ALLERGAN – CONFIDENTIAL

The following contains confidential, proprietary information,
which is the property of Allergan

A PHASE 3, MULTICENTER, OPEN-LABEL, 12-WEEK STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF ORAL ATOGEPANT FOR THE PREVENTION OF MIGRAINE IN CHINESE PARTICIPANTS WITH CHRONIC MIGRAINE

Protocol Number:	3101-311-002
EudraCT Number (if applicable):	N/A
Phase:	3
Name of Study Intervention:	Atogepant
Sponsor:	Allergan Pharmaceuticals International Limited Marlow International The Parkway, Marlow SL7 1YL United Kingdom
China Agent	Allergan Information Consulting (Shanghai) Co., Ltd. Suite 5605, 56F, 1266 West Nanjing Road Jingan District, Shanghai, 200040 China
Emergency Telephone Number(s):	Refer to Study Contacts page
Serious Adverse Event Reporting Fax Number: Back up fax number: Email:	 +1-714-796-9504 +1-714-246-5295 IR-Clinical-SAE@allergan.com
Sponsor Medical Safety Physician Contact Information:	Refer to the Study Contacts Page
Sponsor Signatory:	[redacted] MS, MD Vice President, Neuroscience Development
Original Protocol Date:	18 March 2020
Amendment 1 Date	July 2020

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

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 the sponsor in confidence and, when this information is submitted to an IRB, IEC, or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the study intervention(s), and their trial-related duties and functions.

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

Investigator Printed Name	Signature	Date

Table of Contents

List of Tables

List of Figures

Protocol Summary

Study Compound: Atogepant

Phase: 3

Study Objective:

Safety and tolerability: To evaluate the safety and tolerability of treatment with atogepant 60 mg once daily over a 12-week duration for the prevention of migraine in Chinese participants who completed Study 3101-303-002 (chronic migraine [CM]).

Efficacy: To evaluate the efficacy of treatment with atogepant 60 mg once daily when administered over 12 weeks for the prevention of migraine in Chinese participants with CM.

Clinical Hypotheses:

Atogepant 60 mg once daily is safe and well tolerated when administered over 12 weeks for the prevention of migraine in Chinese participants with CM who completed lead-in study 3101-303-002.

Study Design

Structure: Multicenter, open-label, 12-week, safety extension study conducted in China.
Duration: The study will consist of a 12-week treatment period, followed by a 4-week safety follow-up period, for a total duration of 16 weeks.
Study Intervention: Atogepant 60 mg once daily
Control Intervention: Not applicable
Dosage/Dose Regimen: Atogepant 60 mg orally once daily will be administered for 12 weeks.
Randomization: Not applicable
Visit Schedule: After Visit 1, study visits will occur every 4 weeks during the 12-week treatment period. A safety follow-up visit will occur 4 weeks after the last dose of atogepant. For details, please see Table 1, the Schedule of Visits and Procedures.

Study Population Characteristics

Number of Participants/Sites: All participants who complete Study 3101-303-002, and meet all eligibility requirements, may participate in this study.
Condition/Disease: Migraine with aura or migraine without aura (ICHD-3 Section 1.1 or Section 1.2; see Section 12.1.1)
Key Inclusion Criteria:

- Eligible participants who completed the double-blind treatment period (Visit 7), and the safety 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

Key Exclusion Criteria:

- 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. Concomitant medications with demonstrated efficacy for the prevention of migraine is exclusionary, except that 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 prior to the lead-in study and the participant is willing to continue taking that medication.

- Participants with an ECG indicating clinically significant abnormalities at Visit 1

- Participants with hypertension (sitting systolic BP > 160 mm Hg or sitting diastolic BP > 100 mm Hg) at Visit 1

- Participants with a significant risk of self-harm (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) since the last visit, must be excluded

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

Response Measures

Safety—AEs, physical examinations, clinical laboratory determinations, vital sign measurements, ECG parameters, and the 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, non-headache migraine 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.

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 mITT population, consisting of all participants who received at least 1 dose of study intervention (atogepant) and had at least 1 evaluable post-baseline 4-week period of eDiary data, in this extension study.

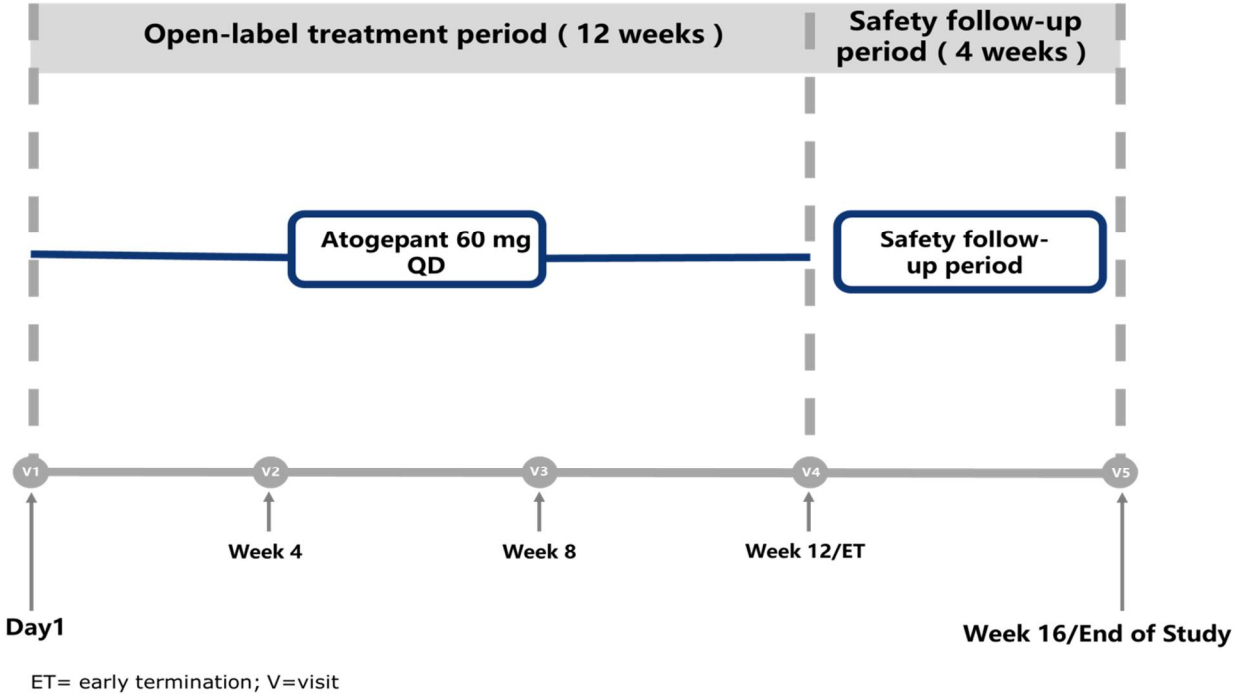
The safety parameters will include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, and the C-SSRS. For each of the clinical laboratory, vital sign, and ECG parameters, the baseline value as defined for the lead-in study (3101-303-002) will be used as the baseline in this extension study. 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.

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. The baseline value as defined for the lead-in study (3101-303-002) will be used as the baseline in this extension study. 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:

Chinese participants who complete Study 3101-303-002, and meet all eligibility requirements, may participate in this extension study. Approximately 120 Chinese participants are expected to participate in this extension study.

Figure 1. Study Diagram



ET= early termination; V=visit

Table 1. Schedule of Visits and Procedures

Study Period	**Open-label Treatment Period (12 weeks)**				**Safety Follow-up Period (4 weeks)**
Visit #	**Visit 1[a]**	**Visit 2**	**Visit 3**	**Visit 4/ET**	**Visit 5/EOS**
Week (Day)	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	N/A	± 3 days	± 3 days	± 3 days	± 3 days
Obtain informed consent and participant privacy	X				
Access IWRS	X	X	X	X	X
Assess inclusion/exclusion criteria	X				
Collect medical history[b]	X				
Perform physical examination	X			X	X
Collect vital sign measurements[c]	X	X	X	X	X
Perform ECG	X		X	X	
Perform urine pregnancy test[d]	X	X	X	X	X
Collect start date (first day) of last menstrual cycle for women having menstrual cycles	X	X	X	X	X
Clinical laboratory determinations[e]	X	X	X	X	X
eDiary instructions and training[f]	X				
Participant eDiary data collection[f,g]	X				
eDiary data (headache duration, frequency, characteristics and symptoms, acute medication use, AIM-D, Activity Level and Activity Limitation) and compliance review[h]		X	X	X	
MSQ v2.1 (eTablet)[i,j]	X	X	X	X	X
C-SSRS (eTablet)[k]	X	X	X	X	X
Collect eDiary				X	
Dispense atogepant	X	X	X		
Review atogepant compliance and accountability		X	X	X	
Adverse events	X				
Concomitant medications/concurrent procedures	X				

a After providing informed consent for this study, Visit 1 will be conducted on the same day as Visit 7/Visit 8 of the lead-in study (Study 3101-303-002 [Phase 3 CM]); procedures conducted as part of Visit 7 of the lead-in study should not be repeated. Visit 1 must be conducted in office. All other visits, should be conducted in office unless it is necessary to conduct a remote visits for the safety of participants (eg, COVID-19 or other pandemic): for details please refer to the Remote Visit Schedule of Assessments in Attachment 12.3).
b Medical history will be collected for participants who have a gap between the last visit of the lead-in study and Visit 1 of this extension study and only new medical history during the gap need to be collected.
c Vital sign measurements: weight, sitting and standing pulse rate, respiratory rate, sitting and standing blood pressure, and body temperature.
d For WOCBP only, a urine pregnancy test will be performed at all visits.
e 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.
f Participants should begin using the eDiary at Visit 1 and for the duration of the treatment period.
g Daily eDiary data collection includes: headache frequency, duration, characteristics, symptoms, acute medication use, AIM-D, Activity Level, and Activity Limitation.
h Participants must bring their eDiary to all visits (except Visit 5).
i Participant will complete on eTablet.
j PRO measures should be administered prior to any tests and/or evaluations unless indicated otherwise in the protocol.
k At all visits, the "Since Last Visit" C-SSRS will be completed for all participants. Clinicians will complete on eTablet.

