirus disease 2019
CM	chronic migraine
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	cytochrome P450 3A4
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EM	episodic migraine
[redacted]	
ET	early termination
eTablet	electronic tablet
FDA	Food and Drug Administration
GBD2010	Global Burden of Disease Survey 2010
GCP	Good Clinical Practices
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
[redacted]	
HIV	human immunodeficiency virus
HSG	hysterosalpingogram
ICF	informed consent form
ICH	International Conference on Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd edition
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone releasing system

Term/Abbreviation	Definition
IV	intravenous
IWRS	interactive web response system
[redacted]	
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
[redacted]	
NSAID	nonsteroidal anti-inflammatory drug
OATP1B1	organic anion transporting polypeptide 1B1
[redacted]	
PK	pharmacokinetic
PRO	patient reported outcomes
QD	daily
QTcF	QT interval corrected for heart rate using Fridericia formula (QTcF = $QT/(RR)^{1/3}$)
ROW	rest of world
SAE	serious adverse event
SAP	statistical analysis plan
SNRI	serotonin norepinephrine reuptake inhibitor
SOC	standard of care
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
VAS	Visual Analogue Scale
VCT	Verified Clinical Trials
WHO	World Health Organization

[redacted]

12.5 Protocol Amendment 1 Summary

Title: A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Long-Term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine

Protocol 3101-302-002

Date of Amendment: 14 Mar 2019

Amendment Summary

This amendment includes changes made to Protocol 3101-302-002 dated 22 August 2018. The protocol was amended to:

- Delete the inclusion of participants from Study 3101-301-002 (rollover participants) from this long-term study and delete any instructions specific for this population throughout the protocol.
- Add the exclusion of participants with clinically significant renal disease to the Protocol Summary, to be consistent with Exclusion Criteria #14 in Section 4.4.

[redacted]

- Add progestogen-only hormonal contraception (with inhibition of ovulation) that are oral, injectable, or implantable as acceptable highly effective contraceptive methods.

[redacted]

- Add that the assessment of causality of any AE or SAE applies to the participants receiving oral SOC migraine prevention medication as well as those receiving atogepant.
- Clarify how new and updated information will be recorded in the eCRF prior to database lock; if an event is an SAE, then it will also be recorded on an SAE reporting form. If new or updated SAE information becomes available after database lock, then the event is only recorded on an SAE reporting.
- Clarify which form that should be used in the event of treatment-emergent elevations in ALT or AST enzyme levels ≥ 3 x ULN.
- Clarify that if a participant meets the Hy's law criteria and has an associated AE that is serious, then an AESI/SAE form is to be completed.
- Make Section 12.2 Examples of Prohibited Medications consistent with Section 4.5.2 Prohibited Medications/Treatments
- Add timing of prohibited non-pharmacological headache interventions to be consistent with Section 4.5.2

[redacted]

The table below provides details related to content changes that were made in the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Protocol Title Page	Added Amendment 1 Date	To indicate that the initial protocol has been amended and when
Global Protocol Deletion Sections affected are: o Protocol Summary and Table 1 Schedule of Visits and Procedures o Section 3.1 o Section 4.2 o Section 4.3 (Inclusion Criteria #11) o Section 4.4 (Exclusion Criteria #10, #13, and #23) o Section 5.5 o Section 5.6.1	Deleted the inclusion of participants from Study 3101-301-002 (rollover participants) as eligible participants in this long-term study and deleted any instructions specific for this population throughout the protocol	The screening period for this study is projected to end prior to participants in Study 3101-301-002 completing Visit 7, the visit where they could rollover into this study. For this reason, the inclusion of rollover participants from Study 3101-301-002 has been eliminated

