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A PHASE 3, MULTICENTER, OPEN-LABEL 52-WEEK EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN JAPANESE PARTICIPANTS WITH CHRONIC OR EPISODIC MIGRAINE

Protocol Number:	3101-306-002
EudraCT Number (if applicable):	
Phase:	3
Name of Study Intervention:	Atogepant (AGN-241689)
Sponsor:	Allergan Pharmaceuticals International Limited (a subsidiary of AbbVie) Marlow International The Parkway, Marlow SL7 1YL United Kingdom
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Original Protocol Date: Amendment 1 Date: Amendment 2 Date: Amendment 3 Date:	15th October 2019 25th November 2019 22nd December 2021 7th July 2022

The following information can be found on the Study Contacts Page: Name and contact information of Sponsor study personnel and Emergency Telephone Numbers.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

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

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

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound: Atogepant (AGN-241689)

Phase: 3

Study Objectives:

Safety and tolerability: To evaluate the safety and tolerability of treatment with atogepant 60 mg once daily when administered over 52 weeks for the prevention of migraine in Japanese participants with chronic migraine (CM) or episodic migraine (EM).

Efficacy: To evaluate the efficacy of treatment with atogepant 60 mg once daily when administered over 52 weeks for the prevention of migraine in Japanese participants with CM or EM.

Clinical Hypotheses:

Atogepant 60 mg once daily is safe and well-tolerated when administered over 52 weeks for the prevention of migraine in Japanese participants with CM or EM.

Study Design:

Structure: Multicenter, open-label, 52-week long-term safety extension study conducted in Japan.
Duration: The study will consist of a 52-week open-label treatment period and a 4-week safety follow-up period for all participants. For De Novo EM Participants only, a 4-week screening/baseline period will be required. Total study duration is 56-60 weeks.
Study Intervention: Atogepant 60 mg tablet
Control Intervention: Not applicable
Dosage/Dose Regimen: Atogepant 60 mg will be administered once daily for 52 weeks.
Randomization: Not applicable
Visit Schedule: There will be a screening visit 4 weeks prior to Visit 1 for De Novo EM Participants only. After Visit 1, study visits will occur every 4 weeks for the duration of the 52-week treatment period for all participants. A safety follow-up visit will occur 4 weeks after the last dose of atogepant. There will be a total of 15 scheduled clinic visits for 3101-303-002 Completers. There will be a total of 16 scheduled clinic visits for De Novo EM Participants. For details, please see Table 1, Schedule of Visits and Procedures.

Study Population Characteristics:

Number of Participants/Sites: All participants who either complete Study 3101-303-002 or are newly recruited and complete the screening/baseline period, and meet all eligibility requirements, may participate in this study. At least 170 participants will be enrolled at approximately 25 centers in Japan, to meet a target of a minimum of 100 participants with EM or CM at 1 year. A minimum of 30 participants enrolled (at selected sites only) must have EM and meet all eligibility criteria.
Condition/Disease: Migraine without aura, migraine with aura, or chronic migraine (ICHD-3 Section 1.1, 1.2 or 1.3; see Section 12.1).

Key Inclusion Criteria:

3101-303-002 Completers:

- Eligible participants who completed Visit 7, and Visit 8 if applicable, of Study 3101-303-002 without significant protocol deviations (eg, noncompliance to protocol-required procedures), and who did not experience an AE that may indicate an unacceptable safety risk.

De Novo EM Participants:

- Male or female participants ages 18 to 80 years, inclusive, at Visit -1.
- Age of the participant at the time of migraine onset < 50 years.
- At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3, 2018 (Section 12.1).
- History of 4 to 14 migraine days per month (see Section 6.2.1 for definition of migraine day) on average in the 3 months prior to Visit -1 in the investigator's judgment.
- 4 to 14 migraine days in the 28-day baseline period per eDiary.
- Completed at least 20 out of 28 days in the eDiary during baseline period and is able to read, understand, and complete the study questionnaires and eDiary per investigator's judgment.

Key Exclusion Criteria (for all participants unless noted otherwise):

- Participants requiring any medication, diet, or nonpharmacological treatment on the list of prohibited concomitant medications or treatments (see Section 4.5.2 and Attachment 12.2), that cannot be discontinued or switched to an allowable alternative. Participants from lead-in study 3101-303-002 taking 1 medication with demonstrated efficacy for the prevention of migraine may participate in the current study provided that the dose was stable and the medication was well-tolerated prior to the lead-in study and the participant is willing and able to continue (Attachment 12.2.2).
- Participants with an ECG indicating clinically significant abnormalities at Visit -1 (De Novo EM Participants) or Visit 1 (3103-303-002 Completers).
- Participants with hypertension (sitting systolic BP > 160 mm Hg or sitting diastolic BP > 100 mm Hg) at Visit -1 (De Novo EM Participants) or Visit 1 (for all participants).
- Participants with a significant risk of self-harm (Columbia-Suicide Severity Rating Scale [C-SSRS]), or of harm to others (investigator opinion); participants who report suicidal ideation with intent, with or without a plan, (ie, Type 4 or 5 on the C-SSRS) or report suicidal behavior in the past 6 months prior to Visit -1 (De Novo EM Participants) or since the last visit at Visit 1 (for all participants), must be excluded.
- Participants with clinically significant hematologic, endocrine, cardiovascular, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease.

De Novo EM Participants only:

- Difficulty distinguishing migraine headaches from tension-type or other headaches.
- Has a history of migraine accompanied by diplopia or decreased level of consciousness or retinal migraine as defined by ICHD-3, 2018.
- Has a current diagnosis of chronic migraine, new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3, 2018.
- Has ≥ 15 headache days per month (see Section 6.2.2 for definition of headache day) on average across the 3 months prior to Visit -1 in the investigator's judgment.
- Has ≥ 15 headache days in the 28-day baseline period per eDiary.
- Usage of opioids or barbiturates > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, NSAIDs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit -1 per investigator's judgment or during the baseline period (barbiturates are excluded 30 days prior to screening and through the duration of the study) (see Section 12.2.1).

Response Measures:

Safety:

AEs, physical examinations, clinical laboratory determinations, vital sign measurements, ECG parameters, and the C-SSRS.

Efficacy:

The efficacy of atogepant for the prevention of migraine will be assessed based on information recorded by the participant. An eDiary will be used daily at home to collect data on headache duration, headache characteristics, symptoms, and acute medication use, which will be collectively applied to define migraine days and headache days per the criteria listed in Sections 6.2.1, 6.2.2 and 6.2.3.

Participants will be administered participant-reported outcome measures collected daily in the eDiary (AIM-D, Activity Level, and Activity Limitation) and at scheduled visits.

General Statistical Methods and Types of Analyses:

All safety analyses will be performed using the safety population which consists of all participants who took at least 1 dose of study intervention (atogepant) in this extension study. All efficacy analyses will be performed using the modified intent-to-treat (mITT) population, consisting of all participants who received at least 1 dose of study intervention (atogepant) in this study, an evaluable baseline (in this study for De Novo EM Participants or in the lead-in study for the rollover participants) and had at least 1 evaluable post-baseline 4-week period of eDiary data, in this extension study.

The safety parameters include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, and the C-SSRS. For each of the clinical, laboratory, vital sign, and ECG parameters, the baseline value in this extension study is defined as:

- The baseline value in the lead-in study (Study 3101-303-002) for 3101-303-002 Completers.
- The last nonmissing safety assessment before the first dose of study drug for De Novo EM Participants.

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

Efficacy endpoints include change from baseline in monthly migraine days, change from baseline in monthly headache days, at least a 50% reduction from baseline in monthly migraine days, and other endpoints.

For monthly endpoints, baseline in this extension study is defined as:

- The baseline value in the lead-in study (Study 3101-303-002) for 3101-303-002 Completers.
- The last 28 days of the screening/baseline period for De Novo EM Participants.

For efficacy endpoints that are assessed at clinical visits, baseline in this extension study is defined as:

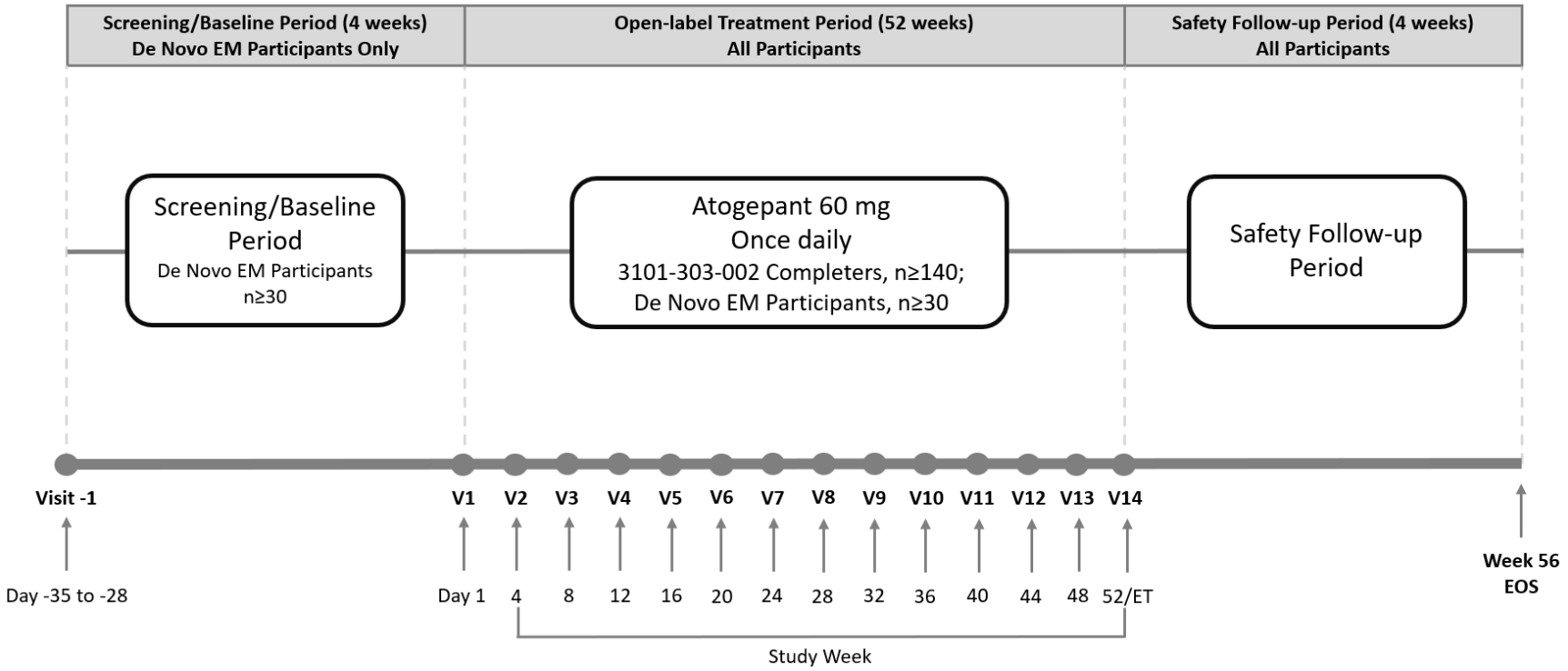
- The last nonmissing efficacy assessment before the first dose of study intervention in the lead-in study (3101-303-002) for 3103-303-002 Completers.
- The last nonmissing efficacy assessment before the first dose of study drug for De Novo EM Participants.

