NCT02873221

Study ID: UBR-MD-04

Title: A Multicenter, Randomized, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine With or Without Aura

Protocol Amd 3 Date: 11-Apr-2018

ALLERGAN – CONFIDENTIAL

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

A MULTICENTER, RANDOMIZED, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF ORAL UBROGEPANT IN THE ACUTE TREATMENT OF MIGRAINE WITH OR WITHOUT AURA

Protocol Number:	UBR-MD-04 Amendment 3
Phase:	3
Name of Investigational Product:	Ubrogepant
Sponsor:	Allergan Pharmaceuticals International Limited Clonshaugh Industrial Estate Coolock Dublin 17 Ireland Authorized US Agent Allergan Sales, LLC 2525 Dupont Drive Irvine, California USA 92612 +1-714-246-4500 +1-800-347-4500
Emergency Telephone Number(s):	Refer to the Study Contacts Page
Serious Adverse Event Reporting Fax Number:	[redacted]
Allergan Medical Safety Physician Contact Information:	Please see Study Contact Sheet
Allergan Signatory:	[redacted]
Original Protocol Date:	02 May 2016
Protocol Amendment 1 Date:	15 Nov 2016
Protocol Amendment 2 Date:	06 Dec 2017
Protocol Amendment 3 Date:	11 Apr 2018

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and Emergency Telephone Numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (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 investigational product(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

[redacted]

Protocol Summary

Study Compound: Ubrogepant

Phase: 3

Study Objective: To evaluate the safety and tolerability of intermittent treatment with ubrogepant for the acute treatment of migraine over 1 year

Clinical Hypotheses: Ubrogepant 50 and 100 mg is safe and tolerable for the acute treatment of migraine over 1 year

Study Design

Structure: multicenter, randomized, open-label, 52-week extension study

Duration: 52 weeks

Study Treatment Groups: usual care, ubrogepant 50 mg, or ubrogepant 100 mg

Controls: Not applicable

Dosage/Dose Regimen: Patients randomized to either of the ubrogepant arms will treat up to 8 migraine attacks (of any pain severity) per every 4-week period at home for a total of 1 year. Patients have the option to take a second dose of ubrogepant if the patient has either a nonresponding migraine or a migraine recurrence. The second dose of ubrogepant will be identical to the first dose.

Patients randomized to the usual-care arm will be instructed to treat their migraine with medications that they routinely use to relieve a migraine attack.

[redacted]

Study Population Characteristics

Number of Patients: Approximately 1200 patients will be randomized (400 patients per arm) from approximately 200 centers in the United States

Condition/Disease: Migraine with or without aura

Key Inclusion Criteria: To be eligible for study participation, patients must have completed 1 of the lead-in studies, UBR-MD-01 or UBR-MD-02, [redacted]

Key Exclusion Criteria: Patients with clinically significant electrocardiogram (ECG), vital sign, physical examination, or laboratory abnormalities, or who require prohibited concomitant medications (see Section 4.5.2)

Response Measures

[redacted]

