Title Page

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A PHASE 3, MULTICENTER, OPEN-LABEL 40-WEEK EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE

Protocol Number:	3101-309-002
EudraCT Number (if applicable):	Not applicable
Phase:	3
Name of Study Intervention:	Atogepant
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Original Protocol Date	22 February 2019

Amendment 1 Date: 15 September 2020

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 confidential.
- 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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Protocol Summary

Study Compound: Atogepant

Phase: 3

Study Objective:
To evaluate the safety and tolerability of treatment with atogepant 60 mg once daily for the prevention of migraine over a 40-week duration.

Clinical Hypotheses:
Atogepant 60 mg once daily is safe and well tolerated when administered over 40 weeks

Study Design

Structure: Multicenter, open-label, 40-week, long-term safety extension study conducted in the United States
Duration: The study will consist of a 40-week treatment period, and a safety follow-up period of an additional 4 weeks, for a total duration of 44 weeks.
Study Intervention: Atogepant 60 mg once daily
Control: Not applicable
Dosage/Dose Regimen: Atogepant 60 mg once daily will be administered for 40 weeks.
Randomization: Not applicable
Visit Schedule: Participants will directly rollover from Study 3101-301-002 (Phase 3 episodic migraine [EM]). As such, participants will have Visit 7 from Study 3101-301-002 function as the Visit 1 for this study after the participant signs the informed consent. After Visit 1, study visits will occur every 4 weeks for the duration of the study. An End of Study (EOS) Visit will occur 4 weeks after the last dose of atogepant. During the COVID-19 pandemic, Visit 12 (Follow-up/End of Study) should be conducted remotely for all participants.

Note, there may be participants who complete Visit 7 in the lead-in Study 3101-301-002 before extension Study 3101-309-002 has been initiated. Those participants should complete Visit 7/ET and Visit 8/EOS Visit (including discontinuation of IP) per the Study 3101-301-002 Schedule of Visits and Procedures.

Depending on the timing of the initiation of this extension study in relation to each participant's planned Visit 8 schedule, Visit 1 Study 3101-309-002 can be conducted on the same day as Visit 8/EOS Visit for Study 3101-301-002 or soon thereafter.

- If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit for Study 3101-301-002 should be conducted on the same day as Visit 1 for Study 3101-309-002.
- If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 and Visit 1), then Visit 8/EOS Visit should be conducted as planned per the Study 3101 301-002 Schedule of Visits and Procedures. When this extension study is initiated, the participant should return to the clinic as soon as possible, and Visit 1 should be conducted per the Study 3101-309-002 Schedule of Visits and Procedures.

For details, please see Table 1, the Schedule of Visits and Procedures.

Study Population Characteristics

Number of Participants/Sites: All participants who complete Study 3101-301-002, and meet all eligibility requirements, may participate in this study. Based on expected completion rates from Study 3101-301-002, it is estimated that approximately 750 participants will be enrolled from approximately 110 centers in the United States.

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

Inclusion Criteria:

- 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.
- Participants must be using a medically acceptable and effective method of birth control during the course of the entire study, as defined in Section 4.4.3.
- Eligible participants who completed the double-blind treatment period (Visit 7) and the follow-up period Visit 8, if applicable depending on the timing of study initiation, of Study 3101-301-002 without significant protocol deviations (eg, noncompliance to protocol-required procedures) and who did not experience an adverse event (AE) that, in the investigator's opinion, may indicate an unacceptable safety risk.

Key Exclusion Criteria:

- 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, electrocardiogram (ECG) parameters, and the Columbia-Suicide Severity Rating Scale (C-SSRS)

Efficacy – Not applicable

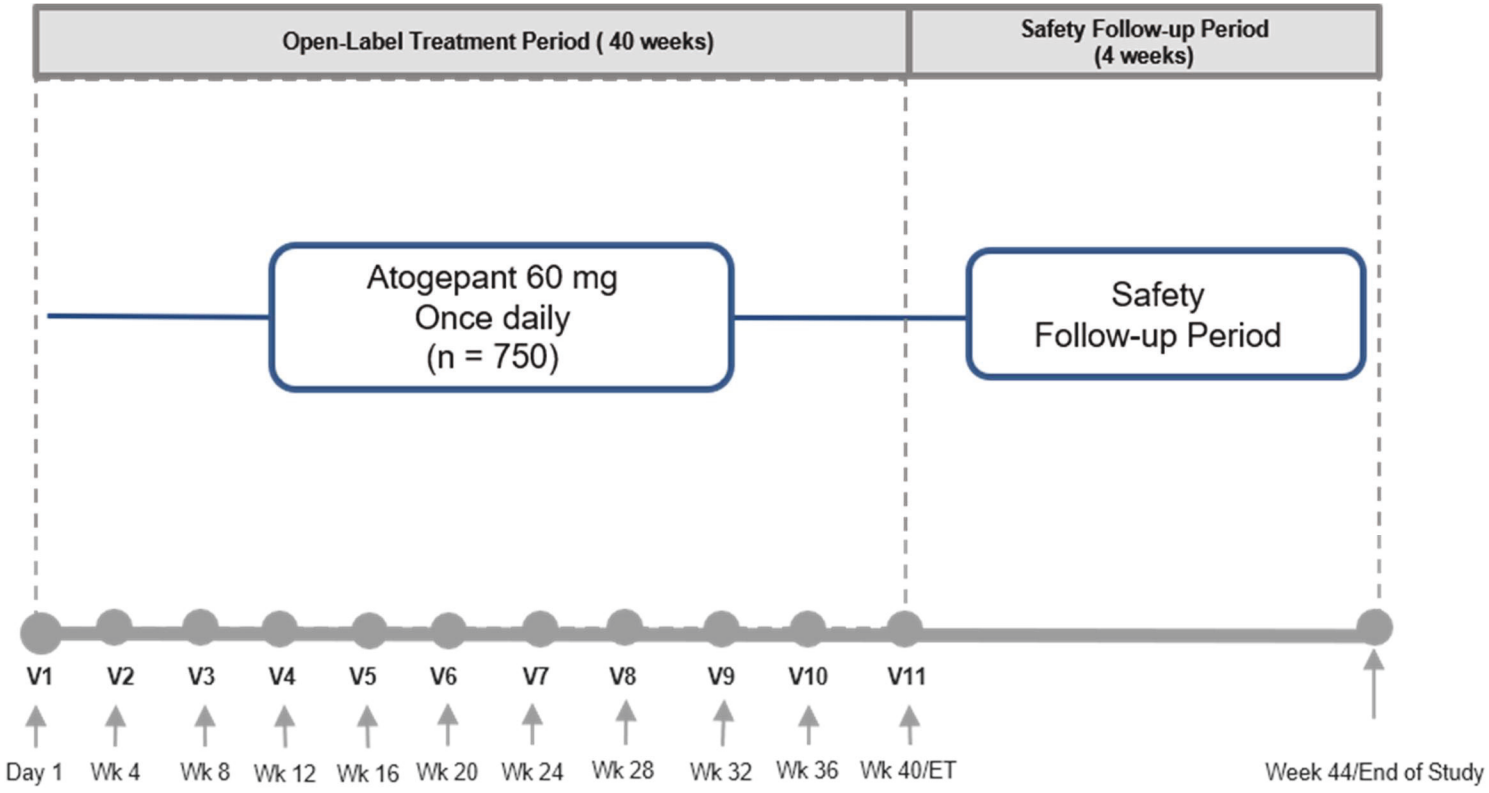
General Statistical Methods and Types of Analyses:

The safety parameters will include AEs, clinical laboratory determinations, vital sign measurements, ECG parameters, and the C-SSRS. For each of the clinical laboratory determinations, vital sign measurements, 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. For all participants, baseline in lead-in study (Study 3101-301-002) will be used. 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:

As this is a safety extension study, all eligible participants from lead-in Study 3101-301-002 may be enrolled.

Figure 1. Study Diagram



ET = early termination; V = visit; Wk = week.

Table 1. Schedule of Visits and Procedures for In-person Visits Conducted Prior to or During the COVID-19 Pandemic

Study Period	**Open-label Treatment Period (40 weeks)**											**Safety Follow-up Period (4 weeks)**
Visit #	**Visit 1[a]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11/ET**	**Visit 12/ EOS[e]**
Day/Week	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***
Visit Windows		± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Obtain Informed Consent and participant privacy	X											
Access IWRS	X	X	X	X	X	X	X	X	X	X	X	X
Assess inclusion/exclusion criteria	X											
Perform physical examination	X										X	X
Collect vital sign measurements[b]	X	X	X	X	X	X	X	X	X	X	X	X
Perform ECG	X			X			X				X	
Perform urine pregnancy test[c]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory determinations[d]	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study intervention (ie, atogepant)	X	X	X	X	X	X	X	X	X	X		
Review of study intervention (ie, atogepant) compliance and accountability		X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X

C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; INR = international normalized ratio; IWRS = interactive web response system.

[a] After providing informed consent for the current study, Visit 1 will be conducted on the same day as Study 3101-301-002 Visit 7; procedures collected as part of Study 3101-301-002 Visit 7 should not be repeated. Visit 1 must be conducted as an in-person visit.

[b] Vital sign measurements: Weight, sitting and standing pulse rate, respiratory rate, sitting and standing blood pressure, and body temperature.

[c] For women of child-bearing potential only, a urine pregnancy test will be performed at all visits.

[d] Clinical laboratory determinations include chemistry, hematology, coagulation parameters (INR), and urinalysis to be collected for all visits. Samples for serology and the urine drug screen will be collected only at screening (Visit 1).