For analysis purposes, 4 weeks (28 days) will be considered as 1 month. Descriptive statistics will be provided by visit for all efficacy endpoints based on the mITT population using the observed cases approach.

Sample Size Calculation:

At least 170 participants will be enrolled into this long-term, open-label, safety extension study including at least 140 participants from the lead-in study (Study 3101-303-002) and approximately 30 De Novo EM Participants (from selected sites only) to meet a target of a minimum of 100 participants at 1 year.

Figure 1. Study Diagram



EM = episodic migraine; EOS = end of study; ET = early termination; V = visit.

Table 1. Schedule of Visits and Procedures

Study Period	**Screening/ Baseline Period (4 weeks)[a]**	**Open-label Treatment Period (52 weeks)**														**Safety Follow-up Period (4 weeks)**
Visit #	**Visit -1**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week -4***	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	***Day -35 to -28***	N/A	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Obtain Informed consent and participant privacy[c]	X	X[d]														
Access IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect demographic information	X															
Assess inclusion/exclusion criteria	X	X[e]														
Collect medical history[f]	X	X[d]														
Collect migraine/headache history and confirm diagnosis	X															
Collect start date (first day) of last menstrual cycle for women having menstrual cycles	X															
Review and record prior medications taken in the past 6 months and all prior headache medications and concomitant medications	X															
Perform physical examination	X	X													X	X
Collect vital sign measurements[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Perform ECG	X	X[d]			X			X			X				X	
Perform urine pregnancy test[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory determinations[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Screening/ Baseline Period (4 weeks)[a]**	**Open-label Treatment Period (52 weeks)**														**Safety Follow-up Period (4 weeks)**
Visit #	**Visit -1**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week -4***	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	***Day -35 to -28***	N/A	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Provide eDiary device with instructions and training[j]	X	X[d]														
Participant eDiary data collection[j,k]	X															
Review eDiary data (headache duration, frequency, characteristics and symptoms, acute medication use, AIM-D, Activity Level, and Activity Limitation) and compliance[l]		X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS (eTablet)[m,n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect ASC-12 (eTablet)[o,p]	X															
HIT-6 (eTablet)[o,p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIC (eTablet)[o,p]					X			X			X			X	X	
PGI-S (eTablet)[o,p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
WPAI:MIGRAINE (eTablet) [o,p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Satisfaction with Study Medication (eTablet)[o,p]			X	X	X	X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L (eTablet)[o,p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MIDAS (eTablet)[o,p]		X			X			X			X			X	X	
MSQ v2.1 (eTablet)[o,p]		X			X			X			X			X	X	X
Collect eDiary		X[q]													X	
Dispense study intervention (ie, atogepant)		X	X	X	X	X	X	X	X	X	X	X	X	X		

Study Period	**Screening/ Baseline Period (4 weeks)[a]**	**Open-label Treatment Period (52 weeks)**														**Safety Follow-up Period (4 weeks)**
Visit #	**Visit -1**	**Visit 1[b]**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week -4***	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	***Day -35 to -28***	N/A	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Review of study intervention (ie, atogepant) compliance and accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events	X															
Concomitant medications/ concurrent procedures	X															

a De Novo EM Participants only.

b After providing informed consent for this study, Visit 7 of the lead-in study (Study 3101-303-002 [Phase 3 CM study]) will function as Visit 1 for this study (see Section 3 for further information)

c Obtained from the participant.

d 3101-303-002 Completers only.

e Review of inclusion/exclusion criteria includes the review of eDiary data and compliance during Screening/Baseline for De Novo EM Participants.

f Medical history will be collected for 3101-303-002 Completers who have a gap between the last visit of the lead-in study and Visit 1 of this extension study and also for De Novo EM Participants.

g 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.

h For WOCBP only, a urine pregnancy test will be performed at all visits. At the first study visit, discuss the method of contraception with WOCBP and document this method. Counsel participants on the importance of maintaining their agreed upon method of contraception throughout the study.

i Clinical laboratory determinations include chemistry, hematology, coagulation parameters (INR), and urinalysis to be collected for all visits. Samples for serology and the urine drug screen will be collected only at Visit 1 for 3101-303-002 Completers and only at Visit-1 for De Novo EM Participants.

j Participants should begin using the eDiary as soon as it is dispensed and for the duration of the screening/baseline (for De Novo EM Participants) and treatment period (for all participants). Training for the eDiary will be provided for qualified participants during the first study visit (Visit -1 for De Novo EM Participants and Visit 1 for 3101-303-002 Completers).

k Daily eDiary data collection includes: headache frequency, duration, characteristics, symptoms, acute medication use, AIM-D, Activity Level, and Activity Limitation.

l Participants must bring their eDiary to all visits (except Visit 15).

m At all visits except Visit -1, the "Since Last Visit" C-SSRS will be completed for all participants. For Visit -1, the 'Screening/Baseline' assessment of the C-SSRS will be completed for the participant's lifetime history and for the 6 months prior to screening.

n Clinicians will complete on eTablet.

o Participant will complete on eTablet.

p PRO measures should be administered prior to any tests and/or evaluations unless indicated otherwise in the protocol.

q eDiary will be collected on Visit 1 for screen failures (De Novo EM Participants only).

Table 2. Schedule of Procedures for Remote Visits

Study Period	**Open-label Treatment Period (52 weeks)**													**Safety Follow-up Period (4 weeks)**
	Potential for Remote Visit[a]													
Visit #	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14/ ET**	**Visit 15/ EOS**
Day/Week	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***	***Week 20 (Day 140)***	***Week 24 (Day 168)***	***Week 28 (Day 196)***	***Week 32 (Day 224)***	***Week 36 (Day 252)***	***Week 40 (Day 280)***	***Week 44 (Day 308)***	***Week 48 (Day 336)***	***Week 52 (Day 364)***	***Week 56 (Day 392)***
Visit Windows	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	+ 3 days	± 3 days
Dispense study intervention (ie, atogepant)[b]	X	X	X	X	X	X	X	X	X	X	X	X		
Review of study intervention (i.e., atogepant) compliance and accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant daily eDiary data collection[c]	X													
Review eDiary data and compliance[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect eDiary[d]													X	X
Perform urine pregnancy test[b,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS (eTablet or web portal)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIT-6[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIC[g] (web portal)			X			X			X			X	X	
PGI-S[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X	X	
WPAI:MIGRAINE[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Satisfaction with Study Medication[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X		
EQ-5D-5L[g] (web portal)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MIDAS[g] (web portal)			X			X			X			X	X	
MSQ v2.1[g] (web portal)			X			X			X			X	X	X
Adverse events	X													
Concomitant medications/ concurrent procedures	X													

a Visit -1 and Visit 1 must be performed onsite.

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, AIM-D, Activity Level, and Activity Limitation.

d Device may be dropped off or returned at Visit 15/EOS.

e WOCBP only are to take an at-home pregnancy test (provided by sites) and report the results during virtual visits.

f The "Since the Last Visit C-SSRS" will be completed. Clinicians will complete the C-SSRS on eTablet or web-based backup portal.

g If available, participants will complete on a web-based portal.

1 Background and Clinical Rationale

1.1 Background

The Global Burden of Disease Survey 2010 (Vos 2013) estimated the global prevalence of migraine to be 14.7%, making it the third most common disease in the world in both males and females. Migraine was ranked seventh highest among specific causes of disability globally (Steiner 2013). 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 observed a 5.9-fold higher risk of migraine than men (Takeshima 2004). Migraine affects 18% of women and 6% of men in the United States with peak prevalence occurring between the ages of 25 and 55 years. Approximately one-third of patients with migraines have 3 or more migraine attacks per month, and over half report severe impairment or the need for bed rest (Lipton 2007). In the United States alone, work loss due to migraine is estimated to cost ~ $13 billion annually (Hu 1999). Prevalence is similar in Europe, with migraine headache affecting on average 17.6% of women and 8% of men (Stovner 2010).

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 in overcoming current barriers to reduce the global burden of migraine.

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

1.2 Overview of Atogepant

Atogepant (AGN-241689) is a potent, selective oral CGRP receptor antagonist being developed for migraine prevention. Additional information on nonclinical pharmacology, toxicology, and PK properties of atogepant can be found in the investigator's brochure.

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

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

Atogepant was approved in the US for the preventive treatment of EM in adults in September 2021.

1.3 Study Rationale

The purpose of this study is to evaluate the safety and tolerability of atogepant 60 mg once daily, in Japanese participants, when taken for 52 weeks for the prevention of CM or EM.

1.4 Rationale for Doses and Dose Regimens Selected

The Phase 3 pivotal studies to evaluate atogepant are testing a maximum total daily dose of 60 mg. For this reason, the dose of 60 mg once daily has been selected for this study to evaluate the long-term safety and tolerability of atogepant in Japanese participants when taken for the prevention of CM or EM.

2 Study Objective and Clinical Hypothesis

2.1 Study Objectives

Safety and tolerability: To evaluate the safety and tolerability of treatment with atogepant 60 mg once daily when administered over 52 weeks for the prevention of migraine in Japanese participants with CM or EM.

Efficacy: To evaluate the efficacy of treatment with atogepant 60 mg once daily when administered over 52 weeks for the prevention of migraine in Japanese participants with CM or EM.

2.2 Clinical Hypothesis

Atogepant 60 mg once daily is safe and well-tolerated when administered over 52 weeks for the prevention of migraine in Japanese participants with CM or EM.

3 Study Design

3.1 Structure

This is a multicenter, open-label, 52-week, long-term safety extension study conducted in Japan and will enroll at least 170 participants from approximately 25 sites, to meet a target of a minimum of 100 participants exposed to atogepant at 1 year. Participants will be treated with atogepant 60 mg once daily.

The study will consist of a 52-week open-label treatment period and a 4-week safety follow-up period for all participants. For De Novo EM Participants only, a 4-week screening/baseline period will be required.

The study will recruit 2 cohorts:

3101-303-002 Completers:

Japanese participants may directly rollover from Study 3101-303-002 (Phase 3 CM study); hereinafter referred to as the lead-in study. As such, participants will have Visit 7 from the

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

Note, there may be participants who complete Visit 7 in the lead-in study before extension Study 3101-306-002 has been initiated. Those participants should complete Visit 7/ET and Visit 8/EOS Visit (including discontinuation of study intervention) per the lead-in study Schedule of Visits and Procedures.

Depending on the timing of the initiation of this extension study, in relation to each participant's planned Visit 8 schedule in the lead-in study, Visit 1 for Study 3101-306-002 can be conducted on the same day as Visit 8/EOS Visit for the lead-in study, or soon thereafter.

1. If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit in the lead-in study should be conducted on the same day as Visit 1 for Study 3101-306-002.

2. If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 and Visit 1), then Visit 8/EOS Visit should be conducted as planned per the lead-in study Schedule of Visits and Procedures. When this extension study is initiated the participant should return to the clinic as soon as possible, and Visit 1 should be conducted per the Study 3101-306-002 Schedule of Visits and Procedures.

De Novo EM Participants:

Japanese participants with EM will be newly recruited at selected sites only. Participation will begin with a 4-week screening/baseline period starting at Visit -1. Participants who complete the 4-week screening/baseline period and meet all entry criteria will be enrolled into the 52-week open-label treatment period at Visit 1.

