Title Page

Protocol Title:	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prophylaxis of Migraine in Participants with Episodic Migraine Who Have Previously Failed 2 to 4 Classes of Oral Prophylactic Treatments (ELEVATE)
Protocol Number:	3101-304-002
Amendment Number:	Amendment 2
Product:	Atogepant (AGN-241689)
Brief Protocol Title:	Atogepant for prophylaxis of migraine in participants who failed previous oral prophylactic treatments
Study Phase:	3
Sponsor Name:	Allergan Limited
Legal Registered Address:	Allergan Limited Ground Floor, Marlow International, Parkway Marlow, Buckinghamshire SL7 1YL United Kingdom
US Agent:	Allergan Sales, LLC 5 Giralda Farms Madison, NJ 07940 USA

Regulatory Agency Identifying Number(s): EudraCT Number: 2019-003448-58; IND: 114780

Allergan Medical Safety Physician Contact Information:	Refer to the Study Contacts Page
Allergan Sponsor Signatory:	[redacted] Vice President, Neuroscience Development
Original Protocol Date:	17 December 2019
Amendment 1 Date	03 April 2020
Amendment 2 Date	01 December 2020

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

SAE Reporting Fax Number/Email:

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Allergan	IR-Clinical-SAE@allergan.com	Not applicable	+1-714-796-9504 Backup: +1-714-246-5295

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, GCP, 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

The signature of the sponsor signatory is collected on the protocol approval page.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	01 December 2020
Amendment 1	03 April 2020
Original Protocol	17 December 2019

Amendment 2 (01 December 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The changes are to remove one atogepant treatment arm and change the study design to a 2-arm study, reduce the sample size, add measures to protect participants or study personnel in pandemic situations (eg, COVID-19, such as, replacing office visits by remote visits if needed, etc) and to enable participants to roll over into long-term extension study 3101-312-002. In addition, the amendment is to simplify inclusion and exclusion criteria, clarify study objectives and endpoints, study assessments, statistical analyses, and resolve discrepancies in the protocol.

Section No. and Name	Description of Change	Brief Rationale
Throughout	Removed the atogepant 30 mg QD treatment arm from the study and reduced the total number of participants from 627 to 300 participants (initial protocol had 209 participants in each of 3 treatment arms, the amended protocol has 150 participants in each of 2 treatment arms).	The results from the Phase 3 Study 3101-301-002 demonstrated that the efficacy of atogepant 10 mg QD, 30 mg QD, and 60 mg QD was significantly higher than placebo for the prevention of migraine in participants with episodic migraine. The atogepant 60 mg QD dose had the highest efficacy while not having a clinically meaningful difference in safety. Therefore, the sponsor decided to eliminate the atogepant 30 mg QD treatment arm in this study and re-estimate the sample size, which reduced the number of participants required to demonstrate a significant difference in atogepant 60 mg QD compared to placebo based on observed responses in Study 3101-301-002.

Section No. and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated in line with changes made throughout the protocol.	To update the synopsis with amended items in the main body of the protocol.
1.3 Schedule of Activities	Updated to clarify that Visit 1 and Visit 2 must be conducted in the office. All other visits should be conducted in the office unless it is necessary to conduct remote visits for safety reasons.	Add measures to protect participants or study personnel in pandemic situations (eg, COVID-19).
	Define the number of scheduled study visits	Add measures for participants rolling over into Study 3101-312-002 (long-term extension study).
	Text was updated to say "Obtain VCT consent and perform verification (United States ~~and Canada~~ only)"	Canada will not utilize the VCT verification
2.2 Background	Updated section with the results from the recently completed Phase 3 studies (Study 3101-301-002 and Study 3101-302-002).	To provide the latest clinical study results and information to the investigators.
3. Objectives and Endpoints	**Secondary:** The first 3 secondary objectives and endpoints have been revised for clarification	To clarify and specify the actual secondary objectives and endpoints.
	Secondary: (*for the United States only*) Added text to clarify the previous secondary objective and endpoints of evaluating the effect of atogepant versus placebo on functioning and activity impairment by specifying the AIM-D domains of Performance of Daily Activities and Physical Impairment.	To further clarify the previous secondary objective and endpoint related to functioning and activity impairment by specifying the Performance of Daily Activities and Physical Impairment domains of the AIM-D score..
	Exploratory: Deletion of CFB in monthly headache-free days at Weeks 1-4, 5-8, and 9-12.	To remove redundancy because monthly headache-free days will be complementary to monthly headache day.
	Exploratory: Deletion of CFB in monthly headache day pain intensity at Weeks 1-4, 5-8, and 9-12.	To remove redundancy because headache pain intensity can be interpreted using monthly moderate/severe days.
	Exploratory: Deleted Week 16 from HIT-6 and MSQ v2.1 assessments as an endpoint for evaluation of efficacy.	Treatment with atogepant or placebo ends at Week 12 (Visit 7) and it is predicted that many participants will enroll in the safety extension Study 3101-312-002. So an assessment at Week 16 will not assess the participant's ability to function while on treatment and the number of participants who will actually have a Week 16 (Visit 8) will be low.

Section No. and Name	Description of Change	Brief Rationale
	Exploratory: Added an additional Exploratory objective and endpoint related to Performance of Daily Activities.	To further clarify the endpoint in CFB in monthly Performance of Daily Activities of the AIM-D.
	Exploratory: Added an Exploratory objective and endpoint related to Physical Impairment.	To further clarify the endpoint related to CFB in monthly Physical Impairment of the AIM-D.
	Exploratory: Added an Exploratory objective and endpoint related to the total score of the AIM-D.	To further clarify the endpoint related to the AIM-D total score.
4.1 Overall Design	Elaboration on how the randomization will be stratified by number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) and the number of classes of failed prior prophylactic treatments (2 and > 2).	Clarification of stratification strategy.
	Adjusted block size for block randomization to accommodate the deletion of the atogepant 30 mg QD treatment arm.	To adjust for the elimination of the atogepant 30 mg QD treatment arm.
	Reference to Subpopulation A removed	To simplify the enrollment requirements
	Added that approximately 50% of randomized participants will have failed >2 classes of prior migraine prophylactic medications	To elaborate on the predicted number of randomized participants in this study that will meet the stratification category of >2 classes of failed prophylactic treatment.
	Define the number of scheduled study visits for participants who will roll over into Study 3101-312-002 (long-term extension study) and those who do not.	Add measures for participants rolling over into Study 3101-312-002 (long-term extension study).
4.2 Justification for Dose	Updated this section with results from Study 3101-301-002 that verifies that the atogepant 60 mg QD dose has a higher efficacy than the atogepant 30 mg QD dose without adding any safety risk.	Verifies the results from Study CGP-MD-01 and justifies the deletion of the atogepant 30 mg QD treatment arm from this study.
5.1 Inclusion Criteria	Inclusion Criterion 2.06.b – Updated to state "Failed <u>at least</u> one ~~AND failed or be not suitable for a second~~treatment from ~~a different medication class as listed~~<u>the list</u> below: i. Propranolol OR metoprolol; ii. Topiramate; iii. Flunarizine;	To simplify the enrollment requirements

Section No. and Name	Description of Change	Brief Rationale
	iv. Amitriptyline”	
	Inclusion Criterion 2.07 removed	To simplify the enrollment requirements
	Inclusion Criterion 3.01, updated to state: “Male participants willing to minimize the risk of inducing pregnancy ~~for the duration of the clinical study and the follow-up period~~ as detailed below” “Female participants willing to minimize the risk of inducing pregnancy ~~for the duration of the clinical study and the follow-up period~~ as detailed below”	To resolve inconsistency in the description of contraception requirements.
5.2 Exclusion Criteria	Revised Exclusion Criterion 3.03 to clarify the use of barbiturate-containing and opioid-containing analgesics on a monthly basis in the 3 months prior to Visit 1	To clarify the conditions of barbiturate- and opioid-containing analgesics that would exclude participants from this study.
	In Exclusion Criterion 3.04, the word “oral” was removed and “or approved” added in the text “any other ~~oral~~ investigational or approved CGRP-RA.”	To clarify that the use of any investigational or approved CGRP-RA is excluded.
	In Exclusion Criterion 3.04, reference to ubrogepant and rimegepant was removed	To clarify that prior use of ubrogepant or rimegepant is not exclusionary.
5.3 Criteria for Determining that Prior Treatment for the Prophylaxis of Migraine Have Been Failed	Deleted text: “Not suitable for the purpose of this study is defined as participant is not considered to be suitable for the treatment for medical reasons such as contraindications or precautions included in local labels, national guidelines or other locally binding documents, or other medically relevant reasons as confirmed by the treating physician. Unsuitability of prior migraine preventive medication categories is to be collected in the eCRF based on: • Contraindications or precautions included in local labels • National guidelines or other locally binding documents • Other medically relevant reasons”	To harmonize with updated inclusion criteria

Section No. and Name	Description of Change	Brief Rationale
5.5 Screen Failures	Updated to state: "Rescreening of screen failures is permitted in certain situations (including failure to adequately screen due to the COVID-19 pandemic), "	To further clarify possibilities for rescreening in pandemic situations (eg, COVID-19)
5.5.1 Procedure for Duplicate Participant Identification – Verified Clinical	Reference to Canada removed.	VCT will not be used in Canada.
6.1.4 Intervention Allocation Ratio	Elaboration on how the randomization will be stratified by number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) and the number of classes of failed prior prophylactic treatments (2 and > 2).	Clarification of stratification strategy.
	Reference to Subpopulation A removed.	To harmonize with updated inclusion criteria.
	Updated with "Approximately 50% of randomized participants will have failed > 2 classes of prior prophylactic treatments.".	To elaborate on the predicted number of randomized participants in this study that will meet the stratification category of > 2 classes of failed prophylactic treatment.
6.1.5 Other Study Supplies	Deleted text in All supplies neded for PK ~~and future biomedical research~~ sample collections.	Clarification
6.3 Measures to Minimize Bias: Randomization and Blinding	Deleted text: "A double-dummy design will be used to maintain study blind".	Revised because there is only one matching placebo for the atogepant 60 mg tablet.
6.5.3 Prohibited Interventions During the Study	Added bulleted text: "Ubrogepant (Ubrelvy®) and rimegepant (Nurtec ODT®) is prohibited from Visit 1 throughout the study period."	Clarification of prohibited concomitant medications
8.3.6 Pregnancy	The text in the first bullet was updated: "Details of all pregnancies in female participants and female partners of male participants will be collected ~~from~~after the ~~signing~~start of ~~the ICF~~study intervention and until ~~3~~the Follow-Up Visit (Visit 8) or 30 days after the last dose of study intervention if the Follow-Up Visit is not done."	To extend the period of pregnancy data collection in order to ensure consistency across the atogepant development program
8.9.1. Activity Impairment in Migraine-Diary (AIM-D)	Description of Activity Impairment in Migraine-Diary (AIM-D) updated	To further clarify the domain structure of Activity Impairment in Migraine-Diary (AIM-D)

Section No. and Name	Description of Change	Brief Rationale
9.1 Statistical Hypothesis	Added the revised hypothesis that atogepant dose has a greater effect than placebo.	To add the alternative statistical hypothesis for the study.
9.2 Sample Size Determination	Revised sample size determination based on the elimination of the atogepant 30 mg QD treatment arm, the estimated efficacy response for the primary endpoint based on the results from Study 3101-301-002, and the primary efficacy endpoint in the United States and in the European Union.	To adjust the sample size to accommodate the elimination of the atogepant 30 mg QD treatment arm and estimated responses in the primary efficacy endpoint based on the responses from participants in the completed study (3101-301-002).
9.4.1.1.2 Secondary efficacy endpoints	Added text to clarify the previous Secondary objective related to Performance of Daily Activities and its respective endpoint. Added an additional Secondary objective and endpoint in this category related to Physical Impairment.	To further clarify the previous Secondary objective and endpoint related to the Performance of Daily Activities of the AIM-D and to add an additional Secondary objective and endpoint related to the effect of Atogepant on Physical Impairment of the AIM-D.
9.4.1.1.3 Exploratory efficacy endpoints	Deleted exploratory endpoint of CFB in monthly headache-free days at Weeks 1-4, 5-8, and 9-12 and average across the 12-week treatment period.	To remove redundancy because monthly headache-free days will be complementary to monthly headache days.
	Deleted exploratory endpoint of CFB in monthly headache day pain intensity at Weeks 1-4, 5-8, and 9-12 and average across the 12-week treatment period.	To remove redundancy because headache pain intensity can be interpreted using monthly moderate/severe days.
	Added an exploratory endpoint related to Performance of Daily Activities.	To further clarify the endpoint in CFB in monthly Performance of Daily Activities of the AIM-D.
	Added an exploratory endpoint related to Physical Impairment.	To further clarify the endpoint related to CFB in monthly Physical Impairment of the AIM-D.
	Added an exploratory endpoint related to the total score of the AIM-D.	To further clarify the endpoint related to the AIM-D total score.
9.4.1.2 Primary Analysis	Added text to further clarify the analysis of the primary efficacy variable and what parameters will be included in the statistical model.	To further clarify which stratification parameters will be included in the statistical model for the analysis and that only data collected during the double-blind period will be included in the analysis.
9.4.1.2.1 Sensitivity Analyses in Missing Data Handling **9.4.1.2.2 Sensitivity Analysis for Possible**	Added 2 new subsections for sensitivity analyses of the primary efficacy data	To further clarify the sensitivity analysis in these 2 situations.

Section No. and Name	Description of Change	Brief Rationale
Violation of Normality Assumption		
9.4.1.3Secondary Analyses	Added text to further define the AIM-D assessment of functioning and activity impairment by using the Performance of Daily Activities and Physical Impairment domain scores and to clarify what parameters will be included in the statistical model for analysis.	To further clarify the analyses used for the secondary objectives.
9.4.1.4 Exploratory Efficacy Analyses	Added text related to the analyses of the exploratory objectives.	To further clarify the analyses used for the exploratory objectives.
9.4.4 Subgroup Analyses	Added text related to the subgroup analyses.	To further clarify the analyses used for the subgroup analyses.
9.6 Off-Treatment Hypothetical Estimand	Added text related to an Off-treatment Hypothetical Estimand	To clarify the analyses used for the Off-treatment Hypothetical Estimand and the subsections.
10.7 Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information	Revised text specifying that nonvasectomized male participants should use contraception during the intervention period and at least 3 days after the last dose of study intervention. Previously, the text just specified the course of the study. Revised text to specify that a male condom can be used with or without spermicide.	Clarification Clarification
10.8.1 Visit 1 (Screening/Baseline) Day -35 to Day 28	Revised VCT consent and verification to be only in the United States instead of the United States and Canada	Clarification
10.8.2 Visit 2 (Randomization) Day 1 **10.8.3 Visits 3 to 6 (Weeks 2 to 8)**	Revised text to remind participant to not only bring e Diary, but also to return the study intervention kits	Clarification
10.8.4 Visit 7/Early Termination (Week 12)	Added text specifying to complete the Healthcare Resource Utilization Questionnaire	Clarification
10.9 Appendix 9: Examples of Prohibited Medications	In table for Drugs with demonstrated efficacy for the prevention of migraine: Added “Locally approved products (eg, oxeterone, pizotifen)”	Clarification of prohibited concomitant medications

Section No. and Name	Description of Change	Brief Rationale
	Added text: "Ubrogepant (Ubrelvy®) and rimegepant (Nurtec ODT®) is prohibited from Visit 1 throughout the study period."	Clarification of prohibited concomitant medications
10.11 Study Visits Conducted Remotely	Added Appendix 11 related to visits conducted remotely.	To further clarify the Schedule of Activities for remote visits and when they are permitted.
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prophylaxis of Migraine in Participants with Episodic Migraine Who Have Previously Failed 2 to 4 Classes of Oral Prophylactic Treatments (ELEVATE)

Protocol Number: 3101-304-002

Brief Title: Atogepant for prophylaxis of migraine in participants who failed previous oral prophylactic treatments

Study Phase: 3

Study Rationale: To prospectively assess the safety, tolerability, and efficacy of atogepant 60 mg QD compared with placebo in the prophylaxis of episodic migraine in participants who previously failed 2 to 4 classes of oral prophylactic treatments.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To prospectively test for superiority of atogepant 60 mg QD versus placebo for the prevention of migraine in participants with episodic migraine who have previously failed 2 to 4 classes of oral medications for the prophylaxis of migraine	Change from baseline (CFB) in mean monthly migraine days across the 12-week treatment period.
Secondary	
To evaluate the effect of atogepant 60 mg QD versus placebo on the proportion of participants with at least 50% reduction from baseline in monthly migraine days	Achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period.
To evaluate the effect of atogepant 60 mg QD versus placebo for the prophylaxis of headache	CFB in mean monthly headache days across the 12-week treatment period.
To evaluate the effect of atogepant 60 mg QD versus placebo on acute medication use	CFB in mean monthly acute medication use days across the 12-week treatment period.
To evaluate the effect of atogepant 60 mg QD versus placebo on the impact of migraine on daily activities as assessed by Migraine Specific Quality of Life Questionnaire (MSQ) v2.1 Role Function-Restrictive domain score	CFB in MSQ v2.1 Role Function-Restrictive domain score at Week 12

Objectives	Endpoints
For the United States only: To evaluate the effect of atogepant 60 mg QD versus placebo on Performance of Daily Activities	*For the United States only:* CFB in mean monthly Performance of Daily Activities domain score of the Activity Impairment in Migraine (AIM-D) across the 12-week treatment period
To evaluate the effect of atogepant 60 mg QD versus placebo on Physical Impairment	CFB in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period
For the European Union only: To evaluate the effect of atogepant 60 mg QD versus placebo on the impact of headaches on daily functioning as assessed by Headache Impact Test (HIT-6)	*For the European Union only:* CFB in the HIT-6 total score at Week 12

Overall Study Design:

- This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel group study in participants with episodic migraine who have previously failed 2 to 4 classes of oral medications for the prophylaxis of migraine

Key Inclusion Criteria

Selected key inclusion criteria are presented below:

Age
Male or female participants ages 18 (or age of legal majority) to 80 years, inclusive, at Visit 1
Type of Participant and Migraine Characteristics
At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3, 2018.
Age of the participant at the time of migraine onset < 50 years
History of 4 to 14 migraine days per month on average in the 3 months prior to Visit 1 in the investigator's judgment
4 to 14 migraine days in the 28-day baseline period per eDiary *(Note: A randomization cap of 20% will be instituted to ensure that the planned randomized participants include no more than 20% of participants with 4 to <8 migraine days at baseline.)*
Completed at least 20 out of 28 days in the eDiary during the baseline period and is able to read, understand, and complete the study questionnaires and eDiary per investigator's judgment.