[e] During the COVID-19 pandemic, Visit 12 (Follow-up/End of Study) should be conducted remotely for all participants.

Table 2. Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID-19 Pandemic

Study Period	**Open-label Treatment Period (40 weeks)[a]**										**Safety Follow-up Period (4 weeks)**
Visit #	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11/ET**	**Visit 12/ EOS[c]**
Day/Week	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***
Visit Windows	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Access IWRS	X	X	X	X	X	X	X	X	X	X	X
Provide urine pregnancy test and instructions[b]	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
Dispense study intervention (ie, atogepant)	X	X	X	X	X	X	X	X	X		
Review of study intervention (ie, atogepant) compliance and accountability	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/concurrent procedures	X	X	X	X	X	X	X	X	X	X	X

C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = end of study; ET = early termination; IWRS = interactive web response system.

[a] For participants who have a study visit replaced by a remote study visit, all missed in-person safety assessments (clinical laboratory determinations, vital signs, and ECGs) will be collected at the next in-person visit. To ensure participant safety, remote study visits can be performed for up to 8 weeks at the discretion of the investigator, after which, participants who cannot attend in-person for a study visit must be discontinued from the study.

[b] For women of childbearing potential only, a urine pregnancy test must be performed within 48 hours prior to the remote visits. Investigators/site staff will provide participants with study-supplied urine pregnancy tests and corresponding written instructions to be used at home by participants for remote study visits. Sites are required to verbally review testing instructions with all participants.

[c] During the COVID-19 pandemic, Visit 12 (Follow-up/End of Study) should be conducted remotely for all participants.

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 (Vos 2013) 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). This study will evaluate the safety and tolerability of atogepant in participants with migraine.

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 IB.

A Phase 2/3 clinical study was conducted, which compared atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 30 mg BID, atogepant 60 mg once daily 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 participants with EM.

1.3 Study Rationale

The purpose of this study is to evaluate the safety and tolerability of atogepant 60 mg once daily, when taken for 40 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 once daily. For this reason, the same dose of 60 mg once daily 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 once daily when administered over 40 weeks for the prevention of migraine in participants with EM.

2.2 Clinical Hypothesis

Atogepant 60 mg once daily is safe and well tolerated when administered over 40 weeks for the prevention of migraine in participants with EM.

3 Study Design

3.1 Structure

This is a multicenter, open-label, 40-week, long-term safety extension study conducted in the United States and will enroll approximately 750 participants from approximately 110 sites. Participants will be treated with atogepant 60 mg once daily.

The study will consist of a 40-week open-label treatment period, and a safety follow-up period of 4 weeks.

Participants will directly rollover from Study 3101-301-002 (Phase 3 EM). As such, participants will have Visit 7 from Study 3101-301-002 function as the Visit 1 for this study after the participant signs the informed consent. After Visit 1, study visits will occur every 4 weeks for the duration of the study. An EOS Visit will occur 4 weeks after the last dose of atogepant.

Note, there may be participants who complete Visit 7 in the lead-in Study 3101-301-002 before extension Study 3101-309-002 has been initiated. Those participants should complete Visit 7/ET and Visit 8/EOS Visit (including discontinuation of study intervention) per the Study 3101-301-002 Schedule of Visits and Procedures.

Depending on the timing of the initiation of this extension study, in relation to each participant's planned Visit 8 schedule, Visit 1 Study 3101-309-002 can be conducted on the same day as Visit 8/EOS Visit for Study 3101-301-002 or soon thereafter.

- If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit for Study 3101-301-002 should be conducted on the same day as Visit 1 for Study 3101-309-002.
- If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 and Visit 1), then Visit 8/EOS Visit should be conducted as planned per the Study 3101-301-002 Schedule of Visits and Procedures. When this extension study is initiated the participant should return to the clinic as soon as possible, and Visit 1 should be conducted per the Study 3101-309-002 Schedule of Visits and Procedures.

After Visit 1, study visits will occur every 4 weeks for the duration of the 40-week treatment period. Participants will return to the clinic for safety assessments at 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40 weeks relative to Visit 1 (Day 1). An EOS Visit will occur 4 weeks after the last dose of atogepant 60 mg once daily. During the COVID-19 pandemic, Visit 12 (Follow-up/End of Study) should be conducted remotely for all participants. For the schedule of visits and procedures conducted in-person, see Table 1.

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 has been updated to allow investigators/appropriately designated study staff to perform study visits remotely. For the schedule of visits and procedures conducted remotely, see Table 2.

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 ≥ 3 × 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 750 participants will be treated with atogepant 60 mg once daily at approximately 110 centers in the United States.

4.2 Inclusion Criteria

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. Participants must be using a medically acceptable and effective method of birth control during the course of the entire study, as defined in Section 4.4.3.

3. Eligible participants who completed the double-blind treatment period (Visit 7) and the follow-up period (Visit 8), if applicable, depending on the timing of study initiation, of Study 3101-301-002 without significant protocol deviations (eg, noncompliance to protocol-required procedures) and who did not experience an AE that, in the investigator's opinion, may indicate an unacceptable safety risk.

4.3 Exclusion Criteria

1. Requirement for any medication, diet (ie, grapefruit juice), that is on the list of prohibited concomitant medications (see Section 4.4.2 and Attachment 12) that cannot be discontinued or switched to an allowable alternative medication. This includes concomitant medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol).

2. 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.

3. An ECG with clinically significant abnormalities at Visit 1 as determined by the investigator.

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

5. Significant risk of self-harm based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator; participants must be excluded if they report suicidal ideation with intent, with or without a plan, (ie, Type 4 or 5 on the C-SSRS) since the last visit.

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

7. Participant has a condition or is in a situation which in the investigator's opinion may put the participant at significant risk, may confound the study results, or may interfere significantly with participation in the study.

8. Any medical or other reasons (eg, unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study) that, in the investigator’s opinion, might indicate that the participant is unsuitable for participation in the study.

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

Medications that are not specifically prohibited in Section 4.4.2 are allowed, with the following clarifications and restrictions.

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

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

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

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

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

4.4.2 Prohibited Medications/Treatments

The following medications are prohibited 30 days prior to Visit 1 (unless otherwise indicated) for all participants and throughout the study (see Attachment 12.1):

- Strong and moderate CYP3A4 inhibitors, including but not limited to: systemic (oral/IV) itraconazole, ketoconazole, fluconazole, erythromycin, clarithromycin, telithromycin, diltiazem, verapamil, aprepitant, cyclosporine, nefazodone, cimetidine, quinine, and HIV protease inhibitors
- Strong and moderate CYP3A4 inducers, including but not limited to: barbiturates (eg, phenobarbital and primidone), systemic (oral/IV) glucocorticoids, nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, and St. John’s wort
- Strong OATP1B1 inhibitors (eg, gemfibrozil)
- Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions (eg, warfarin)
- Medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol). See Attachment 12.2
- CBD oil

- Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, BOTOX®, Myobloc®, Xeomin®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to Visit 1 and for the duration of the study
- Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®) within 6 months prior to Visit 1 and for the duration of the study

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

4.4.3 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 (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.

4.4.4 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.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently treated.

5 Study Intervention

5.1 Study Intervention and Formulations

Tablets containing atogepant 60 mg (Formulation Number: 11281X)

6 Control Intervention

Not applicable.

6.1 Methods for Masking/Blinding

This is an open-label study.

6.2 Treatment Allocation Ratio

All participants will be treated with atogepant 60 mg once daily.

6.3 Method for Assignment to Treatment Groups

Prior to initiation of atogepant in this open-label extension study, each participant who provides informed consent will maintain their lead-in study participant number. This number will serve as the participant identification number on all study documents.

At Visit 1, eligible participants will receive atogepant 60 mg once daily.

Before the study is initiated, log-in information and directions for the IWRS will be provided to each site.

The atogepant bottles will be labeled with kit numbers. The IWRS system will provide the site with the specific medication kit number(s) for each participant at Visit 1. Sites will dispense atogepant according to the IWRS instructions. Sites will also log onto the IWRS at subsequent visits to obtain a kit number for dispensing atogepant. Sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

Atogepant bottles will be dispensed at the study visits summarized in the Schedule of Visits and Procedures. Returned atogepant bottles should not be re-dispensed to the participants.

6.4 Treatment Regimen and Dosing

Participants who meet all of the study entry criteria at Visit 1 will be treated with atogepant 60 mg once daily.

Atogepant to be used in this trial is listed in Table 6-1.

Participants will be instructed to take their atogepant at approximately the same time each day. Atogepant will be administered orally for 40 weeks, and participants will be followed for 4 weeks following completion or discontinuation of the atogepant.

Table 6-1. Study Intervention

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

6.5 Safety Measures

6.5.1 Adverse Events

AEs 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, 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.

6.5.2 Adverse Events of Special Interest

Selected non-serious and SAEs are of special interest (AESI) 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 AESI, ALT or AST elevations, and potential Hy's law cases are outlined in Sections 9.5 and 9.5.1. These AEs or events determined to be SAEs must be reported appropriately via the designated eCRFs and safety forms.

6.5.3 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 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 Visit 1 will be

withdrawn 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 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 6–2.

Table 6–2. 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 study participation.

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.

6.5.4 Vital Signs

Vital sign measurements, including sitting and standing BP, sitting and standing pulse rate, respiratory rate, temperature, and weight 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).

6.5.5 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.

6.5.6 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.