For all participants, after Visit 1 study visits will occur every 4 weeks for the duration of the 52-week treatment period. Participants will return to the clinic for safety assessments at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks relative to Visit 1 (Day 1). An EOS visit will occur 4 weeks after the last dose of atogepant 60 mg once daily. For details, please see Table 1, Schedule of Visits and Procedures.

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

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

3.2 Data Safety Monitoring Board

An independent DSMB will be established to review safety data and summary reports, identify any safety issues and trends, and make recommendations to the Sponsor, including modification or early termination 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 described in a separate DSMB Charter.

3.3 Adjudication Committee

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

4 Study Population and Entry Criteria

4.1 Number of Participants

All participants who either complete Study 3101-303-002 or are newly recruited and complete the screening/baseline period, and meet all eligibility requirements, may participate in this study. At least 170 participants will be enrolled at approximately 25 centers in Japan, to meet a target of a minimum of 100 participants at 1 year. A minimum of 30 participants enrolled (at selected sites only) must be classified as De Novo EM Participants (see definition below).

4.2 Study Population Characteristics

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

1. 3101-303-002 Completers:

   Participants eligible to participate in this study will have completed Visit 7, and Visit 8 if applicable, of Study 3101-303-002 without significant protocol deviations (eg, noncompliance to protocol-required procedures), meet the inclusion criteria and do not meet the exclusion criteria for this study.

2. De Novo EM Participants:

   Participants with EM who meet eligibility criteria.

4.3 Inclusion Criteria

4.3.1 All Participants

The following are inclusion criteria for all participants:

1. Written informed consent and participant privacy information (eg, written authorization for use and release of health and research study information and written data protection consent, per Japan regulations) obtained from the participant prior to initiation of any study-specific procedures.

2. Participants must be using a medically acceptable and effective method of birth control during the course of the entire study, as defined in Section 4.5.3.

4.3.2 3101-303-002 Completers

The following is inclusion criterion for 3101-303-002 Completers only:

3. Eligible participants who completed the double-blind treatment period (Visit 7) and the follow-up period (Visit 8), if applicable, depending on the timing of study initiation, of Study 3101-303-002 without significant protocol deviations (eg, noncompliance to protocol-required procedures) and who did not experience an AE that, in the investigator's opinion, may indicate an unacceptable safety risk.

4.3.3 De Novo EM Participants

The following are inclusion criteria for De Novo EM Participants only:

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

5. At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3, 2018 (Section 12.1).

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

7. History of 4 to 14 migraine days per month (see Section 6.2.1 for definition of migraine day) on average in the 3 months prior to Visit -1 in the investigator's judgment.

8. 4 to 14 migraine days in the 28-day baseline period per eDiary.

9. 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.

4.4 Exclusion Criteria

4.4.1 All Participants

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

1. Requirement for any medication, diet (ie, grapefruit or grapefruit juice), or nonpharmacological treatment that is on the list of prohibited concomitant medications or treatments (see Section 4.5.2 and Attachment 12.2) that cannot be discontinued or switched to an allowable alternative medication or treatment. Participants from lead-in Study 3101-303-002 taking 1 medication with demonstrated efficacy for the prevention of migraine may participate in the current study provided that the dose was stable and the medication was well-tolerated for at least 12 weeks prior to Visit 1 of the lead-in study and the participant is willing and able to maintain taking this medication at a stable dose and dosage regimen throughout the study. (Attachment 12.2.2).

2. Female participant is pregnant, planning to become pregnant during the course of the study, or currently lactating. Women of childbearing potential must have a negative urine pregnancy test at Visit -1 (De Novo EM Participants) and Visit 1 (for all participants).

3. An ECG with clinically significant abnormalities at Visit -1 (De Novo EM Participants) or Visit 1 (3101-303-002 Completers) as determined by the investigator.

4. Hypertension as defined by sitting systolic BP > 160 mm Hg or sitting diastolic BP > 100 mm Hg at Visit -1 (De Novo EM Participants) or Visit 1 (for all participants). Vital sign measurements that exceed these limits may be repeated only once.

5. Significant risk of self-harm based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator; participants must be excluded if they report suicidal ideation with intent, with or without a plan (ie, Type 4 or 5 on the C-SSRS) or report suicidal behavior in the past 6 months prior to Visit -1 (De Novo EM Participants) or since the last visit at Visit 1 (for all participants).

6. Any clinically significant hematologic, endocrine, cardiovascular, 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 (De Novo EM Participants) and is judged by the investigator as not likely to interfere with the participant's participation in the study, the participant may be included.

    - Participants on dialysis for renal failure will be excluded.

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

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

4.4.2 De Novo EM Participants

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

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

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

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

12. Has ≥ 15 headache days per month (see Section 6.2.2 for definition of headache day) on average across the 3 months prior to Visit -1 in the investigator's judgment.

13. Has ≥ 15 headache days in the 28-day baseline period per eDiary.

14. History of an inadequate response to > 4 medications (2 of which have different mechanisms of action) prescribed for the prevention of migraine (see Section 12.2.2 for classification of inadequate response to migraine-preventive medications).

15. Usage of opioids or barbiturates > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, NSAIDs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit -1 per investigator's judgment or during the baseline period (barbiturates are excluded 30 days prior to screening and through the duration of the study) (see Section 12.2.1).

16. QTcF > 450 msec for males and QTcF > 470 msec for females at Visit -1 based on the central reviewer's final ECG report.

17. 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 (Section 12.3).

18. 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.

19. History of acute hepatitis within 6 months of Screening (Visit -1); or chronic liver disease (including nonalcoholic fatty liver disease, viral chronic hepatitis, and cirrhosis); or a positive result on anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti-hepatitis C antibody testing, or anti-hepatitis E IgM antibody.

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

21. 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).

22. 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.

23. History of any GI prior procedures or GI 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 will not be excluded.

24. 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.

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

26. 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).

27. Previous exposure to:

    - Atogepant (AGN-241689 or MK-8031) OR
    - Injectable monoclonal antibodies blocking the CGRP pathway within the last 6 months OR
    - Any other investigational CGRP-receptor antagonist (RA).

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

29. Active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. If a participant has signs/symptoms suggestive of SARS-CoV-2 infection, the participant must have a negative molecular (eg, polymerase chain reaction [PCR]) test result to be considered for inclusion in the study.

(Note: Participants who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria: at least 14 days since first negative PCR test result have passed in asymptomatic participants or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.)

30. Unremitting symptoms of "long COVID" due to prior SARS-CoV-2 infection or any other lasting symptoms 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.

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Medications that are not specifically prohibited in Section 4.5.2 and Attachment 12.2 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

Herbal medications are allowed during the study with the exception of herbal medications for the treatment of migraine.

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

SSRI or SNRI will be permitted, provided that treatment is stable for at least 60 days prior to the first study visit 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 Sponsor.

4.5.2 Prohibited Medications/Treatments

The following medications are prohibited 30 days prior to the first study visit (unless otherwise indicated) for all participants and throughout the study (see Attachment 12.2).

- Strong and moderate CYP3A4 inhibitors, including but not limited to: systemic (oral/IV) itraconazole, ketoconazole, fluconazole, erythromycin, clarithromycin, telithromycin[1], ciprofloxacin, diltiazem, verapamil, aprepitant, cyclosporine, nefazodone[1], cimetidine, quinine, and HIV protease inhibitors
- Strong and moderate CYP3A4 inducers, including but not limited to: barbiturates (eg, phenobarbital and primidone), systemic (oral/IV) glucocorticoids, nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, and St John's wort
- Strong OATP1B1 inhibitors (eg, gemfibrozil[1], 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, topiramate, propranolol), excepting 1 medication with demonstrated efficacy for the prevention of migraine taken at a stable dose and well-tolerated during Study 3101-303-002 which may be continued if the participant is willing and able to do so (see Exclusion Criterion 1, Section 4.4 and Attachment 12.2.2).
- Herbal medications with efficacy for the prevention of migraine (eg, feverfew)
- CBD oil
- Therapeutic or cosmetic botulinum toxin injections (eg, Dysport®, Botox®, Xeomin®, Myobloc®, Jeuveua™) into areas of the head, face, or neck within 6 months prior to the first study visit and throughout the study period

[1] Not approved in Japan

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

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. Sponsor should be notified about administration of prohibited medication/treatment as soon as possible.

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

For purposes of this study, women will be considered of childbearing potential unless they are naturally postmenopausal (ie, no menses for 2 years) or permanently sterilized (ie, bilateral tubal ligation, bilateral tubal occlusion, 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[2], or transdermal[2] (ie, pill, vaginal ring[2], patch[2])
- Progestogen--only hormonal contraception (with inhibition of ovulation) that are oral, injectable[2], or implantable[2]
- IUD or IUS
- Vasectomized partner (provided that the partner is the sole sexual partner of study participant and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse for the duration of the study)

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

- Progestogen-only oral hormonal contraception (where inhibition of ovulation is not the primary mode of action)

[2] Contraceptive methods not approved in Japan.

- Male or female condom with or without spermicide[2] (female and male condoms should not be used together)
- Cap[3], diaphragm[3] or sponge[3] with spermicide
- A combination of male condom with either cap[3], diaphragm[3] or sponge[3] with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

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

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

If a woman becomes pregnant during the study, the investigator will notify Sponsor immediately after the pregnancy is confirmed and the participant will be discontinued from the study after appropriate safety follow-up. The investigator will (1) notify the participant's physician that the participant was being treated with atogepant 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 Sponsor.

4.5.4 Special Diet or Activities

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

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

4.6 Screen Failures

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

[3] Contraceptive methods not approved in Japan.

For De Novo EM Participants only: Rescreening of screen failures is permitted in certain situations, with permission from the Sponsor. However, participants with clinically significant laboratory values at Visit -1 (including ALT or AST > 1 × 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 nondisclosed concomitant medications, are not allowed to be rescreened.

5 Study Intervention

5.1 Study Intervention and Formulations

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

5.2 Control Intervention

Not applicable.

5.3 Methods for Masking/Blinding

This is an open-label study.

5.4 Treatment Allocation Ratio

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

5.5 Method for Assignment to Treatment Groups

Prior to initiation of atogepant in this open-label extension study, each participant who provides informed consent will maintain his/her lead-in study participant number. This number will serve as the participant identification number on all study documents. For De Novo EM Participants, participant identification numbers will be newly assigned at study entry.

At Visit 1, eligible participants will receive one bottle of atogepant 60 mg.

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

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

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

5.6 Treatment Regimen and Dosing

Participants who meet all of the study entry criteria at Visit -1 and/or Visit 1 will be treated with atogepant 60 mg once daily. Atogepant to be used in this study is listed in Table 5-1.

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

Table 5-1. Study Intervention

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

5.7 Storage of Study Intervention

Atogepant bottles must be stored at room temperature in a securely locked cabinet. Further details regarding the storage of atogepant are in the Study Reference Manual.