Participants must meet both criteria below (ie, a and b). Participants must have

a. Failed oral migraine prophylaxis medications from 2 to 4 of the medication classes as listed below:
    i. Propranolol, metoprolol, atenolol, bisoprolol, timolol, or nadolol;
    ii. Topiramate;
    iii. Flunarizine;
    iv. Valproate or divalproex;
    v. Amitriptyline or nortriptyline;
    vi. Venlafaxine or desvenlafaxine;
    vii. Lisinopril;
    viii. Candesartan;
    ix. Locally approved products (eg, oxeterone or pizotifen)
b. Failed at least one treatment from the list below:
    i. Propranolol OR metoprolol;
    ii. Topiramate;
    iii. Flunarizine;
    iv. Amitriptyline;

(*Note: Participant failure of a prophylactic medication can be on the basis of tolerability or efficacy and is based on investigator judgement. Refer to Section 5.3 for more detailed information. Each prior prophylactic medication failure needs to be documented in the Treatment Failure Worksheet, see Section 10.10 [Appendix 10]).*

Contraceptives

Male participants willing to minimize the risk of inducing pregnancy, as detailed below:

A male participant must agree to use contraception as detailed in Section 10.7, Appendix 7 of this protocol during the intervention period and for at least 3 days after the last dose of study intervention and refrain from donating sperm during this period.

Female participants willing to minimize the risk of inducing pregnancy as detailed below.

A female participant is eligible to participate if she is not pregnant (ie, has a negative urine pregnancy result at the Screening Visit (Visit 1) and Randomization Visit (Visit 2), is not planning to become pregnant during the course of the study, is not breastfeeding, and fulfils at least one of the following conditions:

a. Not a woman of childbearing potential (WOCBP) as defined in Section 10.7 (Appendix 7)

OR

b. A WOCBP who agrees to follow the contraceptive guidance of using a medically acceptable and effective contraceptive method as defined in Section 10.7 (Appendix 7) during the intervention period and for 3 days after the last dose of study intervention.

Key Exclusion Criteria

Selected key exclusion criteria are presented below:

Medical Conditions
Any clinically significant hematologic, endocrine, pulmonary, hepatic, gastrointestinal, or neurologic disease • If there is a history of such a disease, but the condition has been stable for more than 1 year prior to Visit 1, and is judged by the investigator as not likely to interfere with the participant's participation in the study, the participant may be included
Participant has any other concurrent pain condition that, in the opinion of the investigator, may significantly impact the current headache disorder (eg, fibromyalgia, facial pain)
In the opinion of the investigator, confounding psychiatric conditions, dementia, epilepsy, or significant neurological disorders other than migraine
Clinically significant cardiovascular or cerebrovascular disease per the investigator's opinion including, but not limited to: • Clinically significant ischemic heart disease (eg, unstable angina pectoris) • Clinically significant cardiac rhythm or conduction abnormalities (eg, atrial fibrillation, second- or third-degree heart block) or risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, bradycardia) • Myocardial infarction, transient ischemic attack, or stroke within 6 months prior to Visit 1 • Heart failure defined as New York Heart Association functional classification system, Class III or IV
At Visit 1, a user of recreational or illicit drugs (including cannabis regardless of legality) or has had a history within the past year of drug or alcohol abuse or dependence
Migraine Characteristics
Has ≥ 15 headache days per month on average across the 3 months prior to Visit 1 in the investigator's judgment
Has ≥ 15 headache days in the 28-day baseline period per eDiary
Difficulty distinguishing migraine headaches from tension-type or other headaches
Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018

Has a current diagnosis of chronic migraine, new persistent daily headache, medication overuse headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018
Prior/Concomitant Therapy
Usage during 30 days prior to Visit 1 (unless otherwise indicated) and throughout the study period of and requirement for any medication, diet (ie, grapefruit juice), or non-pharmacological treatment that is on the list of prohibited concomitant medications or treatments that cannot be discontinued or switched to an allowable alternative medication or treatment. This includes concomitant medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol) regardless of indication. (See Section 6.5.3)
Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, BOTOX®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to Visit 1 and throughout the study period.
Usage of barbiturate-containing or opioid-containing analgesics > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, NSAIDs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline period. *(Note: barbiturate-containing analgesics are excluded 30 days prior to screening, during the screening/baseline period, and for the duration of the study. Opioid-containing analgesics are excluded during the screening/baseline period and throughout the study, however, episodic use of opioids for purposes not related to migraine or headache, eg, surgery, is not exclusionary.)*
Previous exposure to • Atogepant (AGN-241689 or MK-8031) • Injectable monoclonal antibodies blocking the calcitonin gene-related peptide (CGRP) pathway within the last 6 months prior to Visit 1 • Any other investigational calcitonin gene-related peptide receptor antagonist (CGRP-RA)
Diagnostic Assessments
Hypertension as defined by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Visits 1 or Visit 2. Vital sign measurements that exceed these limits may be repeated only once
An ECG with clinically significant abnormalities at screening (Visit 1) as determined by the investigator
QTcF > 450 msec for males and QTcF > 470 msec for females at Visit 1 based on the ECG report of the central reviewer

Clinically significant laboratory values OR any of the following laboratory values at Visit 1: • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1 × the upper limit of normal (ULN) OR • Total bilirubin > 1 × ULN (except for participants with a diagnosis of Gilbert's disease) OR • Serum albumin < 2.8 g/dL [4.06 µmol/L]
Positive result on the urine drug screen at Visit 1 unless explained by concomitant medication use (eg, opioids prescribed for indications other than migraine headache, use of benzodiazepines for insomnia, etc).
History of acute hepatitis within 6 months of screening (Visit 1); or chronic hepatitis (including nonalcoholic steatohepatitis); or a positive result on anti-hepatitis A immunoglobulin M (IgM) antibody, hepatitis B surface antigen, anti–hepatitis C antibody or anti-hepatitis E IgM antibody testing at screening (Visit 1)

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be established to review unblinded safety data and summary reports, identify any safety issues and trends, and make recommendations to the sponsor, including modification or early termination of a trial, if emerging data show unexpected and clinically significant AEs of treatment.

Number of Participants:

Approximately 300 participants will be randomized to one of 2 treatment arms (placebo and atogepant 60 mg QD) in a 1:1 ratio as follows:

- Placebo (n = 150)
- Atogepant 60 mg QD (n = 150)

Randomization will be stratified based on region (North America, Europe and Asia/Pacific), number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) and number of classes of failed prior prophylactic treatments (2 and > 2).

Block randomization will be applied with a block size of 4 (2 treatment arms × 2).

A randomization cap of 20% will be instituted to ensure that the planned randomized participants include no more than 20% of participants with 4 to < 8 migraine days at baseline.

Approximately 50% of randomized participants will have failed > 2 classes of prior prophylactic treatments.

Number of Sites:

This study will be conducted at approximately 125 sites globally (North America, Europe and Asia/Pacific) including both US (investigational new drug [IND]) sites and non-US (non-IND) sites. Data from IND and non-IND study sites will be pooled together for analysis.

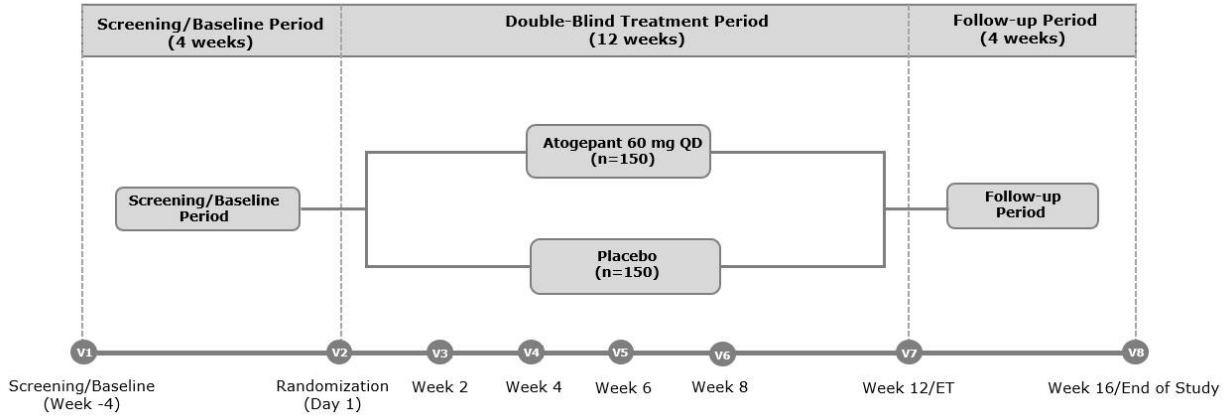
Intervention Groups and Study Duration:

- Patient participation will begin with a 4-week screening/baseline period. Participants who complete the 4-week screening/baseline period and meet all entry criteria will be randomized to the double-blind treatment period of the study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a subsequent safety follow-up period of 4 additional weeks. Total duration of study participation for one participant is approximately 20 weeks.
- There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline Visit), Visit 2 (Randomization Visit), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Week 16/EOS/Safety Follow-up). The Visit 8/EOS/safety follow up period must be completed for all participants who take at least one dose of study intervention, except for participants rolling over into Study 3101-312-002 (long-term safety extension study). For these rollover participants the Follow-up Visit will be performed in the long-term safety extension study. (Please refer to the Schedule of Activities (SoA), Section 1.3).

Data Safety Monitoring Board and Hepatic Events Adjudication Committee: Yes.

1.2. Schema

Figure 1-1 Study Diagram



1.3. Schedule of Activities (SoA)

PRO measures should be administered prior to any tests and/or evaluations with the exception of Visit 1 (Screening/Baseline) and Visit 2 (Randomization) because in those respective visits, the examinations and assessments required for the verification of inclusion/exclusion criteria are to be performed first.

Table 1-1 Schedule of Activities

Study Period	**Screening/Baseline Period (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Safety Follow-up Period (4 weeks)**
Visit Number[a]	**Visit 1 (Screening/Baseline)**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[b]**	**Visit 8 (End of Study)[c]**
Day/Week	***Week -4***	***Day 1***	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	Day -35 to Day -28	NA	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Obtain informed consent	X							
Obtain informed consent for PK (optional)	X							
Randomization		X						
Obtain VCT consent and perform verification (United States only)	X							
Access IWRS	X	X	X	X	X	X	X	X
Assess inclusion/exclusion criteria	X	X						
Collect demographic information	X							
Collect medical history	X							
Collect migraine history	X							
Review prior medications including migraine prophylactic medication use and complete Treatment Failure Worksheet	X							
Perform physical examination	X						X	X
Collect vital sign measurements[d]	X	X	X	X	X	X	X	X
Perform ECG	X				X		X	

Study Period	**Screening/Baseline Period (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Safety Follow-up Period (4 weeks)**
Visit Number[a]	**Visit 1 (Screening/Baseline)**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[b]**	**Visit 8 (End of Study)[c]**
Day/Week	***Week -4***	***Day 1***	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	Day -35 to Day -28	NA	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Perform pregnancy test[e]	X	X	X	X	X	X	X	X
Perform urine drug screen	X							
Clinical laboratory determinations[f]	X	X	X	X	X	X	X	X
PK sample collection (for those participating)[g]		X	X	X	X	X	X	
Provide eDiary, and eDiary instructions and training[h]	X							
Participant daily eDiary data collection	X	X	X	X	X	X	X	X[s]
Review of study intervention compliance			X	X	X	X	X	
Review eDiary data (eg, headache duration, frequency, characteristics, symptoms, acute medication use, AIM-D, activity level and activity limitation) and compliance[i, j]		X	X	X	X	X	X	X[s]
Healthcare Resource Utilization	X	X	X	X	X	X	X	
C-SSRS[k, l]	X	X	X	X	X	X	X	X
ASC-12 (eTablet)[m]	X							
HIT-6 (eTablet)[m]		X		X		X	X	X
PGIC (eTablet)[m]							X	
PGI-S (eTablet)[m]		X		X		X	X	
WPAI: MIGRAINE (eTablet)[m]		X		X		X	X	
PSSM (eTablet)[m]				X		X	X	
EQ-5D-5L (eDiary or eTablet)[m, n]	X	X	X	X	X	X	X	X
MIDAS (eTablet)[m]		X					X	
MSQ v2.1 (eTablet)[m]		X		X		X	X	X

Study Period	**Screening/Baseline Period (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Safety Follow-up Period (4 weeks)**
Visit Number[a]	**Visit 1 (Screening/Baseline)**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[b]**	**Visit 8 (End of Study)[c]**
Day/Week	***Week -4***	***Day 1***	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	Day -35 to Day -28	NA	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
PROMIS-PI (eTablet)[m]		X		X		X	X	
PHQ-9 (eTablet)[m]		X					X	
Dispense study intervention		X[o]	X	X	X	X		
Collect eDiary		X[p]					X[q]	X[r]
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications/concurrent procedures	X	X	X	X	X	X	X	X

ASC-12 = 12-item Allodynia Symptom Checklist; AIM-D = Activity Impairment in Migraine–Diary; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; eDiary = electronic diary; EQ-5D-5L = European Quality of Life – 5 Dimensional; ET = early termination; eTablet = electronic tablet; HIT-6 = Headache Impact Test; INR = international normalized ratio; IWRS = interactive web response system; MIDAS = Migraine Disability Assessment; MSQ v2.1 = Migraine Specific Quality of Life Questionnaire, Version 2.1; PGIC = Patient Global Impression of Change; PGI-S = Patient Global Impression – Severity; PHQ-9 = Patient Health Questionnaire; PK = pharmacokinetic; PRO = patient-reported outcome; PSSM= Patient Satisfaction with Study Medication, PROMIS-PI = Patient-Reported Outcomes Measurement Information System Pain Interference – Short Form 6a; VCT = verified clinical trial; WPAI:MIGRAINE = Work Productivity and Activity Impairment Questionnaire: Migraine V2.0.

[a] Visit 1 and Visit 2 must be conducted in the office. All other visits, should be conducted in the office unless it is necessary to conduct remote visits for the safety of participants or study personnel (eg, COVID-19 or other pandemic situation): for details please refer to the Schedule of Activities for Remote Visits in Section 10.11 (Appendix 11).

[b] Effort should be made by site to not schedule Visit 7 earlier than 12 weeks after Day 1 (Day 84) to ensure that participants complete the full 12 weeks of treatment and have eDiary data through Day 84.

[c] All participants who take at least 1 dose of study intervention must complete the safety follow-up period, except participants rolling over into Study 3101-312-002 (long-term safety extension study). For these rollover participants the Follow-up Visit will be performed at the end of the long-term safety extension study

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

[e] For females of childbearing potential only, urine pregnancy tests will be performed.

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

[g] PK sample should be collected prior to the first dose at Visit 2, 1 sample should be collected prior to the daily dose taken during one of the Visits 3 to 6, and the remaining samples should be collected 1 to 10 hours post the daily dose.

[h] Participant should begin using the eDiary as soon as it is dispensed. If it is subsequently determined that the participant has failed entry criteria, the eDiary should be returned to site.

[i] Participants should bring eDiary to visits and review with coordinators.

[j] Data to be captured in the eDiary on a daily basis

[k] At Visit 1, the *Screening/Baseline* assessment of the C-SSRS will be completed. At all other study visits, the *Since the Last Visit* C-SSRS will be completed.

[l] Clinicians will complete the C-SSRS on eTablet.

[m] PRO measures should be administered prior to any tests and/or evaluations unless indicated otherwise in the protocol (eg, during randomization visit, some tests will be conducted prior to PROs for eligibility).