6.5.7 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 all visits the C-SSRS will be completed for ideation and behavior since last visit for all participants. The C-SSRS will be completed 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 2 through 10 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the ET (Visit 11) and the EOS (Visit 12) visits.

6.6 Other Study Supplies

The following will be provided by Allergan or Allergan designee:

- All supplies needed for blood and urine sampling (central laboratory analysis)
- All supplies needed for on-site urine pregnancy test
- Shipping materials for shipment of laboratory samples to central laboratory
- All supplies needed for ECG assessment including ECG machine

6.7 Summary of Methods of Data Collection

An IWRS will be used to manage atogepant inventory. All office visit data for this study will be collected by eCRFs via an electronic data capture system. Source documents will be used at the sites and may include a participant's medical record, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as laboratory tests, ECGs, etc. A centralized clinical laboratory will be used for the analysis of all blood and urine samples, and for ECG assessments. Additional information on the collection and handling of samples is detailed in the Laboratory Procedure Manual.

7 Statistical Procedures

7.1 Analysis Populations

All safety analyses will be performed using the safety population, consisting of all participants who received at least 1 dose of atogepant in this extension study.

7.2 Hypothesis and Methods of Analysis

7.2.1 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 baseline value as defined for the lead-in study (3101-301-002) will be used as the baseline in this extension study (3101-309-002).

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.

Due to the COVID-19 pandemic, the study conduct and participants may be impacted. As per FDA guidance (FDA 2020), specific tables and listings will be generated to present the impact. In addition, analyses to further address the impact may be conducted.

7.3 Subgroup Analyses

No subgroup analysis is planned.

7.4 Sample Size Calculation

As this is a safety extension study from the lead-in Study 3101-301-002, all participants from the lead-in study who are eligible for this extension study will be enrolled. No separate sample size calculation was performed. Based on expected completion rate from the lead-in Study 3101-301-002, approximately 750 participants will be enrolled into this long-term, open-label, safety extension study.

7.5 Interim Analyses

Interim data-cuts are planned to provide ongoing safety data to support global regulatory submissions.

8 Study Visit Schedule and Procedures

See Table 1 for a schematic of the Schedule of Visits and Procedures conducted in-person, and Table 2 for a schematic of the Schedule of Visits and Procedures conducted remotely due to the COVID-19 pandemic. See 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 4.2 and 4.3 (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.

Participants will maintain their lead-in study participant identification number.

8.2 Washout Intervals/Run-in

This study will not include a washout period.

8.3 Procedures for Final Study Entry

At Visit 1 participants must meet all of the inclusion criteria and must not meet any of the exclusion criteria.

Participants will directly rollover from Study 3101-301-002 (Phase 3 EM). As such, participants will have Visit 7 from Study 3101-301-002 function as the Visit 1 for this study after the participant signs the informed consent. At Visit 1 participants must meet all of the inclusion criteria and must not meet any of the exclusion criteria.

Note, there may be participants who complete Visit 7 in the lead-in Study 3101-301-002 before extension Study 3101-309-002 has been initiated. Those participants should complete Visit 7/ET and Visit 8/EOS Visit (including discontinuation of study intervention) per the Study 3101-301-002 Schedule of Visits and Procedures.

Depending on the timing of the initiation of this extension study in relation to each participant's planned Visit 8 schedule, Visit 1 Study 3101-309-002 can be conducted on the same day as Visit 8/EOS Visit for Study 3101-301-002 or soon thereafter.

If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit for Study 3101-301-002 should be conducted on the same day as Visit 1 for Study 3101-309-002.

If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 and Visit 1), then Visit 8/EOS Visit should be conducted as planned per the Study 3101-301-002 Schedule of Visits and Procedures. When this extension study is initiated, the participant should return to the clinic as soon as possible and Visit 1 should be conducted per the Study 3101-309-002 Schedule of Visits and Procedures.

8.4 Visits and Associated Procedures

There will be 12 scheduled clinic visits: Visit 1 (Day 1), Visit 2 (Week 4), Visit 3 (Week 8), Visit 4 (Week 12), Visit 5 (Week 16), Visit 6 (Week 20), Visit 7 (Week 24), Visit 8 (Week 28), Visit 9 (Week 32), Visit 10 (Week 36), Visit 11/ET (Week 40), and Visit 12/EOS (Week 44).

Refer to Table 1 for assessments to be performed at in-person study visits. Refer to Table 2 for assessments to be performed at study visits conducted remotely due to the COVID-19 pandemic.

For participants who have a study visit replaced by a remote study visit, all missed in-person safety assessments (clinical laboratory determinations, vital signs, and ECGs) will be collected at the next in-person visit. To ensure participant safety, remote study visits can be performed for up to 8 weeks at the discretion of the investigator, after which, participants who cannot attend in person for a study visit must be discontinued from the study.

8.4.1 Open-label Treatment Period (40 Weeks)

8.4.1.1 Visit 1 (Day 1)

- Obtain informed consent and participant privacy.
- Register participant in IWRS.
- Review and record prior medications taken in the past 6 months, and all prior migraine headache medications and concomitant medications.
- Assess inclusion/exclusion criteria.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, and weight).
- Perform physical examination.
- Perform urine pregnancy test for women of child-bearing potential.
- Collect urine for drug screen.
- Perform and transmit ECG
- Collect blood and urine for clinical laboratory determinations including: serology, INR, and urinalysis.
- Review and assess AEs.
- Review and update concomitant medications and concurrent procedures.

- Access IWRS and obtain the kit number for atogepant bottle and dispense atogepant bottle.

8.4.1.2 Visits 2 to Visit 11 (Week 4 to 40)

Refer to Table 2 for assessments to be performed at study visits conducted remotely due to the COVID-19 pandemic.

- Perform urine pregnancy test for women of child-bearing potential.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, and weight).
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Perform and transmit ECG (Visit 4 [Week 12], Visit 7 [Week 24], and Visit 11 [Week 40] only).
- Collect previous visit atogepant bottle, review participant compliance and perform accountability.
- Review and assess AEs.
- Review and update concomitant medications and concurrent procedures.
- Access IWRS to dispense atogepant bottle and enter accountability.

8.4.1.3 Visit 11/Early Termination (Week 40)

Effort should be made by the site to not schedule Visit 11 earlier than 40 weeks after Day 1, to ensure participants complete the full 40 weeks of atogepant treatment.

- Perform physical examination.
- Perform urine pregnancy test for women of child-bearing potential.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, and weight).
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Perform and transmit ECG.
- Review and assess AEs.

- Review and update concomitant medications and concurrent procedures.
- Collect previous visit atogepant bottle, review participant compliance and perform accountability.
- Access IWRS to enter study visit and accountability.

8.4.2 Safety Follow-up Period (4 Weeks)

8.4.2.1 Visit 12/End of Study (Week 44) Conducted Remotely

During the COVID-19 pandemic, Visit 12 (Follow-up/End of Study) should be conducted remotely for all participants. Refer to Table 2 for assessments to be performed at study visits conducted remotely due to the COVID-19 pandemic.

8.4.2.2 Visit 12/End of Study (Week 44) Conducted In-Person Prior to the COVID-19 Pandemic

- Perform physical examination.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, and weight).
- Perform urine pregnancy test for women of child-bearing potential.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Review and assess AEs.
- Update concomitant medications and concurrent procedures.
- Access IWRS to enter study visit.

8.5 Instructions for the Participants

Section 4.4.4 provides diet and activity instructions for participants enrolled in the study. Prohibited medications should be reviewed with the participants. Participants will be instructed to return their atogepant bottle(s), both used and unused at each visit.

Participants should be instructed to take atogepant 60 mg once daily at approximately the same time each day (approximately 24 hours between doses).

Participants should use appropriate contraceptive measures for the duration of their participation in the study (Section 4.4.3).

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 (or Table 2 if conducted remotely due to the COVID-19 pandemic), 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 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 participants who prematurely discontinue from the study, regardless of cause, should

be seen for final study assessments. The final assessments will be defined as the evaluations scheduled for Visit 11/ET and Visit 12/EOS, 4 weeks post the last dose of atogepant.

8.9 Withdrawal Criteria

- **Participants with the following at Visit 1:**
  - **Laboratory Results:**
    - ALT or AST > 1 x ULN OR
    - total bilirubin > 1 x ULN (except for participants with a diagnosis of Gilbert's disease) OR
    - serum albumin < 2.8 g/dL
    - Positive result on the urine drug screen unless explained by concomitant medication use (eg, opioids prescribed for migraine pain).
    - Positive result on anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti–hepatitis C antibody testing, or anti-hepatitis E IgM antibody.
  - **ECG Results:**
    - QTcF > 450 msec for males and QTcF > 470 msec for females on the final central vendor ECG report
    - Clinically significant cardiac rhythm or conduction abnormalities (eg, atrial fibrillation, second- or third-degree heart block)
- **Participants with the following at any study visit:**
  - Female participants who become pregnant (Section 9.4)
  - Participants who meet atogepant 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.
  - 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 2 through 10 must be withdrawn from the study.
  - 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.

All withdrawn participants should receive appropriate follow-up as in routine clinical practice, including the ET (Visit 11) and the EOS (Visit 12) assessments.

8.10 Study Termination

The study may be stopped at the 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, 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. In addition, during Visit 1, AEs will be assessed regardless of the administration of atogepant.

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 the study (see Section 8.8).

All AEs from the signing of the ICF until the EOS Visit (Visit 12), or 30 days after the last dose of atogepant if the EOS Visit is not done, will be collected at the timepoints specified in the Schedule of Visits and Procedures (Table 1 for visits conducted in-person, or Table 2 for visits conducted remotely due to the COVID-19 pandemic), 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 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.