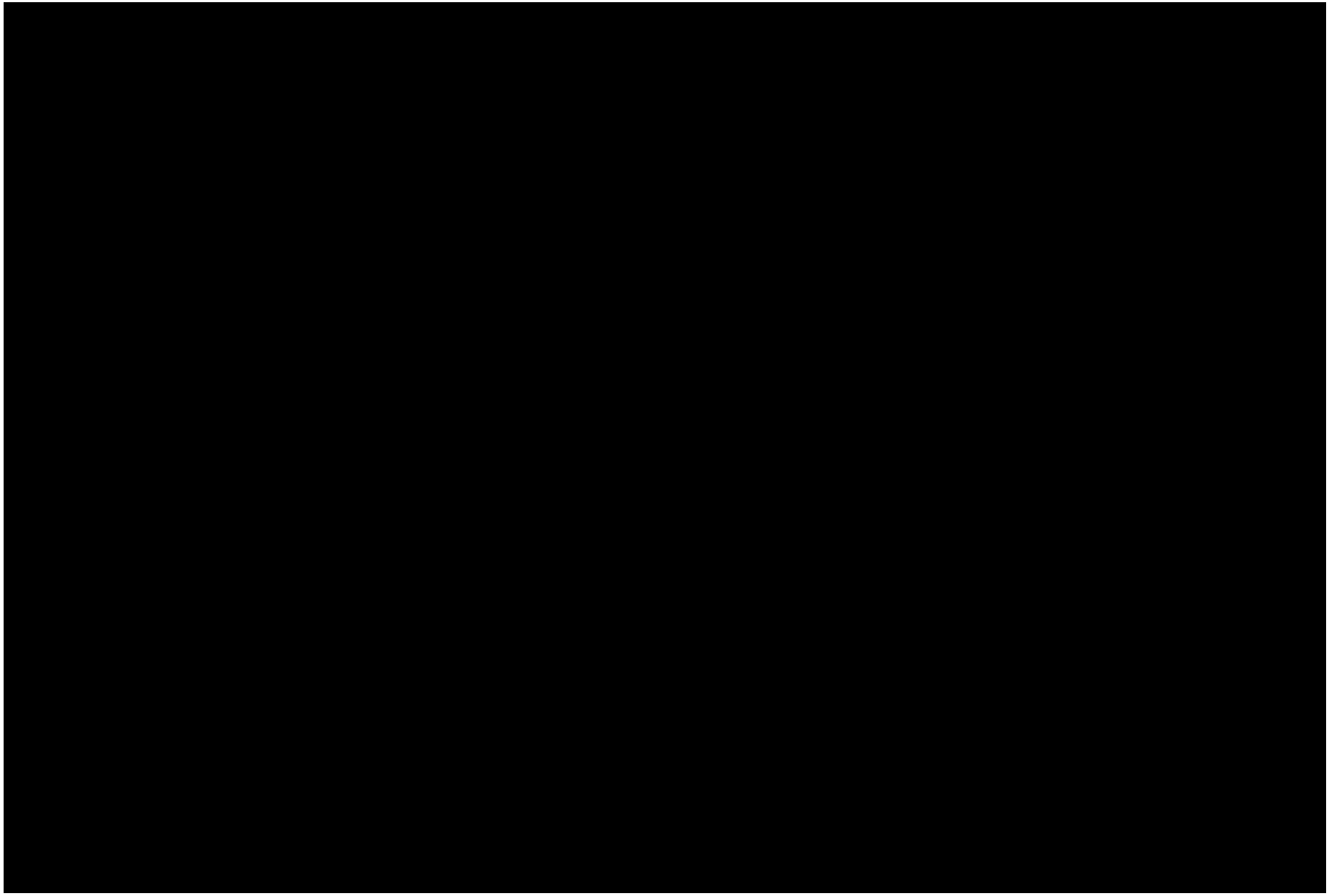
Safety: AEs, physical examinations, clinical laboratory determinations, vital sign measurements, ECG parameters, and the Columbia –Suicide Severity Rating Scale (C-SSRS)

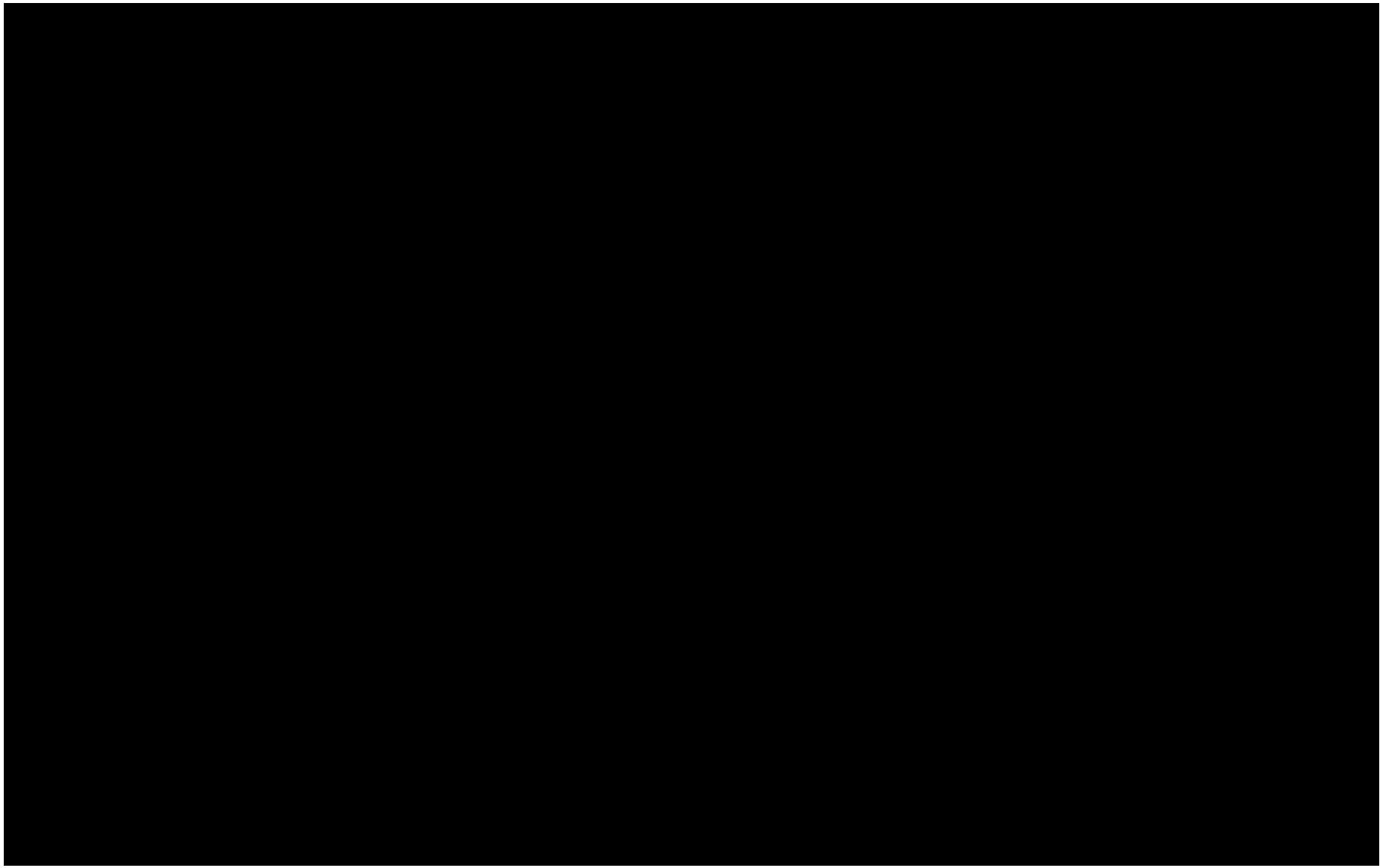
General Statistical Methods and Types of Analyses:

[redacted]

The safety analyses will be performed using the Safety population and will include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, and the C-SSRS. For each of the clinical, laboratory, vital sign, and ECG parameters, the last nonmissing safety assessment before the first dose in the lead-in study will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by the number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

[redacted]





1. Background and Clinical Rationale

What is Migraine and How Prevalent is It?

Migraine affects 18% of women and 6% of men in the United States with a peak prevalence occurring between the ages of 25 to 55 years. Approximately one-third of migraineurs have 3 or more migraine headaches per month, and over half report severe impairment or the need for bed rest during an attack (Lipton 2007). In the United States, work loss due to migraine is estimated to cost ~$13 billion annually (Hu 1999). Prevalence is similar in Europe, with migraine headache affecting 17.6% of women and 8% of men (Stovner 2010). It is currently ranked by the World Health Organization as 19th among causes of disability (Katsarava 2012).

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, migraine headache may be preceded by focal neurological dysfunction (aura). Improving the diagnosis and optimizing treatments for migraine have been recognized as critically important to reduce the global burden of migraine (Katsarava 2012).

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. Chronic migraine is a specific International Classification of Headache Disorders criteria, 3rd edition beta version (ICHD-3 beta) diagnosis applied to a subset of patients with ≥ 15 headache days per month (ICHD-3 beta 2013; Katsarava 2012; Olesen 2006).

What is CGRP and Its Relationship to Migraine?

Calcitonin gene-related peptide (CGRP) is a neuropeptide implicated in the pathophysiology of migraine. CGRP levels in the cranial venous outflow (ie, external jugular vein) are increased during a migraine attack (Goadsby 1993) and exogenously administered CGRP has been shown to trigger migraine-like headache in migraineurs. The majority (80 to 90%) of trigeminal Aδ fibers that innervate the dura contain CGRP, suggesting that these fibers may be involved in sterile neurogenic inflammation and migraine pain transmission. Furthermore, the CGRP receptor is present on human meningeal and cerebral blood vessels. These observations suggest that activation of the trigeminovascular system, with release of CGRP,

may play a key role in migraine pathogenesis and that inhibition of CGRP function may yield a novel therapeutic approach to treating migraine.

Establishment of CGRP Antagonism to Treat Migraine

The ability of CGRP antagonism to relieve pain in the acute treatment of migraine was established by using an intravenous (IV) formulation of olcegepant (Olesen 2004), and replicated by Merck & Co., Inc., with an oral formulation of telcagepant, a highly selective CGRP receptor antagonist (CGRP RA). In Phase 3 studies, telcagepant was superior to placebo in the primary endpoints of 2-hour pain freedom, 2-hour pain relief, and the absence of associated symptoms (photophobia, phonophobia, and nausea), as well as the key secondary endpoint of 24-hour sustained pain freedom (SPF) (Connor 2009). Serum alanine aminotransferase (ALT) increases were observed with telcagepant, as well as with a second CGRP antagonist, MK-3207. For this reason, the development of these compounds was stopped.

What is Ubrogepant?

Ubrogepant, a novel CGRP receptor antagonist that is chemically distinct from both telcagepant and MK-3207, is now being developed for the acute treatment of migraine. Preclinical and clinical studies conducted to date for ubrogepant have shown no evidence of hepatotoxicity.