6 Response Measures and Summary of Data Collection Methods

6.1 Safety Measures

6.1.1 Adverse Events

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

6.1.2 Adverse Events of Special Interest

Selected nonserious and serious adverse events are AESIs and will require immediate reporting, recording and follow-up. The following events will be closely monitored:

- Treatment-emergent suicidal ideations with intent, with or without a plan (ie, Type 4 or 5 on the C-SSRS) or any suicidal behaviors

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

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

6.1.3 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the visits outlined in Table 1. Hematology, chemistry, INR, and urinalysis will be conducted at these visits. Serology and the urine drug screen will only be conducted at Visit -1 (De Novo EM Participants) and at Visit 1 (3101-303-002 Completers). 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 withdrawal criteria, or positive results on the urine drug screen Visit -1 or Visit 1 will be excluded/withdrawn from the study. Women of childbearing potential will be required to have a urine pregnancy test at all visits. A positive pregnancy test at Visit -1 or Visit 1 will exclude the participant from the study.

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

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

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

Table 6-1. Clinical Laboratory Parameters

Category	Parameter
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol. The estimated glomerular filtration rate will be calculated by the central laboratory
Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration), white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count
Urinalysis	Urine dipstick for specific gravity, pH, protein, glucose, ketones, bilirubin, and blood; microscopic examination including red blood cells/high-power field, white blood cells/high-power field, and casts/low-power field
Coagulation	INR
Serology	At Visit -1 (De Novo EM Participants) and Visit 1 (3101-303-002 Completers) 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 (De Novo EM Participants) or Visit 1 (3101-303-002 Completers). Those with a positive result on the Visit -1 or Visit 1 urine drug screen for recreational (including marijuana, regardless of legality) or illicit drugs or nondisclosed concomitant medications are not allowed to be repeated. For all other positive results, the urine drug screen may be repeated with permission from 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 study participation.

IgM = immunoglobulin M; INR = International Normalized Ratio.

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

6.1.4 Vital Signs

Vital sign measurements, including sitting and standing BP, sitting and standing pulse rate, respiratory rate, temperature and weight, will be performed at every visit. Height will be measured only at Visit -1. 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).

6.1.5 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.

6.1.6 Electrocardiograms

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

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

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

ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS at Visits 2 through 13 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the ET (Visit 14) and the safety follow-up (Visit 15).

6.2 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 duration, headache characteristics, symptoms, and acute medication use, which will be collectively applied to define migraine days and headache days per the criteria listed in Sections 6.2.1, 6.2.2 and 6.2.3.

The AIM-D, Activity Level, and Activity Limitation will also be collected daily via an eDiary. Additional health outcome measures, namely, the Patient Satisfaction with Study Medication scale, HIT-6, MIDAS, PGIC, WPAI:MIGRAINE, EQ-5D-5L, PGI-S, and MSQ v2.1 will be administered in an eTablet at specified clinic visits.

6.2.1 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 two of the following 4 characteristics:

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

B. At least 1 of the following:

- Nausea and/or vomiting
- Photophobia and phonophobia
- 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 one criterion from (1) and at least one criterion from (2) **OR** fulfills at least two criteria from (1) and no criteria from (2).

    1) Headache characteristics:
        i. Unilateral location
        ii. Pulsating quality
        iii. Moderate or severe pain intensity
        iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
    2) Symptoms:
        i. Nausea and/or vomiting
        ii. Photophobia and phonophobia
        iii. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins

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

6.2.2 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).

6.2.3 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 eDiary.

6.3 Health Outcome Measures

6.3.1 Activity Impairment in Migraine - Diary (AIM-D)

The AIM–D is an 11-item PRO measure that assesses functioning and activity impairment in migraine patients. Participants are asked to rate the level of difficulty experienced in the past 24 hours with functioning and activity impairment (ie, difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, walking, moving body, bending forward, moving head, concentrating and thinking clearly) using the following 6point 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 2 domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (ie, higher disease burden).

6.3.2 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 scale 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 scale ranging from "Not at all limited – I could do everything" to "Extremely limited".

6.3.3 Patient Satisfaction with Study Medication

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).

6.3.4 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).

6.3.5 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, missed household work days, days at work or school plus days of household work where productivity was reduced by half or more, and missed non-work activity days due to headaches in the last 3 months.

6.3.6 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."

6.3.7 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 six questions related to work productivity. The WPAI measures both presenteeism and absenteeism. The measure yields four scores expressed as impairment percentages ranging from 0% to 100%: Percent work time missed, percent impairment while working, percent overall work impairment, and percent activity impairment due to migraine.

6.3.8 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, 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, visual analogue scale

where the endpoints are labeled "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).

6.3.9 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."

6.3.10 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.

6.4 Other Study Supplies

The following will be provided by Sponsor or Sponsor designee:

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

6.5 Summary of Methods of Data Collection

An IWRS will be used to manage atogepant inventory. All office visit data (ie, nondiary data) for this study will be collected by either the eTablet (eg, questionnaires for PROs) or eCRFs via an

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

All participants will use an eDiary daily to record the daily total duration of headache, headache characteristics, associated symptoms, the worst pain severity, acute medication use, AIM-D, Activity Level, and Activity Limitation during the open-label treatment period until Visit 14. Participants should begin using the eDiary as soon as it is dispensed and for the duration of the screening/baseline (for De Novo EM Participants) and treatment period (for all participants). Training for the eDiary will be provided for qualified participants during the first study visit (Visit -1 for De Novo EM Participants and Visit 1 for 3101-303-002 Completers).

7 Statistical Procedures

7.1 Analysis Populations

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

All efficacy analyses will be performed using the mITT population, consisting of participants who received at least 1 dose of study intervention (atogepant) in this study, an evaluable baseline (in this study for De Novo EM Participants or in the lead-in study for the rollover participants), and had at least 1 evaluable post-baseline 4-week period of eDiary data in this extension study.

7.2 Collection and Derivation of Efficacy Assessments

Since the primary objective of this study is to assess the long-term safety and tolerability of atogepant treatment, efficacy variables are not classified as primary, secondary, or additional.

Efficacy endpoints for long-term efficacy evaluation in the atogepant arm are listed below.

- Change from baseline in monthly migraine days at each monthly period
- Change from baseline in monthly headache days at each monthly period
- Change from baseline in monthly acute medication use days at each monthly period

- ≥ 25%, ≥ 50%, ≥ 75%, and 100% improvement (decrease) in monthly migraine days at each monthly period
- Change from baseline in monthly cumulative headache hours at each monthly period
- Change from baseline in monthly triptan use days at each monthly period
- Change from baseline in monthly moderate/severe headache days at each monthly period
- Change from baseline in monthly severe headache days at each monthly period
- Change from baseline in the HIT-6 total score at each monthly period
- At least a 5-point improvement (decrease) from baseline in total HIT-6 score at each monthly period
- Participants reporting "satisfied" or "extremely satisfied" with study medication for migraine prevention at each monthly period
- Rating of "much better" or "very much better" at Weeks 12, 24, 36, 48, and 52 assessed by the PGIC
- Change from baseline in percent work time missed, percent impairment while working, percent overall impairment, and percent activity impairment due to migraine at each monthly period as assessed by the WPAI:MIGRAINE
- Change from baseline in EQ-5D-5L descriptive system index score at each monthly period
- Change from baseline in the EQ-5D-5L VAS score at each monthly period
- Change from baseline in the MIDAS total score at Weeks 12, 24, 36, 48, and 52
- Change from baseline in MIDAS absenteeism score (Questions 1, 3, and 5) at Weeks 12, 24, 36, 48, and 52
- Change from baseline in MIDAS presenteeism score (Questions 2 and 4) at Weeks 12, 24, 36, 48, and 52
- Change from baseline in PGI-S at each monthly period

- Change from baseline in the MSQ v2.1 Role Function Preventive domain score at Weeks 12, 24, 36, 48, 52, and 56
- Change from baseline in the MSQ v2.1 Role Function Restrictive domain score at Weeks 12, 24, 36, 48, 52, and 56
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 12, 24, 36, 48, 52, and 56
- Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at each monthly period
- Change from baseline in monthly Physical Impairment domain score of the AIM-D at each monthly period
- Change from baseline in monthly AIM-D total score at each monthly period
- Change from baseline in monthly activity level at each monthly period
- Change from baseline in monthly activity limitation at each monthly period

7.3 Hypothesis and Methods of Analysis

7.3.1 Safety Analyses

The safety analyses will be performed using the safety population. The safety parameters will include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters and the C-SSRS. For each of the clinical, laboratory, vital sign, and ECG parameters, the baseline value in this extension study is defined as:

- The baseline value in the lead-in study (Study 3101-303-002) for 3101-303-002 Completers.
- The last nonmissing safety assessment before the first dose of study drug for De Novo EM Participants.

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.

7.3.2 Efficacy Analyses

The efficacy analyses will be based on the mITT population. For analysis purposes, four weeks (28 days) will be considered as 1 month.

For monthly endpoints, baseline in this extension study is defined as:

- The baseline value in the lead-in study (3101-303-002) for 3103-303-002 Completers
- The last 28 days of the screening/baseline period for De Novo EM Participants.

For efficacy endpoints that are assessed at clinical visits, baseline in this extension study is defined as:

- The last nonmissing efficacy assessment before the first dose of study intervention in the lead-in study (3101-303-002) for 3103-303-002 Completers
- The last nonmissing efficacy assessment before the first dose of study drug for De Novo EM Participants.

Monthly efficacy endpoints are defined in a prorated fashion. For example, monthly migraine days are defined as the total number of recorded migraine days in the eDiary divided by the total number of days with eDiary records during each monthly period and multiplied by 28.

Descriptive statistics will be provided by visit for all efficacy endpoints based on the mITT population using the OC approach. No inferential statistical analyses will be performed for the efficacy parameters unless otherwise specified in the Statistical Analysis Plan (SAP).

7.4 Subgroup Analyses

For selected safety and efficacy endpoints, analyses will be performed separately for 3101-303-002 Completers and De Novo EM Participants. Details will be provided in the SAP.

7.5 Sample Size Calculation

The study sample size was driven by regulatory safety requirements for the duration and number of participants exposed rather than statistical considerations. At least 170 participants will be enrolled into this long-term, open-label, safety extension study including at least 140 participants from the lead-in study (Study 3101-303-002) and approximately 30 De Novo EM Participants (from selected sites only) to meet a target of a minimum of 100 participants exposed to atogepant at 1 year.

7.6 Interim Analyses

No interim analyses are 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 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Participant Privacy

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

3101-303-002 Completers will maintain their lead-in study (Study 3101-303-002) participant identification number; this will serve as the participant identification number that will be used on all participant documentation throughout the study. For De Novo EM Participants, participant identification numbers will be newly assigned at study entry.

8.2 Washout Intervals/Run-in

This study will not include a washout period.

8.3 Procedures for Final Study Entry

For 3101-303-002 Completers:

- Participants will directly rollover from their lead-in study (Study 3101-303-002 [Phase 3 CM study]). As such, participants will have Visit 7 from the lead-in study function as Visit 1 for this study after the participant signs the informed consent. At Visit 1 participants must meet all of the inclusion criteria and must not meet any of the exclusion criteria.

- Note, there may be participants who complete Visit 7 in the lead-in study before extension Study 3101-306-002 has been initiated. Those participants should complete Visit 7/ET and Visit 8/EOS Visit (including discontinuation of study intervention) per the lead-in study Schedule of Visits and Procedures.

- Depending on the timing of the initiation of this extension study in relation to each participant's planned Visit 8 schedule in the lead-in study, Visit 1 for Study 3101-306-002 can be conducted on the same day as Visit 8/EOS Visit for the lead-in study, or soon thereafter.