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

Any preplanned 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 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 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 6.5.2) 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 EOS Visit (Visit 12) or 30 days after the last dose of atogepant if the EOS 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 until the EOS Visit (Visit 12) or 30 days after the last dose of atogepant if the EOS 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 Number[s]: +1-714-796-9504 [back up fax number: +1-714-246-5295], email: IR-Clinical-SAE@allergan.com), 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. Any participant with this laboratory result after atogepant was taken must have repeat testing within 48 to 72 hours to confirm the abnormality. For this repeat testing, the following laboratory tests must be performed: hematology and chemistry panels, INR, serum acetaminophen level, urine drugs of abuse screen, and blood alcohol level. An extra blood serology sample must be collected and sent to the central laboratory for further diagnostic testing, at a later date, if needed. In addition, the investigator will perform a complete history and examination to evaluate the participant for possible liver disease.

All AEs of special interest 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 AE of special interest.

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

For these participants, the following laboratory tests must be performed: anti-hepatitis A IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, hepatitis C antibody, hepatitis C

quantitative RNA by polymerase chain reaction, anti-hepatitis E IgM, anti-hepatitis E IgG, Cytomegalovirus IgM antibody and Epstein-Barr Virus IgM antibody. The participant must be followed clinically and further medical evaluation (for other causes of acute hepatic injury) should be done per the judgment of the investigator and in conjunction with medical personnel at Allergan. In general, the chemistry panel should be repeated 1 to 2 times per week to follow the course of ALT/AST elevation.

Atogepant 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 only after consultation with the Allergan Medical Monitor. For participants who are not rechallenged, the participant should be discontinued from the study and complete an ET Visit and an EOS Visit 4 weeks later. 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:

- 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 (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 fax number on the form or the SAE 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, and/or from the participant's legally authorized representative, prior to any study-related activities or procedures in the study.

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

Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as laboratory tests, and ECGs. The investigator's copy of the eCRFs serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

- Participant’s name
- Participant’s contact information

- The date that the participant entered the study, participant number, and participant randomization (or medication kit) number
- The study title and/or the protocol number of the study and the name of Allergan
- A statement that informed consent was obtained (including the date). A statement that written authorization or other country and local participant privacy required documentation for this study has been obtained (including the date)
- Dates of all participant visits
- Participant's medical history
- Information regarding participant's diagnosis of migraine headache
- All concurrent medications (List all prescription and nonprescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Occurrence and status of any AEs
- The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.
- The results of laboratory tests performed by the site (eg, results of urine pregnancy tests).
- Key study variables

Source documentation practices must follow Section 4.0 of ICH E6, GCP: Consolidated Guidance, and ALCOA (ie, records must be Attributable, Legible, Contemporaneous, Original and Accurate).

10.6.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each participant's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan and will be maintained in a central data repository.

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.

For countries falling within the scope of the ICH guidelines, Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of atogepant. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

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

10.7.1 Labeling/Packaging

Atogepant will be supplied in bottles and will be labeled with the protocol number, storage information, warning language, and instructions to take the tablets as directed. The bottle will also include the kit number. Immediately before dispensing the bottle, the investigator or designee will write the participant number and date on the bottle.

10.7.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed or administered to the participants, the number of units returned to the investigator by the participant, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for atogepant. 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

All atogepant and/or supplies will be returned to Allergan or Allergan designee for destruction.

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

Urine pregnancy test kits will be provided by the central laboratory; all urine pregnancy testing will be administered on site according to instructions in the central laboratory manual.

Samples of blood and urine for evaluation of hematology, blood chemistry, urinalysis, urine drug screen, INR, and serology will be analyzed at a central clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology or Clinical Laboratory Improvement Amendments certification).

All samples will be returned to Allergan or Allergan's designee for destruction. Allergan shall have full ownership rights to any biological specimens/samples derived from the study. For additional details regarding handling of biological specimens, please refer to the Study Reference Manual.

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.

11 References

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12 Attachments

12.1 Examples of Prohibited Medications

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

- Strong OATP1B1 inhibitors eg, Gemfibrozil (Lopid™)
- CBD oil

	Strong/moderate CYP3A4 inducers	Strong/moderate CYP3A4 inhibitors
Anti-depressants/ Anti-anxiety	Barbiturates • Amobarbital (Amytal™) • Aprobarbital (Alurate™) • Butalbital (Fiorinal™, Fioricet™) • Butabarbital (Busodium™, Butisol™) • Mephobarbital (Mebaral™) • Pentobarbital (Nembutal™) • Phenobarbital (Luminal™, Solfoton™) • Secobarbital (Seconal™)	Nefazodone (Serzone™)
Anti-seizure	Carbamazepine (Atretol™, Carbatrol™, Epitol™, Equetro™, Tegretol™) Oxcarbazepine (Trileptal™) Phenytoin (Dilantin™, Phenytek™) Primidone (Myidone™, Mysoline™)	
Diabetes	Pioglitazone (Actos™) Troglitazone (Rezulin™, Resulin™)	
Antiemetic		Aprepitant (Emend™)
Anti-hypertension		Diltiazem (Cardizem™) Verapamil (Calan™, Calan SR™)
Glucocorticoid (Systemic)	Betamethasone (Celestone™) Dexamethasone (Baycadron™, DexPak™) Hydrocortisone (Cortef™) Methylprednisolone (Medrol™) Prednisolone (Prelone™) Prednisone (Deltasone™) Triamcinolone (Kenalog™)	
Antibiotics	Rifabutin (Mycobutin™) Rifampicin/Rifampin (Rifadin™, Rifater™, Rimactane™)	Erythromycin (Benzamycin™, EryTab™) Clarithromycin (Biaxin™) Telithromycin (Ketek™)
Anti-fungal		Fluconazole (Diflucan™, Trican™) Itraconazole (Sporanox™) Ketoconazole (Nizoral™)
Anti-HIV	Efavirenz (Stocrin™, Sustiva™) Nevirapine (Viramune™)	Indinavir (Crixivan™) Nelfinavir (Viracept™) Ritonavir (Norvir™) Saquinavir (Fortovase™, Invirase™)
Immune Suppressant		Cyclosporine - Oral/IV only (Neoral™, Sandimmune™)

	Strong/moderate CYP3A4 inducers	Strong/moderate CYP3A4 inhibitors
Others	St. John's wort Enzalutamide (Xtandi™) Modafinil (Provigil™) Armodafinil (Nuvigil™)	Buprenorphine (Cizol™, Subutex™, Suboxone™) Quinine

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

The following medications or treatments are prohibited 6 months prior to Visit 1 and throughout the study:

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

12.2 Classification of Migraine Preventive Medications

Below is a list of migraine preventive medications considered effective or probably effective sorted by mechanism of action. Of note, topiramate and valproic acid derivatives are considered separate categories.

Pharmacologic Category	**Drug Name**
Antiepileptic	Valproic acid, sodium valproate, divalproex sodium Topiramate
Tricyclic antidepressant	Amitriptyline Nortriptyline
Beta-blockers	Metoprolol Bisoprolol Atenolol Nadolol Propranolol Timolol
Calcium channel blocker	Flunarizine
Angiotensin receptor blocker (ARB)	Candesartan
Angiotensin-converting enzyme (ACE) inhibitor	Lisinopril
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine Venlafaxine
Miscellaneous	Country approved products for migraine prevention (eg, oxetrone, pizotifen)

Source: Evers 2009, Hoffmann 2014, Schürks 2008, Silberstein 2012, Steiner 2007.

12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CBD	cannabidiol
CGRP	calcitonin gene-related peptide
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
EM	episodic migraine
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
GBD 2010	Global Burden of Disease Survey 2010
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HSG	hysterosalpingogram
IB	Investigator's Brochure
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
IV	intravenous
IWRS	interactive web response system
NSAID	nonsteroidal anti-inflammatory drug
OATP1B1	organic anion transporting polypeptide 1B1
PK	pharmacokinetic
QTcF	QT interval corrected for heart rate using Fridericia formula (QTcF = $QT/(RR)^{1/3}$)

Term/Abbreviation	Definition
SAE	serious adverse event
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal

12.4 Protocol Amendment 1 Summary

Title: A Phase 3, Multicenter, Open-label, 40-Week Extension Study to Evaluate the Long-term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine

Protocol 3101-309-002

Date of Amendment: 15 September 2020

Amendment Summary

This amendment includes changes made to Protocol 3101-309-002 dated 22 February 2019. The protocol was amended to:

- Add Table 2 for study visits to be conducted remotely to eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic, while ensuring participant safety and maintaining data integrity
- Clarified requirements around the use of remote visits, in particular for Visits 1 and 12.

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
Throughout	Added in following requirements: • Visit 1 must be conducted as an in-person visit. • During the COVID-19 pandemic, Visit 12 (Follow up/End of Study) should be conducted remotely for all participants. • To ensure participant safety, remote study visits can be performed for up to 8 weeks at the discretion of the investigator, after which, participants who cannot attend in person for a study visit must be discontinued from the study.	To clarify requirements in line with remote visits during the COVID-19 pandemic
Protocol Title Page	Added "Amendment 1 Date"	To reflect the approval date of Amendment 1
Table 1	Modified title of Schedule of Visits and Procedures to "Schedule of Visits and Procedures for In-person Visits Conducted Prior to or During the COVID-19	To clarify that this Schedule only applies for in-person visits; remote visits are

	Pandemic", plus added in relevant information on remote visits.	described in Table 2.
	Removal of requirement to measure height at Visit 1.	Correction of error.
Table 2	Addition of "Schedule of Visits and Procedures for Visits Conducted Remotely Due to the COVID 19 Pandemic" to describe remote study visits.	To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity.
Section 7.2.1 Safety Analyses	Addition of a statement that specific tables and listings will be generated to present the impact of the COVID-19 pandemic on study conduct and participants. Analyses to further address the impact may be conducted.	Added in line with FDA guidance.
Section 8.4.1.1 Visit 1	Removal of requirement to measure height at Visit 1.	Correction of error.