A Phase 2b clinical study was conducted, which compared 1, 10, 25, 50, and 100 mg doses of ubrogepant to placebo in the acute treatment of migraine. Overall, all the ubrogepant doses tested were well tolerated and the adverse event (AE) profile of all ubrogepant doses did not differ significantly from placebo. For the primary efficacy endpoint of pain freedom at 2 hours, ubrogepant doses of 1 and 10 mg did not differ from placebo, but doses of 25, 50, and 100 mg were better than placebo. For the primary efficacy endpoint of pain relief at 2 hours none of the ubrogepant doses differed from placebo, probably due to a high placebo response rate.

The absence of migraine-associated symptoms of photophobia, phonophobia, and nausea were assessed as key secondary endpoints. Ubrogepant doses of 50 and 100 mg were significantly better than placebo for absence of phonophobia and photophobia at 2 hours, whereas 25 mg did not differ from placebo. None of the ubrogepant doses differed from placebo for the endpoint of absence of nausea at 2 hours. Measures of sustained migraine headache relief (2 to 24 hours and 2 to 48 hours SPF and sustained pain relief) generally suggested that ubrogepant 50 mg and 100 mg were more effective than the 25 mg dose.

This trial is being conducted to evaluate the long-term safety and tolerability of ubrogepant for the acute treatment of migraine.

The purpose of including the usual-care arm will be to contextualize any safety findings that may occur over the course of a year in the ubrogepant arms. In open-label designs without a comparator arm, it can be difficult to interpret any safety findings that may arise in the experimental treatment arm. The proposed inclusion of the usual-care arm in this study is intended to address this limitation. Because of the stated purpose of the usual-care arm, efficacy data will not be collected from patients randomized to this arm.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To evaluate the safety and tolerability of intermittent treatment with ubrogepant for the acute treatment of migraine over 1 year.

2.2 Clinical Hypothesis

Ubrogepant 50 and 100 mg is safe and tolerable for the acute treatment of migraine over 1 year.

3. Study Design

This multicenter, randomized, open-label, 52-week extension study will enroll approximately 1200 patients from approximately 200 centers in the United States. Patients will be randomized (1:1:1) to 1 of the following 3 treatment groups: usual care, ubrogepant 50 mg, or ubrogepant 100 mg (400 patients per arm). The study is open-label; however, randomization to the ubrogepant arms (50 and 100 mg) will be blinded. If and when an interim analysis occurs, the doses will be unblinded (see Section 7.6).

Patients randomized to either of the ubrogepant arms will treat up to 8 migraine attacks (of any pain severity) per 4-week period at home for a total of 1 year. Patients have the option to take a second dose of ubrogepant or rescue medication if the patient has either a nonresponding migraine or a migraine recurrence. The second dose of ubrogepant will be identical to the first dose. For detailed information on migraine treatment regimens, including optional second dose and rescue medication, see Section 5.6.

Patients randomized to the usual-care arm will be instructed to treat their migraine with medication(s) that they routinely use to relieve a migraine attack. Their usual medication(s)

for acute treatment will be identified at Visit 1 and any changes throughout the study will be recorded in the electronic case report form (eCRF).

[redacted].

The primary outcome is safety and tolerability. The planned safety assessments include collection of AEs, clinical laboratory determinations, ECGs, vital sign measurements, physical examinations, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

3.1 Adjudication Committee and Data Safety Monitoring Board

The Adjudication Charter will be established and will describe the process for the surveillance, monitoring, and adjudication by the Clinical Adjudication Committee of events of post-treatment elevations of ALT and/or aspartate aminotransferase (AST) ≥ 3 times the upper limit of normal (ULN) in the ubrogepant program. The purpose of this committee charter will be to provide a standardized process for the adjudication of data associated with these events in order to determine whether the elevation was due to ubrogepant or not, and to determine whether there was a confounding factor.

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

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 1200 patients will be randomized (400 patients per arm) from approximately 200 centers in the United States.

4.2 Study Population Characteristics

This study will include adult patients with migraine with or without aura who completed Study UBR-MD-01 or UBR-MD-02.

4.3 Inclusion Criteria

To be eligible to participate in the study, patients must meet the following criteria:

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

2. Completed Study UBR-MD-01 or Study UBR-MD-02.

[redacted]

4.4 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

[redacted]

2. Requirement for any medication during the study that is on the list of prohibited concomitant medications (see Sections 4.5.2 and 12.2) that cannot be discontinued or switched to an allowable alternative medication.

[redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Medications that are not specifically prohibited are allowed, with the following clarifications and restrictions for patients taking ubrogepant. Note that for patients assigned to the usual-care arm, these restrictions do not apply.

The following medications are allowed during the study but are prohibited within 48 hours prior to taking ubrogepant:

- any triptan
- any ergot derivative
- any opioid
- any nonsteroidal anti-inflammatory drug (NSAID)
- any other form of analgesic (including acetaminophen)
- any antiemetic agent
- any proton pump inhibitor

The following medications are allowed during the study, but are prohibited within 24 hours prior to taking investigational product (IP):

- any antacid
- any H_2 blocker

Examples of allowed but restricted medications listed above are displayed in Section 12.2.