[n] EQ-5D-5L will be collected via an eDiary for a period of 1 week in the screening period (administered between the 22nd and 28th days of the Screening/baseline period for a total of 7 days), randomization (Study Day 1) until Visit 3 (14 consecutive days from randomization), Visit 4 (± 3 days ie, Study Days 25 to 31 from randomization for a total of 7 days), Visit 5 (± 3 days ie, Study Days 39 to 45 from randomization for a total of 7 days), Visit 6 (± 3 days ie, Study Days 53 to 59 from randomization for a total of 7 days), and Visit 7 (-7 days ie, Study Days 77 to 83 from randomization for a total of 7 days). At Visit 8, the EQ-5D-5L will be administered in an eTablet.

[o] The first dose of study intervention should be taken at the study site

[p] Collected at Visit 2 only for participants who fail screening

[q] Collected at Visit 7/ET only for participants who complete the double-blind treatment period

[r] Collected at Visit 8/EOS only for participants who terminate early from the double-blind treatment period

[s] For participants who terminate early from the double-blind treatment period only.

2. Introduction

Atogepant is a potent, selective oral calcitonin gene-related peptide receptor antagonist (CGRP-RA) being developed for the prophylaxis of migraine.

2.1. Study Rationale

This study is being performed to prospectively assess the safety, tolerability, and efficacy of atogepant 60 mg QD compared with placebo in the prophylaxis of episodic migraine in participants who previously failed 2 to 4 classes of oral prophylactic treatments. This randomized, double-blind, placebo-controlled Phase 3 study is primarily designed to generate data for health technology assessment, and is also a trial to confirm the efficacy of these doses in this patient population. The rationale for the overall study design is in Section 4.1.

2.2. Background

Migraine affects 18% of women and 6% of men in the United States with peak prevalence occurring between the ages of 25 to 55 years. Approximately one-third of these migraineurs have 3 or more migraine headaches 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 and Andree 2010). As of 2016, migraine is the second leading cause of disability worldwide (Global Burden of Disease [GBD] 2017).

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, exam, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnoses and subsequent treatment. Episodic migraine (EM) can be divided into low frequency (LFEM) and high frequency episodic migraine (HFEM) depending on the headache days suffered per month (GBD 2017).

Episodic migraine (EM) is a syndrome diagnosis applied to patients with migraine (with or without aura) who have 1 to 14 headache days per month. Chronic migraine is a specific ICHD-3 diagnosis applied to a subset of patients with ≥15 headache days per month (Katsarava 2012; Olesen 2006; ICHD-3 2018).

This study will include participants with episodic migraine who had failed 2 to 4 classes of prior oral prophylactic medications. The rationale for targeting this population is 2-fold. Firstly, patients on currently available oral prophylactic medications may experience poor tolerability; secondly, many of these treatments have shown insufficient efficacy (did not sufficiently reduce either severity or frequency) of migraine for many patients (Blumenfeld 2013; Hepp 2017).

Discontinuation rates for existing oral prophylactic medications are high for both episodic and chronic migraine (Blumenfeld 2013). The patterns of prophylactic medication use in persons with episodic and chronic migraine were investigated in the cross-sectional, the International Burden of Migraine Study (IBMS-II) with 1165 respondents. Persons with episodic and chronic migraine reported their use of prophylactic migraine medications including antidepressants, anti-epileptic drugs, beta-blockers, calcium channel blockers, and other prophylactic medications specified by respondents. It was concluded by the authors that the most common reasons for discontinuations were lack of efficacy and side effects:

- In persons with episodic migraine, approximately 37% to 48% reported discontinuation of a prophylactic medication due to lack of efficacy, whereas 35% to 49% reported discontinuation due to side effects.

- In persons with chronic migraine, 39% to 48% reported discontinuation due to lack of efficacy, and 34% to 53% reported discontinuation due to side effects.

The consequences of the limitations in current oral prophylactic migraine treatments amount to both poor adherence (Berger 2012; Hepp 2017) and reluctance to initiate prophylactic treatment (Silberstein 2015). In fact, recent studies have indicated that approximately half of migraine patients discontinued their initial oral migraine prophylactic treatment within 60 days, which might be explained by poor tolerability or lack of efficacy (Blumenfeld 2013; Hepp 2017). Moreover, in a US-based retrospective database study it was concluded that approximately 70% of patients who begin migraine prophylaxis with antidepressants, antiepileptics, or beta-blockers are no longer taking these medications at 6 months (Berger 2012). Of those patients who continue to take a prophylactic medication, many still have substantial disease burden (Silberstein 2015).

Therefore, the proposed population for Study 3101-304-002 reflects clinical practice. There is severe unmet need in patients that have failed multiple migraine prophylactic oral medications, and these patients are currently often relying on ineffective treatments and many suffer from intolerability to currently available medications.

Atogepant is a potent, selective oral CGRP-RA being developed for migraine prevention. CGRP is a neuropeptide implicated in the pathophysiology of migraine. CGRP levels in the cranial venous outflow (ie, external jugular vein) are increased during a migraine attack and exogenously administered CGRP has been shown to trigger migraine-like headache in migraineurs. The majority (80% to 90%) of trigeminal Aδ fibers that innervate the dura contain CGRP, suggesting that these fibers may be involved in sterile neurogenic inflammation and migraine pain transmission. Furthermore, the CGRP receptor is present on human meningeal and cerebral blood vessels. These observations suggest that activation of the trigeminovascular system, with release of CGRP, may play a key role in migraine pathogenesis and that inhibition of CGRP may yield a novel therapeutic approach to treating migraine.

The ability of CGRP inhibition to induce pain relief in the acute treatment of migraine was initially observed with an intravenous formulation of olcegepant (Olesen 2004), and replicated by Merck & Co., Inc with an oral formulation of MK-0974 (telcagepant), a highly selective CGRP-RA. In Phase 3 studies, telcagepant was superior to placebo in the primary endpoints of 2-hour pain freedom, 2-hour pain relief, and the absence of associated symptoms

(photophobia, phonophobia, and nausea), as well as the key secondary endpoint of 24-hour sustained pain freedom (Connor 2009). However, serum ALT increases were observed with telcagepant. For this reason, the development of these oral CGRP antagonists was stopped.

Atogepant was chemically designed to minimize the potential for reactive metabolites, thereby reducing the risk of liver toxicity that has been observed with telcagepant, and MK-3027. An extensive Phase 1 program, including a 28-day multiple dose study of doses up to 170 mg QD, has been conducted to assess hepatic effects of atogepant.

A Phase 2/3 clinical study (Study CGP-MD-01) was conducted, which compared atogepant 10 mg QD, atogepant 30 mg QD, atogepant 30 mg BID, atogepant 60 mg QD and atogepant 60 mg BID to placebo in prevention of episodic migraine. Overall, all the atogepant doses tested were well tolerated and the AE profile of all atogepant doses did not significantly differ from placebo. 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 to placebo in participants with episodic migraine.

A recently completed Phase 3 clinical study (Study 3101-301-002) evaluated the efficacy, safety, and tolerability of atogepant 10 mg QD, atogepant 30 mg QD and atogepant 60 mg QD compared to placebo in the prevention of migraine in participants with episodic migraine after 12 weeks of treatment. All atogepant doses demonstrated clinically meaningful and statistically significant improvement over placebo for the primary endpoint of change from baseline in mean monthly migraine days across the 12-week treatment period with LSMD for atogepant vs placebo being -1.21, -1.38, -1.72 days for atogepant 10 mg QD, 30 mg QD, 60 mg QD, respectively. The LS mean change from baseline for monthly migraine days was -2.48, -3.69, -3.86, and -4.20 days for placebo, atogepant 10 mg QD, 30 mg QD, and 60 mg QD, respectively. Furthermore, atogepant 30 mg QD and 60 mg QD demonstrated statistically significant improvement over placebo for all secondary endpoints of the study. Results suggested a clinically relevant dose response relationship and atogepant 60 mg QD demonstrated the highest therapeutic effect. All atogepant doses were well tolerated and no significant difference was detected in the AE profile of the three atogepant doses.

In addition to the 12-week Study 3101-301-002 described above, a 52-week Phase 3 study that evaluated the long-term safety, tolerability, and efficacy of atogepant 60 mg QD compared to standard of care has completed (Study 3101-302-002) in the prevention of episodic migraine. Similar to the 12-week studies, atogepant 60 mg QD dose was safe and well tolerated. A clinically relevant reduction in mean monthly migraine days, mean monthly headache days, mean monthly acute medication use days, and mean monthly triptan use days was achieved within the first month and was sustained over the 1-year treatment period. The LS mean change from baseline in the monthly migraine days was -3.84 days at Weeks 1-4 and -5.19 days at Weeks 49-52.

To date, no safety signal in hepatic lab parameters has been observed in either preclinical or clinical studies conducted with atogepant.

A detailed description of the chemistry, pharmacology, efficacy, and safety of atogepant is provided in the investigator's brochure.

2.3. Benefit/Risk Assessment

The CGP-MD-01 Phase 2/3 study demonstrated that atogepant is efficacious for the prophylaxis of migraine. All doses of atogepant demonstrated significant clinical benefit in reducing the number of mean monthly migraine days and other endpoints. Atogepant was safe and well tolerated in the study. With its mode of action as a CGRP-RA, atogepant is differentiated from the currently available oral prophylactic treatments (ie, beta-blockers, anticonvulsants, etc) by its favorable side effect and safety profile. With its oral route of administration, it also offers a clear benefit if compared to recently approved injectable CGRP-RA monoclonal antibodies.

This study will compare the efficacy, safety, and tolerability of atogepant 60 mg QD to placebo in the prevention of migraine in participants who previously failed 2 to 4 classes of prophylactic oral treatments. This patient population especially requires new therapeutic alternatives.

An independent DSMB will review unblinded safety data throughout the trial and make recommendations to the sponsor, including modification or early termination of the trial, if emerging data show unexpected and clinically significant adverse effects of treatment. Although this is a 12-week placebo-controlled trial, treatment for acute migraine is allowed during the study.

Overall, the benefit-risk assessment supports the clinical investigation of atogepant for the prophylaxis of migraine.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of atogepant may be found in the investigator's brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To prospectively test for superiority of atogepant 60 mg QD versus placebo for the prevention of migraine in participants with episodic migraine who have previously failed 2 to 4 classes of oral medications for the prophylaxis of migraine	CFB in mean monthly migraine days across the 12-week treatment period.
Secondary	
To evaluate the effect of atogepant 60 mg QD versus placebo on the proportion of participants with at least 50% reduction from baseline in monthly migraine days	Achievement of at least a 50% reduction .
To evaluate the effect of atogepant 60 mg QD versus placebo for the prophylaxis of headache	CFB in mean monthly headache days across the 12-week treatment period.
To evaluate the effect of atogepant 60 mg QD versus placebo on acute medication use	CFB in mean monthly acute medication use days across the 12-week treatment period.
To evaluate the effect of atogepant 60 mg QD versus placebo on the impact of migraine on daily activities as assessed by MSQ v2.1 Role Function-Restrictive domain score	CFB in MSQ v2.1 Role Function-Restrictive domain score at Week 12
For the United States only: To evaluate the effect of atogepant 60 mg QD versus placebo on Performance of Daily Activities	*For the United States only:* CFB in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period
To evaluate the effect of atogepant 60 mg QD versus placebo on Physical Impairment	CFB in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period
For the European Union only: To evaluate the effect of atogepant 60 mg QD versus placebo on the impact of headaches on daily functioning as assessed by HIT-6	*For the European Union only:* CFB in the HIT-6 total score at Week 12
Exploratory	
To evaluate the response to atogepant 60 mg QD versus placebo as measured by proportion of participants with ≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100% improvement (decrease) in monthly migraine days	Achievement of ≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100% improvement (decrease) in monthly migraine days at Weeks 1 to 4, 5 to 8, and 9 to 12 Achievement of ≥ 25%, ≥ 30%, ≥ 75%, 100% improvement (decrease) in monthly migraine days across the 12-week treatment period
To evaluate the effect of atogepant 60 mg QD versus placebo for the prevention of migraine	CFB in monthly migraine days at Weeks 1 to 4, 5 to 8, and 9 to 12

Objectives	Endpoints
To evaluate the temporal effect of atogepant 60 mg QD versus placebo for the prevention of headache	CFB in monthly headache days at Weeks 1 to 4, 5 to 8, and 9 to 12
	CFB in monthly cumulative headache hours at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
To evaluate the effect of atogepant 60 mg QD versus placebo on acute migraine-specific medication use	CFB in monthly acute medication use days at Weeks 1 to 4, 5 to 8, and 9 to 12
To evaluate the effect of atogepant 60 mg QD versus placebo on acute triptan use	CFB in monthly triptan use days at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
To evaluate the effect of atogepant 60 mg QD versus placebo on number of monthly moderate/severe and severe headache days	CFB in monthly moderate/severe headache days at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
	CFB in monthly severe headache days at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
To evaluate effects of atogepant 60 mg QD versus placebo on the impact of headaches on daily functioning as assessed by HIT-6	CFB in the HIT-6 total score at Weeks 4, and 8 (*European Union only*)
	CFB in the HIT-6 total score at Weeks 4, 8, and 12 (*United States only*)
To evaluate the response to atogepant 60 mg QD versus placebo as measured by proportion of participants with at least a 5-point improvement (decrease) from baseline in HIT-6 total score	Achievement of at least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, and 12
To evaluate the response to atogepant 60 mg QD versus placebo as measured by proportion of participants *much better* or *very much better* on PGIC	Achievement of a rating of *much better* or *very much better* at Week 12 assessed by the PGIC
To evaluate patient satisfaction with study medication atogepant 60 mg QD versus placebo	Achievement of a rating of *satisfied* or *extremely satisfied* at Weeks 4, 8, and 12 assessed by the PSSM
To evaluate the effect of atogepant 60 mg QD versus placebo on work productivity specific to migraine as measured by WPAI:MIGRAINE	CFB from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Weeks 4, 8, and 12 as assessed by the WPAI:MIGRAINE
To evaluate the effect of atogepant 60 mg QD versus placebo on generic health-related quality of life, as measured by EQ-5D-5L	CFB in EQ-5D-5L descriptive system index score at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, 12, and Week 16
	CFB in the EQ-5D-5L VAS score at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, 12, and Week 16
To evaluate the effect of atogepant 60 mg QD versus placebo on headache-related disability as measured by MIDAS total and domain scores	CFB in the MIDAS total score at Week 12
	CFB in MIDAS absenteeism score (Questions 1, 3, and 5) at Week 12

Objectives	Endpoints
	CFB in MIDAS presenteeism score (Questions 2 and 4) at Week 12
To evaluate the effect of atogepant 60 mg QD versus placebo on participant's global impression of severity in relation to migraine symptoms	CFB in PGI-S score at Weeks 4, 8, and 12
To evaluate the effect of atogepant 60 mg QD versus placebo on how daily social and work-related activities are prevented by migraine as assessed by MSQ v2.1 Role Function-Preventive domain score at Weeks 4, 8, and 12	CFB in the MSQ v2.1 Role Function-Preventive domain score at Weeks 4, 8, and 12
To evaluate the effect of atogepant 60 mg QD versus placebo on the impact of migraine on daily social and work-related activities as assessed by MSQ v2.1 Role Function-Restrictive domain score at Weeks 4 and 8	CFB in the MSQ v2.1 Role Function-Restrictive domain score at Weeks 4 and 8
To evaluate the effect of atogepant 60 mg QD versus placebo on emotions associated with migraine as measured by MSQ v2.1 Emotional Function domain score at Weeks 4, 8, and 12	CFB in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, and 12
To evaluate the effect of atogepant 60 mg QD versus placebo on Performance of Daily Activities	CFB in monthly Performance of Daily Activities domain score of the AIM-D at Weeks 1 to 4, 5 to 8, and 9 to 12 CFB in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period (*European Union only*)
To evaluate the effect of atogepant 60 mg QD versus placebo on Physical Impairment	CFB in monthly Physical Impairment domain score of the AIM-D at Weeks 1 to 4, 5 to 8, and 9 to 12 CFB in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period (*European Union only*)
To evaluate the effect of atogepant 60 mg QD versus placebo on total score of the AIM-D	CFB in monthly AIM-D total score at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
To evaluate the effect of atogepant 60 mg QD versus placebo on activity level and limitation as measured by Activity Level and Activity Limitation items	CFB in monthly activity level at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period CFB in monthly activity limitation at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
To evaluate the effect of atogepant 60 mg QD versus placebo on the interference of pain on relevant aspects of daily life as measured by PROMIS-PI	CFB in PROMIS-PI total score at Weeks 4, 8, and 12
To evaluate the effect of atogepant 60 mg QD versus placebo on symptoms of depression as measured by PHQ-9	CFB in PHQ-9 score at Week 12

Objectives	Endpoints
Safety	
To evaluate the safety and tolerability of atogepant 60 mg QD for the prevention of migraine in participants with episodic migraine who have previously failed 2 to 4 classes of oral medications for the prophylaxis of migraine	AEs, clinical laboratory tests, ECG results, vital signs, C-SSRS

4. Study Design

4.1. Overall Design

This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel group study conducted at approximately 125 sites globally (North America, Europe and Asia/Pacific). Approximately 300 participants will be randomized to one of 2 treatment arms (placebo, and atogepant 60 mg QD) in a 1:1 ratio as follows:

- Placebo (n = 150)
- Atogepant 60 mg QD (n = 150)

Randomization will be stratified based on region (North America, Europe and Asia/Pacific), number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) and number of classes of failed prior prophylactic treatments (2 and > 2).