- If this extension study is initiated prior to the participant's planned Visit 8 in the lead-in study, then Visit 8/EOS Visit for the lead-in study should be conducted on the same day as Visit 1 for Study 3101-306-002.

- If this extension study is not initiated prior to the participant's planned Visit 8 in the lead-in study (ie, there is a gap between Visit 8 and Visit 1), then Visit 8/EOS Visit should be conducted as planned per the lead-in study Schedule of Visits and Procedures. When this extension study is initiated, the participant should return to the clinic as soon as possible and Visit 1 should be conducted per the Study 3101-306-002 Schedule of Visits and Procedures.

For De Novo EM Participants:

- At Visit -1 (Screening/Baseline) and Visit 1, 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 (Section 4.6).

8.4 Visits and Associated Procedures

There will be a total of 15 scheduled clinic visits for 3101-303-002 Completers: Visit 1 (Day 1), Visit 2 (Week 4), Visit 3 (Week 8), Visit 4 (Week 12), Visit 5 (Week 16), Visit 6 (Week 20), Visit 7 (Week 24), Visit 8 (Week 28), Visit 9 (Week 32), Visit 10 (Week 36), Visit 11 (Week 40), Visit 12 (Week 44), Visit 13 (Week 48), Visit 14/ET (Week 52), and Visit 15/EOS. For details, please see Table 1, Schedule of Visit and Procedures.

There will be a total of 16 scheduled clinic visits for De Novo EM Participants: Visit -1, Visit 1 (Day 1), Visit 2 (Week 4), Visit 3 (Week 8), Visit 4 (Week 12), Visit 5 (Week 16), Visit 6 (Week 20), Visit 7 (Week 24), Visit 8 (Week 28), Visit 9 (Week 32), Visit 10 (Week 36), Visit 11 (Week 40), Visit 12 (Week 44), Visit 13 (Week 48), Visit 14/ET (Week 52), and Visit 15/EOS. For details, please see Table 1, Schedule of Visit and Procedures.

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

Visit -1 is to be performed for De Novo EM Participants only.

- Obtain informed consent and participant privacy.
- Register participant in IWRS.
- Collect demographic information.
- Collect medical history.
- Collect migraine/headache history and confirm diagnosis.
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Review and record prior medications taken in the past 6 months and all prior headache medications and concomitant medications.
- Assess C-SSRS on eTablet (the 'Screening/Baseline' assessment of the C-SSRS will be completed); the C-SSRS will be completed for the participant's lifetime history and for the 6 months prior to screening.
- Collect ASC-12 on eTablet.
- Perform physical examination.
- Collect 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.
- Perform and transmit ECG.
- Perform urine pregnancy test for WOCBP. Discuss the method of contraception with WOCBP and document this method. Counsel participants on the importance of maintaining their agreed upon method of contraception throughout the study.
- Collect blood and urine samples for clinical laboratory determinations (chemistry, hematology, INR, urinalysis, and serology).
- Collect urine sample for drug screen.

- Verify if the participant meets inclusion/exclusion criteria at this point.
- Provide eDiary, along with training and instructions. Participants to bring eDiary to all visits.

8.4.2 Open-label Treatment Period (52 Weeks)

8.4.2.1 Visit 1 (Day 1)

- Obtain informed consent and participant privacy (3101-303-002 Completers only).
- Register participant in IWRS (3101-303-002 Completers only).
- Review and update concomitant medications and concurrent procedures.
- Perform urine pregnancy test for WOCBP. Discuss the method of contraception with WOCBP and document this method. Counsel participants on the importance of maintaining their agreed upon method of contraception throughout the study.
- Perform and transmit ECG (3101-303-002 Completers only).
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, and weight).
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect medical history for participants who have a gap between the last visit of the lead-in study and Visit 1 of this extension study (3101-303-002 Completers only).
- Assess inclusion/exclusion criteria.
- Note: review of inclusion/exclusion criteria includes the review of eDiary data and compliance during Screening/Baseline for De Novo EM Participants.

If the participant continues to meet study entry criteria, including acceptable results from Visit 1 ECGs (3101-303-002 Completers only), pregnancy tests and vital sign measurements (see Section 6.1) the following procedures will be carried out at Visit 1.

- Prior to any other test or evaluations, administer the following PRO measures: HIT-6, PGI-S, WPAI:MIGRAINE, EQ-5D-5L, MIDAS, and MSQ v2.1.
- Perform physical examination.

- Collect blood and urine for clinical laboratory determinations including: chemistry, hematology, serology, coagulation parameters (INR), and urinalysis. (Note: serology samples to be collected for 3101-303-002 Completers only).
- Collect urine for drug screen (3101-303-002 Completers only).
- Review and assess AEs.
- Provide eDiary instructions and training (3101-303-002 Completers only).
- Access IWRS and obtain the kit number for atogepant bottle and dispense atogepant bottle.

8.4.2.2 Visits 2 to 13 (Weeks 4 to 48)

- Prior to any other test or evaluations, administer the following PRO measures:
    - HIT-6, PGI-S, WPAI:MIGRAINE, Patient Satisfaction with Study Medication, and EQ-5D-5L (at every visit).
    - PGIC, MIDAS and MSQ v2.1 at Visit 4 (Week 12), Visit 7 (Week 24), Visit 10 (Week 36), and Visit 13 (Week 48).
- Perform urine pregnancy test for women of childbearing potential.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, and weight).
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Perform and transmit ECG (Visit 4 [Week 12], Visit 7 [Week 24] and Visit 10 [Week 36] only).
- Collect previous visit atogepant bottle, review participant compliance and perform accountability.
- Review and assess AEs.
- Review and update concomitant medications and concurrent procedures.

- Review eDiary data and compliance.
- Access IWRS to dispense atogepant bottle and enter accountability.

8.4.2.3 Visit 14/Early Termination (Week 52)

Effort should be made by the site to not schedule Visit 14 earlier than 52 weeks after Day 1, to ensure participants complete the full 52 weeks of atogepant and have eDiary data through Day 364.

- Prior to any other test or evaluations, administer the following PRO measures: HIT-6, PGIC, PGI-S, WPAI:MIGRAINE, Patient Satisfaction with Study Medication, EQ-5D-5L, MIDAS, and MSQ v2.1.
- Perform physical examination.
- Perform urine pregnancy test for women of childbearing potential.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, and weight).
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Perform and transmit ECG.
- Review and assess AEs.
- Review and update concomitant medications and concurrent procedures.
- Review eDiary data and compliance.
- Collect eDiary.
- Collect previous visit atogepant bottle, review participant compliance and perform accountability.
- Access IWRS to enter study visit and accountability.

8.4.3 Safety Follow-up Period (4 Weeks)

8.4.3.1 Visit 15/End of Study (Week 56)

- Prior to any other test or evaluations, administer the following PRO measures: HIT-6, EQ-5D-5L and MSQ v2.1.
- Perform physical examination.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, and weight).
- Perform urine pregnancy test for women of childbearing potential.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Review and assess AEs.
- Update concomitant medications and concurrent procedures.
- Access IWRS to enter study visit.

8.4.4 COVID-19 Pandemic-related Remote Visits

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 2) will be followed. After Visit 1, remote study visits may be performed for up to 8 weeks at the discretion of the investigator after which, participants who cannot attend in-person for a study visit must discontinue from the study. Missed in-person safety assessments (ie, clinical laboratory samples, vital signs and ECGs) should be collected at the next in-person visit. If available, PROs will be collected using a web-based portal during remote visits.

8.5 Instructions for the Participants

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

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

prohibited medications should be reviewed with the participants. Participants will be instructed to bring their eDiary to each clinic visit and return their atogepant bottle(s), both used and unused.

Participants should be instructed to take atogepant 60 mg once daily at approximately the same time each day (approximately 24 hours between doses). 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 (Section 4.5.3).

8.6 Unscheduled Visits

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

8.7 Compliance with Protocol

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

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

8.8 Early Discontinuation of Participants

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

- AE
- Lack of efficacy
- Lost to follow-up
- Noncompliance with study intervention (ie, atogepant)

- 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 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 14/ET and Visit 15/EOS; 4 weeks after the last dose of atogepant.

8.9 Withdrawal Criteria

Study 3101-303-002 Completers with the following at Visit 1 must be withdrawn from the study:

- Laboratory Results:
    - ALT or AST > 1 x ULN OR
    - Total bilirubin > 1 x ULN (except for participants with a diagnosis of Gilbert's disease) OR
    - Serum albumin < 2.8 g/dL
    - Positive result on the urine drug screen unless explained by concomitant medication use (eg, opioids prescribed for migraine pain).
    - Positive result on anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti-hepatitis C antibody, or anti-hepatitis E IgM antibody testing.
- ECG Results:
    - QTcF > 450 msec for males and QTcF > 470 msec for females on the final central vendor ECG report
    - Clinically significant cardiac rhythm or conduction abnormalities (eg, atrial fibrillation, second- or third-degree heart block)

Participants must be withdrawn from the study if they meet any of the following at any study visit:

- Female participants who become pregnant (Section 9.4)
- Participants who meet atogepant discontinuation criteria related to abnormal liver function tests (Section 9.5), and advised not to be rechallenged, will be withdrawn from the study and should refrain from taking atogepant.
- Participants who reply with "yes" to questions 4 or 5 in the suicidal ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS at Visits 2 through 13 must be withdrawn from the study.
- A participant with a condition and/or a situation that, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study should be withdrawn from treatment.

All withdrawn participants should receive appropriate follow-up as in routine clinical practice, including the ET (Visit 14) and the EOS (Visit 15) assessments.

8.10 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. 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 eCRF. If AEs occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical study participant associated with the use of atogepant, whether or not considered related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of atogepant. In addition, during the screening period and Visit 1, AEs will be assessed regardless of the administration of a pharmaceutical product.

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

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

All AEs from the signing of the ICF until the EOS visit (Visit 15), or 30 days after the last dose of atogepant if the EOS visit is not done, will be collected at the timepoints specified in the Schedule of Visits and Procedures (Table 1), and as observed or reported spontaneously by study participants.

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

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

9.1.2 Serious Adverse Event

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

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

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

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

Any preplanned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the participant's entry into the study. If it has not been documented at the time of the participant's entry into the study, then it should be documented as a SAE and reported to 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 1 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	
1.	The investigator is obligated to assess the relationship between atogepant medication and each occurrence of each AE or SAE.
2.	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.
3.	The investigator will use clinical judgment to determine the relationship.
4.	Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to atogepant administration will be considered and investigated.
5.	The investigator will also consult the investigator's brochure in his/her assessment.
6.	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.
7.	There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to 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 Sponsor.**
8.	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.
9.	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 nonserious AEs of special interest (as defined in Section 6.1.2) 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 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 healthcare professionals.

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

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

9.2 Procedures for Reporting Adverse Events

All AEs must be recorded on the appropriate eCRF.

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

9.3 Procedures for Reporting a Serious Adverse Event

Any SAE occurring during the study period (beginning with informed consent) until the EOS visit (Visit 15) or 30 days after the last dose of atogepant if the EOS visit is not done must be immediately reported but no later than 24 hours after learning of an SAE. SAEs must be reported to Sponsor as listed on the Sponsor 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 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 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 (ie, atogepant) under clinical investigation are met. For Japan, the investigator must promptly report the SAE to the head of the study center.