Protocol Approval Form

Protocol Number: 3101-309-002 Amendment 1

Protocol Title: A Phase 3, Multicenter, Open-Label, 40-Week Extension Study to Evaluate the Long-term Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Participants With Episodic Migraine

Approver:

[redacted]

[redacted] Neuroscience Development

September 14, 2020

Date

Title Page

ALLERGAN – CONFIDENTIAL

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which is the property of Allergan

A PHASE 3, MULTICENTER, OPEN-LABEL 40-WEEK EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE

Protocol Number:	3101-309-002
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):	+1-866-438-8820
Serious Adverse Event Reporting Fax Number(s): Back up fax number	+1-714-796-9504 +1-714-246-5295
Email	IR-Clinical-SAE@allergan.com
Allergan Medical Safety Physician Contact Information:	Refer to the Study Contacts Page
Allergan Signatory:	[redacted] Clinical Development
Original Protocol Date	22 February 2019

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 confidential.
- 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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Protocol Summary

Study Compound: Atogepant

Phase: 3

Study Objective:
To evaluate the safety and tolerability of treatment with atogepant 60 mg once daily for the prevention of migraine over a 40-week duration.

Clinical Hypotheses:
Atogepant 60 mg once daily is safe and well tolerated when administered over 40 weeks

Study Design

Structure: Multicenter, open-label, 40-week, long-term safety extension study conducted in the United States
Duration: The study will consist of a 40-week treatment period, and a safety follow-up period of an additional 4 weeks, for a total duration of 44 weeks.
Study Intervention: Atogepant 60 mg once daily
Control: Not applicable
Dosage/Dose Regimen: Atogepant 60 mg once daily will be administered for 40 weeks.
Randomization: Not applicable
Visit Schedule: Participants will directly rollover from Study 3101-301-002 (Phase 3 episodic migraine [EM]). As such, participants will have Visit 7 from Study 3101-301-002 function as the Visit 1 for this study after the participant signs the informed consent. After Visit 1, study visits will occur every 4 weeks for the duration of the study. An End of Study (EOS) Visit will occur 4 weeks after the last dose of atogepant.

Note, there may be participants who complete Visit 7 in the lead-in Study 3101-301-002 before extension Study 3101-309-002 has been initiated. Those patients should complete Visit 7/ET and Visit 8/EOS Visit (including discontinuation of IP) per the Study 3101-301-002 Schedule of Visits and Procedures.

Depending on the timing of the initiation of this extension study in relation to each participant's planned Visit 8 schedule, Visit 1 Study 3101-309-002 can be conducted on the same day as Visit 8/EOS Visit for Study 3101-301-002 or soon thereafter.

- If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit for Study 3101-301-002 should be conducted on the same day as Visit 1 for Study 3101-309-002.
- If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 and Visit 1), then Visit 8/EOS Visit should be conducted as planned per the Study 3101-301-002 Schedule of Visits and Procedures. When this extension study is initiated, the participant should return to the clinic as soon as possible, and Visit 1 should be conducted per the Study 3101-309-002 Schedule of Visits and Procedures.

For details, please see Table 1, the Schedule of Visits and Procedures.

Study Population Characteristics

Number of Participants/Sites: All participants who complete Study 3101-301-002, and meet all eligibility requirements, may participate in this study. Based on expected completion rates from Study 3101-301-002, it is estimated that approximately 750 participants will be enrolled from approximately 110 centers in the United States.

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

Inclusion Criteria:

- 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.
- Participants must be using a medically acceptable and effective method of birth control during the course of the entire study, as defined in Section 4.4.3.
- Eligible participants who completed the double-blind treatment period (Visit 7) and the follow-up period Visit 8, if applicable depending on the timing of study initiation, of Study 3101-301-002 without significant protocol deviations (eg, noncompliance to protocol-required procedures) and who did not experience an adverse event (AE) that, in the investigator's opinion, may indicate an unacceptable safety risk.

Key Exclusion Criteria:

- 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, electrocardiogram (ECG) parameters, and the Columbia-Suicide Severity Rating Scale (C-SSRS)

Efficacy – Not applicable

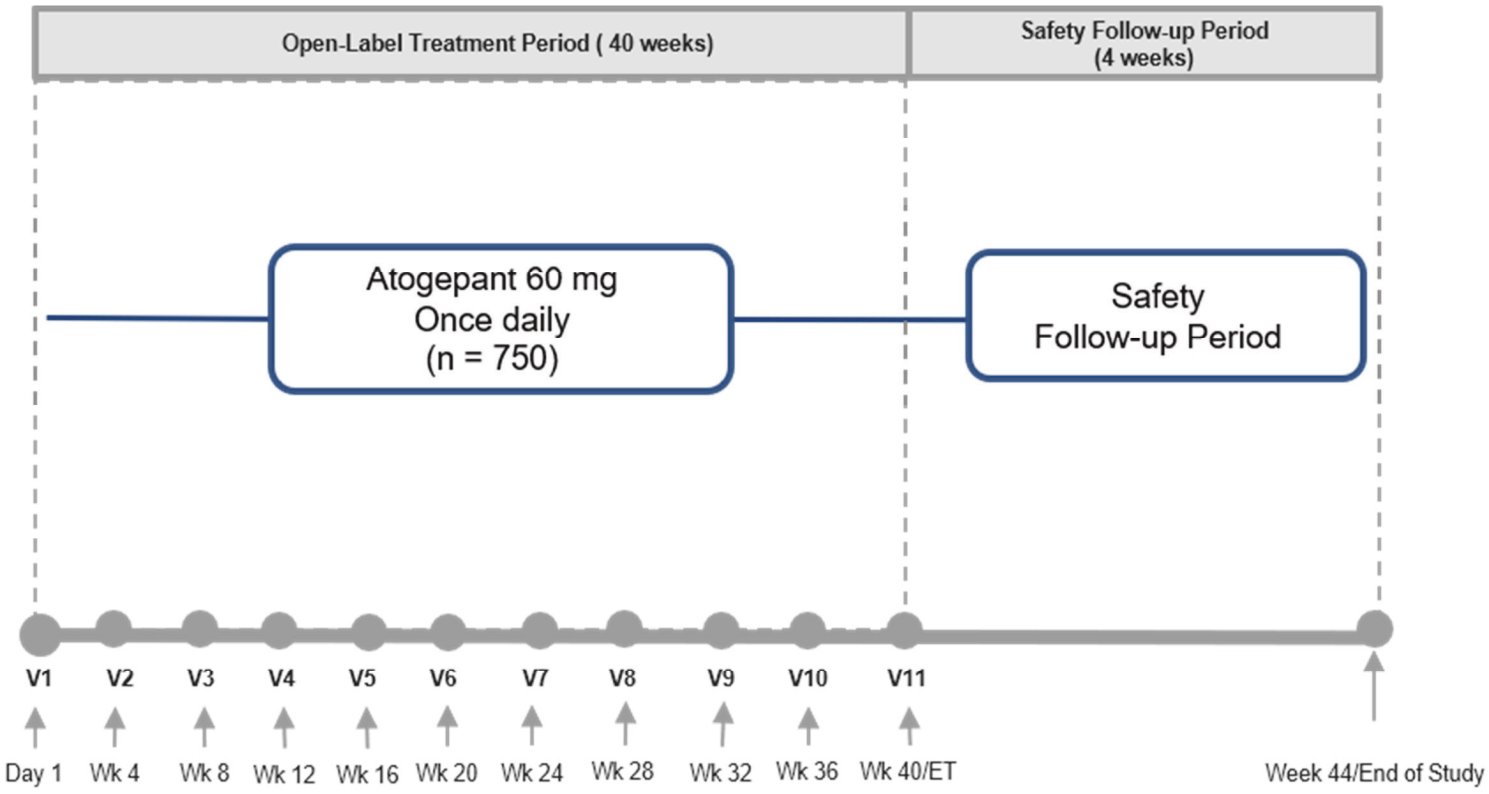
General Statistical Methods and Types of Analyses:

The safety parameters will include AEs, clinical laboratory determinations, vital sign measurements, ECG parameters, and the C-SSRS. For each of the clinical laboratory determinations, vital sign measurements, 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. For all participants, baseline in lead-in study (Study 3101-301-002) will be used. 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:

As this is a safety extension study, all eligible participants from lead-in Study 3101-301-002 may be enrolled.

Figure 1. Study Diagram



ET = early termination; V = visit; Wk = week.