- Aspirin up to 325 mg/day is allowed for cardiac prophylaxis.
- Daily use of pregabalin is allowed.

Patients on a stable prescribed dose of selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) in the lead-in study should continue without change in dose throughout this study.

Patients on migraine prophylactic medication (eg, beta-blocker, tricyclic antidepressant, topiramate, valproic acid, botulinum toxin) in the lead-in study should continue without change in dose throughout this study.

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

4.5.1.1 Acute Treatment/Rescue Medication

Medications for acute treatment of migraine listed above may be taken during the study within the parameters noted in Section 4.5.1 for patients taking ubrogepant. [redacted]

[redacted]

4.5.1.2 Definition of Females of Childbearing Potential and/or Acceptable Contraceptive Methods

For the purposes of this study, females 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 salpingectomy, bilateral oophorectomy or hysterectomy).

For WOCBP who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, vaginal ring, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, intrauterine device, vasectomized partner, or sexual abstinence.

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

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

If a female becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed, and the patient will be withdrawn from the study after appropriate safety follow-up. The investigator will (1) notify the patient's physician that the patient was being treated with investigational drug ubrogepant, 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 Allergan.

4.5.2 Prohibited Medications/Treatments

The following medications are prohibited throughout the study period for patients taking ubrogepant. Note that for patients assigned to the usual-care arm, these restrictions do not apply.

- strong and moderate cytochrome P450 3A4 (CYP3A4) inhibitors, including but not limited to: systemic (oral/IV) itraconazole, ketoconazole, fluconazole, erythromycin, clarithromycin, telithromycin, diltiazem, verapamil, aprepitant, cyclosporine, nefazodone, cimetidine, quinine, and human immunodeficiency virus (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

- inhibitors of the breast cancer resistance protein (BCRP) transporter (eg, rifampin)
- drugs with narrow therapeutic margins (eg, digoxin, warfarin)

Examples of prohibited medications in the classes noted above are displayed in Attachment 12.2.

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

4.5.3 Special Diet or Activities

Patients taking ubrogepant must refrain from consuming grapefruit or grapefruit juice from the time the consent form is signed until completion of the study. In addition, patients will be asked to refrain from sleeping and from consuming caffeine for at least 2 hours after they take IP.

Alcohol intake should be limited to no more than 3 drinks per day throughout the study. A drink is defined as a 12-ounce can/bottle of beer, a 4-ounce glass of wine, or 1 ounce of liquor.

5. Study Treatments

5.1 Study Treatments and Formulations

Ubrogepant [redacted] oral compressed tablets containing 50 mg of ubrogepant.

Ubrogepant placebo [redacted] tablets.

5.2 Control Treatment

This study does not include a control treatment.

5.3 Methods for Masking/Blinding

Ubrogepant will be provided to patients in the ubrogepant arms. A modified double-dummy design will be used to maintain the study blind for the ubrogepant arms. Patients randomized

to the ubrogepant arms will be provided IP in identical blister cards to maintain the blinding, and instructed to take 2 tablets to treat their migraine attack regardless of the dose group to which they are assigned. The patients randomized to the usual-care arm will not be dispensed ubrogepant.

5.4 Treatment Allocation Ratio [redacted]

Patients will be randomized (1:1:1) to 1 of the following 3 treatment groups: usual-care, ubrogepant 50 mg, or ubrogepant 100 mg. The study is open-label; however, randomization to the ubrogepant arms (50 and 100 mg) will be blinded. If and when an interim analysis occurs, the doses will be unblinded (see Section 7.6).

[redacted]

5.5 Method for Assignment to Treatment Groups/Randomization

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

At the time of randomization (ie, Visit 2), eligible patients will be randomly assigned to 1 of 3 treatment arms in a 1:1:1 ratio to receive usual-care, ubrogepant 50 mg, or ubrogepant 100 mg or [redacted].

An automated interactive web response system (IWRS) will be used to manage the randomization and treatment assignment. Allergan Biostatistics (randomization programmer) will prepare the randomization codes.

Investigational product will be labeled with medication kit numbers. The IWRS will provide the site with the specific medication kit number(s) for each randomized patient in the ubrogepant arms at the time of randomization. Sites will dispense IP according to the IWRS instructions. Sites will receive the IWRS confirmation notifications for each transaction. All notifications will be maintained with the study source documents.

5.6 Treatment Regimen and Dosing

5.6.1 Ubrogepant

Table 2 presents the treatments that will be administered in this study. Patients randomized to the ubrogepant arms will be instructed to take 2 tablets to treat their migraine attack regardless of the dose group to which they are assigned.