1 Background and Clinical Rationale

1.1 Background

According to the Guidelines for Prevention and Treatment of Migraine in China (Yu 2016), the prevalence of migraine in China is 9.3%, with a distribution across males and females similar to that of the United States. 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). Globally, migraine is the 3rd leading cause of years lived with disability with an estimated global prevalence of 14.1% (GBD 2016). Migraine was ranked seventh highest among specific causes of disability globally (Steiner 2013).

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

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

1.2 Overview of Atogepant

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

A Phase 2/3 clinical study, CGP-MD-01, compared atogepant 10 mg once daily, atogepant 30 mg once daily, atogepant 30 mg twice a day, atogepant 60 mg once daily, and atogepant 60 mg twice a day 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 episodic migraine.

The ongoing global study 3101-303-002 to evaluate atogepant for the prevention of CM will further explore the dose range that demonstrated statistically significant improvement in the reduction of migraine compared to placebo in Study CGP-MD-01. Study 3101-303-002 will serve as the lead-in study for the current extension study.

1.3 Study Rationale

The purpose of this study is to evaluate the safety and tolerability of atogepant 60 mg once daily, as well as efficacy, when taken for 12 weeks for the prevention of CM.

1.4 Rationale for Doses and Dose Regimens Selected

The Phase 3 pivotal study to evaluate atogepant will test a maximum dose of 60 mg once daily. For this reason, the same dose of 60 mg once daily has been selected to evaluate the safety and tolerability of atogepant for the prevention of CM in this safety extension study.

2 Study Objective and Clinical Hypothesis

2.1 Study Objective

Safety and Tolerability: To evaluate the safety and tolerability of treatment with atogepant 60 mg once daily over a 12-week duration for the prevention of migraine in Chinese participants who completed Study 3101-303-002 (CM).

Efficacy: To evaluate the efficacy of treatment with atogepant 60 mg once daily when administered over 12 weeks for the prevention of migraine in Chinese participants with CM.

2.2 Clinical Hypothesis

Atogepant 60 mg once daily is safe and well tolerated when administered over 12 weeks for the prevention of migraine in Chinese participants with CM who completed lead-in study 3101-303-002.

3 Study Design

3.1 Structure

This is a multicenter, open-label, 12-week, safety extension study conducted in China. Participants will be treated with atogepant 60 mg once daily.

The study will consist of a 12-week treatment period and a 4-week safety follow-up period.

After signing the informed consent, Chinese participants will directly rollover from Study 3101-303-002 (Phase 3 CM); hereafter 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 extension study. After Visit 1, study visits will occur every 4 weeks during the 12-week treatment period. A safety follow-up 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 this extension study (3101-311-002) 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 (3101-311-002) in relation to each participant's planned Visit 8 schedule in the lead-in study, Visit 1 for this extension study 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 in the lead-in study should be conducted on the same day as Visit 1 for this extension study (3101-311-002).

- 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 of the lead-in study and Visit 1 of this extension study), 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 Table 1 Schedule of Visits and Procedures.

Participants will return to the clinic for safety assessments at 4, 8, and 12 weeks relative to Visit 1 (Day 1). A safety follow-up visit will occur 4 weeks after the last dose of atogepant 60 mg once daily. For details, please see Table 1 Schedule of Visits and Procedures.

The primary objective of the study is to assess the safety and tolerability of treatment with atogepant 60 mg once daily over a 12-week duration for the prevention of migraine in Chinese participants who completed Study 3101-303-002. 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

Not applicable

3.3 Adjudication Committee

An Adjudication Charter will be established and will describe the process for the surveillance, monitoring, and adjudication by an 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 complete Study 3101-303-002, and meet all eligibility requirements, may participate in this study. Approximately 120 participants will be enrolled at approximately 25 centers in China.

4.2 Study Population Characteristics

Participants eligible to participate in this study 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.

4.3 Inclusion Criteria

1. Written informed consent and participant privacy information (eg, written authorization for use and release of health and research study information) obtained from the participant prior to initiation of any study-specific procedures.
2. 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.
3. Participants must be using a medically acceptable and effective method of birth control during the course of the entire study, as defined in Section 4.5.3.

4.4 Exclusion Criteria

1. Requirement for any medication, diet (ie, 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 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.
2. Female participant is pregnant, planning to become pregnant during the course of the study, or currently lactating. Women of childbearing potential must have a negative urine pregnancy test at Visit 1.
3. An ECG with clinically significant abnormalities at Visit 1 as determined by the investigator.
4. Hypertension as defined by sitting systolic BP > 160 mm Hg or sitting diastolic BP > 100 mm Hg at Visit 1. Vital sign measurements that exceed these limits may be repeated only once.
5. Significant risk of self-harm based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator; participants must be excluded if they report suicidal ideation with intent, with or without a plan, (ie, Type 4 or 5 on the C-SSRS) since the last visit.

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

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

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

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Medications that are not specifically prohibited in Section 4.5.2 are allowed, with the following clarifications and restrictions.

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

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

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

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

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

4.5.2 Prohibited Medications/Treatments

The following medications are prohibited 30 days prior to Visit 1 (unless otherwise indicated) and throughout the study (see Attachment 12.2):

- Strong CYP3A4 inhibitors, including but not limited to: systemic (oral/IV) itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, nefazodone, 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 and OATP1B3 inhibitors (eg, gemfibrozil, cyclosporine)
- Drugs with narrow therapeutic margins with theoretical potential for CYP drug interactions (eg, warfarin)
- Medications with demonstrated efficacy for the prevention of migraine (eg, amitriptyline, topiramate, propranolol), excepting 1 medication with demonstrated efficacy for the prevention of migraine taken at a stable dose during lead-in 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).
- 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 Visit 1 and throughout the study period
- Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®, Vyepti™) within 6 months prior to Visit 1 and through the study period.
- Herbal and traditional medicine is prohibited from the time the ICF is signed and for the duration of study participation.

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

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

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

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

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

For males who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: post-bilateral vasectomy, barrier contraception, or sexual

abstinence. Male participants must also refrain from donating sperm during the course of the study.

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

If a woman becomes pregnant during the study, the investigator will notify the 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 the 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.

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/Randomization

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

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

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

Atogepant 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 (Table 1). Returned atogepant bottles should not be re-dispensed to the participants.

5.6 Treatment Regimen and Dosing

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

Participants will be provided with atogepant to be taken on an outpatient basis.

Participants will be instructed to take their atogepant at approximately the same time each day. Atogepant will be administered orally for 12 weeks, and participants will be followed for 4 weeks following completion or discontinuation of the atogepant.

Table 5-1. Study Intervention

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

5.7 Storage of Study Intervention

Atogepant tablets 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 study intervention, 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, the sponsor must be notified immediately to meet their reporting obligations to appropriate regulatory authorities.

6.1.2 Adverse Events of Special Interest

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

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

Reporting requirements for ALT or AST elevations and potential Hy's law cases are outlined in Sections 9.5 and 9.5.1. Responses to the C-SSRS that meet the above criterion will be captured in the eTablet and monitored by the 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. 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 (Section 8.9), or positive results on the urine drug screen at 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 will exclude the participant from the study.

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

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

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

Table 6–1. Clinical Laboratory Parameters

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

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. 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 all 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 3 must be withdrawn from the study and should receive appropriate follow-up as in routine clinical practice, including the ET (Visit 4) and the safety follow-up (Visit 5) assessments.

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, non-headache migraine 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. An additional health outcome measure, the MSQ v2.1, will be administered in an eTablet at specified clinic visits (Section 6.3).