Table 1. Schedule of Visits and Procedures

Study Period	**Open-label Treatment Period (40 weeks)**											**Safety Follow-up Period (4 weeks)**
Visit #	**Visit 1[a]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11/ET**	**Visit 12/ EOS**
Day/Week	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***
Visit Windows		± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Obtain Informed Consent and participant privacy	X											
Access IWRS	X	X	X	X	X	X	X	X	X	X	X	X
Assess inclusion/exclusion criteria	X											
Perform physical examination	X										X	X
Collect vital sign measurements[b]	X	X	X	X	X	X	X	X	X	X	X	X
Perform ECG	X			X			X				X	
Perform urine pregnancy test[c]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory determinations[d]	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study intervention (ie, atogepant)	X[e]	X	X	X	X	X	X	X	X	X		
Review of study intervention (ie, atogepant) compliance and accountability		X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/concurrent procedures	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; EM = episodic migraine; EOS = end of study; ET = early termination; INR = international normalized ratio; IWRS = interactive web response system; WOCBP = women of childbearing potential

[a] After providing informed consent for the current study, Visit 1 will be conducted on the same day as Study 3101-301-002 Visit 7; procedures collected as part of Study 3101-301-002 Visit 7 should not be repeated.

[b] Vital sign measurements: height, weight, sitting and standing pulse rate, respiratory rate, sitting and standing blood pressure, and body temperature. Height will be measured only at Visit 1.

[c] For women of child-bearing potential only, a urine pregnancy test will be performed at all visits.

[d] Clinical laboratory determinations include chemistry, hematology, coagulation parameters (INR), and urinalysis to be collected for all visits. Samples for serology and the urine drug screen will be collected only at screening (Visit 1).

[e] The first dose of atogepant must be taken in the office.

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). This study will evaluate the safety and tolerability of atogepant in participants with migraine.

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 IB.

A Phase 2/3 clinical study was conducted, which compared atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 30 mg BID, atogepant 60 mg once daily 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 participants with EM.

1.3 Study Rationale

The purpose of this study is to evaluate the safety and tolerability of atogepant 60 mg once daily, when taken for 40 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 once daily. For this reason, the same dose of 60 mg once daily 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 once daily when administered over 40 weeks for the prevention of migraine in participants with EM.

2.2 Clinical Hypothesis

Atogepant 60 mg once daily is safe and well tolerated when administered over 40 weeks for the prevention of migraine in participants with EM.

3 Study Design

3.1 Structure

This is a multicenter, open-label, 40-week, long-term safety extension study conducted in the United States and will enroll approximately 750 participants from approximately 110 sites. Participants will be treated with atogepant 60 mg once daily.

The study will consist of a 40-week open-label treatment period, and a safety follow-up period of 4 weeks.

Participants will directly rollover from Study 3101-301-002 (Phase 3 EM). As such, participants will have Visit 7 from Study 3101-301-002 function as the Visit 1 for this study

after the participant signs the informed consent. After Visit 1, study visits will occur every 4 weeks for the duration of the study. An EOS Visit will occur 4 weeks after the last dose of atogepant.

Note, there may be participants who complete Visit 7 in the lead-in Study 3101-301-002 before extension Study 3101-309-002 has been initiated. Those participants should complete Visit 7/ET and Visit 8/EOS Visit (including discontinuation of study intervention) per the Study 3101-301-002 Schedule of Visits and Procedures.

Depending on the timing of the initiation of this extension study, in relation to each participant's planned Visit 8 schedule, Visit 1 Study 3101-309-002 can be conducted on the same day as Visit 8/EOS Visit for Study 3101-301-002 or soon thereafter.

- If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit for Study 3101-301-002 should be conducted on the same day as Visit 1 for Study 3101-309-002.

- If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 and Visit 1), then Visit 8/EOS Visit should be conducted as planned per the Study 3101-301-002 Schedule of Visits and Procedures. When this extension study is initiated the participant should return to the clinic as soon as possible, and Visit 1 should be conducted per the Study 3101-309-002 Schedule of Visits and Procedures.

After Visit 1, study visits will occur every 4 weeks for the duration of the 40-week treatment period. Participants will return to the clinic for safety assessments at 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40 weeks relative to Visit 1 (Day 1). An EOS Visit will occur 4 weeks after the last dose of atogepant 60 mg once daily. 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 ≥ 3 × 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 750 participants will be treated with atogepant 60 mg once daily at approximately 110 centers in the United States.

4.2 Inclusion Criteria

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. Participants must be using a medically acceptable and effective method of birth control during the course of the entire study, as defined in Section 4.4.3.

3. Eligible participants who completed the double-blind treatment period (Visit 7) and the follow-up period (Visit 8), if applicable, depending on the timing of study initiation, of Study 3101-301-002 without significant protocol deviations (eg, noncompliance to protocol-required procedures) and who did not experience an AE that, in the investigator's opinion, may indicate an unacceptable safety risk.

4.3 Exclusion Criteria

1. Requirement for any medication, diet (ie, grapefruit juice), that is on the list of prohibited concomitant medications (see Section 4.4.2 and Attachment 12) that cannot be discontinued or switched to an allowable alternative medication. This includes concomitant medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol).

2. 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.

3. An ECG with clinically significant abnormalities at Visit 1 as determined by the investigator.

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

5. Significant risk of self-harm based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator; participants must be excluded if they report suicidal ideation with intent, with or without a plan, (ie, Type 4 or 5 on the C-SSRS) since the last visit.

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

7. Participant has a condition or is in a situation which in the investigator's opinion may put the participant at significant risk, may confound the study results, or may interfere significantly with participation in the study.

8. Any medical or other reasons (eg, unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study) that, in the investigator's opinion, might indicate that the participant is unsuitable for participation in the study.

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

Medications that are not specifically prohibited in Section 4.4.2 are allowed, with the following clarifications and restrictions.

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

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

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

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

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

4.4.2 Prohibited Medications/Treatments

The following medications are prohibited 30 days prior to Visit 1 (unless otherwise indicated) for all participants and throughout the study (see Attachment 12.1):

- Strong and moderate CYP3A4 inhibitors, including but not limited to: systemic (oral/IV) itraconazole, ketoconazole, fluconazole, erythromycin, clarithromycin, telithromycin, diltiazem, verapamil, aprepitant, cyclosporine, nefazodone, cimetidine, quinine, and HIV protease inhibitors
- Strong and moderate CYP3A4 inducers, including but not limited to: barbiturates (eg, phenobarbital and primidone), systemic (oral/IV) glucocorticoids, nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, and St. John’s wort
- Strong OATP1B1 inhibitors (eg, gemfibrozil)
- Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions (eg, warfarin)

- Medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol). See Attachment 12.2
- CBD oil
- Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, BOTOX®, Myobloc®, Xeomin®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to Visit 1 and for the duration of the study
- Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®) within 6 months prior to Visit 1 and for the duration of the study

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

4.4.3 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 (i.e. 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 (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.

4.4.4 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.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently treated.

5 Study Intervention

5.1 Study Intervention and Formulations

Tablets containing atogepant 60 mg (Formulation Number: 11281X)

6 Control Intervention

Not applicable.

6.1 Methods for Masking/Blinding

This is an open-label study.

6.2 Treatment Allocation Ratio

All participants will be treated with atogepant 60 mg once daily.

6.3 Method for Assignment to Treatment Groups

Prior to initiation of atogepant in this open-label extension study, each participant who provides informed consent will maintain their lead-in study participant number. This number will serve as the participant identification number on all study documents.

At Visit 1, eligible participants will receive atogepant 60 mg once daily.

Before the study is initiated, log-in information and directions for the IWRS will be provided to each site.

The atogepant bottles will be labeled with kit numbers. The IWRS system will provide the site with the specific medication kit number(s) for each participant at Visit 1. Sites will dispense atogepant according to the IWRS instructions. Sites will also log onto the IWRS at subsequent visits to obtain a kit number for dispensing atogepant. Sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

Atogepant bottles will be dispensed at the study visits summarized in the Schedule of Visits and Procedures. Returned atogepant bottles should not be re-dispensed to the participants.

6.4 Treatment Regimen and Dosing

Participants who meet all of the study entry criteria at Visit 1 will be treated with atogepant 60 mg once daily.

Atogepant to be used in this trial is listed in Table 6-1.

Participants will be instructed to take their atogepant at approximately the same time each day. Atogepant will be administered orally for 40 weeks, and participants will be followed for 4 weeks following completion or discontinuation of the atogepant.

Table 6-1. Study Intervention

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

6.5 Safety Measures

6.5.1 Adverse Events

AEs 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, 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.

6.5.2 Adverse Events of Special Interest

Selected non-serious and SAEs are of special interest (AESI) 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 AESI, ALT or AST elevations, and potential Hy's law cases are outlined in Sections 9.5 and 9.5.1. These AEs or events determined to be SAEs must be reported appropriately via the designated eCRFs and safety forms.

6.5.3 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 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 Visit 1 will be withdrawn 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 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 6–2.

Table 6–2. 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 study participation.

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.

6.5.4 Vital Signs

Vital sign measurements, including sitting and standing BP, sitting and standing pulse rate, respiratory rate, temperature, and weight 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).

6.5.5 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.

6.5.6 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.

6.5.7 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 all visits the C-SSRS will be completed for ideation and behavior since last visit for all participants. The C-SSRS will be completed 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 2 through 10 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the ET (Visit 11) and the EOS (Visit 12) visits.

6.6 Other Study Supplies

The following will be provided by Allergan or Allergan designee:

- All supplies needed for blood and urine sampling (central laboratory analysis)

- All supplies needed for on-site urine pregnancy test
- Shipping materials for shipment of laboratory samples to central laboratory
- All supplies needed for ECG assessment including ECG machine

6.7 Summary of Methods of Data Collection

An IWRS will be used to manage atogepant inventory. All office visit data for this study will be collected by eCRFs via an electronic data capture system. Source documents will be used at the sites and may include a participant's medical record, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as laboratory tests, ECGs, etc. A centralized clinical laboratory will be used for the analysis of all blood and urine samples, and for ECG assessments. Additional information on the collection and handling of samples is detailed in the Laboratory Procedure Manual.