Block randomization will be applied with a block size of 4 (2 treatment arms × 2).

A randomization cap of 20% will be instituted to ensure that the planned randomized participants include no more than 20% of participants with 4 to < 8 migraine days at baseline.

Approximately 50% of randomized participants will have failed > 2 classes of prior prophylactic treatments.

Participation will begin with a 4-week screening/baseline period. Participants who complete the 4-week screening/baseline period and meet all entry criteria will be randomized to the double-blind treatment period of the study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a subsequent safety follow-up period of 4 additional weeks. Total duration of study participation for one participant is approximately 20 weeks.

There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline Visit), Visit 2 (Randomization Visit), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Week 16/EOS/Safety Follow-up). The Visit 8/EOS/safety follow-up period must be completed for all participants who take at least one dose of study intervention, except for participants rolling over into Study 3101-312-002 (long-term safety extension study). For these rollover participants Visit 8 is not required, because the final Follow-up Visit will be performed at the end of the long-term safety extension study. For participants who screen fail for the long-term safety extension study, the Follow-up Visit of Study 3101-304-002 must be completed. (Please refer to the SoA, Section 1.3).

This study is conducted at US (IND) sites and non-US (non-IND) sites. Data from IND and non-IND study sites will be pooled together for analysis.

4.2. Justification for Dose

This study will test one dose of atogepant, 60 mg QD, selected based on the results from the Phase 2/3 study CGP-MD-01 and the pivotal study 3101-301-002 in participants with episodic migraine. All atogepant doses investigated in Study CGP-MD-01 and Study 3101-301-002 demonstrated good safety and tolerability.

In Study CGP-MD-01, all atogepant doses including 60 mg QD demonstrated a statistically significant reduction from baseline in mean monthly migraine days across the 12-week treatment period compared to placebo; however, there was no clear dose response relationship.

In Study 3101-301-002, a clinically relevant dose response relationship was detected. The highest investigated dose, atogepant 60 mg QD demonstrated the highest treatment difference compared to placebo while there was no clinically significant difference in the AE profile between the atogepant doses. Based on these findings, atogepant 60 mg QD has been selected to be investigated in the current study.

4.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

For Russia, end of study is defined as the last Close Out Visit.

A participant is considered to have completed the study if he/she has not been terminated early and has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

5. Study Population

Approximately 300 participants with episodic migraine with or without aura who previously failed 2 to 4 classes of oral prophylactic treatments will be randomized into the study at approximately 125 sites globally (North America, Europe and Asia/Pacific).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

For further information on participant entry procedures, please see Section 8 (Study Assessments and Procedures).

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Male or female participants ages 18 (or age of legal majority) to 80 years, inclusive, at Visit 1
2.	**Type of Participant and Migraine Characteristics**
2.01	At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3, 2018.
2.02	Age of the participant at the time of migraine onset < 50 years
2.03	History of 4 to 14 migraine days (see Section 8.1.1 for definition) per month on average in the 3 months prior to Visit 1 in the investigator's judgment
2.04	4 to 14 migraine days in the 28-day baseline period per eDiary *(Note: A randomization cap of 20% will be instituted to ensure that the planned randomized participants include no more than 20% of participants with 4 to <8 migraine days at baseline.)*
2.05	Completed at least 20 out of 28 days in the eDiary during the baseline period and is able to read, understand, and complete the study questionnaires and eDiary per investigator's judgment.

2.06	Participants must meet both criteria below (ie, a and b). Participants must have a. Failed oral migraine prophylaxis medications from 2 to 4 of the medication classes as listed below: i. Propranolol, metoprolol, atenolol, bisoprolol, timolol, or nadolol; ii. Topiramate; iii. Flunarizine; iv. Valproate or divalproex; v. Amitriptyline or nortriptyline; vi. Venlafaxine or desvenlafaxine; vii. Lisinopril; viii. Candesartan; ix. Locally approved products (eg, oxeterone or pizotifen) b. Failed at least one treatment from the list below: i. Propranolol OR metoprolol; ii. Topiramate; iii. Flunarizine; iv. Amitriptyline (*Note: Participant failure of a prophylactic medication can be on the basis of tolerability or efficacy and is based on investigator judgement. Refer to Section 5.3 for more detailed information. Each prior prophylactic medication failure needs to be documented in the Treatment Failure Worksheet, see Section 10.10 [Appendix 10]).*

3.	**Contraceptives**
3.01	Male participants willing to minimize the risk of inducing pregnancy as detailed below: A male participant must agree to use contraception as detailed in Section 10.7, Appendix 7 of this protocol during the intervention period and for at least 3 days after the last dose of study intervention and refrain from donating sperm during this period. Female participants willing to minimize the risk of inducing pregnancy as detailed below: A female participant is eligible to participate if she is not pregnant (ie, has a negative urine pregnancy result at the Screening Visit (Visit 1) and Randomization Visit (Visit 2), is not planning to become pregnant during the course of the study, is not breastfeeding, and fulfils at least one of the following conditions: a. Not a WOCBP as defined in Section 10.7 (Appendix 7) OR b. A WOCBP who agrees to follow the contraceptive guidance of using a medically acceptable and effective contraceptive method as defined in Section 10.7 (Appendix 7) during the intervention period and for 3 days after the last dose of study intervention.
4.	**Informed Consent**
4.01	Written informed consent and participant privacy information (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data Protection consent [EU sites]) obtained from the participant prior to any study-related procedures.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	Medical Conditions
1.01	Any clinically significant hematologic, endocrine, pulmonary, hepatic, gastrointestinal, or neurologic disease • If there is a history of such a disease, but the condition has been stable for more than 1 year prior to Visit 1, and is judged by the investigator as not likely to interfere with the participant's participation in the study, the participant may be included
1.02	Participant has any other concurrent pain condition that, in the opinion of the investigator, may significantly impact the current headache disorder (eg, fibromyalgia, facial pain)
1.03	In the opinion of the investigator, confounding psychiatric conditions, dementia, epilepsy, or significant neurological disorders other than migraine
1.04	History of malignancy in the 5 years prior to Visit 1, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer
1.05	History of any prior gastrointestinal procedures or gastrointestinal conditions (eg, diarrhea syndromes, inflammatory bowel disease) that may affect the absorption or metabolism of study intervention; participants with prior gastric bariatric interventions (eg, Lap Band) which have been reversed are not excluded.
1.06	Clinically significant cardiovascular or cerebrovascular disease per the investigator's opinion including, but not limited to: • Clinically significant ischemic heart disease (eg, unstable angina pectoris) • Clinically significant cardiac rhythm or conduction abnormalities (eg, atrial fibrillation, second- or third-degree heart block) or risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, bradycardia) • Myocardial infarction, transient ischemic attack, or stroke within 6 months prior to Visit 1 • Heart failure defined as New York Heart Association functional classification system, Class III or IV
1.07	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) in the past 6 months or report suicidal behavior in the 6 months prior to Visit 1 or Visit 2 assessments
1.08	At Visit 1, a user of recreational or illicit drugs (including cannabis regardless of legality) or has had a history within the past year of drug or alcohol abuse or dependence

2.	**Migraine Characteristics**
2.01	Has ≥ 15 headache days per month on average across the 3 months prior to Visit 1 in the investigator's judgment
2.02	Has ≥ 15 headache days in the 28-day baseline period per eDiary
2.03	Difficulty distinguishing migraine headaches from tension-type or other headaches
2.04	Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018
2.05	Has a current diagnosis of chronic migraine, new persistent daily headache, medication overuse headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018
3.	**Prior/Concomitant Therapy**
3.01	Usage during 30 days prior to Visit 1 (unless otherwise indicated) and throughout the study period of and requirement for any medication, diet (ie, grapefruit juice), or non-pharmacological treatment that is on the list of prohibited concomitant medications or treatments that cannot be discontinued or switched to an allowable alternative medication or treatment. This includes concomitant medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol) regardless of indication. (See Section 6.5.3).
3.02	Usage of therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, BOTOX®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to Visit 1 and throughout the study period.
3.03	Usage of barbiturate-containing or opioid-containing analgesics > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, NSAIDs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline period. *(Note: barbiturate-containing analgesics are excluded 30 days prior to screening, during the screening/baseline period, and for the duration of the study. Opioid-containing analgesics are excluded during the screening/baseline period and throughout the study, however, episodic use of opioids for purposes not related to migraine or headache, eg, surgery, is not exclusionary.)*
3.04	Previous exposure to • Atogepant (AGN-241689 or MK-8031) • Injectable monoclonal antibodies blocking the CGRP pathway within the last 6 months prior to Visit 1 • Any other investigational CGRP-RA
3.05	History of hypersensitivity or clinically significant adverse reaction to a CGRP-RA or hypersensitivity to any component of the study interventions (atogepant or placebo).

4.	**Prior/Concurrent Clinical Study Experience**
4.01	Currently participating or has participated in a study with an investigational compound or device within 30 days prior to Visit 1 (this includes studies using marketed compounds or devices)
5.	**Diagnostic Assessments**
5.01	Hypertension as defined by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Visits 1 or Visit 2. Vital sign measurements that exceed these limits may be repeated only once
5.02	An ECG with clinically significant abnormalities at screening (Visit 1) as determined by the investigator
5.03	QTcF > 450 msec for males and QTcF > 470 msec for females at Visit 1 based on the ECG report of the central reviewer
5.04	Clinically significant laboratory values OR any of the following laboratory values at Visit 1: • ALT or AST > 1 × the ULN OR • Total bilirubin > 1 × ULN (except for participants with a diagnosis of Gilbert's disease) OR • Serum albumin < 2.8 g/dL [4.06 µmol/L]
5.05	Positive result on the urine drug screen at Visit 1 unless explained by concomitant medication use (eg, opioids prescribed for indications other than migraine headache, use of benzodiazepines for insomnia, etc).
5.06	History of acute hepatitis within 6 months of screening (Visit 1); or chronic hepatitis (including nonalcoholic steatohepatitis); or a positive result on anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti–hepatitis C antibody or anti-hepatitis E IgM antibody testing at screening (Visit 1)
6.	**Other**
6.01	Employed by or is an immediate family member (parents, spouses, siblings, or children) of one of the investigators, study staff, or sponsor
6.02	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 the participant's participation in the study
6.03	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 the study

5.3. Criteria for Determining that Prior Treatment for the Prophylaxis of Migraine Have Been Failed

To be eligible for randomization in this study, participants must have failed 2 to 4 classes of prior oral treatments for the prophylaxis of migraine, as described in Section 5.1 Inclusion Criteria.

Participant failure of a prophylactic medication can be on the basis of tolerability or efficacy and is based on investigator judgement.

For *efficacy*, investigators must consider:

- Failure is defined as no meaningful reduction in frequency of migraine days after an adequate trial of at least 2 months at generally accepted therapeutic doses, per investigator judgement and participant interview during the past 7 years prior to screening.

For *tolerability*, investigators should consider:

- Failure is defined as discontinuation of a drug treatment due to adverse effects at any previous time.

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

5.4. Lifestyle Considerations

5.4.1. Meals and Dietary Restrictions

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

5.4.2. Caffeine, Alcohol, and Tobacco

Participants should also refrain from making significant changes to their 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 (approximately 350 mL) can/bottle of beer, a 4-ounce (approximately 120 mL) glass of wine, or 1 ounce (approximately 30 mL) of liquor.

Use of recreational drugs, including cannabis, regardless of legality is prohibited throughout the study.

5.4.3. Activity

No restrictions.

5.5. Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized to treatment. Rescreening of screen failures is permitted in certain situations (including failure to adequately screen due to the COVID-19 pandemic), with permission from Allergan. A participant who is rescreened will be screened again in the IWRS and given a new participant number. However, participants with clinically significant laboratory values at Visit 1 (including ALT or AST > 1 × the ULN, total bilirubin > 1 x ULN or serum

albumin < 2.8 g/dL), or those with a positive result on the Visit 1 urine drug screen for recreational (including marijuana regardless of legality) or illicit drugs or non-disclosed concomitant medications are not allowed to be rescreened.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes indicating screen failure as reason for ending the study, demography, screen failure details, eligibility criteria, and any SAE.

5.5.1. Procedure for Duplicate Participant Identification – Verified Clinical

At participating sites in the United States, a central vendor will be used to verify participants' current and past research study status in order to mitigate safety concerns associated with duplicate enrollment and protocol deviations associated with multiple trial enrollment. Following proper informed consent and after issuing a participant number, each participant will be checked in the VCT database, indicated in the Schedule of Activities (Section 1.3). Partial identifiers will be utilized. Participants who are identified as verification failures by VCT should not be enrolled without documented approval from Allergan.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The investigational medicinal products used in the current study do not have a marketing authorization in any country.

6.1. Study Intervention(s) Administered

6.1.1. Study Interventions and Formulations

Tablets containing atogepant 60 mg.

6.1.2. Control Intervention

Atogepant 60 mg matching placebo.

6.1.3. Study Intervention Regimen and Dosing

Interventions to be used in this study are listed in Table 6-1.

Study intervention will be supplied in blister cards and will be labeled with the protocol number, storage information, warning language, and instructions to take the tablets as directed. The card will also include the medication number.

Participants who meet all of the study entry criteria at Visit 2 will be randomized and provided with study intervention to be taken on an outpatient basis. Sites will subsequently dispense study intervention to participants at Visits 3, 4, 5, and 6. Immediately before dispensing the study intervention, the investigator (or appropriately trained designee) will write the participant's identification number and the date on the label.

Participants will take their first dose study intervention at the clinic at Visit 2 after laboratory sample collection and will be instructed to take their study intervention at approximately the same time each day. Study intervention may be taken with or without food. Water is allowed as desired. Study intervention will be administered orally for 12 weeks, and participants will be followed for 4 weeks following discontinuation of the study intervention.

Table 6-1 Study Interventions

Drug/Dose	Study Intervention Product	Study Intervention Frequency	Route of Administration
Placebo	Placebo	QD (once daily)	Oral
Atogepant 60 mg	Atogepant 60 mg	QD (once daily)	Oral

6.1.4. Intervention Allocation Ratio

Approximately 300 participants will be randomized to the following 2 treatment arms in a 1:1 ratio:

- Placebo (n = 150)
- Atogepant 60 mg QD (n = 150)

Randomization will be stratified based on region (North America, Europe and Asia/Pacific), number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) and number of classes of failed prior prophylactic treatments (2 and > 2).

A randomization cap of 20% will be instituted to ensure that the planned randomized participants include no more than 20% of participants with 4 to < 8 migraine days at baseline.

Approximately 50% of randomized participants will have failed > 2 classes of prior prophylactic treatments.

6.1.5. Other Study Supplies

The following will be provided by Allergan or a delegate of Allergan's:

- All supplies needed for blood and urine sampling (central laboratory analysis, urine, and urine dipstick reagent strips).
- All supplies needed for on-site urine pregnancy test.
- All supplies needed for PK sample collections.
- Shipping materials for shipment of laboratory samples to central laboratory.
- All supplies needed for ECG assessment including ECG machine.
- Electronic diaries.
- Electronic tablet(s)

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Atogepant tablets and matching placebo will be provided in identical blister cards to maintain masking of the study. All participants will be instructed to take study intervention once a day (1 tablet) at approximately the same time each day. Participants will therefore, receive either placebo, or atogepant 60 mg once a day.

Prior to initiation of study intervention, each participant who provides informed consent will be assigned a participant number that will serve as the participant identification number on all study documents.

At the Randomization Visit (Visit 2), eligible participants will be randomly assigned to 1 of 2 treatment arms in a 1:1 ratio to receive atogepant 60 mg QD, or placebo.

An automated IWRS will be used to manage the randomization and intervention assignment based on a randomization scheme prepared by Allergan Biostatistics.

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

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Allergan Medical Monitor prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment of the participant. If a participant's study intervention assignment is unblinded, Allergan Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

6.4. Study Intervention Compliance

For home dosing, study intervention compliance will be closely monitored by participant interview and counting the number of tablets dispensed and returned. Before dispensing new study intervention at each visit, study center personnel will make every effort to collect all unused study intervention and empty blister packs.

The study center will keep an accurate study intervention disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

6.5. Concomitant Therapy

All prior medication for the prophylaxis of migraine, and any medication or vaccine (including over-the-counter, prescription medicines, vitamins, herbal supplements, and/or cannabis or other specific categories of interest) that the participant received during 6 months prior to screening, is receiving at the time of screening, or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.5.1. Permitted Interventions

Therapy considered necessary for the participant's welfare and not specifically prohibited, may be given at the discretion of the investigator, with the following clarifications and restrictions:

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

- SSRIs or SNRIs will be permitted provided that treatment is stable for at least 60 days prior to screening (Visit 1), continues without change in dose throughout the study and is not indicated for the treatment of migraine or headaches, with the exception of venlafaxine or desvenlafaxine (see Section 6.5.3).