Table 2 Treatments Administered for Initial and Optional Second Dose

Drug/Dose	Dose Frequency	Route of Administration	Investigational Product Administered	
			Initial Dose	Optional Second Dose
Ubrogepant 50 mg	Up to 8 times/4 weeks for 1 year (with optional second dose – maximum 16 times/4 weeks)	Oral (tablet)	Ubrogepant 50 mg/ placebo 50 mg	Ubrogepant 50 mg/ placebo 50 mg
Ubrogepant 100 mg	Up to 8 times/4 weeks for 1 year (with optional second dose – maximum 16 times/4 weeks)	Oral (tablet)	Ubrogepant 50 mg/ ubrogepant 50 mg	Ubrogepant 50 mg/ ubrogepant 50 mg

Patients randomized to the ubrogepant arms will be allowed to treat up to 8 qualifying migraine headaches (of any pain severity) per 4-week period throughout the course of a year. Patients will be instructed to treat the migraine headaches as soon as possible when all of the following conditions are met:

- At least 48 hours since the last dose of ubrogepant
- At least 48 hours of pain freedom (ie, no headache for at least 48 hours)
- The migraine headache started less than 4 hours ago
- The migraine headache is not already resolving on its own
- Prohibited medication has not been taken

5.6.2 Usual Care

Patients randomized to the usual-care arm will be instructed to treat their migraine with the medication(s) that they routinely take to relieve a migraine attack. Their usual medication(s) for acute treatment will be identified at Visit 1. At any time during the study, the patient's treating physician or the investigator may instruct these patients to change their migraine treatment. Any changes to the usual medication(s) identified at Visit 1 will be recorded in the

eCRF. There will be no limitations to the number of migraines treated and no qualifiers to treat a migraine for patients in this arm.

5.6.3 Optional Second Dose and Rescue Medication

Patients who took ubrogepant for their initial dose will have the opportunity to take an optional second dose of ubrogepant if they continue to have headache of any pain severity or if headache (of any pain severity) returns. An optional second dose can be taken from 2 to 48 hours after the initial ubrogepant dose.

[redacted]

[redacted]

[redacted]

5.7 Storage of Investigational Products/Treatments

Investigational product at the site must be stored at room temperature in a securely locked cabinet. Further details regarding the storage of the IP are in the Study Reference Manual.

6. Response Measures and Summary of Data Collection Methods

[redacted]

[redacted]

[redacted]

[redacted]

6.2 Safety Measures

6.2.1 Adverse Events

Subjective AEs will be collected throughout the study. For all AEs, the investigator must provide an assessment of the severity, causal relationship to the IP, start and stop date, and seriousness of the event (eg, serious adverse event [SAE]), document all actions taken with regard to the IP, and detail any other treatment measures taken for the AE. For events noted as SAEs, Allergan must be notified immediately to meet their reporting obligations to appropriate regulatory authorities (see Section 9.3).

6.2.2 Events of Clinical Interest

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

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

Reporting requirements for ALT or AST elevations and potential Hy's law cases are outlined in Sections 9.5 and 9.6. Responses to the C-SSRS that meet the above criterion will be captured in the electronic tablet (eTablet) and monitored by Allergan. Events that are determined to be AEs or SAEs must be reported appropriately via the designated eCRF pages and forms.

6.2.3 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the visits outlined in Table 1. Hematology, chemistry, and urinalysis will be conducted at these visits. The investigator will assess the clinical significance of any values outside the reference ranges provided by the central laboratory. 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. Patients with abnormalities judged to be clinically significant at Screening (Visit 1) will be excluded from the study. WOCBP will be required to have a urine pregnancy test at all visits. A positive pregnancy test at Visit 1 or Visit 2 will exclude the patient from participation in the study. Investigators may also perform unscheduled clinical laboratory determinations at any time for the purpose of patient safety. Patients are not required to fast overnight before coming in for their appointments.

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

Table 3 Clinical Laboratory Parameters

Category	Parameter
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol, high density lipoprotein, low density lipoprotein, total triglycerides; 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

6.2.4 Vital Sign Measurements

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

6.2.5 Physical Examinations

A complete physical examination will be performed at the visits outlined in Table 1. A professionally trained physician or healthcare professional licensed to performed physical examinations will examine the patient 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.

6.2.6 Electrocardiograms

A 12-lead ECG will be performed at the visits outlined in Table 1. ECGs will be sent to a central ECG laboratory to be centrally read by a cardiologist. All ECGs should be performed after the patient has been supine for at least 5 minutes. A copy of the ECG 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. The overall interpretation

of the clinical significance of the ECG will be determined by the investigator and recorded in the patient's eCRF in the source notes.