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

- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor 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 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 atogepant and until the EOS visit (Visit 15) or 30 days after the last dose of atogepant if the EOS visit is not done. Study center personnel must report every pregnancy on the Pregnancy Form (within 24 hours of learning of the pregnancy to the Serious Adverse Event Reporting Fax Number[s]: +1-714-796-9504 [back-up fax number: +1-714-246-5295], email: IR-Clinical-SAE@allergan.com), even if no AE has occurred. The pregnancy must be followed to term and the outcome reported by completing a follow-up Pregnancy Form. Abnormal pregnancy outcomes (eg, spontaneous 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 AESI. Any participant with this laboratory result after atogepant was taken must have repeat testing within 48 to 72 hours to confirm the abnormality. For this repeat testing, the following laboratory tests must be performed: hematology and chemistry panels, INR, serum acetaminophen level, urine drugs of abuse screen, and blood alcohol level. A 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 AESIs must be reported to 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 AESI.

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 Sponsor medical personnel. In general, the chemistry panel should be repeated 1 to 2 times per week to follow the course of ALT/AST elevation.

Atogepant must be discontinued if any of the following criteria are met:

- ALT or AST ≥ 3 × ULN and the participant is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
- ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN
- ALT or AST ≥ 3 × ULN and INR > 1.5
- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

The participant may be rechallenged with atogepant only after consultation with the Sponsor Medical Monitor. For participants who are not rechallenged, the participant should be discontinued from the study and complete an ET visit and an EOS Visit 4 weeks later. Participants should receive appropriate follow-up as per standard of care.

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

9.5.1 Potential Hy's Law Cases

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

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

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

A laboratory alert for possible Hy's law cases will be in place and must notify investigators and Sponsor immediately when the above criteria have been met. A possible Hy's law case must be faxed to 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 SAE/Pregnancy fax number, even if no AE has occurred. If the event is serious, please complete the AESI/SAE form. The eCRF for possible Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the Medical Monitor and Medical Safety Physician and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. The participant should return to the study site and be evaluated as soon as possible, preferably within 48 hours from the time the investigator becomes aware of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

10 Administrative Items

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

10.1 Protection of Human Participants

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

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

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

- If the results of the study are published, the participant's identity will remain confidential.
- The anticipated expenses, if any, to the participant for participating in the study
- The anticipated prorated payment, if any, to the participant for participating in the study
- The name, title, and address of the investigator to contact
- The person(s) to contact for further information regarding the clinical study and the rights of participants, and whom to contact in the event of study-related injury
- The type of the IRB engaged in the assessment and deliberation about the acceptability of the study, items subject to the assessment of each IRB, and other IRB-related items relating to the study
- The participant's responsibilities

10.1.2 Compliance with IRB or IEC Regulations

- This protocol is to be conducted in accordance with ethical principles based on the Declaration of Helsinki and the guidance stipulated in Article 14, Paragraph 3 and Article 80-2 of the Pharmaceutical Affairs Law, MHW Ordinance on Good Clinical Practice (MHW Ordinance No 28 [27 Mar 1997]).
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the head of the study center, and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:

    1. Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    2. Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

3. This study is to be conducted in accordance with IRB regulations. The investigator must obtain approval from a properly constituted IRB prior to initiating the study and reapproval or review at least annually. Allergan Japan K.K. (a subsidiary of AbbVie) is to be notified immediately if the responsible IRB has been disqualified or if procedures leading to disqualification have begun. Copies of all IRB correspondence with the investigator should be provided to Allergan Japan K.K (a subsidiary of AbbVie).

10.1.3 Compliance with Good Clinical Practice

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

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

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

10.2 Financial Disclosure

Investigators and subinvestigators will provide Sponsor with sufficient, accurate financial information as requested to allow 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 to the protocol without approval by Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study participants, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.4 Data Protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to 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 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 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 Sponsor 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.

10.5.1 Participant Privacy

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

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

10.6 Documentation

10.6.1 Source Documents

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

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

- Participant's name
- Participant's contact information

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

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

10.6.2 Case Report Form Completion

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

10.6.3 Study Summary

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

10.6.4 Retention of Documentation

Allergan Japan K.K. (a subsidiary of AbbVie) requires that it be notified in writing if the head of the study site 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.

Study Site

The study site should retain the essential documents to be kept at the study site, such as source documents, contracts, informed consent form, protocol, records on control of the study intervention, or other study-related documents until either item 1 or 2 listed below, whichever is later. However, when the sponsor requires that these documents are to be retained for a longer period, the study site should discuss with Allergan Japan K.K. (a subsidiary of AbbVie) the period and method of preservation. The record retainer designated for each record should be responsible for the preservation.

1. The date of approval for manufacturing and marketing applications of the relevant study interventions (in case of discontinuing its development, until at least 3 years after the date of development discontinuation)

2. At least 3 years after the date of termination or completion of the clinical study

The study site and the record retainer should take measures in such a way that these records are not lost or abandoned during the designated period of preservation and that they are presented upon request.

Institutional Review Board

The IRB should retain all relevant records such as SOPs, membership lists (including qualifications of the members), submitted documents, minutes of meetings, and correspondence until either item 1 or 2 listed below, whichever is later. However, when it is necessary to retain longer by Allergan Japan K.K. (a subsidiary of AbbVie), the organizer should discuss with Allergan Japan K.K. (a subsidiary of AbbVie) the period and method of retaining, and make them available upon request from the regulatory authorities.

1. The date of approval for manufacturing and marketing applications of the relevant study interventions (in case of discontinuing its development, until at least 3 years after the date of development discontinuation)

2. At least 3 years after the date of termination or completion of the clinical study

When the study site or the sponsor requests the SOPs and membership lists, the IRB should comply with the request.

Sponsor (Allergan Japan K.K. [a subsidiary of AbbVie])

The sponsor should retain the relevant essential documents until the day specified in item 1 or 2 listed below, whichever is later.

3. At least 5 years after the date of approval for manufacturing and marketing applications of the relevant study intervention (or, in case of a study intervention for which development is prematurely terminated, 3 years after the date on which the termination of development was decided). When the sponsor is required to conduct reexamination for an approved drug, the sponsor must store all GCP study documents until 5 years after approval or reexamination finish, whichever is later.

4. At least 3 years after the date of the premature termination or completion of the clinical study

When the essential documents to be retained by the study site or by the IRB no longer need to be kept, the sponsor should notify the study site and IRB of this fact.

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

10.7.1 Labeling/Packaging

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

10.7.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Sponsor, dispensed or administered to the participants, the number of units returned to the investigator by the participant, and the number of units returned to Sponsor

during and at the completion of the study. A detailed inventory must be completed for atogepant. Atogepant must be dispensed or administered only by an appropriately qualified person to participants in the study. Atogepant is to be used in accordance with the protocol for participants who are under the direct supervision of an investigator.

10.7.3 Return or Disposal of Study Intervention and/or Supplies

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

10.8 Monitoring by the Sponsor

A representative of 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 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.

10.9 Handling of Biological Specimens

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

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

All samples will be returned to Sponsor or Sponsor's designee for destruction. 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.

10.10 Publications

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, Allergan Japan K.K. (a subsidiary of AbbVie), or the governing health

authorities (ie, PMDA) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.11 Coordinating Investigator

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

11 References

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12 Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques: International Classification of Headache Disorders, 3rd Edition

- Migraine
  - Migraine without aura
  - Migraine with aura
    - Migraine with typical aura
      - Typical aura with headache
      - Typical aura without headache
    - Migraine with brainstem aura
    - Hemiplegic migraine
      - Familial hemiplegic migraine (FHM)
        - Familial hemiplegic migraine type 1 (FHM1)
        - Familial hemiplegic migraine type 2 (FHM2)
        - Familial hemiplegic migraine type 3 (FHM3)
        - Familial hemiplegic migraine, other loci
      - Sporadic hemiplegic migraine (SHM)
    - Retinal migraine
  - Chronic migraine
  - Complications of migraine
    - Status migrainosus
    - Persistent aura without infarction
    - Migrainous infarction
    - Migraine aura-triggered seizure
  - Probable migraine
    - Probable migraine without aura
    - Probable migraine with aura
  - Episodic syndromes that may be associated with migraine
    - Recurrent gastrointestinal disturbance
      - Cyclical vomiting syndrome
      - Abdominal migraine
    - Benign paroxysmal vertigo
    - 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 disorder. 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:

- At least five attacks[1] fulfilling criteria B–D
- Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)[2,3]
- Headache has at least two of the following four characteristics:
  - unilateral location
  - pulsating quality
  - moderate or severe pain intensity
  - aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
- During headache at least one of the following:
  - nausea and/or vomiting
  - photophobia and phonophobia
- 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 path- ways, and the possibility that attacks may originate in the central nervous system, have gained increasing attention over the last decades.

At the same time, the circuitry of migraine pain, the trigeminovascular system, and several aspects of its neurotransmission peripherally and in the trigeminal nucleus caudalis, central mesencephalic grey and thalamus, have been recognized. Highly receptor-specific acute medications including 5-$HT_{1B/D}$ 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 provide 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 studies 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:

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

Notes:

- 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.
- Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.
- Scintillations and pins and needles are positive symptoms of aura.

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

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

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

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

Next in frequency are sensory disturbances, in the form of pins and needles moving slowly from the point of origin and 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 headache that does not fulfill criteria for 1.1 *Migraine without aura*, but this is still regarded as a migraine headache because of its relation to the aura. In other cases, migraine aura may occur without headache.

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

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

Prodromal symptoms may begin hours or a day or two before the other symptoms of a migraine attack with aura. They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light and/or sound, nausea, blurred vision, yawning and pallor. The term 'prodrome', which has replaced 'premonitory 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:

1. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
2. Aura with both of the following:
    a. fully reversible visual, sensory and/or speech/ language symptoms
    b. 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 headache with or without migraine characteristics.

Diagnostic criteria:

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

1.2.1.2 Typical aura without headache

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

Diagnostic criteria:

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

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

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

prolonged or very short, other causes, particularly transient ischaemic attacks, should be ruled out.

1.2.2 Migraine with brainstem aura

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

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

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
B. Aura with both of the following:
   - at least two of the following fully reversible brainstem symptoms:
     - dysarthria[1]
     - vertigo[2]
     - tinnitus
     - hypacusis[3]
     - diplopia[4]
     - ataxia not attributable to sensory deficit
     - decreased level of consciousness (GCS ≤13)[5]
   - 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:

1. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
2. Aura consisting of both of the following:
   - fully reversible motor weakness[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 weakness, and at least one first- or second-degree relative has migraine aura including motor weakness.

Diagnostic criteria:

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

Comments: New genetic data have allowed a more precise definition of 1.2.3.1 *Familial hemiplegic migraine* than was previously possible. Specific genetic subforms have been identified: in FHM1 there are mutations in the *CACNA1A* gene (coding for a calcium channel) on chromosome 19; in FHM2 there are mutations in the *ATP1A2* gene (coding for a K/Na-ATPase) on chromo- some 1; and in FHM3 there are mutations in the *SCN1A* gene (coding for a sodium channel) on chromosome 2. There may be other loci not yet identified. When genetic testing is done, the genetic subform (if discovered) should be specified at the fifth digit.