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 four characteristics:
   i. Unilateral location
   ii. Pulsating quality
   iii. Moderate or severe pain intensity
   iv. Aggravated by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

B. At least one of the following:
   i. Nausea and/or vomiting
   ii. Photophobia and phonophobia
   iii. Typical aura (ie, visual, sensory, or speech/language) accompanying or within 60 minutes before headache begins
C. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (ie, triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration will be specified

OR

D. Any headache which fulfills 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 daily diary measure that assesses the impact of migraine and is comprised of two domains that evaluate performance of daily activities (7 items) and physical impairment (4 items). Participants are asked to rate the level of difficulty experienced in the past 24 hours with performance of daily activities (ie, difficulty with household chores, errands, leisure activities at home, leisure or social activities outside the home, strenuous physical activities, concentrating, and thinking clearly) and physical impairment (ie, difficulty walking, moving body, bending forward, moving head) using a 6-point rating scale ranging from "Not difficult at all," "A little difficult," "Somewhat difficult," "Very difficult," "Extremely difficult," and "I could not do it at all." Three items include a response of "I did not…," for example, "I did not have errands planned." The AIM-D was developed as an electronic daily diary with the same set of questions administered in headache and non-headache versions. The Headache version is administered on days when a participant reports a headache and the Non-Headache version is administered on days when a participant does not report having a headache. The AIM-D instructs participants to answer each question based on the level of difficulty experienced in the past 24 hours for both versions, with "during your headache" indicated for the AIM-D Headache version. In addition to the two domain scores, a total score using all 11 items can also be calculated. Each raw daily domain score, as well as the raw daily total score, are transformed to a 0-100 scale, with higher scores indicating greater impact of migraine (ie, higher disease burden).

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

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

6.4 Other Study Supplies

The following will be provided by the sponsor or sponsor's 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
- eTablet(s)
- eDiaries

6.5 Summary of Methods of Data Collection

An IWRS will be used to manage atogepant inventory. All office visit data for this study will be collected by either the eTablet (eg, C-SSRS) 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 4. Training for the eDiary will be provided for qualified participants during Visit 1.

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 extension study 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

7.2.1 Efficacy Variables

Since the primary objective of this study is to assess the safety and tolerability of 12 weeks of atogepant treatment, efficacy variables are not classified as primary, secondary, or additional.

Efficacy endpoints for evaluation in the atogepant arm are listed below.

- Change from baseline in monthly migraine days at each monthly period (ie, each consecutive 4-week 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

7.2.2 Health Outcome Variables

Health outcome endpoints are listed below. The related health outcome analyses will be documented in the health economics and outcomes research statistical analysis plan.

- Change from baseline in the MSQ v2.1 Role Function Restrictive domain score at Weeks 4, 8, 12, and 16
- Change from baseline in the MSQ v2.1 Role Function Preventive domain score at Weeks 4, 8, 12, and 16
- Change from baseline in the MSQ v2.1 Emotional Function domain score at Weeks 4, 8, 12, and 16
- Change from baseline in monthly Performance of Daily Activities domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly Physical Impairment domain score of the AIM-D at Weeks 1-4, 5-8, and 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly AIM-D total score at Weeks 1-4, 5-8, 9-12, and average across the 12-week treatment period.
- Change from baseline in monthly Activity Level at Weeks 1 to 4, 5 to 8, and 9 to 12, and average across the 12-week treatment period
- Change from baseline in monthly Activity Limitation at Weeks 1 to 4, 5 to 8, and 9 to 12, and average across the 12-week treatment 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 as defined for the lead-in study (3101-303-002) will be used as the baseline in this extension study (3101-311-002).

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

7.3.2 Efficacy Analyses

The efficacy analyses will be based on the mITT population. For analysis purposes, 4 weeks (28 days) will be considered as 1 month. The baseline value as defined for the lead-in study will be used as the baseline in this extension study. For monthly endpoints, baseline is defined as assessments during the last 28 days of baseline period in the lead-in study. For efficacy endpoints that are assessed at clinical visits, baseline is defined as the last non-missing efficacy assessment before the first dose of study intervention in the lead-in study.

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 observed cases approach. No inferential statistical analyses will be performed for the efficacy parameters.

7.4 Subgroup Analyses

Not applicable.

7.5 Sample Size Calculation

Chinese participants who complete Study 3101-303-002, and meet all eligibility requirements, may participate in this extension study. Approximately 120 Chinese participants are expected to participate in this extension study.

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

All participants will maintain the lead-in 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.

8.2 Washout Intervals/Run-in

This study will not include a washout period.

8.3 Procedures for Final Study Entry

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

Participants will directly rollover from the lead-in study (3101-303-002 [Phase 3 CM]). 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.

Note, there may be participants who complete Visit 7 in the lead-in study before this extension study (3101-311-002) 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 3101-311-002 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 this extension study (3101-311-002).

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 Table 1 Schedule of Visits and Procedures.

8.4 Visits and Associated Procedures

There will be 5 scheduled clinic visits: Visit 1 (Day 1), Visit 2 (Week 4), Visit 3 (Week 8), Visit 4/ET (Week 12), and Visit 5 (safety follow-up/EOS). For details, please see Table 1, Schedule of Visit and Procedures.

8.4.1 Open-label Treatment Period (12 Weeks)

8.4.1.1 Visit 1 (Day 1)

- Obtain informed consent and participant privacy.
- Register participant in IWRS.
- 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.
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Review and update concomitant medications and concurrent procedures.
- Perform urine pregnancy test for women of childbearing potential.
- Perform and transmit ECG.
- 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).
- Assess inclusion/exclusion criteria.

If the participant continues to meet study entry criteria, including acceptable results from Visit 1 ECG, pregnancy test, 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 MSQ v2.1.
- Perform physical examination.
- Collect blood and urine for clinical laboratory determinations including: chemistry, hematology, serology, INR, and urinalysis.
- Collect urine for drug screen.
- Review and assess AEs.
- Provide eDiary instructions and training
- Access IWRS and obtain the kit number for atogepant bottle and dispense atogepant bottle.

8.4.1.2 Visits 2 and 3 (Week 4 and Week 8)

- Review clinical laboratory results from Visit 1 to confirm continued eligibility (Visit 2 only) (see Section 8.9).
- Prior to any other test or evaluations, administer the MSQ v2.1.
- 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 start date (first day) of last menstrual cycle for women having menstrual cycles.
- 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 3 only).
- Collect previous visit atogepant bottle, review participant compliance, and perform accountability.
- Review and assess AEs.
- Review and update concomitant medications/concurrent procedures.

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

8.4.1.3 Visit 4/Early Termination (Week 12)

Effort should be made by the site to not schedule Visit 4 earlier than 12 weeks after Day 1, to ensure participants complete the full 12 weeks of atogepant.

- Prior to any other test or evaluations, administer the 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 start date (first day) of last menstrual cycle for women having menstrual cycles.
- 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.

8.4.2 Safety Follow-up Period (4 Weeks)

8.4.2.1 Visit 5/End of Study (Week 16)

- Prior to any other test or evaluations, administer the MSQ v2.1.
- Perform physical examination.
- Assess C-SSRS (the "Since Last Visit" assessment of the C-SSRS will be completed).
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, and weight).
- Collect start date (first day) of last menstrual cycle for women having menstrual cycles.
- Perform urine pregnancy test for women of childbearing potential.
- Collect blood and urine samples for chemistry, hematology, INR, and urinalysis.
- Review and assess AEs.
- Review and update concomitant medications and concurrent procedures.
- Access IWRS to enter study visit.

8.5 Instructions for the Participants

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

Prohibited medications should be reviewed with the participants. Participants will be instructed to return their atogepant bottle(s), both used and unused.

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
- Non-compliance with study drug
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by subject

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 4/ET and Visit 5 (safety follow-up/EOS), 4 weeks post the last dose of atogepant.

8.9 Withdrawal Criteria

- **Participants with the following at Visit 1:**
  - **Laboratory Results:**
    - ALT or AST > 1 x ULN OR
    - total bilirubin > 1 x ULN (except for participants with a diagnosis of Gilbert's disease) OR
    - serum albumin < 2.8 g/dL
    - Positive result on the urine drug screen unless explained by concomitant medication use (eg, opioids prescribed for migraine pain).
    - Positive result on anti-hepatitis A IgM antibody, hepatitis B surface antigen, anti–hepatitis C antibody testing, or anti-hepatitis E IgM antibody.
  - **ECG Results:**
    - QTcF > 450 msec for males and QTcF > 470 msec for females on the final central vendor ECG report
    - Clinically significant cardiac rhythm or conduction abnormalities (eg, atrial fibrillation, second- or third-degree heart block)
- **Participants with the following at any study visit:**
  - Female participants who become pregnant (Section 9.4)
  - Participants who meet atogepant discontinuation criteria related to abnormal liver function tests (Section 9.5), and advised not to be rechallenged, will be withdrawn from the study and should refrain from taking atogepant.
  - Participants who reply with "yes" to questions 4 or 5 in the suicidal ideation section or "yes" to any question in the suicidal behavior section of the C-SSRS at Visits 2 and 3 must be withdrawn from the study.
  - A participant with a condition and/or a situation that, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study may be withdrawn from treatment.

