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A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ATOGEPANT FOR THE PREVENTION OF CHRONIC MIGRAINE (PROGRESS)

Protocol Number:	3101-303-002
EudraCT Number:	2018-004337-32
Phase:	3
Name of Study Intervention:	Atogepant (AGN-241689)
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The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of the sponsor 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 the sponsor in confidence and, when this information is submitted to an IRB, IEC or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the study intervention(s), and their trial-related duties and functions.

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

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compounds: Atogepant

Phase: 3

Study Objectives:

To evaluate the safety and tolerability of atogepant 30 mg twice per day (BID) and 60 mg once daily for the prevention of chronic migraine (CM).

To prospectively test for superiority of atogepant 30 mg BID and 60 mg once daily versus placebo for the prevention of CM.

Clinical Hypotheses: In participants with CM, at least one of the following atogepant doses (30 mg BID and 60 mg once daily) is superior to placebo as measured by the change from baseline in mean monthly migraine days across the 12-week treatment period.

Atogepant has an acceptable safety and tolerability profile in participants with CM.

Study Design

Structure: Multicenter, randomized, double-blind, placebo-controlled, parallel-group study

Duration: The study will consist of a 4-week screening and baseline period, a 12-week double-blind treatment period, and a follow-up period of 4 additional weeks, for a total duration of 20 weeks

Study Intervention: Atogepant 30 mg BID and 60 mg once daily tablets

Control: Atogepant-matching placebo

Dosage/Dose Regimen: Atogepant 30 mg BID, atogepant 60 mg once daily, and placebo will be administered for 12 weeks duration.

Randomization/Stratification:

Approximately 750 participants will be randomized to 1 of 3 treatment arms in a 1:1:1 ratio as follows:

- Placebo (n = 250)
- Atogepant 30 mg BID (n = 250)
- Atogepant 60 mg once daily (n = 250)

Participants will be stratified by:

- Randomization will be stratified by use of acute headache medications during the baseline period (acute headache medication overuse Yes or No). Acute headache medication overuse (Yes) will be defined as follows: use of triptans on ≥ 10 days OR use of ergots on ≥ 10 days OR use of simple analgesics (ie, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], or acetaminophen) on ≥ 15 days, OR use of any combination of triptans, ergots or simple analgesics on ≥ 10 days.

- Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy (see Attachment 12.3)[1]. Randomization will be stratified based on migraine prevention medication exposure (Current Use, Past Use, or Never Used) with proven efficacy. Participants with current or past use will be further stratified based on the number of medications failed with unique mechanisms of action: "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" or "failed 2 to 4 medications with different mechanisms of action" (see Attachment 12.3). Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%.
    - Below are examples to illustrate how to implement the stratification based on prior migraine prevention medications:
        - Example 1: Participant has taken metoprolol and propranolol. According to Attachment 12.3, these medications both belong to the beta-blocker pharmacologic category. This participant should be randomized to the "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" stratum.
        - Example 2: Participant has taken metoprolol, propranolol, and topiramate. According to Attachment 12.3, metoprolol and propranolol belong to the beta-blocker pharmacologic category and topiramate belongs to the antiepileptic pharmacologic category. This participant should be randomized to the "failed 2 to 4 medications with different mechanisms of action" stratum.
        - Example 3: Participant has taken metoprolol and topiramate. According to Attachment 12.3, metoprolol belongs to the beta-blocker pharmacologic category and topiramate belongs to the antiepileptic category; however, the patient stopped both of these medications because of a change in health insurance coverage and therefore did not meet the failure definition for either medication. This participant should be randomized to the "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" stratum.
- Randomization will be stratified by regions (ie, North America, Europe, Japan, China, Other)

Visit Schedule: 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 this study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a follow-up period of 4 additional weeks.

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 (Week 12), and Visit 8 (follow-up). The Visit 8 (follow-up) must be completed for all participants who take at least 1 dose of study medication, except for participants rolling over into Study 3101-312-002 (long-term safety extension study in regions excluding Japan and China), Study 3101-306-002 (long-term safety extension study in Japan), or Study 3101-311-002 (open-label safety extension study in China). For these rollover participants Visit 8 of Study 3101-303-002 is not required, because the Follow-up Visit (Visit 8) will be performed after the OL treatment in the respective long-term safety study. For participants who screen fail for the long-term safety study, the Follow-up Visit (Visit 8) of Study 3101-303-002 must be completed. For details, see Table 1, Schedule of Visits and Procedures.

Study Population Characteristics

Number of Participants: Approximately 750 participants will be randomized into this global study (ie, North America, Europe, Japan, China, Other).

[1] All French participants must have taken at least 1 prior migraine prevention medication with proven efficacy to be eligible for Study 3101-303-002.

Condition/Disease: Chronic migraine

Key Inclusion Criteria:

- Male or female participants age 18 to 80 years, inclusive, at Visit 1
- At least a 1-year history of CM consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition (ICHD-3, 2018)
- Age of the participant at the time of migraine onset < 50 years
- Confirmation of headache/migraine headache day frequency as follows:
    a. History of, on average, ≥15 headache days per month in the 3 months prior to Visit 1 in the opinion of the investigator **AND**
    b. ≥ 15 headache days during the 4-week screening/baseline period per the electronic diary (eDiary) **AND**
    c. ≥ 8 days during the 4-week screening/baseline period that qualify as being a migraine day per the eDiary

Key Exclusion Criteria:

- 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 new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018
- History of an inadequate response to > 4 medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine (see Attachment 12.3)
- Usage of opioids and/or barbiturates > 4 days/month in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline period (barbiturates are excluded 30 days prior to screening, and for the duration of the study)(see Attachment 12.2)
- Participants with any clinically significant hematologic, endocrine, cardiovascular, cerebrovascular, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease.

Response Measures

Efficacy: Efficacy assessments will be based on information recorded by the participant. An eDiary will be used daily at home to collect data on headache frequency, duration, characteristics, and symptoms; acute medication use and triptan use, which will be collectively applied to define migraine days and headache days per the criteria listed in Sections 6.1.1, 6.1.2, and 6.1.3.

Health Outcomes: Activity Impairment in Migraine – Diary (AIM-D); Activity Level and Activity Limitation; Patient Satisfaction with Study Medication (PSSM); Headache Impact Test (HIT-6); Migraine Disability Assessment (MIDAS); Patient Global Impression of Change (PGIC); Work Productivity and Activity Impairment Questionnaire: Migraine V2.0 (WPAI:MIGRAINE); European Quality of Life – 5 Dimensional (EQ-5D-5L); Patient Global Impression – Severity (PGI-S); Migraine Specific Quality of Life Questionnaire, Version 2.1 (MSQ v2.1); Patient-Reported Outcomes Measurement Information Systems Pain Interference – Short Form 6a (PROMIS-PI); and Patient Health Questionnaire (PHQ-9).

Pharmacokinetics: Blood samples will be collected for pharmacokinetic (PK) analysis for participants who consent.

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

General Statistical Methods and Types of Analyses:

All efficacy analyses will be performed using the modified intent-to-treat (mITT) population, which consists of all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and at least 1 evaluable postbaseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period. All safety analyses will be performed using the safety population, which consists of all participants who took at least 1 dose of study intervention. The analysis population for off-treatment hypothetical estimand includes all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and at least 1 evaluable postbaseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the study, regardless of whether on study treatment or off study treatment. This population is used for the primary estimand to support filing in Europe.

For all regulatory submissions, the primary efficacy endpoint will be the same. However, secondary efficacy endpoints will differ.

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.

The primary comparison between treatment groups will be done by a mixed-effects model for repeated measures (MMRM) of the change from baseline. The statistical model will include treatment group, visit, region, acute medications during the baseline period (medication overuse Y/N), current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action (Current Use and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action", Current Use and "failed 2 to 4 medications with different mechanisms of action", Past Use only and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action", Past Use only and "failed 2 to 4 medications with different mechanisms of action", and Never Used), and treatment group by visit interaction as categorical fixed effects. The statistical model will also include the baseline score and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-participant repeated measurements. The Kenward-Roger approximation (Kenward 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.

Secondary Efficacy Endpoints for all regions, except Europe and Canada:

- 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
- At least a 50% reduction in 3-month average of monthly migraine days
- 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 Europe and Canada:

- 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
- At least a 50% reduction in 3-month average of monthly migraine days
- Change from baseline in the HIT-6 total score at Week 12
- Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12

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 secondary endpoint of 50% responders, defined as participants 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 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, acute medications during the baseline period (medication overuse Y/N), current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action 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.

A logistic regression model will be used to analyze 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, acute medications during the baseline period (medication overuse Y/N), current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action 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.

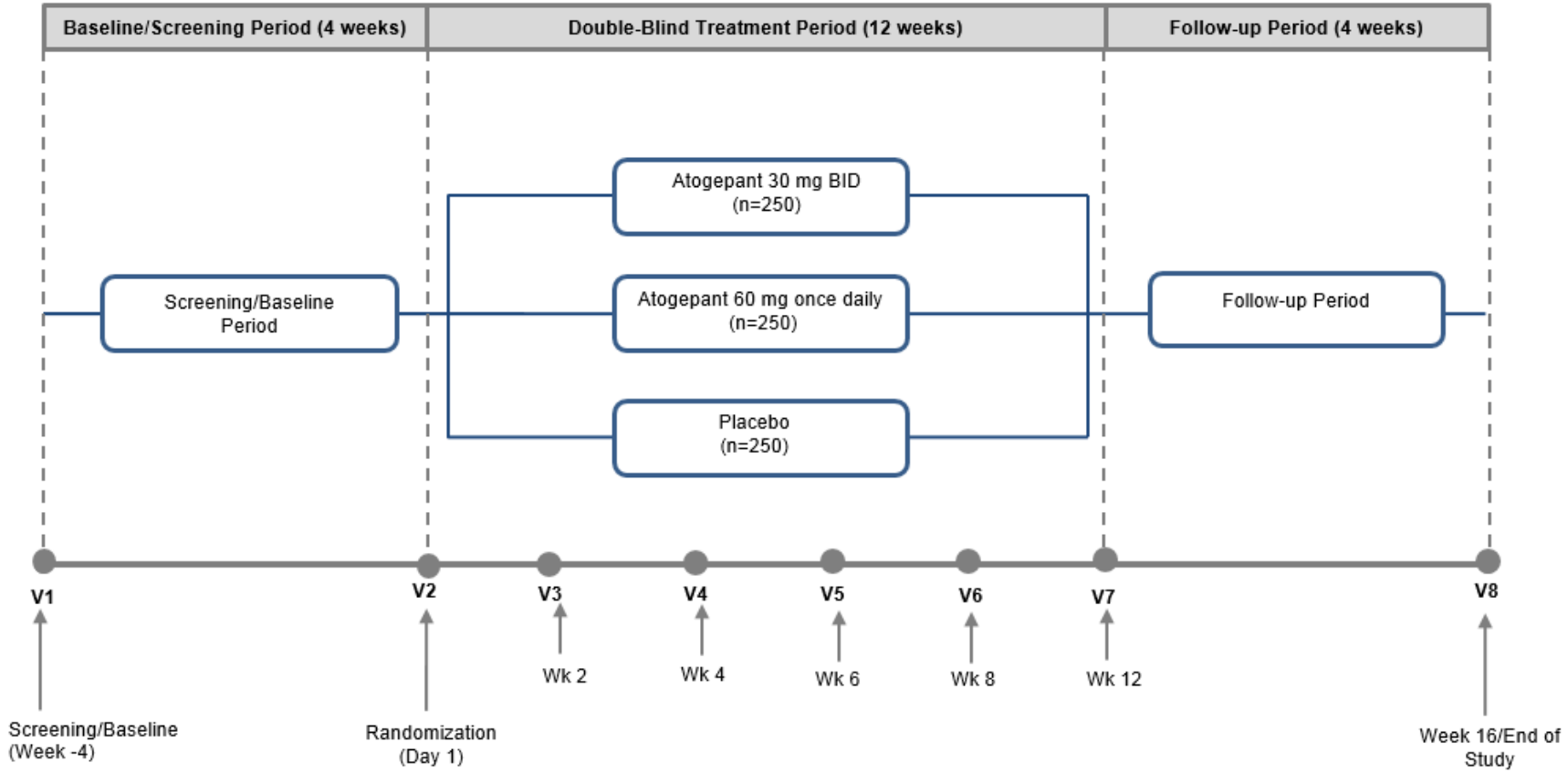
Incidence of treatment emergent adverse events (TEAEs) will be tabulated by primary system organ class (SOC) and by specific event within each primary SOC. TEAEs will be analyzed after treatment start on Day 1 through the end of the study.

Sample Size Calculation: A total sample size of 250 randomized participants per treatment group will provide at least 96% power to detect the treatment difference between each of the 2 atogepant doses (assumed equally effective) and placebo for the primary efficacy endpoint. This sample size was selected to provide sufficient power for the first 3 secondary endpoints. The power calculations are based on the following assumptions:

1) the treatment difference from placebo will be similar to the average value across the CM prevention studies for Botox® (Aurora 2010, Diener 2010) and TEV-48125 (Bigal 2015, Silberstein 2017). In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period is -2 days, and the standard deviation is 5.5 days.

2) the study statistical testing plan controls the overall type I error at 5%. The power calculations of the primary and secondary endpoints have taken the multiple comparisons into consideration by testing each dose versus placebo at a 0.025 significance level, 2-sided. Once the primary endpoint for each dose is significant at 0.025, 2-sided, the secondary endpoints will be tested sequentially.

Figure 1 Study Diagram



BID = twice daily; V = visit.

Table 1 Schedule of Visits and Procedures

Study Period	**Screening/ Baseline (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #[a]	**Visit 1**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[b]**	**Visit 8[c] (End of Study)**
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 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Obtain Informed Consent and participant privacy	X							
Obtain Informed Consent for future biomedical research (optional)	X							
Obtain Informed Consent for PK (optional)	X							
Obtain VCT consent and perform verification (United States and Canada 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	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	
Perform urine pregnancy test[e]	X	X	X	X	X	X	X	X
Collect start date (first day) of last menstrual cycle for women having menstrual cycles	X	X	X	X	X	X	X	X
Collect urine drug screen	X							
Collect clinical laboratory determinations[f]	X	X	X	X	X	X	X	X
Collect PK sample (for those participating)[g]		X	X	X	X	X	X	

Study Period	**Screening/ Baseline (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #[a]	**Visit 1**	**Visit 2 (Randomization)**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7/ET[b]**	**Visit 8[c] (End of Study)**
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 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Collect blood for future biomedical research (for those participating)	X							
Provide eDiary, and eDiary instructions and training[h]	X							
Participant eDiary data collection	X							
Review of medication compliance			X	X	X	X	X	
Review eDiary data (headache duration, frequency, characteristics and symptoms; acute medication use, AIM-D, activity level and activity limitation) and compliance[i]		X	X	X	X	X	X	
C-SSRS (eTablet)[j]	X	X	X	X	X	X	X	X
ASC-12 (eTablet)[k,l]	X							
HIT-6 (eTablet)[k,l]		X		X		X	X	X
PGIC (eTablet)[k,l]							X	
PGI-S (eTablet)[k,l]		X		X		X	X	
WPAI:MIGRAINE (eTablet)[k,l]		X		X		X	X	
PSSM (eTablet)[k,l]				X		X	X	
EQ-5D-5L[m]	X	X	X	X	X	X	X	X
MIDAS (eTablet)[k,l]		X					X	
MSQ v2.1 (eTablet)[k,l]		X		X		X	X	X
PROMIS-PI (eTablet)[k,l]		X		X		X	X	
PHQ-9 (eTablet)[k,l]		X					X	
Collect eDiary		X[n]					X[o]	X[p]
Dispense study intervention		X[q]	X	X	X	X		
Adverse events	X							
Concomitant medications/concurrent procedures	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; OL = open-label; PGIC = Patient Global Impression of Change; PGI-S = Patient Global Impression – Severity; PHQ-9 = Patient Health Questionnaire; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS-PI = Patient-Reported Outcomes Measurement Information System Pain Interference – Short Form 6a; PSSM = Patient Satisfaction with Study Medication; VCT = verified clinical trial; WPAI:MIGRAINE = Work Productivity and Activity Impairment Questionnaire: Migraine V2.0.

[a] Visit 1, Visit 2, and either Visit 3 or Visit 4 must be conducted in office. All other visits, should be conducted in office unless it is necessary to conduct remote visits for the safety of participants (eg, COVID-19 or other pandemic): for details please refer to the Remote Visit Schedule of Assessments in Attachment 12.4.