7 Statistical Procedures

7.1 Analysis Populations

All safety analyses will be performed using the safety population, consisting of all participants who received at least 1 dose of atogepant in this extension study.

7.2 Hypothesis and Methods of Analysis

7.3 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 baseline value as defined for the lead-in study (3101-301-002) will be used as the baseline in this extension study (3101-309-002).

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.

7.4 Subgroup Analyses

No subgroup analysis is planned.

7.5 Sample Size Calculation

As this is a safety extension study from the lead-in Study 3101-301-002, all participants from the lead-in study who are eligible for this extension study will be enrolled. No separate sample size calculation was performed. Based on expected completion rate from the lead-in Study 3101-301-002, approximately 750 participants will be enrolled into this long-term, open-label, safety extension study.

7.6 Interim Analyses

Interim data-cuts are planned to provide ongoing safety data to support global regulatory submissions.

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 4.2 and 4.3 (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.

Participants will maintain their lead-in study participant identification number.

8.2 Washout Intervals/Run-in

This study will not include a washout period.

8.3 Procedures for Final Study Entry

At Visit 1 participants must meet all of the inclusion criteria and must not meet any of the exclusion criteria.

Participants will directly rollover from Study 3101-301-002 (Phase 3 EM). As such, participants will have Visit 7 from Study 3101-301-002 function as the Visit 1 for this study after the participant signs the informed consent. At Visit 1 participants must meet all of the inclusion criteria and must not meet any of the exclusion criteria.

Note, there may be participants who complete Visit 7 in the lead-in Study 3101-301-002 before extension Study 3101-309-002 has been initiated. Those participants should complete Visit 7/ET and Visit 8/EOS Visit (including discontinuation of study intervention) per the Study 3101-301-002 Schedule of Visits and Procedures.

Depending on the timing of the initiation of this extension study in relation to each participant's planned Visit 8 schedule, Visit 1 Study 3101-309-002 can be conducted on the same day as Visit 8/EOS Visit for Study 3101-301-002 or soon thereafter.

If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit for Study 3101-301-002 should be conducted on the same day as Visit 1 for Study 3101-309-002.

If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 and Visit 1), then Visit 8/EOS Visit should be conducted as planned per the Study 3101-301-002 Schedule of Visits and Procedures. When this extension study is initiated, the participant should return to the clinic as soon as possible and Visit 1 should be conducted per the Study 3101-309-002 Schedule of Visits and Procedures.

8.4 Visits and Associated Procedures

There will be 12 scheduled clinic visits: Visit 1 (Day 1), Visit 2 (Week 4), Visit 3 (Week 8), Visit 4 (Week 12), Visit 5 (Week 16), Visit 6 (Week 20), Visit 7 (Week 24), Visit 8 (Week 28), Visit 9 (Week 32), Visit 10 (Week 36), Visit 11/ET (Week 40), and Visit 12/EOS (Week 44).

8.4.1 Open-label Treatment Period (40 Weeks)

8.4.1.1 Visit 1 (Day 1)

- Obtain informed consent and participant privacy.
- Register participant in IWRS.
- Review and record prior medications taken in the past 6 months, and all prior migraine headache medications and concomitant medications.

- Assess inclusion/exclusion criteria.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, height, and weight).
- Perform physical examination.
- Perform urine pregnancy test for women of child-bearing potential.
- Collect urine for drug screen.
- Perform and transmit ECG
- Collect blood and urine for clinical laboratory determinations including: serology, INR, and urinalysis.
- Review and assess AEs.
- Review and update concomitant medications and concurrent procedures.
- Access IWRS and obtain the kit number for atogepant bottle and dispense atogepant bottle.

8.4.1.2 Visits 2 to Visit 11 (Week 4 to 40)

- Perform urine pregnancy test for women of child-bearing potential.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, and weight).
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Perform and transmit ECG (Visit 4 [Week 12], Visit 7 [Week 24], and Visit 11 [Week 40] only).
- Collect previous visit atogepant bottle, review participant compliance and perform accountability.

- Review and assess AEs.
- Review and update concomitant medications and concurrent procedures.
- Access IWRS to dispense atogepant bottle and enter accountability.

8.4.1.3 Visit 11/Early Termination (Week 40)

Effort should be made by the site to not schedule Visit 11 earlier than 40 weeks after Day 1, to ensure participants complete the full 40 weeks of atogepant treatment.

- Perform physical examination.
- Perform urine pregnancy test for women of child-bearing potential.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, and weight).
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Perform and transmit ECG.
- Review and assess AEs.
- Review and update concomitant medications and concurrent procedures.
- Collect previous visit atogepant bottle, review participant compliance and perform accountability.
- Access IWRS to enter study visit and accountability.

8.4.2 Safety Follow-up Period (4 Weeks)

8.4.2.1 Visit 12/EOS (Week 44)

- Perform physical examination.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, and weight).

- Perform urine pregnancy test for women of child-bearing potential.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Review and assess AEs.
- Update concomitant medications and concurrent procedures.
- Access IWRS to enter study visit.

8.5 Instructions for the Participants

Section 4.4.4 provides diet and activity instructions for participants enrolled in the study. Prohibited medications should be reviewed with the participants. Participants will be instructed to return their atogepant bottle(s), both used and unused at each visit.

Participants should be instructed to take atogepant 60 mg once daily at approximately the same time each day (approximately 24 hours between doses). For dosing on Day 1 (Visit 1), the first dose is to be taken at the study site.

Participants should use appropriate contraceptive measures for the duration of their participation in the study (Section 4.4.3)

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 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 participants who prematurely discontinue from the study, regardless of cause, should be seen for final study assessments. The final assessments will be defined as the evaluations scheduled for Visit 11/ET and Visit 12/EOS, 4 weeks post the last dose of atogepant.

8.9 Withdrawal Criteria

- **Participants with the following at Visit 1:**
    - **Laboratory Results:**
        - ALT or AST > 1 x ULN OR
        - total bilirubin > 1 x ULN (except for participants with a diagnosis of Gilbert's disease) OR
        - serum albumin < 2.8 g/dL

- Positive result on the urine drug screen unless explained by concomitant medication use (eg, opioids prescribed for migraine pain).
- Positive result on anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti–hepatitis C antibody testing, or anti-hepatitis E IgM antibody.

- **ECG Results:**
  - QTcF > 450 msec for males and QTcF > 470 msec for females on the final central vendor ECG report
  - Clinically significant cardiac rhythm or conduction abnormalities (eg, atrial fibrillation, second- or third-degree heart block)

- **Participants with the following at any study visit:**
  - Female participants who become pregnant (Section 9.4)
  - Participants who meet atogepant 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.
  - 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 2 through 10 must be withdrawn from the study.
  - 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.

All withdrawn participants should receive appropriate follow-up as in routine clinical practice, including the ET (Visit 11) and the EOS (Visit 12) assessments.

8.10 Study Termination

The study may be stopped at the 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, 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. In addition, during Visit 1, AEs will be assessed regardless of the administration of atogepant.

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 the study (see Section 8.8).

All AEs from the signing of the ICF until the EOS Visit (Visit 12), or 30 days after the last dose of atogepant if the EOS 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 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.

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

Any preplanned 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 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 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 6.5.2) 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 EOS Visit (Visit 12) or 30 days after the last dose of atogepant if the EOS 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 until the EOS Visit (Visit 12) or 30 days after the last dose of atogepant if the EOS 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 Number[s]: +1-714-796-9504 [back up fax number: +1-714-246-5295], email: IR-Clinical-SAE@allergan.com), 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. Any participant with this laboratory result after atogepant was taken must have repeat testing within 48 to 72 hours to confirm the abnormality. For this repeat testing, the following laboratory tests must be performed: hematology and chemistry panels, INR, serum acetaminophen level, urine drugs of abuse screen, and blood alcohol level. An extra blood serology sample must be collected and sent to the central laboratory for further diagnostic testing, at a later date, if needed. In addition, the investigator will perform a complete history and examination to evaluate the participant for possible liver disease.

All AEs of special interest 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 AE of special interest.

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

For these participants, the following laboratory tests must be performed: anti-hepatitis A IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, hepatitis C antibody, hepatitis C quantitative RNA by polymerase chain reaction, anti-hepatitis E IgM, anti-hepatitis E IgG, Cytomegalovirus IgM antibody and Epstein-Barr Virus IgM antibody. The participant must

be followed clinically and further medical evaluation (for other causes of acute hepatic injury) should be done per the judgment of the investigator and in conjunction with medical personnel at Allergan. In general, the chemistry panel should be repeated 1 to 2 times per week to follow the course of ALT/AST elevation.

Atogepant 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 only after consultation with the Allergan Medical Monitor. For participants who are not rechallenged, the participant should be discontinued from the study and complete an ET Visit and an EOS Visit 4 weeks later. 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:

- 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 (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 fax number on the form or the SAE 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, and/or from the participant's legally authorized representative, prior to any study-related activities or procedures in the study.

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

Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as laboratory tests, and ECGs. The investigator's copy of the eCRFs serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

- Participant’s name
- Participant’s contact information
- The date that the participant entered the study, participant number, and participant randomization (or medication kit) number
- The study title and/or the protocol number of the study and the name of Allergan
- A statement that informed consent was obtained (including the date). A statement that written authorization or other country and local participant privacy required documentation for this study has been obtained (including the date)
- Dates of all participant visits
- Participant’s medical history
- Information regarding participant’s diagnosis of migraine headache
- All concurrent medications (List all prescription and nonprescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded.)
- Occurrence and status of any AEs
- The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.
- The results of laboratory tests performed by the site (eg, results of urine pregnancy tests).
- Key study variables

Source documentation practices must follow Section 4.0 of ICH E6, GCP: Consolidated Guidance, and ALCOA (ie, records must be Attributable, Legible, Contemporaneous, Original and Accurate).