6.2.7 Suicidality Assessment

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: Type 1 (wish to be dead), Type 2 (nonspecific active suicidal thoughts), Type 3 (active suicidal ideation with any methods [not plan] without intent to act), Type 4 (active suicidal ideation with some intent to act, without specific plan), and Type 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: Type 0 (no suicidal behavior), Type 1 (preparatory acts or behavior), Type 2 (aborted attempt), Type 3 (interrupted attempt), and Type 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 the previous visit. The C-SSRS will be completed on the eTablet by the investigator or designee with current and valid training in administering the assessment. A patient should not be released from the study center until the results of C-SSRS are reviewed and it is confirmed that the patient is not considered to be at risk.

6.2.8 Cardiovascular Disease Risk

Patients will be classified to 1 of 3 coronary heart disease risk categories (low, moderate, high) based on the National Cholesterol Education Program (NCEP; NIH Publication No. 01-3670, 2001).

- Category 1 (High Risk): > 20% 10-year cardiovascular (CV) risk
- Category 2 (Moderate Risk): 10 to 20% 10-year CV risk
- Category 3 (Low Risk): < 10% 10-year CV risk

Risk of cardiovascular disease will be assessed in the lead-in studies using an algorithm based on NCEP and the Framingham risk factors, along with the presence of cardiovascular heart disease or other clinical forms of atherosclerotic disease, as well as diabetes.

6.3 Other Study Supplies

The following will be provided by Allergan:

- All supplies needed for blood and urine sampling (central laboratory analysis, urine culture/sensitivity), urine dipstick reagent strips, and urine pregnancy tests
- Shipping materials for shipment of laboratory samples to central laboratory
- All supplies needed for ECG assessment, including ECG machine
- eDiary
- eTablet

6.4 Summary of Methods of Data Collection

An IWRS will be used to randomize patients and manage ubrogepant inventory. Data for this study will be collected using eCRFs via an electronic data capture system. Source documents will be used at the sites and may include a patient's medical record, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests, such as laboratory tests, ECGs, etc. Centralized vendors will be used for the analysis of all blood/urine samples and ECG assessments. Additional information on the collection and handling of samples is detailed in respective laboratory manuals.

Patients in the ubrogepant arms will use an eDiary to record details associated with their migraine attack, [redacted]. Patients in the usual-care arm will use the eDiary to record details associated with their migraine attack before it is treated with their usual medication.

The C-SSRS will be conducted as a clinical interview at each visit and recorded by a qualified site staff member via an eTablet.

7. Statistical Procedures

7.1 Analysis Populations

7.1.1 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population will consist of all randomized patients who received at least 1 dose of IP (ubrogepant) and had at least 1 post-treatment efficacy

assessment in this study. The mITT population is only defined for the ubrogepant arms, as no efficacy measurements will be collected from patients in the usual-care arm.

7.1.2 Safety Population

The Safety population will be defined separately for the ubrogepant arms and the usual-care arm.

- Ubrogepant arms: All randomized patients who received ≥ 1 dose of treatment
- Usual-care arm: All randomized patients in the usual-care arm.

The purpose of the usual-care arm is to contextualize any safety findings that may occur in the ubrogepant treated patients over the course of 12 months. As such, data from all patients randomized to the usual-care arm, regardless of whether the patient used medication to treat migraine, will be included in the safety analyses.

[redacted]

7.3 Hypothesis and Methods of Analysis

[redacted]

[redacted]

7.3.2 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 last nonmissing safety assessment before the first dose in the lead-in study will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by the number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

7.3.2.1 Adverse Events

AEs will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities.

An AE will be considered a treatment-emergent adverse event (TEAE) if it was present after the first dose of treatment in the lead-in study or was present before the date of the first dose of treatment in the lead-in study and increased in severity after the first dose of treatment in the lead-in study. If more than 1 AE was reported before the first dose of treatment of the lead-in study and coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring after the first dose of treatment of the lead-in study. An AE that occurs after Visit 16 for patients with Visit 16, or more than 30 days after the last visit or last treatment, whichever is later, for patients without Visit 16 will not be considered as a TEAE.

The number and percentage of patients reporting TEAEs after randomization in each treatment group will be tabulated by descending percentage in the highest dose group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study treatment. If more than 1 AE is coded to the same patient, the patient will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

The incidence of common (≥ 2% of patients in any treatment group) TEAEs will be summarized by system organ class, preferred term, and treatment group.

The total number of TEAEs by severity and causal relationship to the study treatment will be summarized by treatment group.

A SAE that occurred between the date of the first dose of treatment in the lead-in study and Visit 16 for patients with Visit 16, or within 30 days after the last visit or last treatment, whichever is later, for patients without Visit 16, inclusive, will be considered an on-therapy SAE. The number and percentage of patients who have on-therapy SAEs after randomization will be summarized by preferred term and treatment group.