[b] Effort should be made by site to not schedule Visit 7 earlier than Day 85 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 follow-up period, except for participants rolling over into Study 3101-312-002 (long-term safety extension study in regions excluding Japan and China), participants rolling over into Study 3101-306-002 (long-term safety extension study in Japan), or Study 3101-311-002 (open-label safety extension study in China). For these rollover participants the Follow-up Visit will be performed after the completion of the OL treatment in the respective long-term safety extension study.

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

[e] For women of childbearing potential only, a urine pregnancy test will be performed at all visits

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

[g] PK sample should be collected prior to the first dose at Visit 2. One sample should be collected prior to the morning dose during one of the Visits 3 to 7, and the remaining samples should be collected 1 to 10 hours postdose.

[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 the site.

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

[j] Clinicians will complete on eTablet. The screening/baseline assessment of the C-SSRS will be completed. At all other visits, the 'Since Last Visit' C-SSRS will be completed.

[k] Participant will complete on eTablet.

[l] PRO measures should be administered prior to any tests and/or evaluations unless indicated otherwise in the protocol (eg, during Randomization Visit 2, some tests will be conducted prior to the PROs for eligibility).

[m] EQ-5D-5L will be given on eDiary during 7 days in the 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.

[n] eDiary will be collected on Visit 2 for screen failures.

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

[p] Collected at Visit 8/Follow-up only for participants who discontinue from the double-blind treatment period.

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

1. Background and Clinical Rationale

1.1 Background

Migraine affects 18% of women and 6% of men in the United States with peak prevalence occurring between the ages of 25 to 55 years. Approximately one-third of patients with migraines 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 2010). The prevalence of migraine in China is 8.9%, with a similar distribution across males and females as the United States, according to the Guidelines for Prevention and Treatment of Migraine in China (Yu 2016). In Japan, the overall prevalence of migraine was reported as 8.4%; 5.8% was migraine without aura and 2.6% was migraine with aura (Sakai 1997). Like Western countries, migraine is more prevalent among women in Japan; women were observed to have a 5.9-fold higher risk of migraine than men (Takeshima 2004). The Global Burden of Disease Survey 2010 estimated the global prevalence of migraine to be 14.7%, making it the third most common disease in the world in both males and females (Vos 2012). Migraine was ranked seventh highest among specific causes of disability globally (Steiner 2013).

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

Because there are no biological markers for migraine, diagnosis is based on clinical history, examination, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnoses and subsequent treatment. 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. CM 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). Approximately 1.3% of the United States population (approximately 3 million people) and 1.3% to 2.4% of the European population suffer from CM. CM is recognized as the population suffering most from migraine and as a disabling, underdiagnosed, and undertreated disorder (Bigal 2008). Studies have established that those suffering from CM have impaired quality of life and that they suffer substantial socio-economic burden due to increased medical needs, referral to medical specialists,

drug utilization, work absenteeism, and reduced effectiveness at work (Blumenfeld 2011; Munakata 2009).

This study will evaluate the efficacy, safety and tolerability of atogepant in participants with CM.

1.2 Overview of Atogepant

Atogepant is a potent, selective oral CGRP receptor antagonist 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 patients with migraine. 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 IV formulation of olcegepant (Olesen 2004) and replicated by Merck & Co., Inc. with an oral formulation of MK-0974 (telcagepant), a highly selective CGRP receptor antagonist. 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.

A Phase 2/3 clinical study (Study CGP-MD-01) was conducted, which compared atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 30 mg BID, atogepant 60 mg once daily and atogepant 60 mg BID to placebo in EM prevention. 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 patients with EM.

Additional information on nonclinical pharmacology, toxicology, and PK properties of atogepant can be found in the investigator's brochure.

1.3 Study Rationale

The purpose of this study is to prospectively assess the safety, tolerability and efficacy of atogepant doses 30 mg BID and 60 mg once daily compared with placebo in the prevention of CM, in a randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study. This study is designed to be a pivotal trial and will be used to support registration applications.

1.4 Rationale for Doses and Dose Regimens Selected

This study will test 2 doses of atogepant, 30 mg BID and 60 mg once daily, selected based on the results from Study CGP-MD-01 in patients with EM. All atogepant doses investigated in Study CGP-MD-01 demonstrated good safety and tolerability. Whilst all atogepant doses also demonstrated a statistically significant reduction from baseline in mean monthly migraine days across the 12-week treatment period compared to placebo, there was no clear dose-response relationship. However, there was a suggestion that the BID regimen may provide better efficacy than the once-daily regimen. The current study will therefore investigate both atogepant 30 mg BID; and the highest once daily dose previously tested, atogepant 60 mg once daily, with a 12-week treatment period.

1.5 Benefit/Risk Assessment

Based on the currently available data, atogepant has demonstrated efficacy for the prevention of episodic migraine; in addition, atogepant has been well tolerated with no safety concerns to date. The protocol is designed to ensure that patient safety is assessed adequately throughout the study. 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 and patients already receiving a migraine prevention medication at screening can continue treatment during the study. Overall the assessment of benefit/risk is favorable.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To evaluate the safety and tolerability of atogepant 30 mg BID and atogepant 60 mg once daily for the prevention of CM.

To prospectively test for superiority of atogepant (30 mg BID and atogepant 60 mg once daily) versus placebo for the prevention of CM.

2.2 Clinical Hypotheses

In participants with CM, at least one dose of atogepant (30 mg BID and atogepant 60 mg once daily) is superior to placebo as measured by the change from baseline in mean monthly migraine days across the 12-week treatment period.

Atogepant has an acceptable safety profile and is well tolerated in participants with CM.

3. Study Design

3.1 Structure

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study conducted at approximately 140 sites worldwide.

Approximately 750 participants will be randomized to 1 of 3 treatment arms in a 1:1:1 ratio as follows:

- Placebo (n = 250)
- Atogepant 30 mg BID (n = 250)
- Atogepant 60 mg once daily (n = 250)

Participants will be stratified by:

- Randomization will be stratified by use of acute headache medications during the baseline period (acute headache medication overuse Yes or No). Acute headache medication overuse (Yes) will be defined as follows: use of triptans on ≥ 10 days OR use of ergots on ≥ 10 days OR use of simple analgesics (ie, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], or acetaminophen) on ≥ 15 days OR use of any combination of triptans, ergots or simple analgesics on ≥ 10 days.
- Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy (see Attachment 12.3).[2] Randomization will be stratified based on migraine prevention medication exposure (Current Use, Past Use, or Never Used) with proven efficacy. Participants with current or past use will be further stratified based on the number of medications failed

[2] All French participants must have taken at least 1 prior migraine prevention medication with proven efficacy to be eligible for Study 3101-303-002.

with unique mechanisms of action: "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" or "failed 2 to 4 medications with different mechanisms of action" (see Attachment 12.3). Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%.

- Below are examples to illustrate how to implement the stratification based on prior migraine prevention medications:

  - Example 1: Participant has taken metoprolol and propranolol. According to Attachment 12.3, these medications both belong to the beta-blocker pharmacologic category. This participant should be randomized to the "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" stratum.

  - Example 2: Participant has taken metoprolol, propranolol, and topiramate. According to Attachment 12.3, metoprolol and propranolol belong to the beta-blocker pharmacologic category and topiramate belongs to the antiepileptic pharmacologic category. This participant should be randomized to the "failed 2 to 4 medications with different mechanisms of action" stratum.

  - Example 3: Participant has taken metoprolol and topiramate. According to Attachment 12.3, metoprolol belongs to the beta-blocker pharmacologic category and topiramate belongs to the antiepileptic category; however, the patient stopped both of these medications because of a change in health insurance coverage and therefore did not meet the failure definition for either medication. This participant should be randomized to the "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" stratum.

- Randomization will be stratified by regions (ie, North America, Europe, Japan, China, Other)

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 this study at Visit 2 (Randomization Visit). The double-blind treatment period will last 12 weeks, with a follow-up period of 4 additional weeks.

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). The Visit 8 (follow-up) must be completed for all participants who take at least 1 dose of study medication, except for participants rolling over into Study 3101-312-002 (long-term safety extension study in regions, excluding Japan and China), Study 3101-306-002 (long-term safety extension study in Japan), or Study 3101-311-002 (open-label safety extension study in China). For these rollover participants Visit 8 of Study 3101-303-002 is not required,

because the Follow-up Visit (Visit 8) will be performed after the OL treatment in the respective long-term safety study. For participants who screen fail for the long-term safety study, the Follow-up Visit (Visit 8) of Study 3101-303-002 must be completed. For more details on study schedule, please see Table 1, Schedule of Visits and Procedures.

3.2 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 the sponsor, 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.

3.3 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 $\geq 3 \times$ 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.

3.4 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.

4. Study Population and Entry Criteria

4.1 Number of Participants

Approximately 750 participants will be randomized at approximately 140 sites worldwide (North America, Europe, Japan, China, Other).

4.2 Inclusion Criteria

The following are requirements for entry into the study:

1. Written informed consent and participant privacy information (eg, Written Authorization for Use and Release of Health and Research Study Information) obtained from the participant prior to initiation of any study-specific procedures

2. Male or female participants ages 18 to 80 years, inclusive, at Visit 1

3. At least a 1-year history of CM consistent with a diagnosis according to the ICHD-3, 2018

4. Age of the participant at the time of migraine onset < 50 years

5. Confirmation of headache/migraine headache day frequency as follows:

    a. History of, on average, ≥ 15 headache days per month in the 3 months prior to Visit 1 in the opinion of the investigator **AND**
    b. ≥ 15 headache days during the 4-week screening/baseline period per the electronic diary (eDiary) **AND**
    c. ≥ 8 days during the 4-week screening/baseline period that qualify as being a migraine day per the eDiary

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

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

4.3 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1. Difficulty distinguishing migraine headaches from tension-type or other headaches

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

3. Has a current diagnosis of new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018

4. History of an inadequate response to > 4 medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine (see Attachment 12.3)

5. Currently taking more than 1 medication with demonstrated efficacy for the prevention of migraine OR participants who are taking 1 migraine prevention medication, but in the opinion of the investigator:

    - the dose has not been stable and/or the medication has not been well-tolerated for at least 12 weeks prior to Visit 1
    - the participant is not willing or able to maintain taking this medication at a stable dose and dosage regimen throughout the study
    - Note: Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, Botox®, Xeomin®, Myobloc®, Jeuveau™) into areas of the head, face, or neck are excluded 6 months prior to screening and for the duration of the study

6. Requirement for any medication, diet (ie, grapefruit juice), or non-pharmacological treatment that is on the list of prohibited concomitant medications or treatments (see Section 4.4.2 and Attachment 12.2) that cannot be discontinued or switched to an allowable alternative medication or treatment

7. Usage of opioids and/or barbiturates > 4 days/month in the 3 months prior to Visit 1 per investigator's judgment, or during the baseline period (barbiturates are excluded 30 days prior to screening and for the duration of the study) (see Attachment 12.2)

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

9. An ECG with clinically significant abnormalities at screening (Visit 1) as determined by the investigator

10. QTcF > 450 msec for males and QTcF > 470 msec for females at Visit 1 on the final central vendor ECG report

11. 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

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

13. Clinically significant laboratory values OR any of the following laboratory values at Visit 1:

    - ALT or AST > 1 × ULN OR
    - total bilirubin > 1 × ULN (except for participants with a diagnosis of Gilbert's disease) OR
    - serum albumin < 2.8 g/dL

14. Any clinically significant hematologic, endocrine, cardiovascular, cerebrovascular, pulmonary, renal, 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 participation in the study, the participant may be included.
    - Participants on dialysis for renal failure are excluded.

15. 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

16. In the opinion of the investigator, confounding psychiatric conditions, dementia, epilepsy or significant neurological disorders other than migraine

17. 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)

18. 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

19. 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

20. History of any gastrointestinal prior 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.

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

22. Positive result on the urine drug screen at Visit 1 unless explained by concomitant medication use (eg, opioids prescribed for migraine pain)

23. 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)

24. Previous exposure to:

    - atogepant (AGN-241689 or MK8031) OR
    - injectable monoclonal antibodies blocking the CGRP pathway within the past 6 months OR
    - ubrogepant and took more than 3 doses of ubrogepant OR
    - rimegepant and took more than 3 doses of rimegepant

25. History of hypersensitivity or clinically significant adverse reaction to a CGRP receptor antagonist or hypersensitivity to any component of the study interventions (atogepant or placebo)

26. Employed by or is an immediate family member (parents, spouses, siblings or children) of one of the investigators, study staff, or the sponsor

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

28. 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

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

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

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

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

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

SSRIs or SNRIs will be permitted provided that treatment is stable for at least 60 days prior to screening (Visit 1) and continues without change in dose throughout the study.

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

4.4.2 Prohibited Medications/Treatments

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

- Strong and moderate CYP3A4 inhibitors, including but not limited to: systemic (oral/IV) itraconazole, ketoconazole, fluconazole; erythromycin, clarithromycin, telithromycin[3]; diltiazem, verapamil; aprepitant, cyclosporine, nefazodone[3], cimetidine, quinine, and HIV protease inhibitors (see Attachment 12.2)

- Strong and moderate CYP3A4 inducers, including but not limited to: barbiturates (eg, phenobarbital and primidone), systemic (oral/IV) glucocorticoids, nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, and St. John's wort (see Attachment 12.2)

  Strong OATP1B1 inhibitors (eg, gemfibrozil[3], cyclosporine)

- Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions (eg, warfarin)

- Medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, propranolol, topiramate) are prohibited when used for any indication other than migraine prevention. See Attachment 12.3.

    - Participants taking **one** medication with demonstrated efficacy for the prevention of migraine may be randomized provided that in the opinion of the investigator:

        - Dose has been stable and the medication has been well-tolerated for at least 12 weeks prior to Visit 1 AND

        - Participant is willing and able to maintain at a stable dose and dosage regimen during the study, which should be assessed to ensure compliance at each study visit

        - Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%

[3]not approved in Japan

- 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

- Acupuncture, noninvasive neuromodulation devices (eg, transcutanous supraorbital neurostimulator, single pulse transcranial magnetic stimulator, vagus nerve stimulator), cranial traction, nociceptive trigeminal inhibition, occipital nerve block treatments, or dental splints for headache, within 4 weeks prior to entry into the baseline phase at Week – 4 or at any time during the study (including the Week – 4 to Day 1 baseline phase)

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

- For China, South Korea, Japan, and Taiwan, herbal and traditional medicine is prohibited from the time the ICF is signed and for the duration of study participation.

- Cannabidiol (CBD) oil, cannabis.

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

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

For purposes of this study, women will be considered of childbearing potential unless they are naturally postmenopausal (ie, no menses for 2 years) or permanently sterilized (ie, bilateral tubal ligation, bilateral tubal occlusion [eg, Essure® placement[4] with HSG confirmation], bilateral salpingectomy, bilateral oophorectomy, or hysterectomy). For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered highly effective:

- Combined (estrogen and progestogen containing) hormonal contraception such as oral, intravaginal[4], or transdermal[4] (ie, pill, patch[4], vaginal ring[4])

- Progestogen-only hormonal contraception (with inhibition of ovulation) that are oral, injectable[4], or implantable[4]

[4] Contraceptive methods not approved in Japan

- IUD or IUS
- Vasectomized partner (provided that the partner is the sole sexual partner of study participant and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence, defined as refraining from heterosexual intercourse for the entire duration of the study, from Visit 1 through the end of study (Visit 8/Follow-up Visit)
    - Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

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

- Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action)
- Male or women condom with or without spermicide[4] (women and male condoms should not be used together)
- Cap[4], diaphragm[4], or sponge[4] with spermicide
- A combination of male condom with either cap[4], diaphragm[4], or sponge[4] with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

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

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

If a woman becomes pregnant during the study, the investigator will notify the sponsor immediately after the pregnancy is confirmed and the participant will be exited from the study after appropriate follow-up. The investigator will (1) notify the participant's physician that the participant was being treated with an investigational drug atogepant, and (2) follow the progress of the pregnancy. The investigator must document the outcome of the pregnancy and provide a copy of the documentation to the sponsor.

4.4.4 Special Diet or Activities

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 or caffeine intake during the study.

Alcohol intake should be limited to no more than 1 drink per day throughout the study. A drink is defined as a 12-ounce (or 355 mL) can/bottle of beer, a 4-ounce (or 118 mL) glass of wine, or 1 ounce (or 30 mL) of liquor.

4.5 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 (ie, failure to adequately screen due to COVID-19), with permission from the sponsor. However, participants with clinically significant laboratory values at Visit 1 (ie, screening; including ALT or AST >1 × the ULN, total bilirubin > 1 × ULN or serum albumin < 2.8 g/dL), or those with a positive UDS result at Visit 1 for recreational (including marijuana regardless of legality) or illicit drugs or non-disclosed[5] concomitant medications are not allowed to be rescreened.