All withdrawn participants should receive appropriate follow-up as in routine clinical practice, including the Visit 4 (ET) and Visit 5 (safety follow-up/EOS) assessments.

8.10 Study Termination

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

9 Adverse Events

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

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical study participant associated with the use of atogepant, whether or not considered related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of atogepant. In addition, during Visit 1, AEs will be assessed regardless of the administration of 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 study (see Section 8.8).

All AEs from the signing of the ICF until the safety follow-up visit (Visit 5), or 30 days after the last dose of atogepant if the safety follow-up visit is not done, will be collected at the timepoints specified in the Schedule of Visits and Procedures (Table 1), and as observed or reported spontaneously by study participants.

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

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

9.1.2 Serious Adverse Event

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

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

f. Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive intervention in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The sponsor considers all cancer AEs as SAEs. 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).

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

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

9.1.3 Intensity

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

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

9.1.4 Assessment of Causality

Assessment of Causality
• The investigator is obligated to assess the relationship between atogepant and each occurrence of each AE or SAE. • A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to atogepant administration will be considered and investigated. • The investigator will also consult the investigator's brochure in his/her assessment. • For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

9.1.5 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs and non-serious AEs of special interest (as defined in Section 6.1.2) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

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

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 the 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, China regulations, and the governing health authorities. Any AE that is marked ‘ongoing’ at the exit visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any SAE occurring during the study period (beginning with informed consent) until the safety follow-up visit (Visit 5), or 30 days after the last dose of atogepant if the safety follow-up visit is not done, must be immediately reported but no later than 24 hours after learning of an SAE. SAEs must be reported to the sponsor as listed on the Study Contacts Page and recorded on the AESI/SAE form. All participants with an SAE must be followed up and the outcomes reported. The investigator must supply the sponsor and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

9.3.1 Regulatory Reporting Requirements for Serious Adverse Events

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

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

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

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs from the sponsor) will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to China 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 safety follow-up visit (Visit 5) or 30 days after the last dose of atogepant if the safety follow-up visit is not done. Study center personnel must report every pregnancy on the Pregnancy Form (within 24 hours of learning of the pregnancy to the Serious Adverse Event Reporting Fax 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 AESI/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 $\geq 3 \times$ ULN and/or AST $\geq 3 \times$ ULN is considered an AESI. Any participant with this laboratory result after atogepant is taken must have repeat testing within 48 to 72 hours to confirm the abnormality. For this repeat testing, the following laboratory tests must be performed: hematology and chemistry panels, INR, serum acetaminophen level, urine drugs of abuse screen, and blood alcohol level. An extra blood serology sample must be collected and sent to the central laboratory for further diagnostic testing, at a later date, if needed. In addition, the investigator will perform a complete history and examination to evaluate the participant for possible liver disease.

All AESIs must be reported to the sponsor within 24 hours of the time the investigator becomes aware of the event using the abnormal liver function reporting form and the AE eCRF. All new elements of history, physical examination, diagnostic testing results, and other relevant medical reports are to be reported for each 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 the sponsor's 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's Medical Monitor. Participants should receive appropriate follow-up as per standard of care.

The investigator must contact the sponsor's 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 the sponsor immediately when the above criteria have been met. A possible Hy's law case must be faxed to the sponsor on an abnormal liver function reporting form as soon as possible (within 24 hours of learning of the possible Hy's law case) to the 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 and China GCP).

10.1 Protection of Human Participants

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

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

The following process will be followed:

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed

consent that meets the requirements of 21 CFR 50, China regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study if required by the IRB.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.2 Compliance With IRB or IEC Regulations

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

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable China 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 the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.3 Changes to the Protocol

The investigator must not implement any deviation from or changes to the protocol without approval by the 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 identified by a unique identifier assigned during the lead-in study. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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

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

10.5 Participant Privacy

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

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

Source documentation practices must follow Section 4.0 of ICH E6, GCP: Consolidated Guidance, China GCP, 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 the sponsor in a timely manner at the completion of the study, or as otherwise specified by the sponsor and will be maintained in a central data repository.

10.6.3 Study Summary

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

10.6.4 Retention of Documentation

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

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

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

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

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

10.7.1 Labeling/Packaging

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

10.7.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units (atogepant) received from the 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 the 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 the sponsor or sponsor's designee for destruction.

10.8 Monitoring by the Sponsor

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

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

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

10.10 Publications

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

10.11 Coordinating Investigator

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

11 References

GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1211-1259.

Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States. Arch Intern Med. 1999;159:813-818.

ICHD-3: Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.

Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the Differences Between Episodic Migraine and Chronic Migraine. Curr Pain Headache Rep. 2012;16:86–92.

Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68:343-349.

Olesen J, Diener H-C, Husstedt IW, Goadsby PJ, Hall D, Meier U, et al. Calcitonin gene- related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med. 2004;350:1104-1110.

Steiner TJ, Stovner LJ, and Birbeck GL. Migraine: the seventh disabler. J Headache Pain. 2013;14(1):1-2.

Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the Eurolight Project. J Headache Pain. 2010;11:289–299.

Yu S. Guidelines for Prevention and Treatment of Migraine in China. Chinese journal of pain medicine. 2016;22(10):721-727.

12 Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques

12.1.1 International Classification of Headache Disorders, 3rd Edition

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

Coded elsewhere:

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

General comment

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

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

Introduction

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

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

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

1.1 Migraine without aura

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

Diagnostic criteria:

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

Notes:

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

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

feeling tired or weary, difficulty with concentration and neck stiffness, may follow resolution of the headache, persisting for up to 48 hours; these are less well studied.

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

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

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

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

At the same time, the circuitry of migraine pain, the trigeminovascular system, and several aspects of its neurotransmission peripherally and in the trigeminal nucleus caudalis, central mesencephalic grey and thalamus, have been recognized. Highly receptor- specific acute

medications including 5-$HT_{1B/D}$ receptor agonists (triptans), 5-HT_{1F} receptor agonists and CGRP receptor antagonists have demonstrated efficacy in the acute treatment of migraine attacks. Because of their high receptor-specificity, their mechanisms of action pro- vide new insight into migraine mechanisms. It is now clear that 1.1 *Migraine without aura* is a neurobiological disorder, while clinical as well as basic neuroscience stu- dies continue to advance our knowledge of migraine mechanisms.

1.2 Migraine with aura

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

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

Diagnostic criteria:

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

Notes:

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

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

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

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

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

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

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

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

When aura symptoms are multiple, they usually follow one another in succession, beginning with visual, then sensory, then aphasic; but the reverse and other orders have been noted. The accepted

duration for most aura symptoms is one hour, but motor symptoms are often longer lasting.

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

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

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

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

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

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

1.2.1 Migraine with typical aura

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

Diagnostic criteria:

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

1.2.1.1 Typical aura with headache

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

Diagnostic criteria:

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

1.2.1.2 Typical aura without headache

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

Diagnostic criteria:

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

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

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

1.2.2 Migraine with brainstem aura

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

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

Diagnostic criteria:

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

Notes:

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

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

There are typical aura symptoms in addition to the brainstem symptoms during most attacks. Many

patients who have attacks with brainstem aura also report other attacks with typical aura and should be coded for both 1.2.1 *Migraine with typical aura* and 1.2.2 *Migraine with brainstem aura*.

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

1.2.3 Hemiplegic[1] migraine

Description: Migraine with aura including motor weakness.

Diagnostic criteria:

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

Notes:

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

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

1.2.3.1 Familial hemiplegic migraine (FHM)

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

Diagnostic criteria:

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

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

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

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

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

1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)

Diagnostic criteria:

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

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

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

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

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

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

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

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

1.2.3.2 Sporadic hemiplegic migraine (SHM)

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

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*

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

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

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

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

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

1.2.4 Retinal migraine

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

Diagnostic criteria:

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

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

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

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

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

1.3 Chronic migraine

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

Diagnostic criteria:

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

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

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

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

Notes:

1. The reason for singling out 1.3 *Chronic migraine* from types of episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. Such patients are extremely di□cult to keep medication-free in order to observe the natural history of the headache. In

this situation, attacks with and those without aura are both counted, as are both migraine-like and tension-type-like headaches (but not secondary headaches).

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

1.4 Complications of migraine

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

1.4.1 Status migrainosus

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

Diagnostic criteria:

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

Notes:

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

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

1.4.2 Persistent aura without infarction

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

Diagnostic criteria:

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

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

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

1.4.3 Migrainous infarction

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

Diagnostic criteria:

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

Note:

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

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

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

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

1.4.4 Migraine aura-triggered seizure

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

Diagnostic criteria:

A. A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below
B. Occurring in a patient with 1.2 *Migraine with aura*, and during or within one hour after an attack of migraine with aura
C. Not better accounted for by another ICHD-3 diagnosis.

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

1.5 Probable migraine

Previously used term: Migrainous disorder.