○ Section 7.3.1 ○ Section 7.3.2 ○ Section 8.1.2 ○ Section 8.3 ○ Section 8.4 ○ Section 8.4.1 ○ Section 8.4.2.1		
Protocol Summary, *Key Exclusion Criteria*	Added "renal" to the list of clinically significant diseases that exclude participants from enrolling in this study; see	Correction to be consistent with Section 4.4, Exclusion Criteria #14
Section 4.5.2 Prohibited Medications/Treatments (all three items) and	Added CBD oil as a prohibited medication/treatment 30 days prior to Visit 1 for all participants and throughout the study for participants randomized to receive atogepant only Added Mycobloc® and Jeuveua™ as a prohibited therapeutic or cosmetic botulinum toxin injection into areas of the head, face, or neck within 6 months prior to Visit 1 and throughout the study period Added injectable antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®) as prohibited medications/treatments within 6 months prior to Visit 1 and through the study period	The purpose of listing the additional prohibited medications/treatments was to provide a more inclusive list to assist investigators conducting the study
Section 4.5.3 Definition of Women of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods	Added progestogen-only hormonal contraception (with inhibition of ovulation) that are oral, injectable, or implantable as acceptable highly effective contraceptive methods	Some progestogen-only hormonal contraceptives are considered highly effective, therefore women who meet other study criteria can use these effective contraceptive and participate in this study

[redacted]

[redacted]

Section 9.1.4 Assessment of Causality	Added "or oral SOC migraine prevention medication" to 1st and 4th bullet.	Clarification; allows for a general safety comparison between participants who received atogepant versus SOC migraine prevention medication
Section 9.1.5 Follow-up of Adverse Events and Serious Adverse Events	Replaced "New or updated information will be recorded in the originally completed eCRF." with "**Prior to database lock, new or updated information will be recorded in the originally completed eCRF. If the event is an SAE, it will also need to be reported on the SAE reporting form. Post database lock, new or updated SAE information will only be reported on the SAE reporting form.**"	Clarification
Section 9.5 ALT or AST Elevations	Last paragraph: replaced "AESI Form" with "**abnormal liver function reporting form**"	Correction
Section 9.5.1 Potential Hy's Law Cases	Last paragraph: replaced "AESI Form" with "**abnormal liver function reporting form**" and added "**If the event is serious, please complete the AESI/SAE form.**"	Correction and clarification

[redacted]

12.6 Protocol Amendment 2 Summary

Title: A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Long-Term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine

Protocol 3101-302-002

Date of Amendment: April 2020

Amendment Summary
This amendment includes changes made to Protocol 3101-302-002 Amendment 1 dated 14 March 2019.

To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity, the protocol was updated to allow investigators/appropriately designated study staff to perform Visit 14, Visit 15/ET, and Visit 16/SFU as remote study visits (eg, conducted via phone, video conference), as follows:

- Investigators/appropriately designated study staff are allowed to perform Visit 14 and Visit 15/ET as remote study visits.
- Investigators/appropriately designated study staff should conduct Visit 16/SFU Visit remotely for all participants in all cases.
- Safety assessments to be completed at remote study visits include assessment of AEs, concomitant medications, pregnancy test results review, and the C-SSRS.

The protocol also was amended to:

- Update the definition of safety population.

[redacted]

- Remove subgroup analysis by prior treatment failure with oral medications.

[redacted]

The table below provides details related to content changes that were made in the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Table 1 Schedule of Visits and Procedures; 8.4.2.2 Visits 3 to 14 (Week 4 to 48) Section 8.4.2.3 Visit 15/Early Termination (Week 52) 8.4.3.1 Visit 16/End of Study (Week 56) Conducted During In-Person Visit (Prior to the COVID-19 Pandemic) Section 8.4.3.1.1 Visit 16/ End of Study (Week 56) Conducted Remotely (Due to the COVID-19 Pandemic)	Investigators/appropriately designated study staff are allowed to perform Visit 14 and Visit 15/ET Visit as remote study visits (eg, conducted via phone, video conference). Investigators/appropriately designated study staff will perform Visit 16/SFU Visit as a remote study visit (eg, conducted via phone, video conference). Table 1 footnotes t, u, v, w were added for clarity. Safety assessments to be completed at remote study visits include assessment of AEs, concomitant medications, pregnancy test results review, and the C-SSRS. Physical examination, ECG, vital sign measurements, clinical laboratory determinations, and PRO measures will not be performed at the remotely conducted visits. Section 8.4.3.1.1 Visit 16/ End of Study (Week 56) Conducted Remotely (Due to the COVID-19 Pandemic) added for clarity.	To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity

[redacted]

Section	Revision	Rationale
[redacted]		

Electronic Signatures

User	Date	Justification
[redacted]	24-Apr-2020 18:32:15 (GMT)	Manager Approval