5. Study Interventions

5.1 Study Interventions and Formulations

Tablets containing atogepant 30 mg (Formulation Number 11280X) or atogepant 60 mg (Formulation Number 11281X).

5.2 Control Interventions and Formulations

Tablets containing matching placebo 30 mg (Formulation 011326X) for atogepant 30 mg and matching placebo 60 mg for atogepant 60 mg (Formulation 011317X).

[5] For participants in the People's Republic of China, a positive UDS will result in screen failure regardless of disclosed concomitant medications.

5.3 Methods for Masking/Blinding

A double-dummy design will be used to maintain the blind. All study interventions will be provided in identical blister cards to maintain masking of the study.

All participants will be instructed to take their study intervention twice daily (ie, 2 tablets in the morning and 2 tablets in the evening) at approximately the same times each day. Participants, therefore, will receive either placebo BID, atogepant 30 mg BID, or a morning dose of atogepant 60 mg with an evening dose of placebo.

5.4 Treatment Allocation Ratio and Stratification

Approximately 750 participants will be randomized to one of three treatment arms in a 1:1:1 ratio as follows:

- Placebo (n = 250)
- Atogepant 30 mg BID (n = 250)
- Atogepant 60 mg once daily (n = 250)

Participant will be stratified by:

- Randomization will be stratified by use of acute headache medications during the baseline period (acute headache medication overuse Yes or No). Acute headache medication overuse (Yes) will be defined as follows: use of triptans on ≥ 10 days OR use of ergots on ≥ 10 days OR use of simple analgesics (ie, aspirin, NSAIDs, or acetaminophen) on ≥ 15 days OR use of any combination of triptans, ergots, or simple analgesics on ≥ 10 days.
- Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy (see Attachment 12.3)[6]. Randomization will be stratified based on migraine prevention medication exposure (Current Use, Past Use, or Never Used) with proven efficacy. Participants with current or past use will be further stratified based on the number of medications failed with unique mechanisms of action: "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" or "failed 2 to 4 medications with different mechanisms of action" (see Attachment 12.3). Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%.

[6] All French participants must have taken at least 1 prior migraine prevention medication with proven efficacy to be eligible for Study 3101-303-002.

- Below are examples to illustrate how to implement the stratification based on prior migraine prevention medications:
  - Example 1: Participant has taken metoprolol and propranolol. According to Attachment 12.3, these medications both belong to the beta-blocker pharmacologic category. This participant should be randomized to the "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" stratum.
  - Example 2: Participant has taken metoprolol, propranolol, and topiramate. According to Attachment 12.3, metoprolol and propranolol belong to the beta-blocker pharmacologic category and topiramate belongs to the antiepileptic pharmacologic category. This participant should be randomized to the "failed 2 to 4 medications with different mechanisms of action" stratum.
  - Example 3: Participant has taken metoprolol and topiramate. According to Attachment 12.3, metoprolol belongs to the beta-blocker pharmacologic category and topiramate belongs to the antiepileptic category; however, the patient stopped both of these medications because of a change in health insurance coverage and therefore did not meet the failure definition for either medication. This participant should be randomized to the "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" stratum.

- Randomization will be stratified by regions (ie, North America, Europe, Japan, China, Other)

5.5 Method for Assignment to Treatment Groups/Randomization

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 time of randomization (Visit 2), eligible participants will be randomized in a 1:1:1 ratio into the following arms: placebo, atogepant 30 mg BID, or atogepant 60 mg once daily.

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, log in information and directions for the IWRS will be provided to each site.

Study intervention will be labeled with medication 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.

Study intervention will be dispensed at the study visits summarized in Table 1, Schedule of Visits and Procedures. Returned study intervention should not be re-dispensed to the participants.

5.6 Study Intervention Regimen and Dosing

Treatments to be used in this trial are listed in Table 2. Participants who meet all 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. Participants will take their first dose of study intervention at the clinic at Visit 2. All participants will be instructed to take their study intervention twice daily (2 tablets in the morning and 2 tablets in the evening) at approximately the same times each day. Details of PK samples with respect to timing of study intervention are provided in Section 6.3. Study intervention will be administered orally for 12 weeks, and participants will be followed for 4 weeks following study completion or discontinuation of study intervention.

Table 2 Study Interventions

Drug/Dose	Study Intervention Product and Matching Placebo	Study Intervention Frequency	Route of Administration
Placebo	Placebo 30 mg and Placebo 60 mg	BID	Oral
Atogepant 30 mg	Atogepant 30 mg and Placebo 60 mg	BID	Oral
Atogepant 60 mg	AM: Atogepant 60 mg and Placebo 30 mg	BID	Oral
	PM: Placebo 30 mg and Placebo 60 mg		

AM = morning dose; BID = twice daily; PM = evening dose.

5.7 Storage of Study Interventions

The study intervention must be stored at room temperature in a securely locked cabinet. Further details regarding the storage of the study intervention are in the Study Reference Manual.

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

Efficacy assessments will be based on information recorded by the participant. An eDiary will be used daily at home to collect data on headache frequency, duration, characteristics, and symptoms; acute medication use and triptan use, which will be collectively applied to define migraine days and headache days per the criteria listed in Sections 6.1.1, 6.1.2, and 6.1.3.

The AIM-D, Activity Level, and Activity Limitation will also be collected daily via an eDiary. EQ-5D-5L will also be collected via an eDiary for a period of 1 week in the screening period (administered on Study Day 22 through 28 for a total of 7 days after screening), 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 on an eTablet. Additional health outcome measures, namely, the PSSM scale, HIT-6, MIDAS, PGIC, WPAI:MIGRAINE, PGI-S, MSQ v2.1, PROMIS-PI, and PHQ-9 will also be administered on an eTablet at specified clinic visits.

6.1.1 Migraine Day

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

A. Headache has at least 2 of the following 4 characteristics:
   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)

B. At least 1 of the following:
   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
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 fulfills 1 criterion from (1) and at least 1 criterion from (2) **OR** fulfills at least 2 criteria from (1) and no criteria from (2).
   1) Headache characteristics:
      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.

6.1.2 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).

6.1.3 Acute Medication Use Day and Triptan 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, opioids, 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.

6.2 Health Outcomes Measures

6.2.1 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 the 6-point rating scale: "Not difficult at all," "A little difficult," "Somewhat difficult," "Very difficult," "Extremely difficult," and "I could not do it at all." Three items include a response of "I did not…," for example, "I did not have errands planned." 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).

6.2.2 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."

6.2.3 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).

6.2.4 Headache Impact Test (HIT-6)

The HIT-6 is a 6-question assessment used to measure the impact headaches have on a participant's 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 participant's 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).

6.2.5 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.

6.2.6 Patient Global Impression of Change (PGIC)

The PGIC is a single item questionnaire 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."

6.2.7 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 1-week recall and contains 6 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.

6.2.8 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 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against 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).

6.2.9 Patient Global Impression – Severity (PGI-S)

The PGI-S is a single item questionnaire 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."

6.2.10 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 3 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.

6.2.11 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.

6.2.12 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.

6.3 Pharmacokinetics Measures

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 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 1 of the Visits 3 to 6, the sample should be collected prior to the morning dose of study intervention (participant should wait to take the morning 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 morning dose and prior to the evening dose. At Visit 7 the sample should be collected 1 to 10 hours post the morning 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 the 2 doses of 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 Study Reference 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 study report.

6.4 Future Biomedical Research

Blood samples will be collected from all participants who consent to participate in the substudy, for the purposes of future biomedical research. The samples will be obtained at the Screening Visit. All samples will be sent to the designated central laboratory and shipped to a biorepository for storage. Please refer to the Central Laboratory Manual for the genetic blood sampling procedures, shipping instructions, and contact information. Anonymized samples may be stored in the biorepository database for potential analysis under separate protocols for up to 15 years. Samples may be stored for a longer time if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, samples will be stored until these questions have been adequately addressed. The anonymized genetic material from the blood samples may also be used for future, unspecified research, not limited to the disease being studied in this particular clinical study.

All participants enrolled in the clinical trial will be considered for enrollment in the future biomedical research substudy; however, participation is optional and will require a separate ICF. A participant who initially consents can withdraw that consent at any time and have his or her sample destroyed including any by-products of the sample whenever possible.

6.5 Safety Measures

6.5.1 Adverse Events

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

6.5.2 Adverse Events of Special Interest

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

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

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

6.5.3 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the visits outlined in Table 1. Hematology, chemistry, coagulation parameters (INR), and urinalysis will be conducted at these visits. Serology and the urine drug screen will be conducted at screening (Visit 1). The investigator will assess the clinical significance of any values outside the reference ranges provided by the central laboratory. Participants with abnormalities judged to be clinically significant laboratory values that meet exclusionary criteria, or positive results on the urine drug screen at screening (Visit 1), will be excluded from the study.

Women of childbearing potential will be required to have a urine pregnancy test at all visits. A positive pregnancy test at Visit 1 or Visit 2 will exclude the participant from the study.

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

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

The clinical laboratory parameters to be measured are shown in Table 3.

Table 3 Clinical Laboratory Parameters

Category	Parameter
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol. The estimated glomerular filtration rate will be calculated by the central laboratory
Hematology	Hemoglobin; hematocrit; red blood cell count; red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration); white blood cell count including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils); platelet count
Urinalysis	Urine dipstick for specific gravity, pH, protein, glucose, ketones, bilirubin, and blood; microscopic 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. UDS positive for recreational (including marijuana regardless of legality) or illicit drugs or non-disclosed concomitant medications are not allowed to be repeated. All other positive urine drug screens may be repeated with permission from the sponsor; a negative result or an explanation of a positive result due to concomitant medication use (eg, opioids prescribed for migraine pain) will be required for randomization.

IgM = immunoglobulin M.

Please note: For participants in the People's Republic of China, a positive UDS will result in screen failure regardless of disclosed concomitant medications.

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

6.5.4 Vital Signs

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

6.5.5 Physical Examination

A complete physical examination will be performed at the visits outlined in Table 1. A professionally trained physician or healthcare professional licensed to perform physical examinations will examine the participant for any detectable abnormalities of the following body

systems: general appearance, neck (including thyroid), head, eyes, ears, nose, and throat, lungs, heart/cardiovascular, abdomen, neurologic, extremities, back, musculoskeletal, lymphatic, skin, and other. The neurologic examination should be conducted to detect the presence of any significant sensory/motor abnormalities.

6.5.6 Electrocardiograms

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

6.5.7 Columbia-Suicide Severity Rating Scale

The C-SSRS is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts. The C-SSRS will be completed at all study visits. At screening (Visit 1), the C-SSRS will be completed for history of suicidal ideation and suicidal behavior for the participant's lifetime and 6 months prior to screening. At all other visits, the C-SSRS will be completed for ideation and behavior since the previous visit. The C-SSRS will be completed on the eTablet by the investigator or designee with current and valid training in administering the assessment. A participant should not be released from the study center until the results of C-SSRS are reviewed and it is confirmed that the participant is not considered to be at risk. Participants who reply with "yes" to questions 4 or 5 in the suicidal ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS at Visits 3 through 6 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the ET Visit 7 and the follow-up Visit 8. These participants must continue to complete their daily eDiary through Visit 8 follow-up.

6.6 Other Study Supplies

The following will be provided by the sponsor or a delegate:

- 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 and future biomedical research 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)

6.7 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 on the eTablet or, if conducted remotely (Attachment 12.4), utilizing a web-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 Lab Procedure 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. Training for the eDiary will be provided for qualified participants during the Screening/Baseline Visit (Visit 1).

7. Statistical Procedures

7.1 Analysis Populations

The ITT population will consist of all randomized participants. All efficacy analyses will be performed using the mITT population, consisting of 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the double-blind treatment period. All safety analyses will be performed using the safety population, consisting of all participants who received at least 1 dose of study intervention.

The primary efficacy analysis population to support filing in Europe for off-treatment estimand (defined in Section 7.4) includes 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the study, regardless of whether on study treatment or off study treatment.

7.2 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 medication. Participants will be able to report headache data, including absence of headache, for the day of the diary report and for the day immediately prior to the day of the diary report, as long as information reported is for a time subsequent to the participant's most recent report. This is defined as a 1-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 follow-up phase. In practice, there may or may not be exact 2-week or 4-week durations between 2 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 baseline phase for at least 28 days and must report diary data for at least 20 days (including missing recall) during the 28-day 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 postbaseline diary window for a participant has at least 14, but less than 28 days, of reported data, the prorated approach will be used. If a participant reports less than 14 days of eDiary data, the participant's observed counts in that particular 28-day diary window will be set to missing for that window. These prorating rules will be applied to all efficacy analyses of diary data unless otherwise stated.

7.2.1 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.

7.2.2 Secondary Efficacy Endpoints

The Secondary Efficacy Endpoints *for all regions except Europe and Canada*:

- 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
- At least a 50% reduction in 3-month average of monthly migraine days
- 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.

The Secondary Efficacy Endpoints *for Europe and Canada*:

- 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
- At least a 50% reduction in 3-month average of monthly migraine days
- Change from baseline in the HIT-6 total score at Week 12
- Change from baseline in MSQ v2.1 Role Function-Restrictive domain score at Week 12

7.2.3 Additional Efficacy Endpoints

Additional efficacy endpoints for the United States and Europe are provided below. Related analysis will be documented in the statistical analysis plan (SAP).

- ≥ 25%, ≥ 30%, ≥ 50%, ≥ 75%, 100% improvement (decrease) in monthly migraine days at Weeks 1 to 4, 5 to 8, and 9 to 12
- ≥ 25%, ≥ 30%, ≥ 75%, 100% improvement (decrease) in 3-month average of monthly migraine days
- Change from baseline in monthly migraine days at Weeks 1 to 4, 5 to 8, and 9 to 12
- Change from baseline in monthly headache days at Weeks 1 to 4, 5 to 8, and 9 to 12
- Change from baseline in monthly cumulative headache hours at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
- Change from baseline in monthly acute medication use days at Weeks 1 to 4, 5 to 8, and 9 to 12
- Change from baseline in monthly triptan use days at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
- Change from baseline 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
- Change from baseline in monthly severe headache days at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period
- Change from baseline in weekly migraine days at Weeks 1-4

- Participant having a migraine day on the day of initial dose and on each day of the 6 days post the initial dose.
- Change from baseline in the HIT-6 total score at Weeks 4, 8, and 16 (for Europe and Canada)
- Change from baseline in the HIT-6 total score at Weeks 4, 8, 12, and 16 (for all regions except Europe and Canada)
- At least a 5-point improvement (decrease) from baseline in HIT-6 total score at Weeks 4, 8, 12, and 16
- Participant assessed by the PGIC as "much better" or "very much better" at Week 12
- Participant reporting "satisfied" or "extremely satisfied" with study medication for migraine prevention at Weeks 4, 8, and 12
- 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 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-Restrictive domain score at Weeks 4, 8, and 16
- Change from baseline in the MSQ v2.1 Role Function-Preventive domain score at Weeks 4, 8, 12, and 16
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, 12, and 16
- 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 (for Europe and Canada only)

- Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period (for Europe and Canada 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 PHQ-9 score at Week 12

7.2.3.1 Other Health Outcome Variables

Other health outcome endpoints are listed below. The related health outcome analyses will be documented in the health economics and outcomes research SAP.

- 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 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 16
- Change from baseline in PROMIS-PI total score at Weeks 4, 8, and 12

7.3 Hypothesis and Methods of Analysis

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).

7.3.1 Primary Efficacy Analyses

The primary efficacy endpoint is the change from baseline in mean monthly migraine days across the 12-week treatment period. The primary null hypothesis is that atogepant 30 mg BID and 60 mg once daily are each equally effective as placebo in mean change from baseline in mean monthly migraine days across the 12-week treatment period. The alternative hypothesis is that at least 1 of the 2 doses of atogepant has a greater effect than placebo.

The primary comparison between treatment groups will be done by an MMRM of the change from baseline. The statistical model will include treatment group, visit, region, acute migraine medications during the baseline period (medication overuse Y/N), current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action (Current Use and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action", Current Use and "failed 2 to 4 medications with different mechanisms of action", Past Use only and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action", Past Use only and "failed 2 to 4 medications with different mechanisms of action", and Never Used), and treatment group by visit interaction as categorical fixed effects. The statistical model will also include the baseline score and baseline-by-visit interaction as covariates. An unstructured covariance matrix will be used to model the covariance of within-participant repeated measurements. The Kenward-Roger approximation (Kenward 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. This is the primary analysis method for the primary efficacy endpoint in support of US filing. 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.

7.3.1.1 Sensitivity Analyses in Missing Data Handling

Multiple sensitivity analyses for missing data handling will be conducted and summarized below. Details of the sensitivity analyses will be provided in the SAP.