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

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

Diagnostic criteria:

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

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

B. Not fulfilling ICHD-3 criteria for any other 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

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

1.5.2 Probable migraine with aura

Diagnostic criteria:

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

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

1.6 Episodic syndromes that may be associated with migraine

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

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

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

1.6.1 Recurrent gastrointestinal disturbance

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

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

Diagnostic criteria:

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

1.6.1.1 Cyclic vomiting syndrome

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

Diagnostic criteria:

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

Note:

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

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

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

1.6.1.2 Abdominal migraine

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

Diagnostic criteria:

A. At least five attacks of abdominal pain, fulfilling criteria B–D
B. Pain has at least two of the following three characteristics:
   1. midline location, periumbilical or poorly localized

2. dull or 'just sore' quality
3. moderate or severe intensity

C. At least two of the following four associated symptoms or signs:
1. anorexia
2. nausea
3. vomiting
4. pallor

D. Attacks last 2–72 hours when untreated or unsuccessfully treated

E. Complete freedom from symptoms between attacks

F. Not attributed to another disorder.[1]

Note:

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

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

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

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

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

1.6.2 Benign paroxysmal vertigo

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

Diagnostic criteria:

A. At least five attacks fulfilling criteria B and C

B. Vertigo[1] occurring without warning, maximal at onset and resolving spontaneously after minutes to hours without loss of consciousness

C. At least one of the following five associated symptoms or signs:
1. nystagmus
2. ataxia
3. vomiting
4. pallor
5. fearfulness

D. Normal neurological examination and audiometric and vestibular functions between attacks

E. Not attributed to another disorder.[2]

Notes:

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

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

1.6.3 Benign paroxysmal torticollis

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

Diagnostic criteria:

A. Recurrent attacks[1] in a young child, fulfilling criteria B and C

B. Tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days

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

D. Normal neurological examination between attacks

E. Not attributed to another disorder.[3]

Notes:

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

Comments: The child's head can be returned to the neutral position during attacks: some

resistance may be encountered but can be overcome.
These observations need further validation by patient diaries, structured interviews and longitudinal data collection.

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

Bibliography

1 Migraine in general

Arruda MA, Guidetti V, Galli F, et al. Primary head- aches in childhood – a population-based study. *Cephalalgia* 2010; 30: 1056–1064.

Diener HC and Silberstein SD. Medication over- use headache. In: Olesen J, Goadsby PJ, Ramadan NM, et al. (eds) *The headaches, 3rd edition*. Philadelphia: Lippincott Williams & Wilkins, 2006, pp.971–979.

GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990– 2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1545–1602.

Gelfand AA, Fullerton HJ and Goadsby PJ. Child neurology: migraine with aura in children. *Neurology* 2010; 75(5): e16–e19.

Goadsby PJ. Migraine pathophysiology. *Headache* 2005; 45(Suppl 1): S14–S24.

Goadsby PJ. Recent advances in the diagnosis and man- agement of migraine. *BMJ* 2006; 332: 25–29.

Katsarava Z, Manack A, Yoon MS, et al. Chronic migraine: classification and comparisons. *Cephalalgia* 2011; 31: 520–529.

Lipton RB, Bigal ME, Steiner TJ, et al. Classification of primary headaches. *Neurology* 2004; 63: 427–435.

Martelletti P, Haimanot RT, Lainez MJ, et al. The Global Campaign (GC) to Reduce the Burden of Headache Worldwide. The International Team for Specialist Education (ITSE). *J Headache Pain* 2005; 6: 261–263.

Silberstein SD. Migraine. *Lancet* 2004; 363: 381–391.

Vetvik KG, Macgregor EA, Lundqvist C, et al. Prevalence of menstrual migraine: a population-based study. *Cephalalgia* 2014; 34: 280–288.

Vetvik KG, Benth JS̆, MacGregor EA, et al. Menstrual versus non-menstrual attacks of migraine without aura in women with and without menstrual migraine. *Cephalalgia* 2015; 35: 1261–1268.

Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLD) for 1160 sequelae of 289 dis- eases and injuries 1990–2010: a systematic analysis for the global burden of disease study 2010. *Lancet* 2012; 380: 2163–2196.

1.2 Migraine with aura

Cao Y, Welch KM, Aurora S, et al. Functional MRI-BOLD of visually triggered headache in patients with migraine. *Arch Neurol* 1999; 56: 548–554.

Charles A and Brennan K. Cortical spreading depression – new insights and persistent questions. *Cephalalgia* 2009; 29: 1115–1124.

Cologno D, Torelli P and Manzoni GC. Migraine with aura: a review of 81 patients at 10–20 years' follow- up. *Cephalalgia* 1998; 18: 690–696.

Cutrer FM, Sorensen AG, Weissko RM, et al. Perfusion- weighted imaging defects during spontaneous migrainous aura. *Ann Neurol* 1998; 43: 25–31.

Eriksen MK, Thomsen LL, Andersen I, et al. Clinical characteristics of 362 patients with familial migraine with aura. *Cephalalgia* 2004; 24: 564–575.

Eriksen MK, Thomsen LL and Olesen J. The Visual Aura Rating Scale (VARS) for migraine aura diagnosis. *Cephalalgia* 2005; 25: 801–810.

Gi n NJ, Lipton RB, Silberstein SD, et al. The migraine postdrome: an electronic diary study. *Neurology* 2016; 87: 309–313.

Hadjikhani N, Sanchez del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *PNAS* 2001; 98: 4687–4692.

Hansen JM, Lipton R, Dodick D, et al. Migraine head- ache is present in the aura phase – a prospective study. *Neurology* 2012; 79: 2044–2049.

Jensen K, Tfelt-Hansen P, Lauritzen M, et al. Classic migraine. A prospective recording of symptoms. *Acta Neurol Scand* 1986; 73: 359–362.

Kallela M, Wessman M, Farkkila M, et al. Clinical characteristics of migraine in a population-based twin sample: similarities and di erences between migraine with and without aura. *Cephalalgia* 1999; 19: 151–158.

Kelman L. The premonitory symptoms (prodrome): a tertiary care study of 893 migraineurs. *Headache* 2004; 44: 865–872.

Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. *Brain* 1994; 117(Pt 1): 199–210.

Leao AAP. Spreading depression of activity in the cere- bral cortex. *J Neurophysiol* 1944; 7: 359–390.

Lebedeva ER, Gurary NM, Gilev DV, et al. Prospective testing of ICHD-3 beta diagnostic criteria for migraine with aura and migraine with typical aura in patients with transient ischemic attacks. *Cephalalgia*. Epub ahead of print 1 January 2017. DOI: 10.1177/0333102417702121.

Li D, Christensen AF and Olesen J. Field-testing of the ICHD-3 beta/proposed ICD-11 diagnostic criteria for migraine with aura. *Cephalalgia* 2015; 35: 748–756.

Olesen J, Friberg L, Olsen TS, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. *Ann Neurol* 1990; 28: 791–798.

Queiroz LP, Friedman DI, Rapoport AM, et al. Characteristics of migraine visual aura in Southern Brazil and Northern USA. *Cephalalgia* 2011; 31: 1652–1658.

Rasmussen BK and Olesen J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia* 1992; 12: 221–228 (discussion 186).

Salhofer-Polanyi S, Frantal S, Brannath W, et al. Prospective analysis of factors related to migraine aura – The PAMINA Study. *Headache* 2012; 52: 1236–1245.

Schoonman GG, Evers DJ, Terwindt GM, et al. The prevalence of premonitory symptoms in migraine: a questionnaire study in 461 patients. *Cephalalgia* 2006; 26: 1209–1213.

Ulrich V, Gervil M, Kyvik KO, et al. Evidence of a genetic factor in migraine with aura: A population-based Danish twin study. *Ann Neurol* 1999; 45: 242–246.

1.2.1 Migraine with typical aura

Eriksen MK, Thomsen LL and Olesen J. Implications of clinical subtypes of migraine with aura. *Headache* 2006; 46: 286–297.

Hansen JM, Goadsby PJ and Charles AC. Variability of clinical features in attacks of migraine with aura. *Cephalalgia* 2016; 36: 216–224.

Matharu MJ and Goadsby PJ. Post-traumatic chronic paroxysmal hemicrania (CPH) with aura. *Neurology* 2001; 56: 273–275.

Morrison DP. Abnormal perceptual experiences in migraine. *Cephalalgia* 1990; 10: 273–277.

Silberstein SD, Niknam R, Rozen TD, et al. Cluster headache with aura. *Neurology* 2000; 54: 219–221.

Viana M, Linde M, Sances G, et al. Migraine aura symptoms: duration, succession and temporal relationship to headache. *Cephalalgia* 2016; 36: 413–421.

Wijman CA, Wolf PA, Kase CS, et al. Migrainous visual accompaniments are not rare in late life: the Framingham Study. *Stroke* 1998; 29: 1539–1543.

1.2.2 Migraine with brainstem aura

Ambrosini A, D'Onofrio M, Grieco GS, et al. Familial basilar migraine associated with a new mutation in the ATP1A2 gene. Neurology 2005; 65: 1826–1828.