10.6.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each participant's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The

eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan and will be maintained in a central data repository.

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.

For countries falling within the scope of the ICH guidelines, Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of atogepant. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

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

10.7.1 Labeling/Packaging

Atogepant will be supplied in bottles and will be labeled with the protocol number, storage information, warning language, and instructions to take the tablets as directed. The bottle will also include the kit number. Immediately before dispensing the bottle, the investigator or designee will write the participant number and date on the bottle.

10.7.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed or administered to the participants, the number of units returned to the investigator by the participant, and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for atogepant. 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

All atogepant and/or supplies will be returned to Allergan or Allergan designee for destruction.

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

Urine pregnancy test kits will be provided by the central laboratory; all urine pregnancy testing will be administered on site according to instructions in the central laboratory manual.

Samples of blood and urine for evaluation of hematology, blood chemistry, urinalysis, urine drug screen, INR, and serology will be analyzed at a central clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology or Clinical Laboratory Improvement Amendments certification).

All samples will be returned to Allergan or Allergan's designee for destruction. Allergan shall have full ownership rights to any biological specimens/samples derived from the study. For additional details regarding handling of biological specimens, please refer to the Study Reference Manual.

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.

11 References

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12 Attachments

12.1 Examples of Prohibited Medications

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

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

	Strong/moderate CYP3A4 inducers	Strong/moderate CYP3A4 inhibitors
Anti-depressants/ Anti-anxiety	Barbiturates • Amobarbital (Amytal™) • Aprobarbital (Alurate™) • Butalbital (Fiorinal™, Fioricet™) • Butabarbital (Busodium™, Butisol™) • Mephobarbital (Mebaral™) • Pentobarbital (Nembutal™) • Phenobarbital (Luminal™, Solfoton™) • Secobarbital (Seconal™)	Nefazodone (Serzone™)
Anti-seizure	Carbamazepine (Atretol™, Carbatrol™, Epitol™, Equetro™, Tegretol™) Oxcarbazepine (Trileptal™) Phenytoin (Dilantin™, Phenytek™) Primidone (Myidone™, Mysoline™)	
Diabetes	Pioglitazone (Actos™) Troglitazone (Rezulin™, Resulin™)	
Antiemetic		Aprepitant (Emend™)
Anti-hypertension		Diltiazem (Cardizem™) Verapamil (Calan™, Calan SR™)
Glucocorticoid (Systemic)	Betamethasone (Celestone™) Dexamethasone (Baycadron™, DexPak™) Hydrocortisone (Cortef™) Methylprednisolone (Medrol™) Prednisolone (Prelone™) Prednisone (Deltasone™) Triamcinolone (Kenalog™)	
Antibiotics	Rifabutin (Mycobutin™) Rifampicin/Rifampin (Rifadin™, Rifater™, Rimactane™)	Erythromycin (Benzamycin™, EryTab™) Clarithromycin (Biaxin™) Telithromycin (Ketek™)
Anti-fungal		Fluconazole (Diflucan™, Trican™) Itraconazole (Sporanox™) Ketoconazole (Nizoral™)
Anti-HIV	Efavirenz (Stocrin™, Sustiva™) Nevirapine (Viramune™)	Indinavir (Crixivan™) Nelfinavir (Viracept™) Ritonavir (Norvir™) Saquinavir (Fortovase™, Invirase™)
Immune Suppressant		Cyclosporine - Oral/IV only (Neoral™, Sandimmune™)

	Strong/moderate CYP3A4 inducers	Strong/moderate CYP3A4 inhibitors
Others	St. John's wort Enzalutamide (Xtandi™) Modafinil (Provigil™) Armodafinil (Nuvigil™)	Buprenorphine (Cizol™, Subutex™, Suboxone™) Quinine

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

The following medications or treatments are prohibited 6 months prior to Visit 1 and throughout the study:

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

12.2 Classification of Migraine Preventive Medications

Below is a list of migraine preventive medications considered effective or probably effective sorted by mechanism of action. Of note, topiramate and valproic acid derivatives are considered separate categories.

Pharmacologic Category	**Drug Name**
Antiepileptic	Valproic acid, sodium valproate, divalproex sodium Topiramate
Tricyclic antidepressant	Amitriptyline Nortriptyline
Beta-blockers	Metoprolol Bisoprolol Atenolol Nadolol Propranolol Timolol
Calcium channel blocker	Flunarizine
Angiotensin receptor blocker (ARB)	Candesartan
Angiotensin-converting enzyme (ACE) inhibitor	Lisinopril
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine Venlafaxine
Miscellaneous	Country approved products for migraine prevention (eg, oxetrone, pizotifen)

Source: Evers 2009, Hoffmann 2014, Schürks 2008, Silberstein 2012, Steiner 2007.

12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CBD	cannabidiol
CGRP	calcitonin gene-related peptide
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
EM	episodic migraine
EOS	end of study
ET	early termination
FDA	Food and Drug Administration
GBD 2010	Global Burden of Disease Survey 2010
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HSG	hysterosalpingogram
IB	Investigator's Brochure
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
IV	intravenous
IWRS	interactive web response system
NSAID	nonsteroidal anti-inflammatory drug
OATP1B1	organic anion transporting polypeptide 1B1
PK	pharmacokinetic
QTcF	QT interval corrected for heart rate using Fridericia formula (QTcF = $QT/(RR)^{1/3}$)

Term/Abbreviation	Definition
SAE	serious adverse event
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal

To: Atogepant 3101-309-002 Institutional Review Boards & Investigators

From: [redacted]/Clinical Development, CNS

Date: 23 March 2020

Re: **3101- 309-002, A PHASE 3, MULTICENTER, OPEN-LABEL 40-WEEK EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN PARTICIPANTS WITH EPISODIC MIGRAINE**

Please accept this correspondence as notification that due to the COVID-19 pandemic the protocol changes below may be implemented for Investigative Sites to eliminate immediate potential hazards to participants and study staff while ensuring participant safety and maintaining data integrity.

- **Remote Study Visits (Visit 2 - Visit 11)** – Investigators/appropriately designated study staff will be allowed to perform study visits as remote study visits (e.g., conducted via phone, video conference) if participants are unable to attend in-person due to the COVID-19 pandemic. During these remote study visits, the *Schedule of Visits and Procedures for Remote Study Visits* below should be followed. Please note the following clarifications:
  - **Safety Assessments:**
    - Safety assessments to be completed at remote study visits include assessment of adverse events, concomitant medications, pregnancy test results review, and the Columbia-Suicide Severity Rating Scale (C-SSRS).
    - For participants that have a study visit replaced by a remote study visit, all missed in-person safety assessments (i.e., clinical laboratory samples, vital signs and ECGs) will be collected at the next in-person visit.
    - To ensure patient safety, remote study visits can be performed for up to 8 weeks (ie, no in-person study visits for up to 8 weeks) at the discretion of the Investigator after which participants who cannot attend in-person for a study visit must be discontinued from the study.
  - **Columbia-Suicide Severity Rating Scale (C-SSRS)** – Study trained, and delegated raters will perform the C-SSRS remotely and review any positive results with an Investigator-delegated clinician to ensure the participant is not at risk for suicide.
  - **Urine Pregnancy Tests** – Investigators/site staff will provide participants with study supplied urine pregnancy tests and corresponding written instructions to be used at-home by participants for remote study visits. Sites are required to verbally review testing instructions with all participants. Pregnancy tests must be completed according to the *Schedule of Visits and Procedures for Remote Visits* below.
- **Study Medication Dispensation for Remote Study Visits (Visit 2 – Visit 10):**
  - Study medication for remote study visits can be shipped to participants via an overnight courier or provided curbside.
  - Study medication to cover 1 additional remote study visit may be dispensed.
  - Sites are required to provide a documented written process with approval from Allergan prior to performing the first remote visit.

- **Study Visit 12/Follow-Up/End of Study** – Study Visit 12 should be conducted remotely (e.g., conducted via phone, video conference) for **all participants in all cases** following the *Schedule of Visits and Procedures for Remote Study Visits* below.

Training on this protocol clarification will be provided by Allergan. We appreciate your dedication in ensuring participant safety during this challenging time. If you have any questions, please do not hesitate to contact your RSM or the Medical Monitor.

3101-309-002 Schedule of Visits and Procedures for Remote Study Visits

Study Period	Open-label Treatment Period (40 weeks)										Safety Follow-up Period (4 weeks)
Visit #	**Visit 2**	**Visit 3**	**Visit 4**	**Vi it 5**	**V sit 6**	**Visit 7**	**Visi 8**	**Visit 9**	**Visit 10**	**Visit 11/ET**	**Visit 12/ EOS**
Day/Week	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***
Visit Windows	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Provide urine pregnancy test and instructions[a]	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
Access IWRS	X	X	X	X	X	X	X	X	X	X	X
Dispense study intervention	X	X	X	X	X	X	X	X	X		
Review of study intervention compliance and accountability	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/concurrent procedures	X	X	X	X	X	X	X	X	X	X	X

[a] For women of childbearing potential only, a urine pregnancy test must be performed within 48 hours of the remote visits.