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, acute medications during the baseline period (medication overuse Y/N), current or past use of migraine prevention medications and the number of medications failed with unique mechanisms of action, 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 missing at random (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 model (PMM), under which data could be missing not at random (MNAR), with repeated analyses combined via the reference based multiple imputation (MI) 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.

MMRM Based on Primary Measures Collected During the Double-blind and Follow-up Periods

The details for this analysis are provided in Section 7.4. The primary analysis in support of EU filing will serve as one sensitivity analysis in support of US filing.

7.3.1.2 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 MI 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 is referred to as ADAP [R] in Mehrotra 2012. The detail of the sensitivity analyses will be provided in the SAP.

7.3.2 Secondary Efficacy Analyses

The secondary efficacy variables are identified in Section 7.2.2.

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 secondary endpoint of 50% responders, defined as participants 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 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, acute medications during the baseline period (medication overuse Y/N), current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action 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 multiple comparisons across two atogepant doses and the primary and secondary efficacy endpoints will be controlled at the 0.05 level using a graphical approach (Bretz 2011). The primary endpoint will serve as the gatekeeper for the secondary endpoints. A complete graph and details of the graphical multiple comparison procedure will be presented in the SAP.

However, for Japan, the Hochberg procedure (Hochberg 1988) will be used to control the overall Type I error rate at a 0.05 level (2-sided) for multiple comparisons of 2 atogepant doses with placebo for the primary efficacy endpoint only. Detailed procedure is provided below.

Let $p_{(1)}$ and $p_{(2)}$ denote the nominal p-values in increasing order from the 2 comparisons of atogepant doses versus placebo.

Step 1: If $p_{(2)}$ is ≤ 0.05, then both the 2 comparisons are considered statistically significant at the 2-sided significance level of 0.05 and stop here; otherwise, go to Step 2.

Step 2: If $p_{(1)}$ is ≤ 0.025, then the corresponding comparison for $p_{(1)}$ is considered statistically significant at the 2-sided significance level of 0.05; otherwise, stop here.

Adjusted p-values using Hochberg procedure will also be provided.

7.3.3 Additional 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 weekly data analysis purposes, baseline is defined to be the baseline derived in monthly basis divided by 4, and change from baseline in the weekly migraine days will be calculated for consecutive 7-day periods beginning with Day 1. Subsequent to treatment start, the number of headache days will be counted in successive and non-overlapping 1-week (ie, 7-day) windows. Headaches that continue into a subsequent 1-week period will be counted (with recorded severity and duration) as occurring in each period. If any postbaseline eDiary window for a participant has at least 4, but less than 7 days, of reported data, the prorated approach will be used. If a participant reports less than 4 days of headache data, the participant's observed counts in that particular 7-day eDiary window will be set to missing for that window.

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

7.3.4 Safety Analysis

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

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

7.4 Off-treatment Hypothetical Estimand Framework for EMA

This section defines an estimand, termed as off-treatment hypothetical estimand, which will be the primary estimand in support of EU filing and serve as one sensitivity analysis in support of US filing.

7.4.1 Treatment Condition of Interest

Participants take assigned treatment by randomization during the double-blind treatment period. In addition, permissible and prohibited medications are described below:

- Participants are allowed to take acute migraine medications (Section 4.4.1) to keep the participants in the study
- Medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, propranolol, topiramate) are prohibited when used for any indication other than migraine prevention. See Attachment 12.3
    - Participants taking **one** medication with demonstrated efficacy for the prevention of migraine may be randomized provided that in the opinion of the investigator:
        - Dose has been stable and the medication has been well-tolerated for at least 12 weeks prior to Visit 1, AND
        - Participant is willing and able to maintain at a stable dose and dosage regimen during the study, which should be assessed to ensure compliance at each study visit
        - Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%

7.4.2 Population

The target population is patients suffering from CM satisfying the inclusion and exclusion criteria as specified in Section 4.

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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, or 9 to 12) of eDiary data, regardless of whether on study intervention or off study intervention.

7.4.3 Variable

The variable is the same as the primary efficacy endpoint defined in Section 7.2.1, which is the change from baseline in the patient's mean monthly (4-weeks) migraine days across the 12-week treatment period as derived from the eDiary data.

7.4.4 Accounting of Intercurrent Events

Intercurrent events and their handling rules are as follows:

- Participants who started a new migraine prevention treatment after the first dose of double-blind treatment will have their data after the end of the double-blind treatment period following the start of the new migraine prophylaxis treatment excluded from the 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 data will be included in the analysis.

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

7.4.5 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, a MMRM similar to the primary analysis specified in Section 7.3.1, will be performed on observed data including both on-treatment and off-treatment monthly migraine days.

7.4.6 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.

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.

7.5 Subgroup Analyses

7.5.1 Subgroup Analyses for Evaluating the Consistency of Treatment Effects Across Regions and Subpopulations

To estimate the treatment effect on the primary efficacy endpoint for individual regions, the same model as that of the primary MMRM model in primary efficacy analysis in Section 7.3.1 will be utilized. In addition, the model will include region, region by treatment (2-way interaction) and region by treatment by visit (3-way interaction) as categorical fixed effects. An unstructured covariance matrix will be used to model the covariance of within participant repeated measurements. Pairwise contrasts in the MMRM model will be used to compare each atogepant dose to placebo for treatment effect in patients enrolled in each region.

The estimate of the between-group treatment effect (with a 95% CI) for each atogepant dose versus placebo for the primary efficacy endpoint for each region and overall treatment effect will be plotted in a forest plot to visualize the consistency of treatment effect across regions.

For key efficacy endpoints, the estimate of the between-group treatment effect (with 95% CI) for each atogepant dose versus placebo will be summarized overall and for each region in a table to facilitate the comparison. The test of treatment-by-region interaction will be provided as recommended in ICH E17 Section 2.2.7 on Examination of Consistency across Regions and Subpopulations.

Additional analyses to fulfill region specific regulatory requirement will be performed as appropriate. If models do not converge, descriptive statistics for subgroups will be provided. Details will be provided in the SAP.

7.5.2 Other Subgroup Analyses

A subgroup analysis by exposure to migraine prevention medication, preventive medication failures, and acute medication overuse is planned for the following efficacy endpoints:

- Change from baseline 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
- At least a 50% reduction in 3-month average of monthly migraine days
- At least a 75% reduction in 3-month average of monthly migraine days
- A 100% reduction in 3-month average of monthly migraine days

If models do not converge, descriptive statistics for subgroups will be provided. Details will be provided in the SAP.

7.6 Sample Size Calculation

A total sample size of 250 participants will be randomized per treatment group and that will provide at least 96% power to detect the treatment difference between each of the 2 atogepant doses (assumed equally effective) and placebo for the primary efficacy endpoint. The sample size of this study was selected to provide sufficient power for the first 3 secondary endpoints as shown in Table 4. The power calculations are based on the following assumptions:

1) The treatment difference from placebo will be similar to the average value across the CM prevention studies for Botox (Aurora 2010, Diener 2010) and TEV-48125 (Bigal 2015, Silberstein 2017). In particular, the assumed treatment difference from placebo in change from baseline in mean monthly migraine days across the 12-week treatment period is –2 days, and the standard deviation is 5.5 days. Detailed treatment difference and standard deviation assumptions are listed in Table 4.

2) The study statistical testing plan controls the overall type I error at 5%. The power calculations of the primary and secondary endpoints have taken the multiple comparisons into consideration by testing each dose versus placebo at a 0.025 significance level, 2-sided. Once the primary endpoint for each dose is significant at 0.025, 2-sided, the secondary endpoints will be tested sequentially. A detailed graphical multiple comparison procedure will be presented in the SAP.

Table 4 Statistical Power for Primary and the First Three Secondary Endpoints

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	–2	5.5	96%
Secondary 1	Change from baseline in mean monthly headache days across the 12-week treatment period	–2	6.0	93% [a]
Secondary 2	Change from baseline in mean monthly acute medication use days across the 12-week treatment period	–1.8	5.5	92% [a]
Secondary 3	At least a 50% reduction in mean monthly migraine days across the 12-week treatment period	33% Placebo Rate	49% Atogepant Rate	92% [a]

[a]: Statistical powers for secondary endpoints are conditional on success of prior endpoints (assuming independence among the endpoints) in the sequence for the comparisons of each dose versus placebo

7.7 Pharmacokinetics and Exposure-Response 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.

7.8 Interim Analyses

There is no interim analysis planned.

8. Study Visit Schedule and Procedures

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

8.1 Participant Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective participants as defined by the criteria in Sections 4.2 and 4.3 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Participant Privacy

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

Each participant that provides informed consent and/or assent will be assigned a participant identification number that will be used on participant documentation throughout the study.

The investigator or qualified designee will explain the PK and future biomedical research substudy consents to the participant and answer all of his/her questions. Participants will sign separate consent forms to participate in the PK substudy and future biomedical research before performing any procedure related to the substudies, respectively.

8.1.3 Procedure for Duplicate Participant Identification – Verified Clinical Trials

At participating sites, 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 Visits and Procedures (Table 1). Partial identifiers will be utilized. Participants who are identified as verification failures by VCT should not be enrolled without documented approval from the sponsor.

8.2 Washout Intervals

This study will not include a washout period.

8.3 Procedures for Final Study Entry

At the Screening and Randomization Visits (Visits 1 and 2), participants must meet all of the inclusion criteria and must not meet any of the exclusion criteria. Rescreening of participants may be considered with permission from the sponsor. However, participants with clinically significant laboratory values at Visit 1 (including ALT or AST >1 × the ULN, total bilirubin > 1 × 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. 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, confirm that the participant had ≥ 15 headache days per month in the 3 months prior to Visit 1 in the opinion of the investigator, and ≥ 15 headache days during the 4-week screening/baseline period per the eDiary, and ≥ 8 days during the 4-week screening/baseline period that qualify as a migraine day per the eDiary (see Section 6.1.1 for definition), and completed the eDiary for at least 20 of the 28 days.

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

8.4 Visits and Associated Procedures

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, Schedule of Visits and Procedures.

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

- Obtain informed consent and participant privacy.
- Obtain informed consent for future biomedical research (optional).
- Obtain informed consent for PK substudy (optional).
- Obtain VCT consent and perform verification at participating sites (United States and Canada only).
- Register participant in IWRS.
- Assess inclusion/exclusion criteria.
- Collect demographic information.

- Collect medical history.
- Collect migraine history (3-month retrospective) and confirm diagnosis.
- Review prior medications taken in the past 6 months, and all prior headache medications including migraine prophylactic medication use and concomitant medications/procedures.
- Assess C-SSRS on eTablet (the 'Screening/Baseline' assessment of the C-SSRS will be completed).
- Collect ASC-12 on eTablet.
- Perform physical examination.
- Collect vital sign measurements including: height, weight, sitting and standing pulse rate, respiratory rate, sitting and standing BP, and body temperature.
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Perform and transmit ECG.
- Perform urine pregnancy test (for women of childbearing potential only).
- Collect urine for drug screen.
- Collect clinical laboratory determinations including: chemistry, hematology, INR, screening serology, and urinalysis.
- Collect blood for future biomedical research (for those participants who consented)
- Provide eDiary, along with training and instructions. Participants to bring eDiary to all visits.
- Review and assess AEs.

8.4.2 Double-blind Treatment Phase (12 Weeks)

8.4.2.1 Visit 2 (Randomization) Day 1

- Review eDiary data (participants must bring eDiary to visits).
- Perform urine pregnancy test for women of childbearing potential.
- Collect vital sign measurements including: weight, sitting and standing pulse rate, respiratory rate, sitting and standing BP, and body temperature.
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.

- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Assess inclusion/exclusion criteria.

If the participant continues to meet study entry criteria, including acceptable results from Visit 1 clinical laboratory and pregnancy tests and the urine drug screen (see Section 6.5.3) the following procedures will be carried out at the randomization visit (Visit 2):

- Administer PRO measures including: HIT-6, PGI-S, WPAI:MIGRAINE, MIDAS, MSQ v2.1, PROMIS-PI, and PHQ-9.
- Update concomitant medications and concurrent procedures (including all prior headache medications).
- Review and assess AEs.
- Randomize the participant in IWRS and obtain the kit number for study intervention.
- Collect pretreatment PK sample (for those participants who consented).
- Collect pretreatment blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Dispense study intervention. The first dose of study intervention should be taken at the study site.

8.4.2.2 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 on the Schedule of Visits and Procedures.
- Review eDiary data (participants must bring eDiary to visits).
- Perform urine pregnancy test for women of childbearing potential.
- Collect vital sign measurements including: weight, sitting and standing pulse rate, respiratory rate, sitting and standing BP, and body temperature.
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Perform and transmit ECG (Visit 5 [Week 6] only)
- Update concomitant medications and concurrent procedures (including all prior headache medications).

- Review and assess AEs.
- Collect previous visit study intervention, review participant compliance, and perform accountability.
- Collect PK sample (for those participants who consented). During 1 of the Visits 3 to 6, the sample should be collected prior to the morning dose of investigational product (participant should wait to take the morning 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 morning dose and prior to the evening dose.
- Dispense study intervention.
- Collect blood and urine samples for chemistry, hematology, coagulation parameters (INR), and urinalysis.
- Access IWRS and obtain the kit number for study intervention and enter accountability.

8.4.2.3 Visit 7/Early Termination (Week 12)

- 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.
- Perform physical examination.
- Review eDiary data (participants must bring eDiary to visits).
- Collect eDiary from participant, if the participant completed the treatment period (eDiary collection will occur at Visit 8 for participants who discontinue study intervention early [see Section 8.8.1]).
- Perform urine pregnancy test for women of childbearing potential.
- Collect vital sign measurements including: weight, sitting and standing pulse rate, respiratory rate, sitting and standing BP, and body temperature.
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Assess C-SSRS (the “Since Last Visit” assessment of the C-SSRS will be completed).
- Perform and transmit ECG.
- Update concomitant medications and concurrent procedures (including all prior headache medications).
- Collect previous visit study intervention, review participant compliance, and perform accountability.

- Review and assess AEs.
- Access IWRS and enter accountability.
- Collect PK sample (for those participants who consented). The PK sample should be collected 1 to 10 hours post the morning dose.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.

8.4.3 Follow-up Period (4 Weeks)

8.4.3.1 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 participant, if the participant discontinued study intervention early [see Section 8.8.1]).
- Perform physical examination.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect vital sign measurements including: weight, sitting and standing pulse rate, respiratory rate, sitting and standing BP, and body temperature.
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Perform urine pregnancy test for women of childbearing potential.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Update concomitant medications and concurrent procedures (including all prior headache medications).
- Review and assess AEs.
- Access IWRS to enter study visit.

8.5 Instructions for the Participants

Section 4.4.4 provides diet and activity instructions for participants enrolled in the study.

Participants will be provided with instructions on daily completion of the eDiary. A practice session with a hypothetical scenario should be administered to ensure the participant's comprehension of the questions and the information to be entered. In addition, prohibited

medications should be reviewed with the participants. Participants will be instructed to bring their eDiary to each clinic visit and return their study intervention (used and unused blister packs).

Participants should be instructed to take study intervention BID at approximately the same times each day (approximately 12 hours between doses). For dosing on Day 1 (Visit 2), the first dose is to be taken at the study site, and participants should be advised to take the second dose depending on the time of the site visit and the participant's usual routine. Study intervention may be taken with or without food. Water is allowed as desired.

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

8.6 Unscheduled Visits

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

8.7 Compliance with Protocol

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

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

8.8 Early Discontinuation of Participants

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

- AE
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study intervention
- Other (specify reason)
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by participant

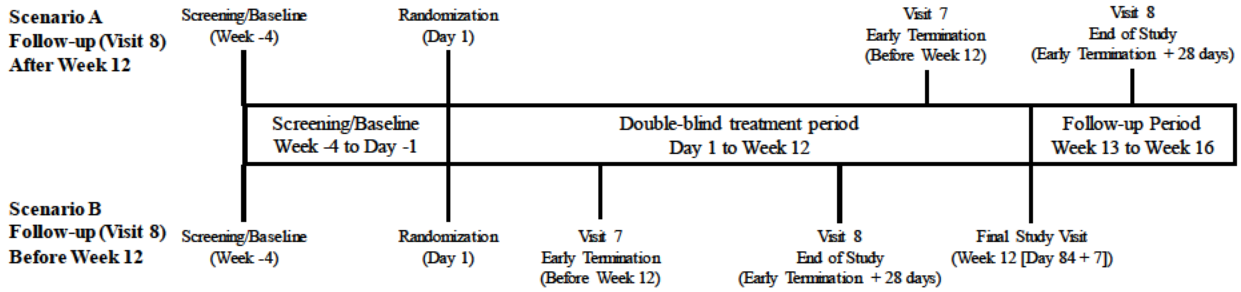
Participants may voluntarily withdraw from the study at any time. Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF. All randomized participants who prematurely discontinue from the study, regardless of cause, should be seen for final study assessments. The final assessments will be defined as completion of the evaluations scheduled for Visit 7/ET and Visit 8 (follow-up), 4 weeks post the last dose of study intervention.