Bickerstaff ER. Basilar artery migraine. Lancet 1961; i:15–17.

Caplan LR. Migraine and vertebrobasilar ischemia. *Neurology* 1991; 41: 55–61.

Eriksen MK, Thomsen LL and Olesen J. Implications of clinical subtypes of migraine with aura. *Headache* 2006; 46: 286–297.

Kirchmann M, Thomsen LL and Olesen J. Basilar-type migraine: clinical, epidemiologic, and genetic features. *Neurology* 2006; 66: 880–886.

Lempert T, Neuhauser H and Daroff RB. Vertigo as a symptom of migraine. *Ann NY Acad Sci* 2009; 1164: 242–251.

Li D, Christensen AF and Olesen J. Field-testing of the ICHD-3 beta/proposed ICD-11 diagnostic criteria for migraine with aura. *Cephalalgia* 2015; 35: 748–756.

Sturzenegger MH and Meienberg O. Basilar artery migraine: a follow-up study of 82 cases. *Headache* 1985; 25: 408–415.

Swanson JW and Vick NA. Basilar artery migraine 12 patients, with an attack recorded electroencephalographically. *Neurology* 1978; 28: 782–786.

Thomsen LL, Eriksen MK, Roemer SF, et al. A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. *Brain* 2002; 125: 1379–1391.

Thomsen LL, Ostergaard E, Olesen J, et al. Evidence for a separate type of migraine with aura: sporadic hemiplegic migraine. *Neurology* 2003; 60: 595–601.

1.2.3 Hemiplegic migraine

Ambrosini A, D'Onofrio M, Grieco GS, et al. Familial basilar migraine associated with a new mutation in the *ATP1A2* gene. *Neurology* 2005; 65: 1826–1828.

De Fusco M, Marconi R, Silvestri L, et al. Haploinsu□ciency of *ATP1A2* encoding the $Na^þ/K^þ$ pump a2 subunit associated with familial hemiplegic migraine type 2. *Nat Genet* 2003; 33: 192–196.

De Vries B, Frants RR, Ferrari M, et al. Molecular genetics of migraine. *Hum Genet* 2009; 126: 115–132.

Dichgans M, Freilinger T, Eckstein G, et al. Mutation in the neuronal voltage-gated sodium channel *SCN1A* in familial hemiplegic migraine. *Lancet* 2005; 366: 371–377.

Dreier JP, Jurkat-Rott K, Petzold GC, et al. Opening of the blood–brain barrier preceding cortical edema in a severe attack of FHM type II. *Neurology* 2005; 64: 2145–2147.

Eriksen MK, Thomsen LL and Olesen J. Implications of clinical subtypes of migraine with aura. *Headache* 2006; 46: 286–297.

Hansen JM, Schytz HW, Larsen VA, et al. Hemiplegic migraine aura begins with cerebral hypoperfusion: imaging in the acute phase. *Headache* 2011; 51: 1289–1296.

Hansen JM, Thomsen LL, Olesen J, et al. Coexisting typical migraine in familial hemiplegic migraine. *Neurology* 2010; 74: 594–600.

Iizuka T, Takahashi Y, Sato M, et al. Neurovascular changes in prolonged migraine aura in FHM with a novel *ATP1A2* gene mutation. *J Neurol Neurosurg Psychiatry* 2012; 83: 205–212.

Jurkat-Rott K, Freilinger T, Dreier JP, et al. Variability of familial hemiplegic migraine with novel A1A2 $Na^þ/K^þ$-ATPase variants. *Neurology* 2004; 62: 1857–1861.

Kirchmann M, Thomsen LL and Olesen J. Basilar-type migraine: clinical, epidemiologic, and genetic features. *Neurology* 2006; 66: 880–886.

Leo L, Gherardini L, Barone V, et al. Increased susceptibility to cortical spreading depression in the mouse model of familial hemiplegic migraine type 2. *PloS Genet* 2011; 7: e1002129.

Thomsen LL, Eriksen MK,Roeme SF, et al. A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. *Brain* 2002; 125: 1379–1391.

Thomsen LL, Kirchmann M, Bjornsson A, et al. The genetic spectrum of a population-based sample of familial hemiplegic migraine. *Brain* 2007; 130: 346–356.

Thomsen LL, Ostergaard E, Olesen J, et al. Evidence for a separate type of migraine with aura: sporadic hemiplegic migraine. *Neurology* 2003; 60: 595–601.

Vanmolkot KRJ, Kors EE, Turk U, et al. Two *de novo* mutations in the Na,K-ATPase gene *ATP1A2* associated with pure familial hemiplegic migraine. *Eur J Hum Genet* 2006; 14: 555–560.

1.2.4 Retinal migraine

Carroll D. Retinal migraine. *Headache* 1970; 10: 9–13. Chronicle EP and Mulleners WM. Visual system dysfunction in migraine: a review of clinical and psychophysical findings. *Cephalalgia* 1996; 16: 525–535.

Grosberg BM, Solomon S, Friedman DI, et al. Retinal migraine reappraised. *Cephalalgia* 2006; 26: 1275–1286.

Hedges TR. Isolated ophthalmic migraine in the di erential diagnosis of cerebroocular ischemia. *Stroke* 1976; 7: 379–381.

Hill DL, Daroff RB, Ducros A, et al. Most cases labeled as ‘‘retinal migraine’’ are not migraine. *J Neuroophthalmol* 2007; 27: 3–8.

Martin TJ and Corbett JJ. Disorders of the eye. In: Silberstein SD, Lipton RB and Dalessio DJ (eds) *Wolff's headache and other head pain*. New York: Oxford University Press, 2001, pp.459–474.

Troost T and Zagami AS. Ophthalmoplegic migraine and retinal migraine. In: Olesen J, Tfelt-Hansen P and Welch KMA (eds) *The headaches, 2nd edition*. Philadelphia: Lippincott Williams & Wilkins, 2000, pp.511–516.

1.3 Chronic migraine

Aurora SK. Is chronic migraine one end of a spectrum of migraine or a separate entity? *Cephalalgia* 2009; 29: 597–605.

Bigal ME and Lipton RB. Concepts and mechanisms of migraine chronification. *Headache* 2008; 48: 7–15.

Bigal M, Rapoport A, Sheftell F, et al. The International Classification of Headache Disorders revised criteria for chronic migraine – field testing in a headache specialty clinic. *Cephalalgia* 2007; 27: 230–234.

Bigal ME, Serrano D, Reed M, et al. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology* 2008; 71: 559–566.

Bigal ME, Sheftell FD, Rapoprt AM, et al. Chronic daily headache in a tertiary care population: correlation between the International Headache Society diagnostic criteria and proposed revisions of criteria for chronic daily headache. *Cephalalgia* 2002; 22: 432–438.

Bloudek LM, Stokes M, Buse DC, et al. Cost of health- care for patients with migraine in five European countries: results from the International Burden of Migraine Study (IBMS). *J Headache Pain* 2012; 13: 361-378.

Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors. Results from the

American Migraine Prevalence and Prevention Study. *Headache* 2012; 52: 1456-1470.

Buse D, Manack A, Serrano D, et al. Headache impact of chronic and episodic migraine: results from the American Migraine Prevalence and Prevention study. *Headache* 2012; 52: 3–17.

Diamond S. A view of chronic daily headache. *Headache Q* 2000; 11: 177.

Diener HC, Dodick DW, Goadsby PJ, et al. Chronic migraine – classification, characteristics and treatment. *Nat Rev Neurol* 2012; 8: 162–171.

Goadsby PJ and Hargreaves R. Refractory migraine and chronic migraine: pathophysiological mechanisms. *Headache* 2008; 48: 799–804.

Katsarava Z, Manack A, Yoon MS, et al. Chronic migraine: classification and comparisons. *Cephalalgia* 2011; 31: 520–529.

Manzoni GC, Bonavita V, Bussone G, et al.; ANIRCEF (Associazione Neurologica Italiana Ricerca Cefalee). Chronic migraine classification: current knowledge and future perspectives. *J Headache Pain* 2001; 12: 585–592.

Mathew NT, Stubits E and Nigam MP. Transformed or evolutive migraine. Headache 1987; 27: 102–106.

Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia 2010; 30: 599–609.

Scher AI, Stewart WF, Liberman J, et al. Prevalence of frequent headache in a population sample. *Headache* 1998; 38: 497–506.

Scher AI, Stewart WF, Ricci JA, et al. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain* 2003; 106: 81–89.

Silberstein SD, Lipton RB and Sliwinski M. Classification of daily and near-daily headaches: field trial of revised IHS criteria. *Neurology* 1996; 47: 871–875.

Silberstein SD, Lipton RB, Solomon S, et al. Classification of daily and near-daily headaches: proposed revisions to the IHS criteria. *Headache* 1994; 34: 1–7.

Stewart WF, Scher AI and Lipton RB. Stressful life events and risk of chronic daily headache: results from the frequent headache epidemiology study. *Cephalalgia* 2001; 21: 279. Abstract no: OR32.