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

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

1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)

Diagnostic criteria:

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

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

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

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

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

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

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

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

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

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

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

1.2.3.2 Sporadic hemiplegic migraine (SHM)

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

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*

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

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

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

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

1.2.4 Retinal migraine

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

Diagnostic criteria:

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

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

- Headache (migraine-like or tension-type-like[1]) on 15 days/month for >3 months, and fulfilling criteria B and C
- 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*
- On 8 days/month for >3 months, fulfilling any of the following[2]:
  - criteria C and D for 1.1 *Migraine without aura*
  - criteria B and C for 1.2 *Migraine with aura*
  - believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
- Not better accounted for by another ICHD-3 diagnosis.[3–5]

Notes:

A. 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).

B. 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.

C. 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.

D. 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*.

E. 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:

- Remissions of up to 12 hours due to medication or sleep are accepted.
- Milder cases, not meeting criterion C2, are coded

1.5.1 *Probable migraine without aura.*

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

1.4.2 Persistent aura without infarction

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

Diagnostic criteria:

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

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

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

1.4.3 Migrainous infarction

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

Diagnostic criteria:

1 A migraine attack fulfilling criteria B and C
2 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]
3 Neuroimaging demonstrates ischaemic infarction in a relevant area
4 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 subtype 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 headache disorder

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

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

1.5.1 Probable migraine without aura Diagnostic criteria:

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

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

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

1.5.2 Probable migraine with aura

Diagnostic criteria:

1. Attacks fulfilling all but one of criteria A–C for 1.2 M*igraine with aura* or any of its subtypes
2. Not fulfilling ICHD-3 criteria for any other headache disorder
3. 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:

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

1.6.1.1 Cyclic vomiting syndrome

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

Diagnostic criteria:

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

Note:

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

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

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

1.6.1.2 Abdominal migraine

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

Diagnostic criteria:

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

Note:

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

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

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

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

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

1.6.2 Benign paroxysmal vertigo

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

Diagnostic criteria:

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

Notes:

- 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.

- 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:

1. Recurrent attacks[1] in a young child, fulfilling criteria B and C
2. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days
3. At least one of the following five associated symptoms or signs:
   - pallor
   - irritability
   - malaise
   - vomiting
   - ataxia[2]
4. Normal neurological examination between attacks
5. 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 Prohibited Medications

12.2.1 Examples of Prohibited Medications

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

- Strong OATP1B1 inhibitors eg, gemfibrozil[a], cyclosporine
- CBD oil

	Strong/moderate CYP3A4 inducers	Strong/moderate CYP3A4 inhibitors
Anti-depressants/ Anti-anxiety	Barbiturates Amobarbital Aprobarbital[a] Butalbital[a] Butabarbital[a] Mephobarbital[a] Pentobarbital Phenobarbital Secobarbital	Nefazodone[a]
Anti-seizure	Carbamazepine Oxcarbazepine[a] Phenytoin Primidone	
Diabetes	Pioglitazone Troglitazone[a]	
Antiemetic		Aprepitant
Anti-hypertension		Diltiazem Verapamil
Glucocorticoid (Systemic)	Betamethasone Dexamethasone Hydrocortisone Methylprednisolone Prednisolone Prednisone[a] Triamcinolone	
Antibiotics	Rifabutin Rifampicin/Rifampin[a]	Erythromycin Clarithromycin Telithromycin[a] Ciprofloxacin
Anti-fungal		Fluconazole Itraconazole Ketoconazole
Anti-HIV	Efavirenz Nevirapine	Indinavir Nelfinavir Ritonavir Saquinavir
Immune Suppressant		Cyclosporine - Oral/IV only
Antacid/heartburn		Cimetidine

	Strong/moderate CYP3A4 inducers	Strong/moderate CYP3A4 inhibitors
Other	St John's wort Enzalutamide Modafinil Armodafinil[a]	Buprenorphine Quinine

Drugs with narrow therapeutic margins with potential for CYP drug interactions	Warfarin Digoxin Cisapride[a] Pimozide
Nonpharmacologic headache interventions	Acupuncture Noninvasive 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 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)

a Not approved in Japan.

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

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

12.2.2 List of Migraine Preventative Medications With Proven Efficacy and Criteria for Determining Inadequate Response to a Prior Migraine Preventive Medication

Medications with demonstrated efficacy for the prevention of migraine are prohibited for all participants for 30 days prior to the first study visit and throughout the study, excepting 1 medication with demonstrated efficacy for the prevention of migraine taken at a stable dose and well-tolerated during Study 3101-303-002. This medication which may be continued if the participant is willing and able to do so.

Below is a list of migraine preventative medications considered effective or probably effective sorted by mechanism of action during Study 3101-303-002.

Pharmacologic Category	**Drug Name**
Antiepileptic	Valproic acid, sodium valproate, divalproex sodium[a] Topiramate
Tricyclic antidepressant	Amitriptyline Nortriptyline
Beta-blockers	Metoprolol Bisoprolol Atenolol Nadolol Propranolol Timolol[a]
Calcium channel blocker	Flunarizine[a], lomerizine, verapamil
Angiotensin receptor blocker (ARB)	Candesartan
Angiotensin-converting enzyme (ACE) inhibitor	Lisinopril
Serotonin-norepinephrine reuptake inhibitor (SNRI)	Desvenlafaxine[a] Venlafaxine
Miscellaneous	Pizotifen[a]

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

a Not approved in Japan.

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

For efficacy:

- 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 judgment and participant interview.
- Medications must have been started within the past 7 years.

For tolerability:

- 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.

12.3 New York Heart Association Functional Classification

The table below describes the New York Heart Association Functional Classification system (adapted from Criteria Committee NY Heart Association 1994). It places patients in 1 of 4 categories based on how much they are limited during physical activity.

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

12.4 Glossary of Abbreviations

Term/Abbreviation	Definition
ASC-12	12-item Allodynia Symptom Checklist
AE	adverse event
AESI	adverse event of special interest
AIM-D	Activity Impairment in Migraine - Diary
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CBD	Cannabidiol,
CGRP	calcitonin gene-related peptide
CGRP-RA	calcitonin gene-related peptide-receptor antagonist
CM	chronic migraine
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A4	cytochrome P450 3A4
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EM	episodic migraine
EOS	end of study
EQ-5D-5L	European Quality of Life - 5 Dimensional
ET	early termination
eTablet	electronic tablet
FDA	Food and Drug Administration
GBD2010	Global Burden of Disease Survey 2010
GCP	Good Clinical Practice
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HIT-6	Headache Impact Test
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders, 3rd edition
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IRB	institutional review board

Term/Abbreviation	Definition
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWRS	interactive web response system
LSMD	least squares mean
MIDAS	Migraine Disability Assessment
mITT	modified intent-to-treat
MSQ v2.1	Migraine Specific Quality of Life Questionnaire, Version 2.1
NSAID	nonsteroidal anti-inflammatory drug
OATP1B1	organic anion transporting polypeptide 1B1
OC	observed cases
PCR	polymerase chain reaction
PGIC	Patient Global Impression of Change
PGI-S	Patient Global Impression – Severity
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	patient-reported outcome
QTcF	QT interval corrected for heart rate using Fridericia formula (QTcF = $QT/(RR)^{⅓}$)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SNRI	serotonin norepinephrine reuptake inhibitor
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
V	Visit
VAS	Visual Analogue Scale
Wk	Week
WOCBP	women of childbearing potential
WPAI:MIGRAINE	Work Productivity and Activity Impairment Questionnaire: Migraine V2.0

12.5 Protocol Amendment 1 Summary

Title: A PHASE 3, MULTICENTER, OPEN-LABEL 52-WEEK EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN JAPANESE PARTICIPANTS WITH CHRONIC OR EPISODIC MIGRAINE

Protocol 3101-306-002

Date of Amendment 1: 25th November 2019

Amendment Summary

This amendment includes changes made to Protocol 3101-306-002, dated 15 October 2019. This protocol was amended to clarify Japan-specific approvals and to correct minor editorial errors.

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

Section	Revision	Rationale
4.5.3 Definition of (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods:	Footnotes amended to clarify contraceptive methods not approved in Japan	Clarification
Section 12.2.1 Examples of Prohibited Medications	Indication of specified medications that are not approved in Japan	Clarification
12.2.2 List of Migraine Preventative Medications With Proven Efficacy *(Text above Table)*	Below is a list of migraine preventative medications considered effective or probably effective sorted by mechanism of action **during Study 3101-303-002.** ~~Of note, topiramate and valproic acid derivatives are considered separate categories.~~	Clarification
12.2.2 List of Migraine Preventative Medications With Proven Efficacy *(Table)*	Indication added of specified medications that are not approved in Japan	Clarification

12.6 Protocol Amendment 2 Summary

Title: A PHASE 3, MULTICENTER, OPEN-LABEL 52-WEEK EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN JAPANESE PARTICIPANTS WITH CHRONIC OR EPISODIC MIGRAINE

Protocol 3101-306-002

Date of Amendment 2: 22 December 2021

Amendment Summary

This amendment includes changes made to Protocol 3101-306-002 Amendment 1, dated 25 November 2019. This protocol was amended to add De Novo EM Participants and to correct minor editorial errors.

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

Section	Revision	Rationale
Title Page	*Left cell:* Allergan **(AbbVie Company)** Signatory: *Right cell:* [redacted], ~~Clinical~~ **Neuroscience** Development	Allergan was acquired by AbbVie.
Protocol Summary	Updated.	To reflect changes in the body of the protocol.
Table 1 Schedule of Visits and Procedures	Updated.	To reflect changes in the body of the protocol.
Table 2 Schedule of Procedures for Remote Visits *(Amendment 2 table)*	New table was added.	To outline remote visit procedures in the event of a COVID-19 infection.
1.2 Overview of Atogepant	Recent study results and approval of atogepant for the preventive treatment of EM in adults were added.	To reflect the current status of the atogepant program.

Section	Revision	Rationale
3.1 Structure	Updated.	To reflect addition of De Novo EM Participants, which created 2 cohorts (De Novo EM Participants and 3101-303-002 Completers), a 4-week screening/baseline period for De Novo EM Participants only, and a larger sample size (changed from 140 participants to 170 participants [30 De Novo EM Participants enrolled at selected sites only]). All references to lead-in Study 3101-305-002 were removed from the protocol.
3.2 Data Safety Monitoring Board	Updated.	To reflect the involvement of a DSMB.
4.1 Number of Participants	Updated.	To reflect addition of De Novo EM Participants.
4.2 Study Population Characteristics	Updated.	To reflect the 2 cohorts.
4.3.1 Inclusion Criteria	Updated.	To reflect inclusion criteria applicable for all participants.
4.3.2 3101-303-002 Completers *(Amendment 2 section)*	New section was added.	To reflect inclusion criteria for 3101-303-002 Completers only.
4.3.3 De Novo EM Participants *(Amendment 2 section)*	New section was added.	To reflect inclusion criteria for De Novo EM Participants only.
4.4 Exclusion Criteria	Updated.	To reflect exclusion criteria applicable for all participants (unless noted otherwise).
4.4.1 De Novo EM Participants *(Amendment 2 section)*	New section was added.	To reflect exclusion criteria applicable for De Novo EM Participants.
4.6 Screen Failures	Updated.	To allow rescreening of screen failures for De Novo EM Participants.
5.5 Method for Assignment to Treatment Groups	**For De Novo EM Participants, participant identification numbers will be newly assigned at study entry.**	To account for De Novo EM Participants.
5.6 Treatment Regimen and Dosing	Updated.	To incorporate Visit -1 for De Novo EM Participants only.
6.1.3 Clinical Laboratory Determinations	Updated.	To incorporate Visit -1 for De Novo EM Participants only and to clarify Visit 1 serology and urine drug screen are for 3101-303-002 Completers only.