8.8.1 Participants Who Discontinue Study Intervention Early

All participants who discontinue study intervention early (defined as prior to Week 12 [Visit7]) for reasons other than withdrawal of consent or lost to follow-up should remain in the study for the purpose of collecting efficacy data to support the estimand framework for EMA. These participants should return to the clinic for ET procedures (Visit 7) and the Follow-up Visit (Visit 8) per the Schedule of Visits and Procedures (Table 1). If Visit 8 occurs on or after Week 12 (relative to randomization), no Final Study Visit is required (Figure 2, Scenario A). If Visit 8 occurs before Week 12 (relative to randomization) participants should return to the clinic

for an additional Final Study Visit to be scheduled 12 weeks after randomization (Day 84 +7 days, Figure 2, Scenario B).

Figure 2 Study Diagram for Estimand Framework



Note the following changes to the Schedule of Visits and Procedures for participants who discontinue study intervention early:

- Participants should continue to complete eDiary assessments daily until Visit 8 or the Final Study Visit (if required) to allow for the collection of at least 12 weeks of efficacy data.
- eDiaries should be collected at the participant's last study visit (Visit 8 or at the Final Study Visit [if required]).
- PROs should be administered on the eTablet as follows:
    - Scenario A - Visit 8 is the final study visit:
        - Visit 7/ET PROs should be collected as per the Schedule of Visits and Procedures
        - Visit 8 PROs will include those expected to be collected per the Schedule of Visits and Procedures and the HIT-6
    - Scenario B – Visit 8 is not the final study visit:
        - Visit 7/ET PROs should be collected as per the Schedule of Visits and Procedures
        - Visit 8 PROs should be collected as per the Schedule of Visits and Procedures
        - Final Study Visit PROs will include MSQ v2.1 and HIT-6
- If a Final Study Visit is required, concomitant medications/concurrent procedures should also be assessed.

8.9 Withdrawal Criteria

Women who become pregnant (Section 9.4) and participants who meet study intervention discontinuation criteria related to abnormal liver function tests (Section 9.5), and advised not to be rechallenged, will be withdrawn from the study and should refrain from taking study intervention. The participant should return to the clinic for ET procedures (Visit 7) and the Follow-up Visit (Visit 8). Participants who reply with "yes" to questions 4 or 5 in the suicidal ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS at Visits 3 through 6 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the ET Visit (Visit 7) and the Follow-up Visit (Visit 8).

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

8.10 Study Termination

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

9. Adverse Events

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

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study participant 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. In addition, during the screening period, AEs will be assessed regardless of the administration of a pharmaceutical product.

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

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

All AEs must be collected once informed consent has been obtained, regardless of whether or not the participant has been administered study intervention, 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. These will be collected at the timepoints specified in the Schedule of Visits and Procedures (Table 1), and as observed or reported spontaneously by study participants. Investigators are not obligated to actively seek AE information after conclusion of the study participation.

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

9.1.2 Serious Adverse Event

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, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.

d.	**Results in persistent disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	**Is a congenital anomaly/birth defect**
f.	**Other situations:** • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The sponsor considers all cancer AEs as SAEs. The sponsor considers any spontaneous abortion as an SAE. Elective abortions can be SAEs or AEs depending on the reason for the elective abortion (eg, fetal death, still birth, congenital anomalies, ectopic pregnancy, which would make the elective abortion an SAE).

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

Any pre-planned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the participant's entry into the study. If it has not been documented at the time of the participant's entry into the study, then it should be documented as a SAE and reported to the sponsor.

9.1.3 Intensity

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

Assessment of Intensity	
MILD	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.	

9.1.4 Assessment of Causality

Assessment of Causality
• The investigator is obligated to assess the relationship between 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's brochure in his/her assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality. 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 the sponsor. 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.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.1.5 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs and non-serious AEs of special interest (as defined in Section 6.5.2) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.8).

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

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

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

9.1.6 Adverse Reactions, Serious Adverse Reactions, and Suspected Unexpected Serious Adverse Reactions

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, see below). Also, seriousness criteria for AEs/ARs (as would apply to SARs and SUSARs) are currently included in the protocol, listed in Section 9.1.2.

- 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 9.1.2 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).

9.2 Procedures for Reporting Adverse Events

Any AE must be recorded on the appropriate CRF.

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

9.3 Procedures for Reporting a Serious Adverse Event

Any SAE occurring during the study period (beginning with informed consent) until the Follow-up Visit (Visit 8) or 30 days after the last dose of study intervention if the Follow-up Visit is not done must be immediately reported but no later than 24 hours after learning of an SAE.

SAEs must be reported to the sponsor (or agent of the sponsor) as listed on the Study Contacts Page and recorded on the SAE form. All participants with an SAE must be followed up and the outcomes reported. The investigator must supply the sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

9.3.1 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to 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

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

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs from 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.

9.4 Exposure to Study Intervention During Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of 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. Study center personnel must report every pregnancy on the Pregnancy Form (within 24 hours of learning of the pregnancy to the Serious Adverse Event Reporting Fax Number: +1-714-796-9504 [back up fax number: +1-714-246-5295], email: IR-Clinical-SAE@allergan.com), even if no AE has occurred. The pregnancy must be followed to term and the outcome reported by completing a follow-up Pregnancy Form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Elective abortions can be SAEs or AEs depending on the reason for the elective abortion (eg, fetal death, still birth, congenital anomalies, ectopic pregnancy, which would make the elective abortion an SAE). For pregnancy related SAEs, in addition to the Pregnancy Form, a separate SAE Form must be filed as described in Section 9.3 with the appropriate serious criterion (eg, hospitalization) indicated.

9.5 ALT or AST Elevations

A treatment-emergent ALT ≥ 3 × ULN and/or AST ≥ 3 × ULN is considered an 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 and chemistry panels, INR, serum acetaminophen level, urine drugs of abuse screen, and blood alcohol level. An extra blood serology sample must be collected and sent to the central laboratory for further diagnostic testing, at a later date, if needed. In addition, the investigator will perform a complete history and examination to evaluate the participant for possible liver disease.

All AEs of special interest must be reported to 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, and Epstein-Barr Virus IgM antibody. The participant must be followed clinically and further medical evaluation (for other causes of acute hepatic injury) should be done per the judgment of the investigator and in conjunction with medical personnel at the sponsor. 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 medical monitor. For participants who are not rechallenged with study intervention, the

participant should be discontinued from the study and complete an ET visit (Visit 7/ET) and 4-week follow-up visit. Participants should receive appropriate follow-up as per standard of care.

The investigator must contact the sponsor 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.

9.5.1 Potential Hy's Law Cases

Sites must report every participant who meets the following potential Hy's law criteria if this occurs within the time the participant signs the ICF until 30 days after the last dose of investigational product:

- ALT or AST ≥ 3 × ULN **AND**
- Total bilirubin ≥ 2 × ULN **AND**
- Alkaline phosphatase < 2 × 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 and must notify investigators and the sponsor immediately when the above criteria have been met. A possible Hy's law case must be faxed 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.

9.6 Procedures for Unmasking of Study Medication

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 sponsor 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, the sponsor 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.

10. Administrative Items

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

10.1 Protection of Human Participants

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

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

The following process will be followed:

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

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

10.1.2 Compliance With IRB or IEC Regulations

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

10.1.3 Compliance With Good Clinical Practice

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

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

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

10.2 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.

10.3 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC (and the appropriate regulatory agency, if required by national law) of a protocol amendment, except where necessary to eliminate immediate hazards to study participants, or

when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.4 Data Protection

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

The participant must be informed that his/her personal study-related data will be used by 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.

10.5 Participant Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study intervention may ultimately be marketed, but the participant's name will not be disclosed in these documents. The participant's name may be disclosed to the sponsor of the study, or the governing health authorities or the FDA if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.6 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.

10.7 Documentation

10.7.1 Source Documents

Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as 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 the sponsor
- A statement that informed consent was obtained (including the date). A statement that written authorization (United States sites only), data protection consent (European Union 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 (ie, records must be Attributable, Legible, Contemporaneous, Original and Accurate).

10.7.2 Case Report Form Completion

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

10.7.3 Study Summary

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

10.7.4 Retention of Documentation

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

For countries falling within the scope of the ICH guidelines, the sponsor-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 the sponsor.

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.

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

10.8 Labeling, Packaging, and Return or Disposal of Study Interventions/Treatments

10.8.1 Labeling/Packaging

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. Immediately before dispensing the blister card, the investigator or designee will write the participant number and date dispensed on the blister card.

10.8.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from the sponsor, dispensed or administered to the participants, the number of units returned to the investigator by the participant (if applicable), and the number of units returned to the sponsor during and at the completion of the study. A detailed inventory must be completed for the study medication. The study intervention must be dispensed or administered only by an appropriately qualified person to participants in the study. The medication is to be used in accordance with the protocol for participants who are under the direct supervision of an investigator.

10.8.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All clinical study interventions/treatments and/or supplies will be returned to the sponsor or designee for destruction.

10.9 Monitoring by the Sponsor

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

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

10.10 Handling of Biological Specimens

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

Samples of blood and urine for evaluation of hematology, blood chemistry, urinalysis, urine drug screen, INR, and serology will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology or Clinical Laboratory Improvement Amendments certification). All samples for future biomedical research will be sent to the designated central laboratory and shipped to a biorepository for storage.

PK samples obtained from participants in the PK substudy will be stored at the centralized clinical laboratory until ready for PK analyses by the sponsor's Pharmacokinetics and Drug Distribution department using a validated method. This laboratory meets GLP requirements.

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

10.11 Publications

The sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and the sponsor 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 the sponsor.

10.12 Coordinating Investigator

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

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12. Attachments

12.1 International Classification of Headache Disorders, 3rd Edition

1. Migraine
1.1 Migraine without aura
1.2 Migraine with aura
1.2.1 Migraine with typical aura
1.2.1.1 Typical aura with headache
1.2.1.2 Typical aura without headache
1.2.2 Migraine with brainstem aura
1.2.3 Hemiplegic migraine
1.2.3.1 Familial hemiplegic migraine (FHM)
1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)
1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)
1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)
1.2.3.1.4 Familial hemiplegic migraine, other loci
1.2.3.2 Sporadic hemiplegic migraine (SHM)
1.2.4 Retinal migraine
1.3 Chronic migraine
1.4 Complications of migraine
1.4.1 Status migrainosus
1.4.2 Persistent aura without infarction
1.4.3 Migrainous infarction
1.4.4 Migraine aura-triggered seizure
1.5 Probable migraine
1.5.1 Probable migraine without aura
1.5.2 Probable migraine with aura
1.6 Episodic syndromes that may be associated with migraine
1.6.1 Recurrent gastrointestinal disturbance
1.6.1.1 Cyclical vomiting syndrome
1.6.1.2 Abdominal migraine
1.6.2 Benign paroxysmal vertigo
1.6.3 Benign paroxysmal torticollis

Coded elsewhere:

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

General comment

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

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

Introduction

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

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

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

1.1 Migraine without aura

Previously used terms: Common migraine; hemicrania simplex

Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

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

Notes:

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

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

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

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

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

Very frequent migraine attacks are distinguished as 1.3 *Chronic migraine*. When there is associated medication overuse, both of the diagnoses 1.3 *Chronic migraine* and 8.2 *Medication-overuse headache* should be applied. 1.1 *Migraine without aura* is the disease most prone to accelerate with frequent use of symptomatic medication.

Regional cerebral blood flow imaging shows no changes suggestive of cortical spreading depression (CSD) during attacks of 1.1 *Migraine without aura*, although blood flow changes in the brainstem may occur, as may cortical changes secondary to pain activation. This contrasts with the pathognomonic spreading oligaemia of 1.2 *Migraine with aura*. While the bulk of the literature suggests that CSD does not occur in 1.1 *Migraine without aura*, some recent studies disagree. Furthermore, it has been suggested that glial waves or other cortical phenomena may be involved in 1.1 *Migraine without aura*. The messenger molecules nitric oxide (NO), serotonin (5-hydroxytryptamine;5-HT) and calcitonin gene-related peptide (CGRP) are involved.

While the disease was previously regarded as primarily vascular, the importance of sensitization of pain pathways, and the possibility that attacks may originate in the central nervous system, have gained increasing attention over the last decades. At the same time, the circuitry of migraine pain, the trigeminovascular system, and several aspects of its neurotransmission peripherally and in the trigeminal nucleus caudalis, central mesencephalic grey and thalamus, have been recognized. Highly receptor-specific acute medications including 5-$HT_{1B/D}$ receptor agonists (triptans), 5-HT_{1F} receptor agonists and CGRP receptor antagonists have demonstrated efficacy in the

acute treatment of migraine attacks. Because of their high receptor-specificity, their mechanisms of action pro- vide new insight into migraine mechanisms. It is now clear that 1.1 *Migraine without aura* is a neurobiological disorder, while clinical as well as basic neuroscience stu- dies continue to advance our knowledge of migraine mechanisms.

1.2 Migraine with aura

Previously used terms: Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagne´ e; complicated migraine.
Description: Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.
Diagnostic criteria:

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

Notes:

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

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

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

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

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

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

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

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

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

Patients with aura symptoms arising from the brain- stem are coded as 1.2.2 *Migraine with brainstem aura*, but

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

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

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

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

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

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

1.2.1 Migraine with typical aura

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

Diagnostic criteria:

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

1.2.1.1 Typical aura with headache

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

Diagnostic criteria:

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

1.2.1.2 Typical aura without headache

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

Diagnostic criteria:

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

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

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

1.2.2 Migraine with brainstem aura

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

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

Diagnostic criteria:

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

Notes:

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

Comments: Originally the terms *basilar artery migraine* or *basilar migraine* were used but, since involvement of the basilar artery is unlikely, the term *migraine with brainstem aura* is preferred.

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

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

1.2.3 Hemiplegic[1] migraine

Description: Migraine with aura including motor weakness.

Diagnostic criteria:

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

Notes:

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

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

1.2.3.1 Familial hemiplegic migraine (FHM)

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

Diagnostic criteria:

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

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

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

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

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

1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)

Diagnostic criteria:

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

B. A mutation on the *CACNA1A* gene has been demonstrated.

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

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

B. A mutation on the *ATP1A2* gene has been demonstrated.

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

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

B. A mutation on the *SCN1A* gene has been demonstrated.

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

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

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

1.2.3.2 Sporadic hemiplegic migraine (SHM)

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

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*

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

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

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

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

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

1.2.4 Retinal migraine

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

Diagnostic criteria:

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

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

c. accompanied, or followed within 60 minutes, by headache

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

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

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

1.3 Chronic migraine

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

Diagnostic criteria:

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

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

C. On 8 days/month for >3 months, fulfilling any of the following[2]:

1. criteria C and D for 1.1 *Migraine without aura*

2. criteria B and C for 1.2 *Migraine with aura*

3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis.[3–5]

Notes:

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

1.4 Complications of migraine

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

1.4.1 Status migrainosus

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

Diagnostic criteria:

A. A headache attack fulfilling criteria B and C

B. Occurring in a patient with 1.1 *Migraine without aura* and/or 1.2 *Migraine with aura*, and typical of previous attacks except for its duration and severity

C. Both of the following characteristics:
   1. unremitting for >72 hours[1]
   2. pain and/or associated symptoms are debilitating[2]
D. Not better accounted for by another ICHD-3 diagnosis.

Notes:

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

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

1.4.2 Persistent aura without infarction

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

Diagnostic criteria:

A. Aura fulfilling criterion B
B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous auras except that one or more aura symptoms persists for 1 week
C. Neuroimaging shows no evidence of infarction
D. Not better accounted for by another ICHD-3 diagnosis.

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

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

1.4.3 Migrainous infarction

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

Diagnostic criteria:

A. A migraine attack fulfilling criteria B and C
B. Occurring in a patient with 1.2 *Migraine with aura* and typical of previous attacks except that one or more aura symptoms persists for >60 minutes[1]
C. Neuroimaging demonstrates ischaemic infarction in a relevant area
D. Not better accounted for by another ICHD-3 diagnosis.

Note:

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

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

1.4.3 Migrainous infarction mostly occurs in the posterior circulation and in younger women.

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

1.4.4 Migraine aura-triggered seizure

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

Diagnostic criteria:

A. A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below
B. Occurring in a patient with 1.2 *Migraine with aura*, and during or within one hour after an attack of migraine with aura

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

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

1.5 Probable migraine

Previously used term: Migrainous disorder.