Yalın OO¨, Uluduz D, O¨zge A, et al. Phenotypic features of chronic migraine. *J Headache Pain* 2016; 17: 26.

Zeeberg P, Olesen J and Jensen R. Probable medication-overuse headache: the effect of a 2-month drug- free period. *Neurology* 2006; 66: 1894–1898.

Zeeberg P, Olesen J and Jensen R. Medication overuse headache and chronic migraine in a specialized headache centre: field-testing proposed new appen- dix criteria. *Cephalalgia* 2009; 29: 214–220.

1.4.1 Status migrainosus

Akhtar ND, Murray MA and Rothner AD. Status migrainosus in children and adolescents. *Semin Pediatr Neurol* 2001; 8: 27–33.

Beltramone M and Donnet A. Status migrainosus and migraine aura status in a French tertiary-care center: An 11-year retrospective analysis. *Cephalalgia* 2014; 34: 633–637.

Couch JR and Diamond S. Status migrainosus. Causative and therapeutic aspects. *Headache* 1983; 23: 94–101.

Cure J and Rothrock J. Prolonged status migrainosus complicated by cerebellar infarction. *Headache* 2007; 47: 1091–1092.

Gentile S, Rainero I, Daniele D, et al. Reversible MRI abnormalities in a patient with recurrent status migrainosus. *Cephalalgia* 2009; 29: 687-690.

Lanfranconi S, Corti S, Bersano A, et al. Aphasic and visual aura with increased vasogenic leakage: an atypical migrainosus status. *J Neurol Sci* 2009; 285: 227–229.

Perucca P, Terzaghi M and Manni R. Status epilepticus migrainosus: clinical, electrophysiologic, and imaging characteristics. *Neurology* 2010; 75: 373–374.

Raskin NH. Treatment of status migrainosus: the American experience. *Headache* 1990; 30(Suppl 2): 550–553.

1.4.2 Persistent aura without infarction

Ambrosini A, de Noordhout AM and Schoenen J. Neuromuscular transmission in migraine patients with prolonged aura. *Acta Neurol Belg* 2001; 101: 166–170.

Bento MS and Esperanca P. Migraine with prolonged aura. *Headache* 2000; 40: 52–53.

Chen WT, Fuh JL, Lu SR, et al. Persistent migrainous visual phenomena might be responsive to lamotrigine. *Headache* 2001; 41: 823–825.

Chen WT, Lin YY, Fuh JL, et al. Sustained visual cortex hyperexcitability in migraine with persistent visual aura. *Brain* 2011; 134(Pt 8): 2387–2395.

Evans RW and Lay CL. A persistent migraine aura. *Headache* 2000; 40: 696–698.

Haan J, Sluis P, Sluis IH, et al. Acetazolamide treatment for migraine aura status. *Neurology* 2000; 55: 1588–1589.

Haas DC. Prolonged migraine aura status. *Ann Neurol* 1982; 11: 197–199.

Lebedeva ER, Gurary NM, Gilev DV, et al. Prospective testing of ICHD-3 beta diagnostic criteria for migraine with aura and migraine with typical aura in patients with transient ischemic

attacks. *Cephalalgia*. Epub ahead of print 1 January 2017. DOI: 10.1177/0333102417702121.

Liu GT, Schatz NJ, Galetta SK, et al. Persistent positive visual phenomena in migraine. *Neurology* 1995; 45: 664–668.

Luda E, Bo E, Sicuro L, et al. Sustained visual aura: a totally new variation of migraine. *Headache* 1991; 31: 582–583.

Relja G, Granato A, Ukmar M, et al. Persistent aura without infarction: description of the first case studied with both brain SPECT and perfusion MRI. *Cephalalgia* 2005; 25: 56–59.

Rothrock JF. Successful treatment of persistent migraine aura with divalproex sodium. *Neurology* 1997; 48: 261–262.

San-Juan OD and Zermen˜ o PF. Migraine with persistent aura in a Mexican patient: case report and review of the literature. Cephalalgia 2007; 27: 456–460.

Smith M, Cros D and Sheen V. Hyperperfusion with vasogenic leakage by fMRI in migraine with pro- longed aura. *Neurology* 2002; 58: 1308–1310.

Wang YF, Fuh JL, Chen WT, et al. The visual aura rating scale as an outcome predictor for persistent visual aura without infarction. *Cephalalgia* 2008; 28: 1298–1304.

1.4.3 Migrainous infarction

Bono G, Minonzio G, Mauri M, et al. Complications of migraine: migrainous infarction. *Clin Exp Hypertens* 2006; 28: 233–242.

Bousser MG, Conard J, Kittner S, et al. Recommendations on the risk of ischemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine. The International Headache Society Task Force on Combined Oral Contraceptives & Hormone Replacement Therapy. *Cephalalgia* 2000; 20: 155–156.

Chang CL, Donaghy M and Poulter N. Migraine and stroke in young women: case–control study. The World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *BMJ* 1999; 318: 13–18.

Connor CCR. Complicated migraine. A study of permanent neurological and visual defects. *Lancet* 1962; ii: 1072–1075.

Laurell K, Artto V, Bendtsen L, et al. Migrainous infarction: a Nordic multicenter study. *Eur J Neurol* 2011; 18: 1220–1226.

MacGregor EA and Guillebaud J. Combined oral contraceptives, migraine and ischemic stroke. Clinical and Scientific Committee of the Faculty of Family Planning and Reproductive Health Care and the Family Planning Association. *Br J Fam Plann* 1998; 24: 55–60.

Olesen J, Friberg L, Olsen TS, et al. Ischaemia-induced (symptomatic) migraine attacks may be more frequent than migraine induced ischemic insults. *Brain* 1993; 116: 187–202.

Rothrock JF, Walicke P, Swenson MR, et al. Migrainous stroke. *Arch Neurol* 1988; 45: 63–67.

Schulz UG, Blamire AM, Davies P, et al. Normal cortical energy metabolism in migrainous stroke: A ^{31}P-MR spectroscopy study. *Stroke* 2009; 40: 3740–3744.

Tietjen GE. The relationship of migraine and stroke.

Neuroepidemiology 2000; 19: 13–19.

Tzourio C, Kittner SJ, Bousser MG, et al. Migraine and stroke in young women. *Cephalalgia* 2000; 20: 190–199.

Vollbracht S, Robbins MS and Kister I. Classification challenge in migrainous infarction. *Headache* 2014; 54: 170–171.

Wolf ME, Szabo K, Griebe M, et al. Clinical and MRI characteristics of acute migrainous infarction. *Neurology* 2011; 76: 1911–1917.

1.4.4 Migraine aura-triggered seizure

Belcastro V Striano P, Kasteleijn-Nolst Trenite´ DG et al. Migralepsy, hemicrania epileptica, postictal headache and ‘‘ictal epileptic headache’’: a proposal for terminology and classification revision. *J Headache Pain* 2011; 12: 289–294.

Davies PT and Panayiotopoulos CP. Migraine triggered seizures and epilepsy triggered headache and migraine attacks: a need for re-assessment. *J Headache Pain* 2011; 12: 287–288.

Friedenberg S and Dodick DW. Migraine-associated seizure: a case of reversible MRI abnormalities and persistent nondominant hemisphere syndrome. *Headache* 2000; 40: 487–490.

Maggioni F, Mampreso E, Ru□atti S, et al. Migralepsy: is the current definition too narrow? *Headache* 2008; 48: 1129–1132.

Marks DA and Ehrenberg BL. Migraine-related seizures in adults with epilepsy, with EEG correlation. *Neurology* 1993; 43: 2476–2483.

Merlino G, Valente MR, D’Anna S, et al. Seizures with prolonged EEG abnormalities during an attack of migraine without aura. *Headache* 2007; 47: 919–922.

arisi P and Kasteleijn-Nolst Trenite` DGA. ‘‘Migralepsy’’: a call for revision of the definition. *Epilepsia* 2010; 51: 932–933.

Rogawski MA. Common pathophysiologic mechanisms in migraine and epilepsy. *Arch Neurol* 2008; 65: 709–714.

Sances G, Guaschino E, Perucca P, et al. Migralepsy: a call for revision of the definition. *Epilepsia* 2009; 50: 2487–2496.

Ter Berg HW. Migraine-associated seizure: a case of reversible MRI abnormalities and persistent non-dominant hemisphere syndrome. *Headache* 2001; 41: 326–328.

Velioglu SK and Ozmenoglu M. Migraine-related seizures in an epileptic population. *Cephalalgia* 1999; 19: 797–801.

Verrotti A, Coppola G, Di Fonzo A, et al. Should ''migralepsy'' be considered an obsolete concept? A multicenter retrospective clinical/EEG study and review of the literature. *Epilepsy Behav* 2011; 21: 52–59.

1.5 Probable migraine

Granella F, Alessandro RD, Manzoni GC, et al. International Headache Society classification: inter- observer reliability in the diagnosis of primary head- aches. *Cephalalgia* 1994; 14: 16–20.