See also Section 6.5.2.

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

6.5.2. Rescue Interventions

Participants can apply "best supportive care" for the treatment of acute migraine attacks. This can include both pharmacological interventions (ie, abortive treatments for acute attacks, see below) and non-pharmacological interventions (eg, biofeedback, psychotherapy, acupuncture, vagus nerve stimulation, transcutaneous supraorbital nerve stimulation, single-pulse transcranial magnetic stimulator or other locally accepted and endorsed non-invasive interventions for acute migraine).

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

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

Use of rescue medication must be recorded in the eDiary. Relevant non-pharmacological therapies as part of "best supportive care" use for acute migraine attacks should be recorded in the eCRF.

6.5.3. Prohibited Interventions During the Study

The following medications are prohibited 30 days prior to Visit 1 (unless instructed otherwise in the study protocol) and throughout the study period (see also Section 10.9, Appendix 9) for examples of prohibited medications):

- Strong and moderate CYP3A4 inhibitors, including but not limited to: systemic (oral/intravenous) 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, butalbital, phenobarbital and primidone), systemic (oral/intravenous) glucocorticoids, nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, and St. John's wort
- Strong P-gp inhibitors (eg, clarithromycin, itraconazole, quinidine, verapamil)
- Strong OATP1B1/OATP1B3 inhibitors (eg, gemfibrozil, cyclosporine)
- Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions (eg, warfarin)
- Medications with demonstrated efficacy for the prophylaxis of migraine, regardless of indication:
    - Propranolol, metoprolol, atenolol, bisoprolol, timolol, or nadolol;
    - Topiramate;
    - Flunarizine;
    - Valproate or divalproex;
    - Amitriptyline or nortriptyline;
    - Venlafaxine or desvenlafaxine;

  - Lisinopril;
  - Candesartan;
  - Products approved locally for the prophylaxis of migraine (eg, oxeterone or pizotifen)

- CBD oil

- Cannabis

- Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®) within 6 months prior to Visit 1 and through the study period.

- Ubrogepant (Ubrelvy®) and rimegepant (Nurtec ODT®) is prohibited from Visit 1 throughout the study period.

- Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, BOTOX®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck within 6 months prior to Visit 1 and throughout the study period.

- Cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache, within 4 weeks prior to Visit 1 or at any time during the study (including the baseline period).

- Use of acupuncture, non-invasive neuromodulation devices (eg, transcutaneous supraorbital neurostimulator, single-pulse transcranial magnetic stimulator, vagus nerve stimulator, etc) for the prophylaxis of migraine within 4 weeks prior to Visit 1 or at any time during the study (including the baseline period).

- Any opioid-containing medication is prohibited during the screening/baseline period and any time during the study. *(Note: episodic use for purposes not related to migraine or headache, eg, surgery is allowed. The medical monitor is to be notified.)*

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. The sponsor representative should be notified about the administration of prohibited medication/treatment as soon as possible.

6.6. Dose Modification

This protocol does not allow for any modification from the currently outlined dosing schedule.

6.7. Intervention after the End of the Study

No study intervention will be administered after the end of the study.

Following the end of study, the participant may be treated as per usual practice and standard of care or referred to the participant's treating physician/general practitioner for further medical care at the investigator's discretion.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and receives study medication ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

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.

Participants can be prematurely discontinued from the study for one of the following reasons:

- Adverse Event
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study drug
- Other
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by subject

All randomized participants who prematurely discontinue from the study, regardless of cause, should be seen for final study assessments. The final assessments will be defined as completion of the evaluations scheduled for Visit 7/ET and Visit 8 EOS (Safety Follow-up Visit), 4 weeks post the last dose of study intervention. These participants must continue to complete their eDiary through Visit 8 EOS (Safety Follow-up Visit).

7.1. Discontinuation of Study Intervention

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 receiving study intervention. Discontinuation of study intervention also requires discontinuation from the study. Please see appropriate sections regarding final assessments to be completed for discontinuation from study.

The following conditions require participants to be withdrawn from study:

- Women who become pregnant will be withdrawn from the study and should refrain from taking further study intervention. The participant should return to the clinic for ET study procedures (Visit 7/ET), including the Safety Follow-up Visit (Visit 8) if study intervention was taken.

- Participants who reply with yes to Questions 4 or 5 in the suicidal ideation section indicating having suicidal ideation with intent (with or without plan) or yes to any question in the suicidal behavior section of the C-SSRS should receive appropriate follow-up as in routine clinical practice. The participant should return to the clinic for ET study procedures (Visit 7/ET), including the Safety Follow-up Visit (Visit 8) if study intervention was taken.

- Participants who meet any of the below study intervention discontinuation criteria related to abnormal liver function tests and are advised not to be rechallenged (see also Section 10.3.1):

    - 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

7.1.1. Criteria for Study Termination

The sponsor may stop the study (and/or the study site) for any reason with appropriate notification.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator

- Discontinuation of further study intervention development

If a study is prematurely terminated or suspended due to safety issues, the sponsor shall inform all investigators and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC is also to be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator, as specified by

the applicable regulatory requirements. If a premature termination or suspension occurs, the sponsor shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of participants enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled participants, if applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's source data.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1 (Appendix 1).

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All assessments will be conducted at the appropriate visits as outlined in Section 1.3, the SoA, 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.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Rescreening of participants may be considered with permission from Allergan (Section 5.5). Also, all women of childbearing potential must have negative results on the urine pregnancy test at the Screening and Randomization Visits (Visits 1 and 2, prior to the first administration of study intervention).

- Prior to randomization, it must be confirmed that the participant had 4 to 14 migraine days and < 15 headache days during the 28-day baseline period (see Section 8.1.1 for definition) and completed the eDiary for at least 20 of the 28 days.

- There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline), Visit 2 (Randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Follow-up).

- 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.

8.1. Efficacy and Descriptive Assessments

Efficacy assessments (including Health Outcome measures) will be based on information recorded by the participant. An eDiary will be used daily at home to collect data on headache duration, headache characteristics, symptoms, and acute medication use, which will be collectively applied to define migraine and headache days per the criteria listed in Sections 8.1.1 and 8.1.2. Efficacy assessments being also Health Outcome measures are presented in Section 8.9.

8.1.1. Migraine Day

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

A. Headache has at least two of the following four characteristics:
   a. Unilateral location
   b. Pulsating quality
   c. Moderate or severe pain intensity
   d. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

B. At least one of the following:
   a. Nausea and/or vomiting
   b. Photophobia and phonophobia
   c. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

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

OR

D. Any headache which fulfils one criterion from (1) and at least one criterion from (2) **OR** fulfils at least two criteria from (1) and no criteria from (2).
   1) Headache characteristics:
      i. Unilateral location
      ii. Pulsating quality
      iii. Moderate or severe pain intensity
      iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
   2) Symptoms:
      i. Nausea and/or vomiting
      ii. Photophobia and phonophobia
      iii. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

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

8.1.2. Headache Day

A headache day is defined as any calendar day on which headache pain lasting 2 hours or longer occurs unless an acute headache medication (eg, ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration will be specified. Calendar days begin at midnight and last until 11:59 PM (23:59).

8.1.3. Acute Medication Use Day

An acute medication use day is defined as any day on which a participant reports, per eDiary, the intake of allowed medication(s) to treat an acute migraine. The allowed medications include the following categories of drugs: triptans, ergots, analgesics (including acetaminophen), NSAIDs (including aspirin), and antiemetics.

A triptan use day is defined as any day on which a participant reports intake of a triptan to treat a migraine per participant diary.

8.1.4. Allodynia Symptom Checklist (ASC-12)

The ASC-12 measures overall allodynia and subtypes. Cutaneous allodynia affects patients with migraine and is associated with frequency, severity, disability and associated symptoms of migraine. ASC-12 includes 12 questions about the frequency of various allodynic symptoms in association with headache attacks. Each item is scored as “0” (ie, very rarely or does not apply to me), “1” (less than half the time), or “2” (half the time or more). The ASC-12 will be administered (or completed) on the eTablets at the screening visit (visit 1).

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

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.

8.2.2. Vital Signs

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

8.2.3. Electrocardiograms

A 12-lead ECG will be performed at the visits outlined in the SoA (Section 1.3). 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.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency. Hematology, chemistry, coagulation parameters (INR), and urinalysis will be conducted at each visit. Serology and the urine drug screen will be conducted at Screening (Visit 1). 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.

At screening, the investigator or subinvestigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

Positive results with the urine drug screen at Visit 1, unless explained by previously reported concomitant medication use, will be excluded from the study. Urine drug screens positive for recreational (including cannabis regardless of legality) or illicit drugs or non-disclosed concomitant medications are not allowed to be repeated. All other positive urine drug screens may only be repeated with permission from the Sponsor.

A positive pregnancy test at Visit 1 or Visit 2 will exclude the participant from participation in the study. Participants who are confirmed to be pregnant during the study will be withdrawn.

All laboratory tests with values considered clinically significant during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the SoA.

8.2.5. Suicidal Risk Monitoring

Atogepant is considered to be CNS active and participants being treated should be monitored appropriately and observed closely for suicidal ideation and behavior. 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 [no plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

The C-SSRS will be completed at all Study Visits. At screening, the C-SSRS will be completed for the participant's history of suicidal ideation and behavior in lifetime and in the past 6 months. At all other administrations, it will be completed for suicidal ideation and suicidal behavior since the previous visit. The C-SSRS will be administered on the eTablet by a clinician who has been certified to administer the C-SSRS. 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.

Refer to Section 10.3 (Appendix 3) for more information.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3 (Appendix 3).

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 the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs from the signing of the ICF must be collected until 30 days after the last dose of study, regardless of whether or not the participant has been administered study intervention, until the Follow-up Visit (Visit 8) (Section 1.3) and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 10.3 (Appendix 3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs [and AEs of special interest (as defined in Section 8.3.9)] will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee 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.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Adverse Reactions, Serious Adverse Reactions, and Suspected Unexpected Serious Adverse Reactions – Expedited reporting within the EU

For the purposes of expedited reporting within the EU, the Sponsor will follow the applicable definitions for ARs, SARs, and SUSARs (for example, as outlined in Article 2 [n,o,p] of Directive 2001/20/EC). Also, seriousness criteria for AEs/ARs (as would apply to SARs and SUSARs) are currently included in the protocol, listed in Section 10.3, Appendix 3.

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Serious Adverse Reaction: an adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect (see Section 10.3, Appendix 3) for further details pertaining to seriousness criteria).

Suspected Unexpected Serious Adverse Reaction: a serious adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, the investigator's brochure).

8.3.6. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the Follow-Up Visit (Visit 8) or 30 days after the last dose of study intervention if the Follow-Up Visit is not done.

- If a pregnancy is reported, the investigator should inform the sponsor or designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.7 (Appendix 7).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.3.7. Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Signs and symptoms associated with acute migraine attack, eg, aura symptoms, headache pain, nausea and vomiting, sensitivity to light or sound, are considered to be manifestations of migraine and will be captured in the eDiary as symptoms of the disease but they will not be reported as AEs, unless they change in severity or frequency, when they are to be considered as AE. If those events meet SAE criteria, they need to be reported as AEs and SAEs as appropriate.

If the investigator considers these manifestations to have a reasonable possibility of relationship to the study intervention(s), then they should be reported as AEs or SAEs, respectively.

Please also see Section 10.3 (Appendix 3).

8.3.8. Protocol-specific AEs

Not applicable.

8.3.9. AEs of Special Interest

AEs of special interest that warrant ongoing monitoring and rapid communication by the investigator to the sponsor are outlined and specific liver safety guidelines to be followed for this protocol are outlined in Section 10.3 (Appendix 3).

8.3.10. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration, including wrong site of administration (eg, wrong eye)
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study intervention.

Overdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is above the maximum recommended dose according to the reference safety information or protocol for the study intervention or comparator as applicable. This also takes into account cumulative effects due to overdose.

An overdose is any unintentional administration of atogepant above 60 mg per day as per the protocol.

Underdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is under the minimum recommended dose according to the reference safety information or protocol.

8.4. Treatment of Overdose

For this study, any dose of atogepant greater than 60 mg within a 24-hour time period will be considered an overdose.

At present, specific information regarding treatment of overdose of atogepant is not available. In case of an overdose, it may be considered that the stomach be emptied and oral gavage with activated charcoal be used to help reduce absorption of atogepant.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical safety physician immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until atogepant can no longer be detected systemically (at least 2 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the medical safety physician (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical safety physician based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Blood PK Sampling Procedure

A blood sample for PK analysis will be collected on site at Visits 2, 3, 4, 5, 6, and 7/ET from participants who consent to participate in the PK substudy. Participants can withdraw consent to participate in the PK substudy at any time and should have no further PK samples collected. Each participant in the PK substudy will be asked to provide a total of 6 blood samples (1 per visit). At Visit 2, the sample should be collected prior to the initial dose of study intervention taken at the clinic. During one of the Visits 3 to 6, the sample should be collected prior to the daily dose of study intervention (participant should wait to take the dose in the clinic after PK sample collection), and the samples collected at the remaining visits should be collected 1 to 10 hours post the daily dose. At Visit 7 the sample should be collected 1 to 10 hours post the daily dose.

The date and time of collection of each PK sample will be recorded in the eCRF. In addition, for each of the PK samples collected (except the Visit 2 sample) the date and time of taking study intervention prior to the PK sample should be recorded. PK samples will be collected, stored (frozen), and shipped according to instructions provided in the laboratory manual.

The treatment codes will be provided to the bioanalytical lab using a secure process, ensuring no one outside the bioanalytical team is unblinded, to allow only atogepant-treated participant PK samples to be analyzed. The bioanalytical method for the determination of individual plasma concentrations of atogepant and the performance of the assay during validation and sample analysis will be summarized in a separate bioanalytical report, including the results obtained

from analysis of the PK samples. The bioanalytical report will be appended to the integrated clinical trial report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Bioanalytical representatives will be unblinded for PK sample bioanalysis during the conduct of the study. The unblinding of bioanalytical representatives is to be carried out in a secure manner following the sponsor's standard operating procedures. Extreme care and diligence will be taken to ensure no other individuals outside the bioanalytical team will be unblinded.

8.5.2. PK Sample Bioanalysis

Plasma concentrations of atogepant will be determined using validated liquid chromatography-tandem mass spectrometry methods.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Biomarkers are not evaluated in this study.

8.9. Health Outcome Measures and Health Resource Utilization

8.9.1. Activity Impairment in Migraine-Diary (AIM-D)

The AIM-D is an 11-item daily diary measure that assesses the impact of migraine and is comprised of two domains that evaluate performance of daily activities (7 items) and physical impairment (4 items). Participants are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities (ie, difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and physical impairment (ie, difficulty walking, moving body, bending forward, moving head) using a 6 point rating scale ranging from "Not difficult at all," "A little difficult," "Somewhat difficult," "Very difficult," "Extremely difficult," and "I could not do it at all." Three items include a response of "I did not…," for example, "I did not have errands planned." The AIM-D was developed as an electronic daily diary with the same set of questions administered in headache and non-headache versions. The Headache version is administered on days when a participant reports a headache and the Non-Headache version is administered on days when a participant does not report having a headache. The AIM-D instructs participants to answer each question based on the level of difficulty experienced in the past 24 hours for both versions, with "during your headache" indicated for the AIM-D Headache version. In addition to the two domain scores, a total score using all 11 items can also be

calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (ie, higher disease burden).

The AIM-D will be collected daily via the eDiary.

8.9.2. Activity Level and Activity Limitation

Two items based on a 24-hour recall will be administered daily using Headache and Non-Headache versions as additional health outcome measures and for evaluation of the AIM-D. The first item will be used to assess activity level within the past 24 hours with a 5-level response ranging from "No activity –Spent all day lying down" to "Exercised – Brisk walk, running, jogging, biking or other activity for 30 or more minutes." The second item will be used to evaluate activity limitation with a 5-level response ranging from "Not at all limited –I could do everything" to "Extremely limited."

Activity Level and Activity Limitation will be collected daily via the eDiary.

8.9.3. Patient Satisfaction with Study Medication (PSSM)

Overall satisfaction with the study medication for prevention of migraine will be assessed using a single item and a 7-point rating scale ranging from extremely satisfied (0) to extremely dissatisfied (6).

The PSSM scale will be administered in the eTablet at the clinic visits as indicated in the SoA (Section 1.3).

8.9.4. Headache Impact Test (HIT-6)

The HIT is a 6-question assessment used to measure the impact headaches have on participants' ability to function on the job, at school, at home and in social situations. It assesses the effect that headaches have on normal daily life and the participants' ability to function. Responses are based on frequency using a 5-point scale ranging from "never" to "always." The HIT-6 total score, which ranges from 36 to 78, is the sum of the responses – each of which is assigned a score ranging from 6 points (never) to 13 points (always).