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

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

Diagnostic criteria:

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

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

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

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

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

1.5.1 Probable migraine without aura Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A–D for 1.1 *Migraine without aura*

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

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

1.5.2 Probable migraine with aura

Diagnostic criteria:

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

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

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

1.6 Episodic syndromes that may be associated with migraine

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

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

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

1.6.1 Recurrent gastrointestinal disturbance

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

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

Diagnostic criteria:

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

1.6.1.1 Cyclic vomiting syndrome

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

Diagnostic criteria:

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

Note:

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

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

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

1.6.1.2 Abdominal migraine

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

Diagnostic criteria:
and evaluation

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

Note:

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

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

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

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

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

1.6.2 Benign paroxysmal vertigo

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

Diagnostic criteria:

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

Notes:

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

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

1.6.3 Benign paroxysmal torticollis

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

Diagnostic criteria:

A. Recurrent attacks[1] in a young child, fulfilling criteria B and C
B. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
C. At least one of the following five associated symptoms or signs:
   1. pallor
   2. irritability
   3. malaise
   4. vomiting
   5. ataxia[2]
D. Normal neurological examination between attacks
E. Not attributed to another disorder.[3]

Notes:

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

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

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

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12.2 Examples of Prohibited Medications

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

Strong OATP1B1 inhibitors, eg, gemfibrozil (Lopid™)*, cyclosporine

	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™)
Non-pharmacologic headache interventions:	Acupuncture Non-invasive neuromodulation devices (eg, transcutaneous supraorbital neurostimulator single pulse transcranial magnetic stimulator vagus nerve stimulator) Cranial traction Nociceptive trigeminal inhibition Occipital nerve block treatments Dental splints for headache

*not approved in Japan

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®)

12.3 List of Migraine Preventive Medications With Proven Efficacy & Criteria for Determining that a Prior Migraine Preventive Medication Has Been Failed

12.3.1 List of Migraine Preventive Medications With Proven Efficacy

Below is a list of migraine preventive medications considered effective or probably effective sorted by mechanism of action. Of note, topiramate and valproic acid derivatives are considered separate categories. A history of inadequate response (based on inadequate efficacy or inadequate tolerability) to more than 4 of these medications (2 of which have different mechanisms of action) will exclude the participant from the study.

Pharmacologic Category	**Drug Name (all regions unless otherwise noted)**
Antiepileptic	Valproic acid, sodium valproate, divalproex sodium Topiramate
Tricyclic antidepressant	Amitriptyline Nortriptyline
Beta-blockers	Metoprolol Bisoprolol Atenolol Nadolol Propranolol Timolol
Calcium channel blocker	Flunarizine Lomerizine (Japan) Verapamil (Japan)
Angiotensin receptor blocker (ARB)	Candesartan
Angiotensin-converting enzyme (ACE) inhibitor	Lisinopril
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine Venlafaxine
Miscellaneous	Oxetorone (Europe), pizotifen (Japan, Taiwan, Korea, Australia, and Europe)

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

12.3.2 Criteria for Determining That a Prior Migraine Preventive Medication has Been Failed

The criteria below should be used to determine how to stratify each participant based on the number of prior migraine preventive medications failed with unique mechanisms of action. Failure of a migraine preventive medication can be assessed on the basis of tolerability or efficacy and is based on investigator judgment.

- 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.
    - Medications must have been started within the past 7 years.
    - Note the following for participants who are currently taking a stable dose of one of the migraine prevention medications listed and meet the efficacy criteria:
        - If the participant meets all study entry criteria, this participant is eligible to be randomized provided that the participant agrees to continue to take this migraine preventive medication for the duration of the study.
        - This medication should be considered as one of the failed drugs for the prevention of migraine.
        - Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%.
- For tolerability, investigators should consider:
    - Failure is defined as discontinuation of a drug treatment due to adverse effects.
    - 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.

12.4 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 Remote Visit Schedule of Assessments (Table 5) should be followed. Remote visits may be conducted between Visit 3 – Visit 8 but participants must attend in office assessments at 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 on the eTablet during in-office visits, will be collected using a web-based portal during remote visits, if available.

Table 5 Remote Visits Schedule of Assessments (ie, Schedule of Visits and Procedures)

Study Period	**Screening/ Baseline (4 weeks)**	**Double-blind Treatment Period (12 weeks)**						**Follow-up Period (4 weeks)**
Visit #	**Visit 1[a]**	**Visit 2[a] (Randomization)**	**Visit 3[a]**	**Visit 4[a]**	**Visit 5**	**Visit 6**	**Visit 7/ET**	**Visit 8 (End of Study)**
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 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Dispense study intervention (ie, atogepant)[b]		X	X	X	X	X		
Review of atogepant compliance			X	X	X	X	X	
Participant eDiary Data Collection[c]	X							
Review eDiary data and compliance		X	X	X	X	X	X	
Perform urine pregnancy test[b,d]	X	X	X	X	X	X	X	X
C-SSRS (eTablet or web portal)	X	X	X	X	X	X	X	X
HIT-6 (web portal)[e]		X		X		X	X	X
PGIC (web portal)[e]							X	
PGI-S (web portal)[e]		X		X		X	X	
WPAI:MIGRAINE (web portal)[e]		X		X		X	X	
PSSM (web portal)[e]				X		X	X	
EQ-5D-5L [f]	X	X	X	X	X	X	X	X
MIDAS (web portal)[e]		X					X	
MSQ v2.1 (web portal)[e]		X		X		X	X	X
PROMIS-PI (web portal)[e]		X		X		X	X	
PHQ-9 (web portal)[e]		X					X	
Adverse events	X							
Concomitant medications/concurrent procedures	X							

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; 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, Visit 2, and either Visit 3 or Visit 4 must be conducted in office, to ensure laboratory assessments are performed within the first 4 weeks of study intervention.

[b] 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.

[c] Daily eDiary data collection includes: Headache Frequency, Duration, Characteristics, and Symptoms; Acute Medication Use and Triptan Use; AIM-D; Activity Level and Activity Limitation.

[d] Female participants are to take an at-home pregnancy test (provided by sites) and report the results during virtual visits.

[e] If available, participants will complete on a web-based portal.

[f] Participants will complete in eDiary on Visit 1 to 7 and on the web-based portal (if available) at Visit 8 (Week 16).

12.5 Glossary of Abbreviations

Term/Abbreviation	Definition
AE	adverse event
AIM-D	Activity Impairment in Migraine – Diary
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
ASC-12	allodynia symptom checklist
AST	aspartate aminotransferase
BID	twice daily
BP	blood pressure
CBD	cannabidiol
CGRP	calcitonin gene-related peptide
CM	chronic migraine
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	cytochrome P450 3A4
DSMB	Data Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EM	episodic migraine
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life – 5 Dimensional
ET	early termination
eTablet	electronic tablet
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HIT-6	Headache Impact Test
HSG	hysterosalpingogram
HIV	Human immunodeficiency virus

Term/Abbreviation	Definition
ICF	informed consent form
ICH	International Conference on Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd edition
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IV	intravenous
IWRS	interactive web response system
MAR	missing-at-random
MI	multiple imputation
MIDAS	Migraine Disability Assessment
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
MNAR	missing-not-at-random
MSQ v2.1	Migraine Specific Quality of Life Questionnaire, Version 2.1
NSAID	nonsteroidal anti-inflammatory drug
OATP1B1	organic anion transporting polypeptide 1B1
OL	open-label
PD	pharmacodynamic
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression – Severity
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetic
PMM	pattern-mixture model
PRO	patient-reported outcomes
PROMIS-PI	Patient-Reported Outcomes Measurement Information System Pain Interference – Short Form 6a
PSSM	Patient Satisfaction with Study Medication
QTcF	QT interval corrected for heart rate using Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
ROW	rest of world

Term/Abbreviation	Definition
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAR	serious adverse reaction
SNRI	serotonin norepinephrine reuptake inhibitor
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
UDS	urine drug screen
ULN	upper limit of normal
VAS	Visual Analogue Scale
VCT	verified clinical trials
WPAI:MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine Version V2.0

12.6 Protocol Amendment 1 Summary

Title: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ATOGEPANT FOR THE PREVENTION OF CHRONIC MIGRAINE (PROGRESS)

Protocol 3101-303-002

Date of Amendment: 08 April 2019

Amendment Summary

This amendment includes changes made to Protocol 3101-303-002 dated 13 December 2018. The protocol was amended to:

- Add instructions for study conduct in China and Canada
- Clarify primary and secondary endpoints for China, and Canada
- Clarify prohibited medications
- Update laboratory parameters
- Update the subgroup analyses
- Correct the study diagram for the estimand framework
- Update the definition of failed migraine preventive medication

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

Section	Revision	Rationale
Protocol Title Page	Added "Protocol Amendment 1 Date" to the title page	To reflect the approval date of Amendment 1
Protocol Summary	Changed the Condition/Disease from "CM with aura or migraine without aura" to "Chronic migraine"	For clarity
Protocol Summary	Changed text with regard to the primary efficacy endpoint to clarify that the primary efficacy endpoint is the same for all regulatory authorities	For clarity
Protocol Summary	Added text to clarify the secondary efficacy endpoints for China	Study will also be conducted in China
Protocol Summary	Added text to clarify the secondary efficacy endpoints for Canada	Study will also be conducted in Canada
Protocol Summary, Table 1 Schedule of Visits and Procedures	Clarified that VCT is applicable for United States and Canada only	For clarity
Protocol Summary, Table 1 Schedule of Visits and Procedures	Added HIT-6 to Visit 8	HIT-6 collection at Visit 8 is needed for estimand framework
Section 1.1 Background	Added background information for China	Study will also be conducted in China
Section 3.1 Structure	Updated number of sites to approximately 140	For accuracy
Section 4.1 Number of Participants	Updated number of sites to approximately 140	For accuracy
Section 4.3 Exclusion Criteria, criterion 5	Added recently approved botulinum toxin injections, Myobloc® and Jeuveau™	For clarity and completeness
Section 4.3 Exclusion Criteria, criterion 24	Corrected a typographical error in the developmental name of atogepant (MK8031)	To correct an error
Section 4.4.2 Prohibited Medications/Treatments	Added language to exclude use of medications with demonstrated efficacy for the prevention of migraine for indications other than migraine prevention	For clarity
Section 4.4.2 Prohibited Medications/Treatments	Added recently approved botulinum toxin injections, Myobloc® and Jeuveau™	For clarity and completeness
Section 4.4.2 Prohibited Medications/Treatments	Added: • For China, South Korea, and Taiwan, herbal and traditional medicine is prohibited from the time the ICF is signed and for the duration of study participation.	To clarify that herbal and traditional medicines are prohibited in countries where they are commonly used
Section 6.1 Efficacy Measures	Corrected the Study Days and visit windows for the EQ-5D-5L	To correct an error
Section 6.5.3 Clinical Laboratory Determinations, Table 6-1 Clinical Laboratory Parameters	Deleted gamma glutamyl transferase	Parameter is not measured
Section 7.2.2 Secondary Efficacy Endpoints	Added text to clarify the secondary efficacy endpoints for China	Study will also be conducted in China
Section 7.2.2 Secondary Efficacy Endpoints	Added text to clarify the secondary efficacy endpoints for Canada	Study will also be conducted in Canada

Section	Revision	Rationale
Section 7.2.3 Additional Efficacy Endpoints	Deleted text concerning countries for additional efficacy endpoints	For clarity, because additional efficacy endpoints are the same for all countries
Section 7.2.3 Additional Efficacy Endpoints	Added ≥ 30% as an additional range for responders	To add granularity to the analysis of additional efficacy endpoints
Section 7.2.3 Additional Efficacy Endpoints	Added Canada to the countries where "Change from baseline in the HIT-6 total score at Weeks 4 and 8" will be analyzed	Canada is using the European Union endpoints
Section 7.2.3 Additional Efficacy Endpoints	Added China to the countries where "Change from baseline in the HIT-6 total score at Weeks 4, 8, and 12" will be analyzed	China is using the United States endpoints
Section 7.2.3 Additional Efficacy Endpoints	Added Canada to the countries where "Change from baseline in mean monthly performance of daily activities domain score of the AIM-D across the 12-week treatment period" and "Change from baseline in mean monthly physical impairment domain score of the AIM-D across the 12-week treatment period" are analyzed	Canada is using the European Union endpoints
Section 7.5 Subgroup Analyses	Updated text for subgroup analysis	For clarity
Section 8.1.3 Procedure for Duplicate Participant Identification – Verified Clinical Trials	Changed ROW to Canada	VCT only used in the United States and Canada
Section 8.4.1 Visit 1 (Screening/Baseline) Day -35 to Day -28	Changed "if applicable" to United States and Canada only	VCT only used in the United States and Canada
Section 8.4.3.1 Visit 8/End of Study (Week 16)	Added HIT-6	HIT-6 is being collected for all participants at Week 16
Section 8.8.1 Participants Who Discontinue Study Intervention Early, Figure 2 Study Diagram for Estimand Framework	Replaced the study diagram	To correct an error
Section 10 Administrative Items	Added text to clarify that relevant local regulations should be followed	For clarity
Section 11 References	Added references for China background	Migraine background in China was added to Section 1.1
Section 12.2 Examples of Prohibited Medications	Aligned text for treatments prohibited 6 months prior to screening and throughout the study period with the text in the protocol body	For clarity and internal consistency

Section	Revision	Rationale
Section 12.3.1 List of Migraine Preventive Medications With Proven Efficacy	Added "(non-United States only)" to Miscellaneous category	For clarity
Section 12.3.2 Criteria for Determining That a Prior Migraine Preventive Medication has Been Failed	Updated the failure definition	The definition of failure has changed

12.7 Protocol Amendment 2 Summary

Title: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ATOGEPANT FOR THE PREVENTION OF CHRONIC MIGRAINE (PROGRESS)

Protocol 3101-303-002

Date of Amendment 2: 23 September 2019

Amendment Summary
This amendment includes changes made to Protocol 3101-303-002 Amendment 1, dated 08 April 2019. The protocol was amended to:

- Add instructions for study conduct in Japan
- Add instruction regarding Visit 8 (follow-up) for participants in Japan and China who may rollover to a regional, long-term, extension, safety study
- Clarify secondary efficacy endpoints for Europe and Canada, and for all other regions except Europe and Canada
- Update description of the AIM-D health outcomes measure and endpoints
- Describe the Hochberg procedure to be used to control the overall Type I error rate at a 0.05 level (2-sided) for multiple comparisons of 2 atogepant doses with placebo for the primary efficacy endpoint, only for the analysis in Japan
- Describe weekly data analysis procedures for other efficacy analyses
- Describe planned subgroup analyses to evaluate consistency of treatment across regions and subpopulations
- Update description of safety analysis
- Clarify criteria for sexual abstinence to be considered as a highly effective contraceptive method
- Add a benefit/risk assessment

- Add definition of the end of the study
- Clarify exclusion criterion based on hypersensitivity to study interventions
- Clarify the instructions regarding prohibited medication/treatments
- Clarify instructions for the participants
- Clarify instructions regarding assessment of causality of adverse events
- Add definition of adverse reaction, serious adverse reaction, and suspected unexpected serious adverse reaction
- Clarify instruction regarding changes to the protocol.