Section	Revision	Rationale
Table 6-1 Clinical Laboratory Parameters	Updated.	To incorporate Visit -1 for De Novo EM Participants only and to clarify Visit 1 serology and urine drug screen are for 3101-303-002 Completers only.
6.1.4 Vital Signs	Vital sign measurements, including sitting and standing BP, sitting and standing pulse rate, respiratory rate, temperature and weight, will be performed at every visit. **Height will be measured only at Visit -1.**	For clarification.
6.1.7 Columbia-Suicide Severity Rating Scale (C-SSRS)	**At Visit -1 (Screening/Baseline, De Novo EM Participants only), the C-SSRS will be completed for the participant's lifetime history and for the 6 months prior to screening.**	To account for De Novo EM Participants.
6.3.1 Activity Impairment in Migraine – Diary (AIM-D)	**In addition to the 2 domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (ie, higher disease burden).**~~AIM-D scores range from 0 to 5 with higher scores indicating greater impact in functioning and activity impairment.~~	For clarification.
7.1 Analysis Populations	All efficacy analyses will be performed using the mITT population, consisting of participants who received at least 1 dose of study intervention (atogepant) in this study**, an evaluable baseline (for the De Novo EM Participants),** and had at least 1 evaluable post-baseline 4-week period of eDiary data in this extension study.	To account for De Novo EM Participants.

Section	Revision	Rationale
7.2 Collection and Derivation of Efficacy Assessments	The efficacy endpoints of change from baseline in monthly headache-free days, and headache day pain intensity at each monthly period were removed from the protocol. The efficacy endpoints of participants reporting "satisfied" or "extremely satisfied" with study medication for migraine prevention and change from baseline in monthly AIM-D total score at each monthly period were added. Other edits include: 1 Change from baseline in the MSQ v2.1 Role Function Preventive domain score at Weeks 12, 24, 36, 48, ~~and~~ 52**, and 56** 2 Change from baseline in the MSQ v2.1 Role Function Restrictive domain score at Weeks 12, 24, 36, 48, ~~and~~ 52**, and 56** 3 Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 12, 24, 36, 48, ~~and~~ 52**, and 56** 4 Change from baseline in ~~AIM-D~~ monthly ~~functioning~~ **Performance of Daily Activities domain score of the AIM-D at each monthly period** 5 **Change from baseline in ~~and~~ monthly Physical Impairment domain score of the AIM-D** ~~and activity impairment score~~ at each monthly period	No longer completing these measures. For clarification.
7.3.1 Safety Analyses	Definition of baseline value was edited.	To account for De Novo EM Participants and for clarification.
7.3.2 Efficacy Analyses	Definition of baseline value was edited.	To account for De Novo EM Participants and for clarification.
7.4 Subgroup Analyses	**For selected safety and efficacy endpoints, analyses will be performed separately, for 3101-303-002 Completers and De Novo EM Participants. Details will be provided in the SAP.** ~~No subgroup analysis is planned.~~	For clarification.

Section	Revision	Rationale
7.5 Sample Size Calculation	Updated.	To reflect addition of De Novo EM Participants
8.1.2 Informed Consent and Participation Privacy	Updated.	To incorporate Visit -1 and assignment of participant identification numbers for De Novo EM Participants.
8.3 Procedures for Final Study Entry	Updated.	To incorporate Visit -1 and clarified Visit 1 study entry procedures applicable to 3101-303-002 Completers only.
8.4 Visits and Associated Procedures	Updated.	To clarify the visits for the 2 cohorts.
8.4.1 Visit -1 (Screening/Baseline) Day -35 to Day -28 *(Amendment 2 section)*	New section was added.	To detail Visit -1 procedures.
8.4.2.1 Visit 1 (Day 1) *(Amendment 2 section)*	Updated.	To clarify which Visit 1 procedures are for 3101-303-002 Completers only and that review of eligibility criteria includes the review of eDiary data and compliance during Screening/Baseline for De Novo EM Participants.
8.4.4 COVID-19 Pandemic-related Remote Visits *(Amendment 2 section)*	New section was added.	To outline remote visit procedures in the event of a COVID-19 infection.
8.9 Withdrawal Criteria	Updated.	To reflect withdrawal criteria pertaining to 3101 303-002 Completers only with the addition of positive result on anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti-hepatitis C antibody, or anti-hepatitis E IgM antibody testing.
11 References	Criteria Committee of the New York Heart Association reference was added.	As needed for De Novo EM Participants exclusion criteria.
Section 12.2.2 List of Migraine Preventative Medications With Proven Efficacy **and Criteria for Determining Inadequate Response to a Prior Migraine Preventive Medication** *(Amendment 2 section)*	Updated.	To include criteria for determining inadequate response to a prior migraine preventive medication and to add ciprofloxacin.
Section 12.3 New York Heart Association Functional Classification *(Amendment 2 section)*	New attachment was added to describe the New York Heart Association Functional Classification system.	As needed for De Novo EM Participants exclusion criteria.

12.7 Protocol Amendment 3 Summary

Title: A PHASE 3, MULTICENTER, OPEN-LABEL 52-WEEK EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN JAPANESE PARTICIPANTS WITH CHRONIC OR EPISODIC MIGRAINE

Protocol 3101-306-002

Date of Amendment 3: 07 July 2022

Amendment Summary

This amendment includes changes made to Protocol 3101-306-002 Amendment 2, dated 22 December 2021. This protocol was amended to correct Visit 1 to Visit -1 for select inclusion and exclusion criteria; clarify the visits associated with eDiary training, permissible and prohibited medications language, and discussion of the method of contraception with WOCBP; update consent of participants aged 18 or 19 and the Sponsor name; incorporate formatting edits from protocol administrative change 1, dated 17 February 2022; and correct minor editorial errors.

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

Section	Revision	Rationale
Global change	"(a subsidiary of AbbVie" was added after "Allergan" or "Allergan" was changed to "Sponsor" as applicable.	Allergan was acquired by AbbVie
Protocol Summary and Section Section 4.3.3 De Novo EM Participants	History of 4 to 14 migraine days per month (see Section 6.2.1 for definition of migraine day) on average in the 3 months prior to Visit -1 in the investigator's judgment.	Corrected Visit 1 to Visit -1
Protocol Summary and Section 4.4.2 De Novo EM Participants	Has ≥ 15 headache days per month (see Section 6.2.2 for definition of headache day) on average across the 3 months prior to Visit -1 in the investigator's judgment.	Corrected Visit 1 to Visit -1

Section	Revision	Rationale
Protocol Summary and Section 4.4.2 De Novo EM Participants	Usage of opioids or barbiturates > 2 days/month, triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, NSAIDs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit **-**1 per investigator's judgment or during the baseline period (barbiturates are excluded 30 days prior to screening and through the duration of the study) (see Section 12.2.1).	Corrected Visit 1 to Visit -1
Section 4.4.2 De Novo EM Participants	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~~).	Corrected as this is an open-label study with no placebo.
Table 1. Schedule of Visits and Procedures	Participant eDiary data collection was extended to include Visit -1.	Clarification
Global change (Table 1. Schedule of Visits and Procedures footnote c, Section 4.3.1 All Participants, Section 8.1.2 Informed Consent and Participant Privacy, Section 8.4.1 Visit -1 [Screening/Baseline] Day -35 to Day -28), and Section 10.5.1 Participant Privacy	Consent should have been obtained from legally authorized representatives of 3101-303-002 Completers aged 18 or 19 only at Visit 1. No longer required for De Novo EM Participants aged 18 or 19 at Visit -1.	Updated or Deleted (Section 8.4.1 only) as per the change of Japan's legal age of adulthood age to 18, starting from 1 Apr 2022.
Table 1. Schedule of Visits and Procedures footnote h	For WOCBP only, a urine pregnancy test will be performed at all visits. **At the first study visit**~~For Visit -1~~, discuss the method of contraception with WOCBP and document this method. Counsel participants on the importance of maintaining their agreed upon method of contraception throughout the study.	Clarification
Table 1. Schedule of Visits and Procedures footnote j	Participants should begin using the eDiary as soon as it is dispensed and for the duration of the **screening/baseline (for De Novo EM Participants) and** treatment period **(for all participants)**. **Training for the eDiary will be provided for qualified participants during the first study visit (Visit -1 for De Novo EM Participants and Visit 1 for 3101-303-002 Completers).**	Clarification

Section	Revision	Rationale
Section 4.4.2 De Novo EM Participants	QTcF > 450 msec for males and QTcF > 470 msec for females at Visit -1 based on the central reviewer's final ECG report.	Corrected Visit 1 to Visit -1
Global change within Section 4.5 Permissible and Prohibited Medications/Treatments and Section 12.2 Prohibited Medications	Updated "Visit 1" to "the first study visit" for prohibited medications.	Clarification
Section 6.5 Summary of Methods of Data Collection	All participants will use an eDiary daily to record the daily total duration of headache, headache characteristics, associated symptoms, the worst pain severity, acute medication use, AIM-D, Activity Level, and Activity Limitation during the open-label treatment period until Visit 14. **Participants should begin using the eDiary as soon as it is dispensed and for the duration of the screening/baseline (for De Novo EM Participants) and treatment period (for all participants).** Training for the eDiary will be provided for qualified participants during ~~Visit 1~~**the first study visit (Visit -1 for De Novo EM Participants and Visit 1 for 3101-303-002 Completers).**	Clarification
Section 8.4.2.1 Visit 1 (Day 1)	Perform urine pregnancy test for ~~women of childbearing potential~~**WOCBP**. **Discuss the method of contraception with WOCBP and document this method. Counsel participants on the importance of maintaining their agreed upon method of contraception throughout the study.**	Clarification
Section 8.4.2.1 Visit 1 (Day 1)	If the participant continues to meet study entry criteria, including acceptable results from Visit 1 ECGs **(3101-303-002 Completers only)**, pregnancy tests and vital sign measurements (see Section 6.1) the following procedures will be carried out at Visit 1.	Clarification

Section	Revision	Rationale
Section 8.5 Instructions for the Participants	Participants will be provided with instructions on daily completion of the eDiary **at their first study visit**. A practice session with a hypothetical scenario should be administered to ensure the participant's comprehension of the questions and the information to be entered. In addition, prohibited medications should be reviewed with the participants. Participants will be instructed to bring their eDiary to each clinic visit and return their atogepant bottle(s), both used and unused.	Clarification
Section 8.9 Withdrawal Criteria	**Study** 3101-303-002 Completers with the following at Visit 1 **must be withdrawn from the study**:	Clarification
Section 8.9 Withdrawal Criteria	Participants **must be withdrawn from the study if they meet any of**~~with~~ the following at any study visit:	Clarification
Section 9.1.1 Adverse Events	An AE is any untoward medical occurrence in a clinical study participant associated with the use of atogepant, whether or not considered related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of atogepant. In addition, during **the screening period and** Visit 1, AEs will be assessed regardless of the administration of a pharmaceutical product.	Clarification
Section 12.2.1 Examples of Prohibited Medications	The superscript "a" (for footnote a) was added to Prednisone and Rifampicin/Rifampin**.**	To indicate these medications are not approved in Japan.