HIT-6 will be administered in the eTablet at the clinic visits as indicated in the Schedule of Activities (Section 1.3).

8.9.5. Migraine Disability Assessment (MIDAS)

The MIDAS is a 7-item questionnaire designed to quantify headache-related disability over a 3-month period. The MIDAS score is the sum of missed work or school days, days at work or school plus days of household work where productivity was reduced by half or more, missed household work days, and missed non-work activity days due to headaches in the last 3 months.

MIDAS will be administered in the eTablet at the clinic visits as indicated in the SoA (Section 1.3).

8.9.6. Patient Global Impression of Change (PGIC)

The PGIC is a single item used to measure the participant's impression of overall change in migraine since the first dose of study medication. The measure uses a 7-point rating scale with responses ranging from "very much better" to "very much worse."

PGI-C will be administered in the eTablet at the clinic visits as indicated in the SoA (Section 1.3).

8.9.7. Work Productivity and Activity Impairment Questionnaire: Migraine V2.0 (WPAI:MIGRAINE)

The WPAI:MIGRAINE will be used to assess work productivity specific to migraine. The measure uses a one-week recall and contains six questions related to work productivity. The WPAI measures both presenteeism and absenteeism. The measure yields four scores expressed as impairment percentages ranging from 0 to 100%: Percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to migraine.

WPAI-MIGRAINE will be administered in the eTablet at the clinic visits as indicated in the SoA (Section 1.3).

8.9.8. European Quality of Life – 5 Dimensional (EQ-5D-5L)

EQ-5D-5L is a generic instrument for use as a measure of health status. The EQ-5D-5L consists of 2 components – the EQ-5D descriptive system and the EQ VAS. The descriptive system comprises of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The respondent is asked to indicate his/her health state by marking the box for the most appropriate statement in each of the 5 dimensions. The scoring range of the EQ-5D descriptive system is typically from 0 (dead) to 1 (full health). The EQ VAS records the respondent's self-rated health on a vertical, VAS where the endpoints are labelled "Best imaginable health state" and "Worst imaginable health state." The scoring range of the EQ VAS is from 0 (worst imaginable health) to 100 (best imaginable health).

EQ-5D-5L will be captured on eDiary during 7 days in the screening/baseline period and during specific time periods for Visit 1 to 7, except at Visit 8 (Week 16) where it will be administered on an eTablet. For details please refer to Schedule of Activities (Section 1.3) as indicated in the Schedule of Activities (Section 1.3).

8.9.9. Patient Global Impression – Severity (PGI-S)

The PGI-S is a single item used to measure the participant's impression of severity in relation to migraine symptoms overall at the time of administration of the measure. The measure uses a 5-point rating scale with responses ranging from "none" to "very severe".

PGI-S will be administered in the eTablet at the clinic visits as indicated in the Schedule of Activities (Section 1.3).

8.9.10. Migraine Specific Quality of Life Questionnaire, Version 2.1 (MSQ v2.1)

The MSQ v2.1 is a 14-item questionnaire designed to measure health-related quality-of-life impairments attributed to migraine in the past 4 weeks. It is divided into three domains: Role Function Restrictive assesses how migraines limit one's daily social and work-related activities; Role Function Preventive assesses how migraines prevent these activities; and the Emotional Function domain assesses the emotions associated with migraines. Participants respond to items using a 6-point scale ranging from "none of the time" to "all of the time." Raw dimension scores are computed as a sum of item responses and rescaled to a 0 to 100 scale, where higher scores indicate better quality of life.

MSQ V2.1 will be administered in the eTablet at the clinic visits as indicated in the SoA (Section 1.3).

8.9.11. Patient-Reported Outcomes Measurement Information System Pain Interference –Short Form 6a (PROMIS-PI)

The PROMIS-PI measures self-reported interference of pain on relevant aspects of daily life (ie, social, cognitive, emotional, physical, recreational) over the past 7 days. A 5-level response scale for all six items ranges from "Not at all" to "Very much." Scores range from 6 to 30, with higher scores indicating greater pain interference. The raw scores are translated into a T-score where the T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation of 10.

PROMIS-PI will be administered in the eTablet at the clinic visits as indicated in the SoA (Section 1.3).

8.9.12. Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a concise, self-administered, validated, screening and diagnostic tool for mental health disorder, which has been field-tested in office practice. The screener is quick and user friendly, improves the recognition rate of depression, and facilitates diagnosis and treatment. The PHQ-9 consists of the 9 diagnostic criteria for depressive disorders in the past 2 weeks from the DSM-IV. Participants are asked to indicate the frequency with which they have been bothered by 9 symptoms of depressive disorders over the previous 2 weeks, on a 4-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 27 (from best to worst). A score of 15 to 19 is considered as moderately severe depression and 20 to 27 as severe depression.

PHQ-9 will be administered in the eTablet at the clinic visits as indicated in the SoA (Section 1.3).

8.9.13. Healthcare Resource Utilization

Healthcare resource utilization questions will be completed in the source documents at the sites based on the investigator's interview with the participant at each study visit. This data will then be transcribed into the eCRF thereafter. Healthcare resource utilization questions will include use of migraine-specific healthcare resources due to migraine attack (eg, visits to any general practitioner, specialist, emergency room, or hospital, and any diagnostic procedures prescribed by health care providers).

Resource utilization data will be collected paper based at the study visits.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary null hypothesis is that atogepant treatment dose (atogepant 60 mg QD) is equally effective to placebo in decreasing from baseline in mean monthly migraine days across the 12-week treatment period. The alternative hypothesis is that atogepant dose has a greater effect than placebo.

For efficacy analyses, data will be analyzed according to participants' randomization assignments, regardless of actual treatment received.

For safety data analyses, the participants will be analyzed according to actual treatment received (rather than as randomized).

9.2. Sample Size Determination

A sample size of 150 randomized participants per treatment group will provide a 97% and 95% power to detect the treatment difference of -1.7 or -1.6 between atogepant and placebo for the primary efficacy endpoint for the United States or the EU, respectively. This sample size was selected to provide sufficient power for each of the secondary endpoints in Table 9-1 for the United States and Table 9-2 for the EU.

Table 9-1 Statistical Power for Primary and Secondary Endpoints for the United States

Hypothesis Testing	Endpoint	Treatment Difference from Placebo	Standard Deviation	Statistical Power
Primary	Change from baseline in mean monthly migraine days across the 12-week treatment period	-1.7	3.5	97%
Secondary 1	Achievement of at least 50% reduction in mean monthly migraine days across the 12-week treatment period	29% Placebo rate	60% atogepant rate	99%
Secondary 2	Change from baseline in mean monthly headache days across the 12-week treatment period	-1.7	3.7	95%
Secondary 3	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	-1.5	3.1	97%
Secondary 4	Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12	10.8	22.6	96%
Secondary 5	Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period	-3.3	7.3	93%
Secondary 6	Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period	-2.4	6.4	81%

Table 9-2 Statistical Power for Primary and Secondary Endpoints for the EU

Hypothesis Testing	Endpoint	Treatment Difference from Placebo*	Standard Deviation[a]	Statistical Power
Primary	Change from baseline in mean monthly migraine days across the 12-week treatment period	-1.6	3.5	95%
Secondary 1	≥ 50% reduction in in mean monthly migraine days across the 12-week treatment period	30% Placebo rate	59% atogepant rate	99%
Secondary 2	Change from baseline in mean monthly headache days across the 12-week treatment period	-1.6	3.7	92%
Secondary 3	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	-1.4	3.2	93%
Secondary 4	Change from baseline in HIT-6 total score at Week 12	-3.9	7.6	98%
Secondary 5	Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12	10.9	22.8	96%

[a] The assumptions applied for the EU were estimated using off-treatment hypothetical estimand approach based on Advance Study data.

The power calculations are based on the following assumptions:

1) Table 9-3 provides the results from two atogepant studies (CGP-MD-01 and 3101-301-002 [Advance Study]) and Liberty Study (Reuter 2018) for the primary endpoint. The treatment difference for atogepant 60mg QD versus placebo is assumed to be observed treatment difference in the atogepant Advance study, which is a relative conservative assumption in term of primary endpoint. The standard deviation assumptions were based on the variance in Liberty Study and monthly variance observed in Advance Study for the primary endpoint. In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period is -1.7 days for the United States and is -1.6 days for the EU, and the standard deviation is 3.5 days. Detailed treatment difference and standard deviation assumptions for secondary endpoints are listed in Table 9-1 for the United States and in Table 9-2 for the EU, which are based on the results from the atogepant Advance study.

Table 9-3 Observed Treatment Effect for Primary Endpoint in Atogepant Program and Liberty

Study	Population	Atogepant 60 mg QD Treatment Difference from Placebo	Standard Deviation
Advance	mITT population	-1.72	3.00
	Participants with Prior exposure to migraine preventive treatment = Yes	-2.16	3.01
	Participants with one treatment failures	-1.94	3.04
	Participants with two or more treatment failures	-2.91	3.34
CGP-MD-01	Participants with Prior exposure to migraine preventive treatment = Yes	-1.41	2.97
Liberty	Efficacy Population for Treatment Failure study	-1.93 (Average of 12 Weeks)	3.47[a]
	Efficacy Population for Treatment Failure study	-1.6 (At month 3)	4.6

[a] SD was calculated using variance in liberty and correlation matrix from Advance study

2) A fixed-sequence procedure will be used for multiple comparisons to control the family-wise Type I error rate at a 0.05 level. The testing sequence is specified in Table 9-1 and Table 9-2. Once the primary endpoint for atogepant dose is significant at 0.05 (2-sided), the secondary endpoints will be tested sequentially. Statistical powers for secondary endpoints are conditional on success of prior endpoints (assuming independence among the endpoints) in the sequence.
3) The dropout rate is assumed to be 15% for endpoints other than AIM-D related endpoints. The dropout rate for AIM-D endpoints is 21%. A higher missing rate for AIM-D endpoints was observed in the Advance Study because the related measure was collected only in Today's eDiary instead of both Yesterday and Today's eDiary, If the participants may provide less than 14 records of Today's eDiary within a 28-day period, it would lead to missing data.

The assumptions of sample size calculation such as SD and dropout rate will be monitored while the study is ongoing and sample size will be adjusted. This blinded analysis of variability in the pooled treatment groups will be performed using the primary efficacy analysis model for the primary endpoint as described in Section 9.4.1.2 but excluding the terms treatment and treatment by visit interaction from model terms.

9.3. Populations for Analyses

The analysis populations will consist of participants as defined below:

- The ITT population includes all randomized participants. Participants will be summarized according to the randomized study intervention.
- The mITT population includes all randomized participants who received at least one dose of study intervention, had an evaluable baseline period of eDiary data and had at least one evaluable post-baseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period. Participants will be summarized according to the randomized study intervention.
- The safety population includes all treated participants who received ≥ 1 administration of study intervention. Participants will be summarized according to the study intervention they actually received.
- The PK population includes all participants who have evaluable PK parameters.

The population for EU filing in the estimand framework is defined in Section 9.6.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

The efficacy analyses will be based on the mITT population. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects and all CIs will be 2-sided 95% CIs, unless stated otherwise.

9.4.1.1. Analysis Endpoints

The primary, secondary and exploratory efficacy endpoints are listed below and analyses will be defined in the following sections. Analysis of all endpoints listed below will be defined in the SAP.

9.4.1.1.1. Primary efficacy endpoint:

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

9.4.1.1.2. Secondary efficacy endpoints:

Secondary efficacy endpoints for the United States:

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

Secondary efficacy endpoints for the EU:

- Achievement of at least a 50% reduction in mean monthly migraine days across the 12-week treatment period
- Change from baseline in mean monthly headache days across the 12-week treatment period
- Change from baseline in mean monthly acute medication use days across the 12-week treatment period
- Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12
- Change from baseline in the HIT-6 total score at Week 12

9.4.1.1.3. Exploratory efficacy endpoints:

Exploratory efficacy endpoints for the United States and the EU are provided below. Related analysis will be documented in the SAP.

- Achievement of ≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100% improvement (decrease) in monthly migraine days at Weeks 1-4, 5-8, and 9-12
- Achievement of ≥ 25%, ≥30%, ≥ 75%, 100% improvement (decrease) in monthly migraine days across the 12-week treatment period
- Change from baseline in monthly migraine days at Weeks 1-4, 5-8, and 9-12
- Change from baseline in monthly headache days at Weeks 1-4, 5-8, and 9-12
- Change from baseline in monthly cumulative headache hours at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period

- Change from baseline in monthly acute medication use days at Weeks 1-4, 5-8, and 9-12
- Change from baseline in monthly triptan use days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period
- Change from baseline in monthly moderate/severe headache days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period
- Change from baseline in monthly severe headache days at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period
- Change from baseline in the HIT-6 total score at Weeks 4 and 8 (*EU only*)
- Change from baseline in the HIT-6 total score at Weeks 4, 8, and 12 (*United States only*)
- Achievement of at least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, and 12
- Achievement of a rating of "*much better*" or "*very much better*" at Week 12 assessed by the PGIC
- Achievement of a rating of "*satisfied*" or "*extremely satisfied*" at Weeks 4, 8, and 12 as assessed by the PSSM
- Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at Weeks 4, 8, and 12 as assessed by the WPAI:MIGRAINE
- Change from baseline in EQ-5D-5L descriptive system index score at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, 12, and Week 16
- Change from baseline in the EQ-5D-5L VAS score at Weeks 1 to 2, at specified windows around Weeks 4, 6, 8, 12, and Week 16
- Change from baseline in the MIDAS total score at Week 12
- Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Week 12
- Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Week 12
- Change from baseline in PGI-S score at Weeks 4, 8, and 12
- Change from baseline in the MSQ v2.1 Role Function-Preventive domain score at Weeks 4, 8, and 12
- Change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at Weeks 4 and 8

- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, and 12
- Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at Weeks 1 to 4, 5 to 8, and 9 to 12
- Change from baseline in monthly Physical Impairment domain score of the AIM-D at Weeks 1 to 4, 5 to 8, and 9 to 12
- Change from baseline in mean monthly Performance of Daily Activities domain score of the AIM-D across the 12-week treatment period (*EU only*)
- Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period (*EU only*)
- Change from baseline in monthly AIM-D total score at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
- Change from baseline in monthly activity level at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
- Change from baseline in monthly activity limitation at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
- Change from baseline in PROMIS-PI total score at Weeks 4, 8, and 12
- Change from baseline in PHQ-9 score at Week 12

9.4.1.1.4. Collection and Derivation of Primary and Secondary Efficacy Assessments

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

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

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

If any eDiary window for a participant has at least 12 but less than 28 days of reported data, the prorated approach will be used. If a participant reports less than 12 days of headache data, the participant's observed counts in that particular 28-day eDiary window will be set to missing for that window. These prorating rules will be applied to all efficacy analyses of eDiary data unless otherwise stated.

9.4.1.2. Primary Analyses

The primary efficacy analysis is the change from baseline in mean monthly migraine days across the 12-week treatment period.

The primary comparison between treatment groups will be done by a MMRM of the change from baseline. The statistical model will include treatment group, visit, region, number of classes of failed prior prophylactic treatments, and treatment group by visit interaction as categorical fixed effects. It will also include the baseline value and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-participant repeated measurements. Note that baseline monthly migraine is included in the primary model, therefore the stratification of number of migraine days during the screening/baseline period (4 to < 8 and ≥ 8) will be excluded in the primary model. On the other hand, this stratification will be included in the secondary and exploratory analyses if baseline values other than monthly migraine days are included in the corresponding models. The Kenward-Roger approximation (Kenward and Roger 1997) will be used to estimate the denominator degrees of freedom. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. Pairwise contrasts in the MMRM model will be used to make the pairwise comparisons of each atogepant dose to placebo. Only data collected during the double-blind period will be included in the analysis. Participants are always analyzed based on the treatment group assigned by randomization.

9.4.1.2.1 Sensitivity Analyses in Missing Data Handling

Multiple sensitivity analyses for missing data handling will be conducted and are summarized below. Details of the sensitivity analyses will be provided in the statistical analysis plan.

ANCOVA Model Based on 3-month Average of the Monthly Migraine Days

A supportive analysis will be performed on the primary endpoint using an ANCOVA model. The response variable for the ANCOVA model is the change from baseline in the calculated average monthly migraine days during the 12-week treatment period for each participant. The ANCOVA model includes terms for treatment, region, number of classes of failed prior prophylactic treatments, and baseline score. The treatment difference for atogepant doses versus placebo will

be estimated and reported along with the corresponding 95% CI and nominal p-value for superiority testing.

Within-group Imputation Based on Observed Data

Sensitivity analysis will be performed based on imputation using participants from the same treatment group with observed data under the MAR assumption. Missing data for participants who prematurely discontinued are assumed to copy the profile of participants in the same treatment group with observed data.

Copy-Reference Approach

Copy-reference approach will be performed on the primary endpoint to assess the robustness of the MMRM analysis to possible violation of the MAR assumption. This sensitivity analysis is one type of pattern mixture models (PMM), under which data could be missing not at random (MNAR), with repeated analyses combined via the reference based multiple imputation procedure. Participants who discontinued in the atogepant groups are assumed to have no treatment effect after the discontinuation. Participants are assumed to copy the profile of placebo arm and missing values are imputed based on the distribution estimated from the placebo group under the MAR using copy reference approach.