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

Section	Revision	Rationale
Protocol Summary	Bolded text added to *Number of Participants*: Approximately 750 participants will be randomized into this **global study (North America, Europe, Japan, China, Other)**.	Clarification
Protocol Summary, Table 1 Schedule of Visits and Procedures, Section 3.1 Structure	Clarified end of study visit schedule for participants in Japan and China who may rollover to a regional, long-term, extension, safety study	Clarification
Table 1 Schedule of Visits and Procedures	Consolidated rows pertaining to eDiary, AIM-D and activity level and activity limitation: "Review eDiary data (headache duration, frequency, characteristics and symptoms, acute medication use, AIM-D, activity level and activity limitation) and compliance[i]"	Clarification, as AIM-D, activity level and activity limitation data are also recorded on eDiary
Table 1 Schedule of Visits and Procedures, Section 8.4.2.3 Visit 7/ Early Termination Week 12), Section 8.4.3.1 Visit 8/ End of Study (Week 16)	Clarified when the eDiary is to be collected for participants who complete the double-blind treatment period and for those patients who discontinue study intervention early	Clarification
Section 1.1 Background	Added background information for Japan	Study will also be conducted in Japan
Section 1.5 Benefit/ Risk Assessment	Added Section 1.5 Benefit/Risk Assessment	Added in accordance with EU protocol review
Section 3.4 End of Study Definition	Added Section 3.4 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."	Added in accordance with EU protocol review
Section 4.3 Exclusion Criteria	Bolded text added to exclusion criterion #25: 25. History of hypersensitivity or clinically significant adverse reaction to a CGRP receptor antagonist **or hypersensitivity to any component of the study interventions (atogepant or placebo)**.	Clarification
Section 4.4.2 Prohibited Medications/Treatments	Bolded text added and strikethrough text removed: **Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator**. The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. ~~When possible, Allergan should be notified before the prohibited medication/treatment is administered~~. **The sponsor should be notified about administration of prohibited medication/treatment as soon as possible.** Asterisks added to indicate the specified medications that are not approved in Japan. Clarified that herbal and traditional medicine is also prohibited in Japan.	Clarification

Section	Revision	Rationale
Section 4.4.3 Definition of Women of (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods	Bolded text added to definition of sexual abstinence Sexual abstinence, defined as refraining from heterosexual intercourse for the **entire** duration of the study, **from Visit 1 through the end of study (Visit 8/Safety Follow-up Visit).** o **Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.**	Clarification in accordance with UK's MHRA request
Section 4.4.4 Special Diet or Activities	Added mL equivalents to the definition of an alcohol drink.	Clarification
Protocol Summary, Section 6.1 Efficacy Measures, Section 6.2.1 Activity Impairment in Migraine – Diary (AIM-D), Section 6.2.2 Activity Level and Activity Limitation	Updated description of AIM-D Patient Difficulty in Concentrating and Difficulty in Thinking Clearly items are no longer considered stand-alone items but part of the AIM-D	Based on psychometric (quantitative) analyses, AIM-D is now an 11-item PRO measure that includes the items 'patient difficulty in concentrating' and 'difficulty in thinking clearly'.
Protocol Summary, Section 7.2.2 Secondary Efficacy Endpoints	Clarify secondary efficacy endpoints for Europe and Canada, and for all other regions except Europe and Canada Updated secondary efficacy endpoints related to AIM-D	To specify key secondary endpoints by region. To align with updated AIM-D description
Section 7.2.3 Additional Efficacy Endpoints	Updated additional efficacy endpoints for HIT-6. Added change from baseline in weekly migraine days at Weeks 1-4. Updated additional efficacy endpoints related to AIM-D	To align with the estimand framework To understand the onset effect To align with updated AIM-D description
Section 7.3.2 Secondary Efficacy Analyses	Updated description of AIM-D endpoints Added description of the Hochberg procedure to be used to control the overall Type I error rate at a 0.05 level (2-sided) for multiple comparisons of 2 atogepant doses with placebo for the primary efficacy endpoint only for the analysis in Japan.	To align with updated AIM-D description To align with PMDA's feedback
Section 7.3.3 Additional Efficacy Analyses	Describe weekly data analysis procedures for other efficacy analyses.	To understand the onset effect
Section 7.3.4 Safety Analysis	Updated description of safety analyses.	Clarification

Section	Revision	Rationale
Section 7.5.1 Subgroup Analyses for Evaluating the Consistency of Treatment Effects Across Regions and Subpopulations	Added description of subgroup analyses to evaluate consistency of treatment effects across regions and subpopulation. Description of other subgroup analyses was moved to Section 7.5.2.	Study will be conducted in multiple regions.
Section 8.1.3 Procedure for Duplicate Participant Identification – Verified Clinical Trials, Section 8.4.1 Visit 1 (Screening/Baseline) Day --5 to Day -28	Added the phrase "at participating sites" to text describing VCT.	For clarification, as VCT is optional for sites in Canada
Section 8.4.2.2 Visits 3 to 6 (Week 2 to 8), Section 8.4.2.3 Visit 7/Early Termination (Week 12)	Removed duplicate bullet: • ~~Review medication compliance~~	Clarification, as review of medication compliance is included in bullet that states: "Collect previous visit study intervention, review participant compliance, and perform accountability"
Section 8.5 Instructions for the Participants	Bolded text added to instruction for taking study intervention: **Study intervention may be taken with or without food. Water is allowed as desired.**	Clarification
Section 9.1.4 Assessment of Causality	Bolded text added to bullet point below: • 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.**	Clarification

Section	Revision	Rationale
Section 9.1.6 Adverse Reactions, Serious Adverse Reactions, and Suspected Unexpected Serious Adverse Reactions	Added Section 9.1.6 Adverse Reactions, Serious Adverse Reactions, and Suspected Unexpected Serious Adverse Reactions with the following text: "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, see below). Also, seriousness criteria for AEs/ARs (as would apply to SARs and SUSARs) are currently included in the protocol, listed in Section 9.1.2. • 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 9.1.2 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)."	Added in accordance with EU protocol review
Section 9.4 Exposure to Study Intervention During Pregnancy	Strikethrough font removed from statement below: Abnormal pregnancy outcomes (eg, spontaneous ~~or elective~~ abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Elective abortions can be SAEs or AEs depending on the reason for the elective abortion (eg, fetal death, still birth, congenital anomalies, ectopic pregnancy, which would make the elective abortion an SAE).	Clarification
Section 10.3 Changes to the Protocol	Bolded text added: The investigator must not implement any deviation from or changes of the protocol without approval by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC **(and the appropriate regulatory agency, if required by national law)** of a protocol amendment, except where necessary to eliminate immediate hazards to study participants, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).	Clarification
Section 11 References	Updated reference list.	In accordance with amendment revisions
Section 12.2 Examples of Prohibited Medications	Asterisks added to indicate the specified medications that are not approved in Japan.	Clarification

12.8 Protocol Amendment 3 Summary

Title: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ATOGEPANT FOR THE PREVENTION OF CHRONIC MIGRAINE (PROGRESS)

Protocol 3101-303-002

Date of Amendment 3: 29 May 2020

Amendment Summary

This amendment includes changes made to Protocol 3101-303-002 Amendment 2, dated 23 September 2019.

The following is a summary of changes that were made to each section of the protocol, and a brief rationale for these changes.

Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Protocol Summary, Study Design: *Randomization/ Stratification*	Added footnote 2: • Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy (see Attachment 12.3).**[2]** **[2]: All French participants must have taken at least 1 prior migraine prevention medication with proven efficacy to be eligible for Study 3101-303-002.**	Requirement by French authorities.
	Added text: • Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy (see Attachment 12.3).[2] Randomization will be stratified based on migraine prevention medication exposure (Current Use, Past Use, or Never Used) with proven efficacy. Participants with current or past use **will be further stratified based** on the number of medications failed with unique mechanisms of action: "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" or "failed 2 to 4 medications with different mechanisms of action" (see Attachment 12.3). **Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%.**	Based on data review of recent migraine prevention studies
	Added bullet: • **Randomization will be stratified by region (ie, North America, Europe, Japan, China, Other)**	Clarification of the randomization and stratification process to include region

Section	Revision	Rationale
Protocol Summary, Study Design: *Visit Schedule*	Revised text: 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~~ **this** study at Visit 2 (Randomization Visit). The double blind treatment period will last 12 weeks, with a ~~subsequent~~ follow-up period of 4 additional weeks. 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 (Week 12), and Visit 8 (follow-up). The Visit 8 (follow-up) must be completed for all participants who take at least 1 dose of study medication, except for participants rolling over **into Study 3101-312-002 (long-term safety extension study in regions, excluding Japan and China)**, Study 3101-306-002 (long-term safety extension study in Japan), or Study 3101-311-002 (open-label safety extension study in China). For these **rollover** participants Visit 8 of Study 3101-303-002 is not required, **because** the Follow-up Visit **(Visit 8)** will be performed **after the OL treatment in the respective** long-term safety study. For participants who screen fail for the long-term safety study, the Follow-up Visit **(Visit 8)** of Study 3101-303-002 must be completed. For more details, see Table 1, Schedule of Visits and Procedures.	Clarified participation in Visit 8/EOS for rollover participants, by region and respective long-term safety extension study, and added information to allow for participants to roll over to the respective OL long-term extension study.
Protocol Summary, Study Population Characteristics, *Number of Participants*	Revised text: (North America, Asia/Pacific, and Europe) was changed to: (ie, North America, **Europe, Japan, China, Other**)	Adapted description of regions for consistency with stratification
Protocol Summary, General Statistical Methods and Types of Analyses	Revised text: All efficacy analyses will be performed using the modified intent-to-treat (mITT) population, which consists of all randomized participants who received at least 1 dose of study intervention, had an evaluable baseline period of eDiary data and at least 1 evaluable postbaseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data during the **double-blind treatment period**. All safety analyses will be performed using the safety population, which consists of all participants who took at least 1 dose of study intervention. **The analysis population for Off-treatment Hypothetical Estimand includes 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the study, regardless of whether on study treatment or off study treatment. This population is used for the primary estimand to support filing in Europe.**	Clarification and description of the ITT and mITT population, and the analysis population for off-treatment hypothetical estimand for the primary efficacy analysis to support filing in Europe.
Protocol Summary, General Statistical Methods and Types of Analyses, *Primary Efficacy Endpoint*	Added subsection on primary endpoint definition (matching protocol Section 7.2.1): ***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.** And edited sentence to add 'region' to statistical model: The statistical model will include treatment group, visit, **region,** acute medications during the baseline period (medication overuse Y/N), current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action (Current Use and "failed 0 medications or failed 1 or more medication(s) with the same	Clarification of primary endpoint and added the statistical model term 'region' to the MMRM model for primary analysis.

Section	Revision	Rationale
	mechanism of action", Current Use and "failed 2 to 4 medications with different mechanisms of action", Past Use only and "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action", Past Use only and "failed 2 to 4 medications with different mechanisms of action", and Never Used), and treatment group by visit interaction as categorical fixed effects.	
Protocol Summary, General Statistical Methods and Types of Analyses, *Secondary Efficacy Endpoints for all regions, except Europe and Canada*:	Revised text: • ~~Change from baseline in mean AIM-D monthly functioning and activity impairment score across the 12-week treatment period~~ Changed the above/previous AIM-D endpoint to the following 2 endpoints: • **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.**	Clarification of the AIM-D related secondary endpoint, based on psychometric evidence of the AIM-D consisting of 2 domains, performance of daily activities and physical impairment
Protocol Summary, General Statistical Methods and Types of Analyses, *Secondary Efficacy Endpoints* for all regions	Changed wording of secondary endpoints for all regions to: • At least a 50% reduction **in 3-month average of monthly migraine days**	To clarify secondary endpoints
Protocol Summary, General Statistical Methods and Types of Analyses, *Secondary Efficacy Endpoints*	Revised text: The secondary endpoints for headache days, acute medication use days, MSQ v2.1 Role Function-Restrictive domain score, ~~AIM-D functioning and activity impairment 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 secondary endpoint of 50% responders, defined as participants with at least a 50% reduction from baseline in the 3-month average of monthly migraine days, will be assessed for each individual.**~~The secondary endpoint of at least a 50% reduction from baseline in monthly migraine days will be summarized for each 4-week period during the 12-week treatment period.~~ A **logistic regression**~~generalized linear mixed~~ model will be used to analyze 50% responders~~ as repeated measures~~ 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**~~visit~~, acute medications during the baseline period (medication overuse Y/N), current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action~~, and treatment group-by-visit interaction~~ as categorical fixed effects; baseline value~~ and baseline-by-visit interaction~~ will be included as **a** covariate~~s~~. ~~Participants will be included as random effects with unstructured covariance matrix in the model to account for the correlation among repeated measurements.~~ 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.	Clarification that 50% responder will be assessed for each individual. The corresponding model is changed consequently. Clarification of statistical analysis model for secondary analysis

Section	Revision	Rationale
Table 1 Schedule of Visits and Procedures	Added table footnote [a]: **[a]: Visit 1, Visit 2, and either Visit 3 or Visit 4 must be conducted in office. All other visits, should be conducted in office unless it is necessary to conduct remote visits for the safety of participants (eg, COVID-19 or other pandemic): for details please refer to the Remote Visit Schedule of Assessments in Attachment 12.4)** Added table footnote [c]: **[c]: All participants who take at least 1 dose of study intervention must complete the follow-up period, except for participants rolling over into Study 3101-312-002 (long-term safety extension study in regions excluding Japan and China), participants rolling over into Study 3101-306-002 (long-term safety extension study in Japan), or Study 3101-311-002 (open-label safety extension study in China). For these rollover participants the Follow-up Visit will be performed after the completion of the OL treatment in the respective long-term safety extension study.** Added to table footnote [j]: **[j]: Clinicians will complete on eTablet.** The screening/baseline assessment of the C-SSRS will be completed. At all other visits, the 'Since Last Visit' C SSRS will be completed. Added table footnote [k]: **[k]: Participant will complete on eTablet.** Added table footnote [n]: **[n]: eDiary will be collected on Visit 2 for screen failures.** Added table footnote [q]: **[q]: The first dose of study intervention should be taken at the study site.**	To add flexibility and safety for participants and staff to the conduct of this study, when remote visits are necessary due to COVID-19 or other pandemic Clarified participation in Visit 8/EOS for rollover participants, by region and respective long-term safety extension study, added information to allow for participants to roll over to the respective OL long-term extension study. Clarifications
Section 3 Study Design, Section 3.1 Structure	Added footnote 2: • Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy (see Attachment 12.3).[2] **[2]: All French participants must have taken at least 1 prior migraine prevention medication with proven efficacy to be eligible for Study 3101-303-002.**	Requirement by French authorities.
	Added text: • Approximately 70% of randomized participants will have taken at least 1 prior migraine prevention medication with proven efficacy (see Attachment 12.3).[2] Randomization will be stratified based on migraine prevention medication exposure (Current Use, Past Use, or Never Used) with proven efficacy. Participants with current or past use **will be further stratified based** on the number of medications failed with unique mechanisms of action: "failed 0 medications or failed 1 or more medication(s) with the same mechanism of action" or "failed 2 to 4 medications with different mechanisms of action" (see Attachment 12.3). **Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%.**	Based on data review of recently published migraine prevention studies
	Added bullet: • **Randomization will be stratified by region (ie, North America, Europe, Japan, China, Other)**	To clarify the randomization stratification process.

Section	Revision	Rationale
	Changed text: 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~~ **this** study at Visit 2 (Randomization Visit). The double blind treatment period will last 12 weeks, with a ~~subsequent~~ follow-up period of 4 additional weeks. 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 (Week 12), and Visit 8 (follow-up). **The Visit 8 (follow-up) must be completed for all participants who take at least 1 dose of study medication, except for participants rolling over into Study 3101-312-002 (long-term safety extension study in regions, excluding Japan and China), Study 3101-306-002 (long-term safety extension study in Japan), or Study 3101-311-002 (open-label safety extension study in China). For these rollover participants Visit 8 of Study 3101-303-002 is not required, because the Follow-up Visit (Visit 8) will be performed after the OL treatment in the respective long-term safety study. For participants who screen fail for the long-term safety study, the Follow-up Visit (Visit 8) of Study 3101-303-002 must be completed.** For more details on ~~details~~study schedule, please see Table 1, Schedule of Visits and Procedures. ~~Only Japanese or Chinese participants completing the double-blind treatment period in this study may be eligible to continue in either Study 3101-306-002 (long-term safety extension study in Japan) or Study 3101-311-002 (long-term safety extension study in China). For these rollover participants, a Visit 8 is not required in the present study, as the Follow-up Visit will be performed in the long-term safety study. For participants who screen fail for the long-term safety study, the Follow-up Visit must be completed.~~	Clarified participation in Visit 8/EOS for rollover participants, by region and respective long-term safety extension study. And added information to allow for participants to roll over into the respective OL long-term extension study.
Section 3.4 End of Study Definition	Added sentence: 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.**	To comply with Russian requirement to call it Close Out Visit
Section 4.1 Number of Participants	Revised text: (North America, Asia/Pacific, and Europe) was changed to: (ie, North America, **Europe, Japan, China, Other**)	Adapted description of regions for consistency with stratification
Section 4.3, Exclusion Criterion number 14.	Changed text: 14. Any clinically significant hematologic, endocrine, **cardiovascular, cerebrovascular**, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease	Clarification

Section	Revision	Rationale
Section 4.4.2 Prohibited Medications/ Treatments	Revised text and added bullet: ● Medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, propranolol, topiramate) are prohibited when used for any indication other than migraine prevention. See Attachment 12.3. o Participants taking **one** medication with demonstrated efficacy for the prevention of migraine may be randomized provided that in the opinion of the investigator: ▪ Dose has been stable and the medication has been well-tolerated for at least 12 weeks prior to Visit 1 AND ▪ Participant is willing and able to maintain at a stable dose and dosage regimen during the study**, which should be assessed to ensure compliance at each study visit** ▪ **Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%** ● … ● **Cannabidiol (CBD) oil, cannabis.**	Clarification
Section 4.5 Screen Failures	Revised text: 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 **(ie, failure to adequately screen due to COVID-19)**, with permission from the sponsor. However, participants with clinically significant laboratory values at Visit 1 (**ie, screening;** including ALT or AST >1 × the ULN, total bilirubin >1 × ULN or serum albumin < 2.8 g/dL), or those with a **positive UDS** result at Visit 1 for recreational (including marijuana regardless of legality) or illicit drugs or non-disclosed[5] concomitant medications are not allowed to be rescreened. Footnote [5]**: For participants in the People's Republic of China, a positive UDS will result in screen failure regardless of disclosed concomitant medications.** And for Table 3 in Section 6.5.3, the same footnote was added as table footnote	Clarification
Section 5.2 Control Intervention(s)	Revised text: **5.2 Control Interventions *and Formulations*** **Tablets containing** matching **placebo 30 mg** (Formulation 011326X) **for** atogepant 30 mg and matching **placebo 60 mg** (Formulation 011317X) **for** atogepant 60 mg .	Clarification
Section 5.3 Methods for Masking/Blinding	Revised text: All participants will be instructed to take their study intervention twice daily (2 tablets in the morning and 2 tablets in the evening) at approximately the same time**s** each day. Participants, therefore, will receive either placebo **BID**, **atogepant 30 mg BID, or** a morning dose of atogepant 60 mg with an evening dose of placebo.	Clarification of blinded study intervention taken by eligible participants
Section 5.4 Treatment Allocation Ratio and Stratification	Added bullet: • **Randomization will be stratified by region (ie, North America, Europe, Japan, China, Other)**	Clarification of the randomization and stratification process to include region

<table>
<tr><th>Section</th><th>Revision</th><th>Rationale</th></tr>
<tr><td>Section 5.6 Study Intervention Regimen and Dosing</td><td>Revised text and Table 2:
Treatments to be used in this trial are listed in Table 2. Participants who meet all 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. Participants will take their first dose of study intervention at the clinic at Visit 2. All participants will be instructed to take their study intervention twice daily (2 tablets in the morning and 2 tablets in the evening) at approximately the same times each day. Details of PK samples with respect to timing of study intervention are provided in Section 6.3. Study intervention will be administered orally for 12 weeks, and participants will be followed for 4 weeks following study completion or discontinuation of study intervention.