Rains JC, Penzien DB, Lipchik GL, et al. Diagnosis of migraine: empirical analysis of a large clinical sample of atypical migraine (IHS 1.7) patients and proposed revision of the IHS criteria. *Cephalalgia* 2001, 21: 584–595.

Rasmussen BK, Jensen R and Olesen J. A population- based analysis of the diagnostic criteria of the International Headache Society. *Cephalalgia* 1991; 11: 129–134.

Russell MB and Olesen J. Migrainous disorder and its relation to migraine without aura and migraine with aura. A genetic epidemiological study. *Cephalalgia* 1996; 16: 431–435.

1.6.1 Recurrent gastrointestinal disturbance

Abu-Arafeh I and Russel G. Prevalence and clinical features of abdominal migraine compared with those of migraine headache. *Arch Dis Child* 1995; 72: 413–417.

Al-Twaijri WA and Shevell MI. Pediatric migraine equivalents: occurrence and clinical features in prac- tice. *Pediatr Neurol* 2002; 26: 365–368.

Dignan F, Abu-Arafeh I and Russell G. The prognosis of childhood abdominal migraine. *Arch Dis Child* 2001; 84: 415–418.

Drossman DA and Dumitrascu DL. Rome III: new standard for functional gastrointestinal disorders. *J Gastrointestin Liver Dis* 2006; 15: 237–241.

Farquar HA. Abdominal migraine in children. *BMJ* 1956; i: 1082–1085.

Fleisher DR. Cyclic vomiting syndrome and migraine. *J Pediatr* 1999; 134: 533–535.

Haan J, Kors EE and Ferrari MD. Familial cyclic vomiting syndrome. *Cephalalgia* 2002; 22: 552-554.

Li BU. Cyclic vomiting syndrome: age-old syn- drome and new insights. *Semin Pediatr Neurol* 2001; 8: 13–21.

Li BUK, Lefevre F, Chelimsky GG, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr* 2008; 47: 379–393.

Rashed H, Abell TL, Familoni BO, et al. Autonomic function in cyclic vomiting syndrome and classic migraine. *Dig Dis Sci* 1999; 44(Suppl 8): 74S-78S.

Russell G, Abu-Arafeh I and Symon DN. Abdominal migraine: evidence for existence and treatment options. *Paediatr Drugs* 2002; 4: 1–8.

Thiessen PN. Recurrent abdominal pain. *Pediatr Rev* 2002; 23: 39–46.

Welch KM. Scientific basis of migraine: speculation on the relationship to cyclic vomiting. *Dig Dis Sci* 1999; 44(Suppl 8): 26S–30S.

1.6.2 Benign paroxysmal vertigo

Drigo P, Carli G and Laverda AM. Benign paroxysmal vertigo of childhood. *Brain Dev* 2001; 23: 38–41.

Dunn DW and Snyder CH. Benign paroxysmal vertigo of childhood. *Am J Dis Child* 1976; 130: 1099–1100.

Fenichel GM. Migraine as a cause of benign paroxysmal vertigo of childhood. *J Pediatr* 1967; 71: 114–115.

1.6.3 Benign paroxysmal torticollis

Drigo P, Carli G and Laverda AM. Benign paroxysmal torticollis of infancy. Brain Dev 2000; 22: 169–172.

Giffin NJ, Benton S and Goadsby PJ. Benign paroxysmal torticollis of infancy: four new cases and linkage to CACNA1A mutation. Dev Med Child Neurol 2002; 44: 490–493.

Rosman NP, Douglass LM, Sharif UM, et al. The neurology of benign paroxysmal torticollis of infancy: report of 10 new cases and review of the literature. *J Child Neurol* 2009; 24: 155–160.

12.2 Examples of Prohibited Medications

- The following medications are prohibited 30 days prior to Visit 1 (unless otherwise indicated) and throughout the study:
    - Strong OATP1B1 and OATP1B3 inhibitors (eg, gemfibrozil, cyclosporine)
    - CBD oil

	Strong/moderate CYP3A4 inducers	Strong CYP3A4 inhibitors
Anti-depressants/ Anti-anxiety	Barbiturates • Amobarbital • Aprobarbital • Butalbital • Butabarbital • Mephobarbital • Pentobarbital • Phenobarbital • Secobarbital	Nefazodone
Anti-seizure	Carbamazepine Oxcarbazepine Phenytoin Primidone	
Diabetes	Pioglitazone Troglitazone	
Glucocorticoid (Systemic)	Betamethasone Dexamethasone Hydrocortisone Methylprednisolone Prednisolone Prednisone Triamcinolone	
Antibiotics	Rifabutin Rifampicin/Rifampin	Erythromycin Clarithromycin Telithromycin
Anti-fungal		Itraconazole Ketoconazole
Anti-HIV	Efavirenz Nevirapine	Indinavir Nelfinavir Ritonavir Saquinavir
Others	St. John's wort Enzalutamide Modafinil Armodafinil	

Drugs with narrow therapeutic margins with potential for CYP drug interactions	Warfarin Digoxin Cisapride Pimozide
For participants from lead-in study 3101-303-002 already taking 1 medication with demonstrated efficacy for the prevention of migraine are allowed to maintain previous preventive medication at a stable dose during this study.	Topiramate Valproic acid, sodium valproate, divalproex sodium Amitriptyline Nortriptyline Metoprolol Atenolol Nadolol Propranolol Timolol Flunarizine Candesartan Lisinopril Desvenlafaxine Venlafaxine

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

- Botulinum toxin injections into areas of the head, face, or neck (eg, Dysport®, Botox®, Xeomin®, Myobloc®, Jeuveau™)
- Injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®, Vyepti™)

12.3 Study Visits Conducted Remotely

Remote study visits, conducted virtually or by phone, are permitted if the Investigator determines there to be a public health risk due to viral infection (eg, COVID-19) to the participant or site staff. During remote study visits, the Remote Visit Schedule of Assessments (Table 12–1) 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.

Table 12–1. Remote Visits Schedule of Assessments (ie, Schedule of Visits and Procedures)

Study Period	**Open-label Treatment Period (12 weeks)**				**Safety Follow-up Period (4 weeks)**
		Potential for Remote Study Visit			
Visit #	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4/ET**	**Visit 5/EOS**
Week (Day)	***Day 1***	***Week 4 (Day 28)***	***Week 8 (Day 56)***	***Week 12 (Day 84)***	***Week 16 (Day 112)***
Visit Windows	N/A	± 3 days	± 3 days	± 3 days	± 3 days
Perform urine pregnancy test[a,b]	X	X	X	X	X
Collect start date (first day) of last menstrual cycle for women having menstrual cycles	X	X	X	X	X
Participant eDiary data collection	X				
eDiary data and compliance review		X	X	X	
MSQ v2.1 (web portal)	X	X	X	X	X
C-SSRS	X	X	X	X	X
Dispense atogepant[a]	X	X	X		
Review atogepant compliance and accountability		X	X	X	
Adverse events	X				
Concomitant medications/concurrent procedures	X				

[a] 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.

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

12.4 Glossary of Abbreviations

Term/Abbreviation	Definition
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
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CM	chronic migraine
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EOS	end of study
ET	early termination
eTablet	electronic tablet
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on 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
IUD	intrauterine device
IUS	intrauterine hormone releasing system
IV	intravenous
IWRS	interactive web response system
mITT	modified intent to treat
MSQ v2.1	Migraine Specific Quality of Life Questionnaire, Version 2.1

Term/Abbreviation	Definition
NSAID	nonsteroidal anti-inflammatory drug
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
PK	pharmacokinetic
PRO	patient reported outcome
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RNA	ribonucleic acid
SAE	serious adverse event
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
WOCBP	women of childbearing potential

12.5 Protocol Amendment 1 Summary

Title: A Phase 3, Multicenter, Open-Label, 12-Week Study to Evaluate the Safety and Tolerability of Oral Atogepant for the Prevention of Migraine in Chinese Participants With Chronic Migraine

Protocol 3101-311-002

Date of Amendment: July 2020

Amendment Summary

This amendment includes changes made to Protocol 3101-311-002 dated 18 March 2020. The protocol was amended to:

- Remove reference to Study 3101-305-002 (regional study of preventive treatment of episodic migraine in China and Japan)
- Add Attachment 12.3 for study visits to be conducted remotely to eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic, while ensuring participant safety and maintaining data integrity

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

Section	Revision	Rationale
Throughout	Removal of episodic migraine as an indication in this study.	Removed in line with removal of Study 3101-305-002.
Throughout	Removal of lead-in Study 3101-305-002 (episodic migraine) from protocol.	Due to business decision.
Section 7.4	Removal of statement that subgroup analyses will be performed for selected endpoints.	Removal of Study 3101-305-002 as lead-in study.
Attachment 12.3	Addition of "Attachment 12.3 Study Visits Conducted Remotely" to describe remote study visits, including a Remote Visits Schedule of Assessments.	To eliminate immediate potential hazards to participants and study staff due to the COVID-19 pandemic while ensuring participant safety and maintaining data integrity.