9.4.1.2.2 Sensitivity Analysis for Possible Violation of Normality Assumption

The normality test is performed on the residuals which are generated by the same MMRM as used for the primary efficacy analysis. The residuals are scaled by the inverse Cholesky root of its estimated variance-covariance matrix. The Kolmogorov-Smirnov test for normality is applied to the de-correlated and scaled residuals and normality test is rejected if p-value from the Kolmogorov-Smirnov test is less than 0.01.

If the normality test is rejected, the sensitivity analysis uses multiple imputation in conjunction with robust regression to assess the robustness of the primary MMRM analysis to the possible violation of normality assumption. This method has been described and referred as ADAP [R] in Mehrotra 2012. The detail of the sensitivity analyses will be provided in the SAP.

9.4.1.3. Secondary Analyses

The secondary endpoints for headache days, acute medication use days, MSQ v2.1 Role Function-Restrictive domain score, Performance of Daily Activities domain score of the AIM-D, Physical Impairment domain score of the AIM-D, and HIT-6 total score will be analyzed in the same manner as that used to analyze the primary endpoint.

The 50% responder, defined as a participant with at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each individual. A logistic regression model will be used to analyze the proportion of 50% responders across the 12-week treatment period. This model assumes a binary distribution for the response and uses a logit link. The analysis model will include treatment group, region, and number of classes of failed prior prophylactic treatments as categorical fixed effects; baseline value will be included as a covariate. The analysis will be performed based on all postbaseline values using only the observed cases without imputation of missing values. The treatment difference in terms of odds

ratio between each atogepant dose group and placebo will be estimated and tested from this model.

The overall type I error rate for the primary and secondary efficacy endpoints will be controlled at the 0.05 level using the fixed sequence procedure following the testing order pre-specified in Table 9-1 for the United States and Table 9-2 for the EU. Once one efficacy endpoint is not significant, all subsequent endpoints will not be tested.

9.4.1.4. Exploratory Efficacy Analyses

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

Other efficacy variables will be analyzed as follows:

For selected diary variables with a continuous response range, the baseline score will be included as a covariate in an MMRM analysis of the change from baseline. These analyses will be performed similarly to the primary MMRM, with focus again on the pairwise contrasts of each dose group to placebo.

- For variables where the data are essentially binary, comparisons between treatment groups will be done with logistic regression for variables with only one post-baseline assessment or using generalized linear mixed model for variables with multiple post-baseline assessments.

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

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs, clinical laboratory, vital signs, ECG parameters, and C-SSRS.

For each of the clinical laboratory, vital signs, and ECG parameters, the last nonmissing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter.

9.4.2.1. Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of study intervention. TEAEs will be analyzed after treatment start on day 1 through the end of the study. An AE that occurs more than 30 days after the last dose of double-blind study treatment or Visit 8 whichever comes later will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

MedDRA nomenclature will be used to code AEs.

The number and percentage of participants with TEAEs in each study intervention group will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants with treatment related TEAEs in each study intervention group will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

AEs will also be summarized separately for the double-blind treatment and safety follow up phases of the study.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation if 5 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Section 10.3 (Appendix 3).

9.4.2.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline (screening) and changes from baseline at each assessment will be presented by study intervention for each clinical laboratory assessment.

9.4.2.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, weight, respiration rate, and temperature) at baseline (screening) and changes from baseline at each assessment will be presented by study intervention.

9.4.2.4. Electrocardiograms

A 12-lead ECG will be performed at the visits outlined in the SoA, Section 1.3. 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.

9.4.2.5. Suicidality Assessment

For the C-SSRS, the number of participants with suicidal ideation and suicidal behavior in lifetime history, 6 months prior to screening, and after the initial dose of study intervention will be summarized by study intervention for the safety population. The Safety Follow-up Visit assessment will be presented in the last study intervention the participant received. A supportive listing of participants with suicidal ideation or suicidal behavior will be provided for the safety population.

9.4.3. PK Analyses

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

9.4.4. Subgroup Analyses

Subgroup analyses will be performed to evaluate the consistency of treatment effects on the primary efficacy endpoint for individual regions (North America, Europe, and Asia/Pacific as well as the following subpopulations defined by prior oral prophylactic treatment failure:

- Participants who have failed ≥2 prior oral prophylactic treatments with 2 different class of treatments
- Participants who have failed ≥3 prior oral prophylactic treatments with 2 different class of treatments
- Participants who have failed ≥ 3 prior oral prophylactic treatments with 3 different class of treatments
- Participants who have failed ≥3 prior oral prophylactic treatments, irrespective of class
- Participants who have failed ≥ 4 prior oral prophylactic treatments, irrespective of class

If the sample size for one region is small, the subgroup analysis will be performed after pooling one or more regions. Details of the subgroup analysis will be provided in the SAP.

9.5. Interim Analyses

No interim analysis is planned.

9.6. Off-treatment Hypothetical Estimand

9.6.1. Treatment Condition of Interest

Participants take assigned treatment by randomization during the double-blind treatment period. In addition, permitted intervention, rescue interventions and prohibited interventions are described below:

- Participants are allowed to take therapies considered necessary for the participant's welfare (Protocol Section 6.5.1) or to apply "best supportive care" including both acute migraine

medications and acute non-pharmacological interventions to keep the participants in the study (Protocol Section 6.5.2).
- The protocol prohibits participants from starting any new migraine preventive treatments during the study (Protocol Section 6.5.3).

9.6.2. Population

The target population is participants suffering from migraine with aura or migraine without aura satisfying the inclusion and exclusion criteria as specified in Section 5.

The analysis population is defined to be all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and had at least 1 evaluable post-baseline 4-week period (Weeks 1-4, 5-8, 9-12) of eDiary data, regardless of whether on study intervention or off study intervention.

9.6.3. Variable

The variable is the same as the primary efficacy endpoint defined in Section 9.4.1.1.1, which is the change from baseline in the participant's mean monthly (4-weeks) migraine days across the 12-week treatment period as derived from the eDiary data.

9.6.4. Accounting of Intercurrent Events

Intercurrent events and their handling rules are as follows:

- Participants who start a new migraine prophylaxis treatment during the double-blind or safety follow-up period will have their data during the safety follow-up period after starting the new migraine prophylaxis treatment excluded from the data analysis.

- Participants who discontinue study intervention due to all reasons other than starting a new migraine prophylaxis treatment will have their data collected after discontinuation of study intervention and those off-treatment will be included in the analysis.

Detailed methods and procedures will be documented in the SAP prior to study completion.

9.6.5. Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between each atogepant group and placebo.

Participants are always analyzed based on their treatment assignment by randomization. To obtain the estimate of treatment effect defined in the off-treatment hypothetical estimand, an MMRM similar to the primary analysis specified in Section 9.4.1.2 will be performed on observed data including both on-treatment and off-treatment monthly migraine days.

9.6.6. Off-treatment Hypothetical Estimand Approach for the Secondary Endpoints

Continuous secondary endpoints will be handled using the same estimand approach defined above for the primary endpoint.

The secondary endpoint of 50% responders will be derived using both on-treatment and off-treatment observed data as defined in the primary endpoint above. The population-level summary for this endpoint is the odds ratio for each atogepant group relative to placebo.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the CIOMS International Ethical Guidelines
  - Applicable ICH/ISO GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval (and approval of the appropriate regulatory agency, if required by national law) before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor 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.

10.1.3. Informed Consent Process

- 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 re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Written informed consent is to be obtained from each participant prior to enrollment into the study and/or from the participant's legally authorized representatives. The informed consent form includes explanation of the following:

1. That the study involves research
2. The objectives of the study
3. The study procedures
4. The expected duration of the participant's participation in the study
5. The approximate number of participants involved in the study
6. The reasonably foreseeable risks or inconveniences to the participant
7. The alternative procedures or courses of interventions that may be available to the participant, and their important potential benefits and risks
8. The compensation and/or intervention available to the participant in the event of study-related injury
9. That the participant's participation in the study is voluntary and that the participant may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which the participant is otherwise entitled
10. That the participant will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study
11. The foreseeable circumstances and/or reason under which the participant's participation in the study may be terminated
12. That the monitors, auditors, the IRB, and the regulatory authorities may provide direct access to the participant's original medical records. In such cases, the confidentiality of the participant should be protected, and by signing and sealing an informed consent form, the participant is authorizing such access.
13. If the results of the study are published, the participant's identity will remain confidential.
14. The anticipated expenses, if any, to the participant for participating in the study

15. The anticipated prorated payment, if any, to the participant for participating in the study
16. The name, title, and address of the investigator to contact
17. The person(s) to contact for further information regarding the clinical study and the rights of participants, and whom to contact in the event of study-related injury
18. The type of the IRB engaged in the assessment and deliberation about the acceptability of the study, items subject to the assessment of each IRB, and other IRB-related items relating to the study
19. The participant's responsibilities

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that 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 the sponsor 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 the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Data Safety Monitoring Board

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

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.

10.1.5.2. Hepatic Event Adjudication Committee

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

10.1.6. Posting Clinical Study Data

Study information and tabular study results will be posted to the US National Institutes of Health website www.clinicaltrials.gov. and other publicly accessible sites. Study data and information

may be published in non-promotional, peer-reviewed publications either by or on behalf of the sponsor. Clinical study reports, safety updates, and annual reports will be provided to the regulatory authorities as required.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- 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 the study intervention. 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.

10.1.8. Summary of Methods of Data Collection

An IWRS will be used to randomize participants and manage study intervention inventory. All visit data (ie, non-diary data) for this study will be collected by either the eTablet or, if conducted remotely (see Section 10.11, Appendix 11), utilizing a web-based portal (eg, questionnaires for PROs) or 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 manual.

Participants will use an eDiary daily to record the daily total duration of headache, headache characteristics, associated symptoms, the worst pain severity, and acute medication use both in the screening/baseline period and double-blind treatment period until Visit 7/ET. They also will record AIM-D, Activity level and Activity limitation, EQ-5D-5L in the eDiary during the double-blind treatment period and the safety follow-up period as indicated in the SoA, Section 1.3. Training for the eDiary will be provided for qualified participants during the Screening/Baseline Visit (Visit 1).

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data is presented below:

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 X-rays, laboratory tests, and ECGs. The investigator's copy of the CRFs 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 study intervention kit numbers
- 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 (United States sites only), data protection consent (EU sites only), or other country and local participant privacy required documentation for this study has been obtained (including the date)
- Dates of all participant visits
- Participants medical history
- Information regarding participant's diagnosis of migraine headache
- All concurrent medications (List all prescription and non-prescription 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-C (ie, records must be Attributable, Legible, Contemporaneous, Original Accurate and Complete).

10.1.10. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If a study is prematurely terminated or suspended due to safety issues, the sponsor shall inform all investigators and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC is also to be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, the sponsor shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of participants enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.11. Publication Policy

- 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.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.12. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.1.13. Participant Privacy

Written authorization (United States sites only), data protection consent (European sites only), 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, European Union Data Protection Directive 95/46/EC ["EU Directive"]).

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

10.1.14. Coordinating Investigator

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

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10-1 below will be performed by the central laboratory. Blood and urine samples will be collected, processed, and stored according to the instructions provided by the laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

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

Investigators must document their review of each laboratory safety report.

Table 10-1 Protocol-required Laboratory Assessments

Category	Parameter
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, lactate dehydrogenase, creatine kinase, total protein, serum 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 exam including red blood cells/high-power field, white blood cells/high-power field, and casts/low-power field.
Coagulation	International normalized ratio
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. Urine drug screens positive for recreational (including cannabis regardless of legality) or illicit drugs or non-disclosed concomitant medications are not allowed to be repeated. All other positive urine drug screens may only be repeated with permission from the Sponsor. A negative result or an explanation of a positive result due to concomitant medication use (eg, benzodiazepines for insomnia) will be required for randomization.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- 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 study intervention.

AE of Special Interest

An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study intervention or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESI(s) have been identified for the study intervention(s) in this protocol:

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

Participants with any AESI(s) will be closely monitored. Selected nonserious and serious adverse events are of special interest and will require immediate reporting, recording, and follow-up.

Reporting requirements for ALT or AST elevations and potential Hy's law cases are outlined in Section 10.3.1. and 10.3.2. below. Responses to the C-SSRS that meet the above criterion will be captured in the eTablet and monitored by the sponsor. These AEs or events determined to be SAEs must be reported appropriately via the designated eCRFs and safety forms.

10.3.1. ALT or AST Elevations

A treatment-emergent ALT ≥ 3 × ULN and/or AST ≥ 3 × ULN is considered an AE of special interest.

Any participant with this laboratory result after study intervention 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 drawn:

- hematology panel
- 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 the sponsor 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
- 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 the sponsor site. In general, the chemistry panel should be repeated 1 to 2 times per week to follow the course of ALT/AST elevation.

Study intervention 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 study intervention only after consultation with the sponsor's Medical Monitor. For participants who are not rechallenged with study intervention, they should be discontinued from the study and complete an ET Visit (Visit 7/ET assessments) and 4-week Follow-up Visit. Participants should receive appropriate follow-up as per SoC.

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

10.3.2. 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 study intervention:

- 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 study intervention (if the final visit does not occur). A laboratory alert for possible

Hy's law cases will be in place, to notify investigators and the sponsor immediately when the above criteria have been met. A possible Hy's law case must be faxed by the investigator to the sponsor 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 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.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease); for example:
  - The test result is associated with accompanying symptoms, and/or
  - The test result requires additional diagnostic testing or medical/surgical intervention, and/or
  - The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
  - The test result is considered to be an AE by the investigator or sponsor.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/ self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE. • The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition • The following events are considered to be manifestations of migraine and will be captured in the eDiary as symptoms of the disease but they will not be reported as AEs, unless they change in severity or frequency warranting an AE, or meet criteria of SAE: • Signs and symptoms associated with acute migraine attack, eg, aura symptoms, headache pain, nausea and vomiting, sensitivity to light or sound. If the investigator considers these manifestations to have a reasonable possibility of relationship to the study intervention(s), then they should be reported as AEs or SAEs, respectively. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

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 that 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 fulfils 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.

Recording and Follow-up of AEs and/or SAEs

AE and SAE Recording

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE or SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE or SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event 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 adverse event 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 adverse event 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.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention 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 study intervention administration will be considered and investigated. • The investigator will also consult the investigator 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. In evaluating causality, the investigator will need to make a Yes/No assessment (ie, related or not related) regarding a reasonable possibility that the study intervention caused the event. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. 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 the sponsor or designee.** • 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.

Follow-up of AEs and SAEs
• See Section 8.3.3.

Reporting of SAEs

SAE Reporting within 24 hours
• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone (see the study contact list) is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AIM-D	Activity Impairment in Migraine
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
ASC-12	Allodynia Symptom Checklist
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0-\infty}$	area under the plasma concentration-vs-time curve from time 0 to infinity
AUC_{0-Tau}	area under the plasma concentration-vs-time curve from time 0 to the end of the dosing period
BP	blood pressure
CBD	cannabidiol
CDISC	Clinical Data Interchange Standards Consortium
CFB	change from baseline
CGRP	calcitonin gene-related peptide
CGRP-RA	calcitonin gene-related peptide receptor antagonist
CIOMS	Declaration of Helsinki and Council for International Organizations of Medical Sciences
$C_{min,ss}$	minimum plasma drug concentration at steady state
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials

Abbreviation	Definition
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome
CYP3A4	cytochrome P450 3A4
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EM	episodic migraine
EOS	end of study
EQ-5D-5L	European Quality of Life – 5 Dimensional
ET	early termination
eTablet	electronic tablet
EU	European Union
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HFEM	high frequency migraine
HIT-6	Headache Impact Test
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council on Harmonisation
ICHD-3	International Classification of Headache Disorders 3rd edition
IEC	independent ethics committee
IND	investigational new drug
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IRB	institutional review board
ISO	International Organization for Standardization
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
LFEM	low frequency migraine
LS	least squares
LSMD	least squares mean difference
MAR	missing at random

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MIDAS	Migraine Disability Assessment
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
MSQ	Migraine Specific Quality of Life Questionnaire
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
OATP	organic-anion-transporting polypeptides
OATP1B1	organic-anion-transporting polypeptides 1B1 subtype
OATP1B3	organic-anion-transporting polypeptides 1B3 subtype
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic
PRO	patient-reported outcome
PROMIS-PI	Patient-Reported Outcomes Measurement Information System Pain Interference
PSSM	Patient Satisfaction with Study Medication
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SNRI	serotonin norepinephrine reuptake inhibitor
SoA	schedule of activities
SoC	standard of care
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
VAS	Visual analogue scale
VCT	verified clinical trial
WOCBP	woman of childbearing potential
WPAI:MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine

10.5. Appendix 5: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion, or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Atogepant for the Prophylaxis of Migraine in Participants with Episodic Migraine Who Have Previously Failed 2 to 4 Classes of Oral Prophylactic Medications (ELEVATE)
	Clinical Study Sponsor	Allergan Pharmaceuticals International Limited
	Trial Phase Classification	Phase 3 trial
	Trial Indication	Prophylaxis of Migraine in Participants with Episodic Migraine Who Have Previously Failed 2 to 4 Classes of Oral Prophylactic Medications
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	Approximately 20 weeks
	Planned Country of Investigational Sites	Approximately 125 sites globally including both US (IND) sites and non-US (non-IND) sites.
	Planned Number of Subjects	300
	FDA-regulated Device Study	No
	FDA-regulated Drug Study	No
	Pediatric Study	No
Subject information	Diagnosis Group	Participants with Episodic Migraine who have previously failed 2 to 4 classes of oral prophylactic medications
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	80

Parameter Group	Parameter	Value
	Sex of Participants	Both
	Stable Disease Minimum Duration	At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3, 2018
Treatments	Investigational Therapy or Treatment	Atogepant
	Intervention Type	Drug
	Pharmacological Class of Investigational Therapy	Selective oral calcitonin gene-related peptide receptor antagonist (CGRP-RA)
	Dose per Administration	1 (1 tablet)
	Dose Units	Atogepant: 60 mg
	Dosing Frequency	QD
	Route of Administration	Oral
	Current Therapy or Treatment	Not applicable
	Added on to Existing Treatments	No
	Control Type	Placebo
	Comparative Treatment Name	Not applicable
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2
	Trial Is Randomized	Yes
	Randomization Quotient	1:1 ratio
	Trial Blinding Schema	Double-blind
	Stratification Factor	Not applicable
	Adaptive Design	No
	Study Stop Rules	Based on investigator or sponsor determination

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal

2. Premenopausal female with 1 of the following:

    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

      Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

    - A postmenopausal state is defined as no menses for 24 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Male Participants

Nonvasectomized male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the intervention period and for at least 3 days after the last dose of study intervention:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom with or without spermicide
- In addition, nonvasectomized male participants must refrain from donating sperm

Nonvasectomized male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the course of the study.