Table 2 Study Interventions
<table>
<tr><th>Drug/ Dose</th><th>Study Intervention Product and Matching Placebo</th><th>Study Intervention Frequency</th><th>Route of Admini-stration</th></tr>
<tr><td>Placebo</td><td>Placebo 30 mg and Placebo 60 mg</td><td>BID</td><td>Oral</td></tr>
<tr><td>Atogepant 30 mg</td><td>Atogepant 30 mg and Placebo 60 mg</td><td>BID</td><td>Oral</td></tr>
<tr><td rowspan="2">Atogepant 60 mg</td><td>AM: Atogepant 60 mg and Placebo 30 mg</td><td rowspan="2">BID</td><td rowspan="2">Oral</td></tr>
<tr><td>PM: Placebo 30 mg and Placebo 60 mg</td></tr>
</table>
AM = morning dose; BID = twice daily; PM = evening dose.</td><td>Clarification of blinded study intervention taken by eligible participants</td></tr>
<tr><td>Section 6.2.1 Activity Impairment in Migraine – Diary (AIM-D)</td><td>Revised text:
The AIM-D is an 11-item daily diary<s>PRO</s> measure that assesses the impact of migraine<s> functioning</s> and is comprised of two domains that evaluate performance of daily activities (7 items) and physical<s>activity</s> impairment (4 items)<s> in migraine patients</s>. Participants are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities<s>functioning and activity impairment</s> (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)<s>, concentrating, and thinking clearly)</s> using the 6-point rating scale:<s> ranging from</s> “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<s>a</s> daily d<s>e</s>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<s>AIM-D</s> scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total</td><td>Clarification of the AIM-D diary questionnaire, based on psychometric evidence of the AIM-D consisting of 2 domains, performance of daily activities and physical impairment</td></tr>
</table>

Section	Revision	Rationale
	score, are transformed to a ~~range from~~ 0-**100 scale**, ~~to 5~~ with higher scores indicating greater impact of **migraine (ie, higher disease burden).** ~~in functioning and activity impairment.~~	
Section 6.7 Summary of Methods of Data Collection	Revised text: An IWRS will be used to randomize participants and manage study intervention inventory. All ~~office~~ visit data (ie, non-diary data) for this study will be collected by either **on** the eTablet **or, if conducted remotely (Attachment 12.4), utilizing a web-portal** (eg, questionnaires for PROs) or eCRFs via an electronic data capture system.	To adapt text to remote visits necessary due to COVID-19
Section 7.1 Analysis Populations	Added text to first paragraph: The ITT population will consist of all randomized participants. All efficacy analyses will be performed using the mITT population, consisting of 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, and 9 to 12) of eDiary data **during the double-blind treatment period**. All safety analyses will be performed using the safety population, consisting of all participants who received at least 1 dose of study intervention. Added 2nd paragraph: **The primary efficacy analysis population to support filing in Europe for off-treatment estimand (defined in Section 7.4) includes 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 postbaseline 4-week period (Weeks 1 to 4, 5 to 8, 9 to 12) of eDiary data during the study, regardless of whether on study treatment or off study treatment.**	Clarification and description of the ITT and mITT population, and the analysis population for off-treatment hypothetical estimand for the primary efficacy analysis to support filing in Europe.
Section 7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments	Revised text: On a daily basis during the 28-day baseline period and throughout the **study**~~double-blind treatment period~~, 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 medication. Therefore, for data analysis purposes, the number of migraine days during the last 28 days **prior to the randomization date** ~~of the baseline phase (ie, Day -28 to -1)~~, 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**~~Day 1~~.	Clarification of collection of migraine days and baseline for migraine days
Section 7.2.1 Primary Efficacy Endpoint	Revised text: 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.** ~~of the baseline phase (ie, Day -28 to -1)~~	Clarification of primary endpoint
Section 7.2.2 Secondary Efficacy Endpoints <u>for all regions, except Europe and Canada</u>	Revised text: • ~~Change from baseline in mean AIM-D monthly functioning and activity impairment score across the 12-week treatment period~~ Changed the above/previous AIM-D endpoint to the following 2 endpoints: • **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.**	Clarification of the AIM-D related secondary endpoint, based on psychometric evidence of the AIM-D consisting of 2 domains, performance of daily activities and physical impairment

Section	Revision	Rationale
Section 7.2.2 Secondary Efficacy Endpoints Secondary Efficacy Endpoints for all regions, except Europe and Canada, and for Europe and Canada	Changed wording of secondary endpoints to: • At least a 50% reduction **in 3-month average of monthly migraine days**	To clarify that 50% responder will be assessed for each individual. The corresponding model is changed consequently.
Section 7.2.3 Additional Efficacy Endpoints	Added text: **Additional efficacy endpoints for the United States and the Europe are provided below. Related analysis will be documented in the SAP.**	Added text for clarification
Section 7.2.3 Additional Efficacy Endpoints	Changed, added, and deleted additional efficacy endpoints: • ≥ 25%, ≥ 30%, ≥ 75%, 100% improvement (decrease) in **3-month average of monthly migraine days** ~~across the 12-week treatment period~~ • ~~Change from baseline in monthly headache-free days at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period~~ • ~~Change from baseline in monthly headache day pain intensity at Weeks 1 to 4, 5 to 8, 9 to 12, and average across the 12-week treatment period~~ • **Participant having a migraine day on the day of initial dose and on each day of the 6 days post the initial dose.** • **Participant** assessed by the PGIC as "much better" or "very much better" at Week 12 • **Participant reporting** "satisfied" or "extremely satisfied" with study medication for migraine prevention at Weeks 4, 8, and 12 • ~~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 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 (for Europe and Canada only)** • **Change from baseline in mean monthly Physical Impairment domain score of the AIM-D across the 12-week treatment period (for Europe and Canada 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 AIM-D monthly functioning and activity impairment score at Weeks 1 to 4, 5 to 8, and 9 to 12~~ • ~~Change from baseline in mean AIM-D monthly functioning and activity impairment score across the 12-week treatment period (for Europe and Canada)~~ • ~~Change from baseline in PROMIS-PI total score at Weeks 4, 8, and 12~~	To remove redundancy because monthly headache free days will be complementary to monthly headache day, and headache pain intensity can be interpreted using monthly moderate/severe days. To add the endpoint for evaluating the onset effect.

Section	Revision	Rationale
Section 7.2.3.1 Other Health Outcome Variables	Moved the following additional efficacy endpoints from Section 7.2.3 to this subsection: • **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 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 16** • **Change from baseline in PROMIS-PI total score at Weeks 4, 8, and 12**	To classify other health outcomes together because related analyses will be described in the health economics and outcomes research SAP.
Section 7.3.1 Primary Efficacy Analysis	Added 2 sentences to the 2nd paragraph in this section (description of the primary analysis with the MMRM model): **This is the primary analysis method for the primary efficacy endpoint in support of the US filing. 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.** Added the following 2 new subsections, each describing a different sensitivity analysis, as outlined below (no **bold font** used, for preserving the overview on subsections): **7.3.1.1 Sensitivity Analyses in Missing Data Handling** Multiple sensitivity analyses for missing data handling will be conducted and summarized below. Details of the sensitivity analyses will be provided in the SAP. <u>ANCOVA Model Based on 3-month Average of the Monthly Migraine Days</u> 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, acute medications during the baseline period (medication overuse Y/N), current or past use of migraine prevention medications and the number of medications failed with unique mechanisms of action, 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. <u>Within-group Imputation Based on Observed Data</u> 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. <u>Copy-Reference Approach</u> Copy-reference approach will be performed on the primary endpoint to assess the robustness of the MMRM analysis to possible violation of the missing at random (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 (MI) 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. <u>MMRM Based on Primary Measures Collected during the Double-blind and Follow-up Periods</u>	Added text to the description of the primary analysis with the MMRM model. To align with the atogepant clinical program.

Section	Revision	Rationale
	The details for this analysis are provided in Section 7.4. The primary analysis in support of EU filing will serve as one sensitivity analysis in support of US filing. **7.3.1.2 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 MI 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.	
Section 7.3.2 Secondary Efficacy Analysis	Changed 1st and 2nd paragraph: The secondary endpoints for headache days, acute medication use days, MSQ v2.1 Role Function-Restrictive domain score, ~~AIM-D functioning and activity impairment 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 secondary endpoint of 50% responders, defined as participants 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**~~generalized linear mixed~~ model will be used to analyze 50% responders~~ as repeated measures~~ 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**~~visit~~, acute medications during the baseline period (medication overuse Y/N), current and past use of migraine prevention medications and the number of medications failed with unique mechanisms of action~~, and treatment group-by-visit interaction~~ as categorical fixed effects; baseline value~~ and baseline-by-visit interaction~~ will be included as **a covariate**~~s~~. ~~Participants will be included as random effects with unstructured covariance matrix in the model to account for the correlation among repeated measurements.~~ 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.	Clarification of the AIM-D related secondary endpoint, based on psychometric evidence of the AIM-D consisting of 2 domains, performance of daily activities and physical impairment. To clarify that 50% responder will be assessed for each individual. The corresponding model is changed consequently.
Section 7.3.3 Additional Efficacy Analysis	Changed paragraph: 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. ~~For ASC-12, the number and percentage of randomized participants will be summarized by presence of allodynia as measured by the sum of score (absence: 0 to 2, presence > 2).~~ Details will be specified in the SAP.	Clarification

Section	Revision	Rationale
Section 7.4 **Off-treatment Hypothetical** Estimand Framework for EMA	Clarified section title and added text with subsections (no **bold font** used to preserve overview over subsections) as follows: **7.4 Off-Treatment Hypothetical Estimand Framework for EMA** This section defines an estimand, termed as off-treatment hypothetical estimand, which will be the primary estimand in support of EU filing and serve as one sensitivity analysis in support of US filing. **7.4.1 Treatment Condition of Interest** Participants take assigned treatment by randomization during the double-blind treatment period. In addition, permissible and prohibited mediations are described below: • Participants are allowed to take acute migraine medications (Section 4.4.1) to keep the participants in the study • Medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, propranolol, topiramate) are prohibited when used for any indication other than migraine prevention. See Attachment 12.3 o Participants taking one medication with demonstrated efficacy for the prevention of migraine may be randomized provided that in the opinion of the investigator: ▪ Dose has been stable and the medication has been well-tolerated for at least 12 weeks prior to Visit 1 AND ▪ Participant is willing and able to maintain at a stable dose and dosage regimen during the study, which should be assessed to ensure compliance at each study visit ▪ Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%	To align with ICH E9R1 (issued on Nov 20, 2019) Section A.3.3.
Section 7.4.4 Accounting of Intercurrent Events	Changed text: Intercurrent events and their handling rules are as follows: • **Participants who started a new migraine prevention treatment after the first dose of DB treatment will have their data after the end of DB treatment period following the start of the new migraine prophylaxis treatment excluded from the analysis.**~~Participants who discontinue study intervention and switch to other prophylaxis treatment will have their data collected after switching treatment, but such data collected after discontinuation of study intervention will be excluded from the analysis.~~ • Participants who discontinue study intervention due to all reasons other than **starting a new migraine prophylaxis treatment**~~switching treatment~~ will have their data collected after discontinuation of study intervention, and **those off-treatment data will be** included in the analysis. ~~Participants with missing data up to 12-week treatment period will have their data imputed using participants in the same treatment group who provide data while off study intervention.~~ Detailed methods and procedures will be documented in the SAP prior to the study completion.	To align with atogepant clinical program
Section 7.4.5 Population-Level Summary	Added the following text as 2nd paragraph: **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, a MMRM similar to the primary analysis specified in Section 7.3.1 will be performed on observed data including both on-treatment and off-treatment monthly migraine days.**	To propose the analysis method to obtain the population-level summary for the primary endpoint.

Section	Revision	Rationale
Section 7.4.6 **Off-treatment Hypothetical** Estimand Approach for the Secondary Endpoints	Clarified text in 2nd paragraph: 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.	Clarification
Section 7.5.2 Other Subgroup Analyses	Changed first sentence to: A subgroup analysis by exposure to migraine prevention medication**, preventive medication failures, and by acute medication overuse** is planned for the following efficacy endpoints: Changed wording of secondary endpoints to: • At least a 50% reduction **in 3-month average of monthly migraine days** • At least a 75% reduction **in 3-month average of monthly migraine days** • A 100% reduction **in 3-month average of monthly migraine days** Deleted the following text: ~~Subgroup analyses by number of preventive medications failed with unique mechanisms of action, by ≥ 1, ≥ 2, and ≥ 3 preventive medication failures (irrespective of class) and by medication overuse are also planned for the following efficacy endpoints:~~ • ~~Change from baseline 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~~ • ~~At least a 50% reduction in 3-month average of monthly migraine days~~	Modified the description of responders to be consistent with Sections 7.2.2 and 7.2.3 Subgroup analyses for presence of allodynia will be included in SAPs in support of business objectives such as a separate SAP relevant to health technology assessment and publications.
Section 11. References	Added reference: **Mehrotra DV, Li X, Liu J, Lu K. Analysis of longitudinal clinical trials with missing data using multiple imputation in conjunction with robust regression. Biometrics. 2012;68(4):1250-1259.**	As per text additions in Section 7.3.1

Section	Revision	Rationale
Attachment 12.3	Added bullet: The criteria below should be used to determine how to stratify each participant based on the number of prior migraine preventive medications failed with unique mechanisms of action. Failure of a migraine preventive medication can be assessed on the basis of tolerability or efficacy and is based on investigator judgment. • For efficacy, investigators must consider: o 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. o Medications must have been started within the past 7 years. o Note the following for participants who are currently taking a stable dose of one of the migraine prevention medications listed and meet the efficacy criteria: ▪ If the participant meets all study entry criteria, this participant is eligible to be randomized provided that the participant agrees to continue to take this migraine preventive medication for the duration of the study. ▪ This medication should be considered as one of the failed drugs for the prevention of migraine. ▪ **Enrollment of participants with current use of a migraine prevention medication will be capped at ~15%**	Clarification
Additional Attachment 12.4	Added Attachment 12.4 with text (see below) and Table 5 Remote Visits Schedule of Assessments, to explain in more detail the conduct of remote study visit for the safety of participants and site staff (ie, COVID-19 or other pandemic). **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 Remote Visit Schedule of Assessments (Table 12 1) should be followed. Remote visits may be conducted between Visit 3 – Visit 8 but participants must attend in office assessments at 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 on the eTablet during in-office visits, will be collected using a web-based portal during remote visits, if available.**	To outline conduct of study when remote visits are necessary due to COVID-19