Female Participants

- Female participants of childbearing potential are eligible to participate if they agree to use a highly effective or acceptable method of contraception consistently and correctly as described in Table 10-2.

Table 10-2 Highly Effective and Acceptable Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg, Essure®, bilateral tubal ligation) • Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
Acceptable Methods *ceptable birth control methods that result in a failure of more than 1% per year include:*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device 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.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

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

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test at screening (Visit 1) and also a negative urine test on Day 1 (Visit 2).
- Additional pregnancy testing should be performed at each study visit during the study intervention period and at the EOS visit (Visit 8), 4 weeks after the last dose of study intervention and as required locally.

Collection of Pregnancy Information:

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and will be withdrawn from the study.

10.8. Appendix 8: Study Schedule Supplement

There will be 8 scheduled clinic visits: Visit 1 (Screening/Baseline), Visit 2 (Randomization), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8), Visit 7/ET (Week 12), and Visit 8 (Follow-up). For details, please see Table 1-1 Schedule of Activities.

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

- Obtain informed consent and participant privacy
- Obtain informed consent for PK substudy (optional)
- Obtain VCT consent and perform verification (United States only)
- Collect demographic information
- Collect medical history
- Collect migraine history (3-month retrospective) and confirm diagnosis
- Review and record all prior prophylactic headache medications for the lifetime of the participant
- Complete Treatment Failure Worksheet.
- Register participant in IWRS
- Review and record prior medications taken in the past 6 months, and all concomitant medications and concurrent procedures.
- Collect ASC-12
- Assess C-SSRS on eTablet (the 'Screening/Baseline' assessment of the C-SSRS will be completed).
- Perform physical examination
- Collect vital sign measurements (height, weight, pulse rate, respiratory rate, blood pressure, and body temperature). Height will be measured only at Visit 1.
- Perform and transmit ECG
- Perform urine pregnancy test for women of childbearing potential. Discuss the method of contraception with women of childbearing potential and document this method.
- Counsel participants on the importance of maintaining their agreed upon method of contraception throughout the study.
- Collect blood and urine samples for clinical laboratory determinations (chemistry, hematology, INR, urinalysis, and serology).
- Collect urine sample for drug screen
- Verify if the participant meets inclusion/exclusion criteria at this point

- Provide eDiary, along with training and instructions. Remind participant to bring eDiary to next visit.
- Complete Healthcare Resource Utilization Questionnaire.
- Review and assess AEs

10.8.2. Visit 2 (Randomization) Day 1

- Review eDiary data and compliance for eligibility.
- Perform urine pregnancy test for women of childbearing potential.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, pulse rate, respiration rate, temperature, and weight).
- Assess C-SSRS on eTablet (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Verify if participant meets inclusion/exclusion criteria and is eligible for the study at this point.

If the participant continues to meet study entry criteria, including acceptable results from Visit 1 clinical laboratory tests, pregnancy tests and the urine drug screen (Section 5) the following procedures will be carried out at the Randomization Visit (Visit 2):

- Prior to any other test or evaluations, administer PRO measures including: HIT-6, PGI-S, WPAI:MIGRAINE, MIDAS, MSQ v2.1, PROMIS-PI and PHQ-9.
- Complete Healthcare Resource Utilization Questionnaire.
- Update concomitant medications and concurrent procedures.
- Review and assess AEs.
- Randomize the participant in IWRS and obtain the kit number for study intervention.
- Collect pre-treatment blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Collect pre-treatment PK sample (for participants who consented).
- Dispense study intervention. Participants must take their first dose of study intervention at the study site on this day.
- Remind participant to bring eDiary and to return study intervention kits (used and unused) to all visits.

10.8.3. Visits 3 to 6 (Weeks 2 to 8)

- Prior to any other test or evaluations, administer PRO measures, including: HIT-6, PGI-S, WPAI:MIGRAINE, PSSM, MSQ v2.1, and PROMIS-PI, at the times outlined in Section 1.3 SoA.
- Complete Healthcare Resource Utilization Questionnaire.
- Review eDiary data and compliance.
- Perform urine pregnancy test for women of childbearing potential.
- Collect vital sign measurements (weight, pulse rate, respiratory rate, blood pressure, and body temperature).
- Assess C-SSRS on eTablet (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Perform and transmit ECG (Visit 5 only).
- Update concomitant medications and concurrent procedures.
- Review and assess AEs.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Collect PK sample (for participants who consented). During 1 of the Visits 3 to 6, the sample should be collected prior to the daily dose of study intervention (participant should wait to take the dose in the clinic after PK sample collection), and the samples collected at the remaining visits should be collected 1 to 10 hours post the daily dose.
- Collect previous visit study intervention, review participant compliance, and perform accountability.
- Access IWRS to dispense study intervention and enter accountability.
- Dispense study intervention.
- Remind participant to bring eDiary and to return study intervention kits (used and unused) to all visits.

10.8.4. Visit 7/Early Termination (Week 12)

- Effort should be made by the site to not schedule Visit 7 earlier than 12 weeks after Day 1 to ensure participants complete the full 12 weeks of treatment and have eDiary data through Day 83. Prior to any other test or evaluations, administer PRO measures, including: HIT-6, PGIC, PGI-S, WPAI:MIGRAINE, PSSM, MIDAS, MSQ v2.1, PROMIS-PI and PHQ-9.
- Review eDiary data and compliance.
- Complete Healthcare Resource Utilization Questionnaire
- Collect eDiary, only from participants who completed the double-blind treatment period (Visit 2 to Visit 7/ET; for participants who discontinue study, eDiary collection will occur at Visit 8)
- Perform physical examination.
- Perform urine pregnancy test for women of childbearing potential.
- Collect vital sign measurements (weight, pulse rate, respiratory rate, blood pressure, and body temperature).
- Assess C-SSRS on eTablet (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Perform and transmit ECG.
- Update concomitant medications and procedures.
- Review and assess AEs.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Collect post-dose PK sample (for participants who consented). The PK sample should be collected 1 to 10 hours post the daily dose.
- Collect previous visit study intervention, review participant compliance, and perform accountability.
- Access IWRS and enter accountability.
- Advise participants who early terminated from the double-blind treatment period to continue completing their eDiary through the Follow-up Visit. Remind participant to bring eDiary to next visit.

10.8.5. Visit 8 (End of Study) Week 16

- Prior to any other test or evaluations, administer PRO measures, including: EQ-5D-5L, HIT-6, and MSQ v2.1.
- Collect eDiary from participants who early terminated from the double-blind treatment period, review eDiary data and compliance.
- Perform physical examination.
- Assess C-SSRS on eTablet (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect vital sign measurements (weight, pulse rate, respiratory rate, blood pressure, and body temperature).
- Perform urine pregnancy test for women of childbearing potential.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Update concomitant medications and procedures.
- Review and assess AEs.
- Access IWRS to enter study visit.

10.8.6. 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.

10.9. Appendix 9: Examples of Prohibited Medications

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

- Strong OATP1B1/OATP1B3 inhibitors eg, gemfibrozil (Lopid™)
- Strong P-gp inhibitors (eg, clarithromycin (Biaxin™), itraconazole (Sporanox™), quinidine, verapamil (Calan™, Calan SR™)
- 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™)
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™) Locally approved products (eg, oxeterone, pizotifen)
Non-pharmacologic headache interventions	Acupuncture, if used for prophylaxis of migraine Non-invasive neuromodulation devices (eg, transcutaneous supraorbital neurostimulator, single-pulse transcranial magnetic stimulator, vagus nerve stimulator), if used for prophylaxis of migraine Cranial traction Nociceptive trigeminal inhibition Occipital nerve block treatments Dental splints for headache

Ubrogepant (Ubrelvy®) and rimegepant (Nurtec ODT®) is prohibited from Visit 1 throughout the study.

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

- 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®).

10.10. Appendix 10: Documentation of prior prophylactic treatment failures

10.10.1. Source documents

For the source documentation of prior treatment failure, prior medical records with compound name, treatment duration, dose and reason for discontinuation, are primarily to be obtained.

If obtaining prior medical records is not possible, the investigator is requested to provide an affidavit confirming the above information about prior treatment failures according to the protocol definition. For these affidavits, if the principal investigator is the treating physician, the investigator must provide a dated and signed written note with all required information regarding the previously failed medication(s); if the principal investigator is not the treating physician, all effort should be made by the investigator to interview the treating physician to confirm the required information and provide dated documentation of the interview.

10.10.2. Treatment Failure Worksheet

The investigator is required to transcribe data confirming previous oral prophylactic migraine treatment failure in the Treatment Failure Worksheet as detailed in the Study Reference Manual. If requested by the Medical Monitor, the investigator communicates key screening information including the Treatment Failure Worksheet to the Medical Monitor. Decisions regarding inclusion of participants at time of enrollment primarily remain at the discretion of the investigator. The medical monitor may be consulted if there are questions about whether prior treatment failures meet relevant protocol criteria.

10.11. Appendix 11: Study Visits Conducted Remotely

Remote study visits, conducted virtually or by phone, are permitted if the Investigator determines there to be a public health risk due to viral infection (eg, COVID-19) to the participant or site staff. During remote study visits, the Schedule of Activities for Remote Study Visits (Table 10-3) should be followed.

Remote visits may be conducted between Visit 3 – Visit 8 but participants must attend in office assessments at either Visit 3 or Visit 4 to ensure laboratory samples are obtained within the first 4-weeks of treatments and remote visits should not be performed for greater than 8 weeks.

Missed in-person safety assessments (ie, clinical laboratory samples, vital signs and ECGs) should be collected at the next in-person visit. Patient reported outcomes collected using the eTablet during in-office visits will be collected using a web-based portal during remote visits.

Table 10-3 Schedule of Activities for Remote Study Visits

Study Period	**Double-blind Treatment Period (12 weeks)**					**Safety Follow-up Period (4 weeks)**
Visit Number	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[a]**	**Visit 8 (End of Study)[b]**
Day/Week	***Week 2 (Day 14)***	***Week 4 (Day 28)***	***Week 6 (Day 42)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	± 3 day	± 3 day	± 3 day	± 3 days	+ 3 days	± 3 days
Access IWRS	X	X	X	X	X	X
Perform pregnancy test [c, d]	X	X	X	X	X	X
Participant daily eDiary data collection	X	X	X	X	X	X[h]
Review eDiary data (eg, headache duration, frequency, characteristics, symptoms, acute medication use, AIM-D, activity level and activity limitation) and compliance	X	X	X	X	X	X[h]
Healthcare Resource Utilization	X	X	X	X	X	
C-SSRS (eTablet or web portal) [e]	X	X	X	X	X	X
HIT-6 (web portal) [f]		X		X	X	X
PGIC (web portal) [f]					X	
PGI-S (web portal) [f]		X		X	X	
WPAI: MIGRAINE (web portal) [f]		X		X	X	
PSSM (web portal) [f]		X		X	X	
EQ-5D-5L (eDiary or eTablet/ web portal) [f, g]	X	X	X	X	X	X
MIDAS (web portal) [f]					X	
MSQ v2.1 (web portal) [f]		X		X	X	X
PROMIS-PI (web portal) [f]		X		X	X	
PHQ-9 (web portal) [f]					X	
Review of study intervention compliance	X	X	X	X	X	
Dispense study intervention [d]	X	X	X	X		
Adverse events	X	X	X	X	X	X
Concomitant medications/concurrent procedures	X	X	X	X	X	X

AIM-D = Activity Impairment in Migraine–Diary; C-SSRS = Columbia Suicide Severity Rating Scale; eDiary = electronic diary; EQ-5D-5L = European Quality of Life – 5 Dimensional; ET = early termination; eTablet = electronic tablet; HIT-6 = Headache Impact Test; IWRS = interactive web response system; MIDAS = Migraine Disability Assessment; MSQ v2.1 = Migraine Specific Quality of Life Questionnaire, Version 2.1; PGIC = Patient Global Impression of Change; PGI-S = Patient Global Impression – Severity; PHQ-9 = Patient Health Questionnaire; PRO = patient-reported outcome; PSSM= Patient Satisfaction with Study Medication, PROMIS-PI = Patient-Reported Outcomes Measurement Information System Pain Interference – Short Form 6a; WPAI:MIGRAINE = Work Productivity and Activity Impairment Questionnaire: Migraine V2.0.

[a] Effort should be made by site to not schedule Visit 7 earlier than 12 weeks after Day 1 (Day 84) to ensure that participants complete the full 12 weeks of treatment and have eDiary data through Day 84.

[b] All participants who take at least 1 dose of study intervention must complete the safety follow-up period, except participants rolling over into Study 3101-312-002 (long-term safety extension study). For these rollover participants the final Follow-up Visit will be performed at the end of the long-term safety extension study.

[c] For females of childbearing potential only, at home urine pregnancy tests will be performed (provided by sites) and results reported during the remote visits

[d] Study medication to cover 1 remote study visit and urine pregnancy tests may be dispensed at an office visit (if the next visit is anticipated to be remote), for curbside pick-up or shipped to participants via an overnight courier.

[e] The *Since the Last Visit* C-SSRS will be completed. Clinicians will complete the C-SSRS on eTablet or web backup portal.

[f] PRO measures should be administered prior to any tests and/or evaluations.

[g] EQ-5D-5L will be collected via an eDiary for a period of 1 week around Visit 4 (± 3 days ie, Study Days 25 to 31 from randomization for a total of 7 days), Visit 5 (± 3 days ie, Study Days 39 to 45 from randomization for a total of 7 days), Visit 6 (± 3 days ie, Study Days 53 to 59 from randomization for a total of 7 days), and Visit 7 (-7 days ie, Study Days 77 to 83 from randomization for a total of 7 days). At Visit 8, the EQ-5D-5L will be administered in an eTablet (office visit), or via web portal (remote visit).

[h] For participants who terminate early from the double-blind treatment period only.

10.12. Appendix 12: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

Amendment 1 (03 April 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The changes are to clarify the study rationale, exclusion criteria, primary and secondary statistical analyses, in response to the Grounds for Non-Acceptance (GNA) addressed to Allergan during the VHP (Voluntary Harmonisation Procedure) in Europe.

Section No. and Name	Description of Change	Brief Rationale
1.1 Synopsis	Key Exclusion Criteria- added the diagnosis of "medication overuse headache."	Added to clarify that patients with "medication overuse headache" will not be enrolled and to further clarify this is in accordance with inclusion criteria 2.04 and 2.05.
2.1 Study Rationale	Added text to clarify the study rationale.	Clarification that the purpose of this Phase 3 study is primarily to generate data for health technology assessment, but is also a pivotal trial to confirm the efficacy of the selected doses in this patient population.
4.1 Overall Design	Block randomization will be applied with a block size of 6 (3 treatment arms × 2). A block can be shared by sites within the same region (stratification factor).	To further clarify to the block randomization procedure.
5.2 Exclusion Criteria 2.05	Same as above	Same as above.
9.4.1.2 Primary Analysis **9.4.1.3 Secondary Analysis**	Added "region" to the analysis model.	To further clarify the protocol, region is added in the longitudinal model as a factor for both the primary and secondary efficacy endpoints in sections 9.4.1.2 and 9.4.1.3

11. References

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