The number and percentage of patients who had AEs leading to premature discontinuation of the study treatment will be summarized by preferred term and treatment.

For all screened patients, separate tabular displays will be presented for patients who died, patients with SAEs, and patients with AEs leading to premature discontinuation.

The number and percentage of patients with TEAEs of clinical interest will be summarized by preferred term and treatment group. TEAEs of clinical interest include triptan-associated TEAEs, abuse-related TEAEs, hepatic injury TEAEs, cardiac arrhythmias TEAEs, central nervous system TEAEs, vascular disorders TEAEs, embolic and thrombotic events TEAEs, hypertension TEAEs, ischemic heart disease TEAEs, and suicide/self-injury TEAEs.

7.3.2.2 Cardiovascular Risk

Patients will be categorized into 1 of 3 coronary heart disease (CHD) risk subgroups based on National Cholesterol Education Program Adult Treatment Panel III Guidelines (NCEP ATP III) (Grundy 2004; NIH Publication No. 01-3670, 2001). An algorithm will be used for assigning patients to a CV risk category (low, moderate, or high risk) in the lead-in studies.

A summary of adverse experiences will be provided for the CV risk factor subgroups listed above.

7.3.2.3 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment timepoint will be presented by treatment group for clinical laboratory parameters. In addition, descriptive statistics for values and changes from the baseline values in conventional units at each assessment timepoint will be presented for selected clinical laboratory parameters. Patient narratives will also include the values in conventional units for the selected laboratory parameters.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria. PCS criteria will be specified in the Statistical Analysis Plan (SAP). The number and percentage of patients who have PCS postbaseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non PCS baseline values and at least 1 PCS postbaseline value. A supportive tabular display of patients with PCS postbaseline values will be provided, including the

patient number, baseline, and all postbaseline (including non-PCS) values. In addition, a tabular display showing all AEs that occurred in patients who had PCS postbaseline clinical laboratory values will be provided.

Shift tables from baseline to end of study for clinical laboratory parameters will be presented by treatment group for the following categories: low, normal, and high, which are provided by the lab vendor.

Any post-treatment ALT and/or AST results that are ≥ 3 times the ULN are considered events of clinical interest in this study and are subject to blinded adjudication by the Clinical Adjudication Committee to determine whether the elevation is due to treatment or not, and to determine whether there is a confounding factor. Patients with liver function laboratory findings that meet predetermined criteria will be summarized by treatment group along with the adjudication results. A detailed listing of all patients with any liver function laboratory findings will be provided.

7.3.2.4 Vital Sign Measurements

Descriptive statistics for vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiratory rate, temperature, weight, and BMI) and changes from baseline values at each visit and at the end of study will be presented by treatment group.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria. PCS criteria will be specified in the SAP. The number and percentage of patients with PCS postbaseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive tabular display of patients with PCS postbaseline values will be provided, including the patient number, baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in patients who had PCS postbaseline vital sign values will be provided.

7.3.2.5 Electrocardiogram

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS interval, QT interval, and QTc) and changes from baseline values at each assessment timepoint to the end of study will be presented by treatment group.

Electrocardiographic parameter values are considered PCS if they meet or exceed the higher-limit PCS criteria. PCS criteria will be specified in the SAP. The number and percentage of patients with PCS postbaseline ECG values will be tabulated by treatment group. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator is the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive tabular display of patients with PCS postbaseline values will be provided, including the patient number, baseline, all postbaseline (including non-PCS) values, and change from baseline. In addition, a tabular display showing all AEs that occurred in patients who had postbaseline PCS ECG values will be provided.

A shift table from baseline to the end of study in the investigator's overall interpretation of the ECG will be presented by treatment group for the following categories: normal, abnormal, not clinically significant, abnormal, clinically significant. A tabular display showing patients with postbaseline clinically significant ECG abnormalities according to the investigator's overall interpretation will be provided.

7.3.2.6 Suicidality Assessment

For the C-SSRS, the number of patients with suicidal ideation and suicidal behavior in lifetime history, during the treatment period, and during the Safety Follow-up period will be summarized by treatment group for the Safety population. Supportive tabular display of patients with all values will be provided, including patient number, treatment group, visit number, intensity of suicidal ideation, suicidal behavior type, and lethality of suicidal behavior.

7.3.2.7 Potential Hy's Law

Potential Hy's Law criteria within a 24-hour window is defined by a postbaseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times the ULN, along with total bilirubin (TBL) ≥ 2 times the ULN and a nonelevated alkaline phosphatase (ALP) < 2 times the ULN, all based on blood draws collected within a 24-hour period.

Potential Hy's Law criteria without time window (evaluation of drug-induced serious hepatotoxicity [eDISH]) is defined by maximum of postbaseline elevation of ALT or AST ≥ 3 times the ULN, along with maximum of postbaseline elevation of TBL ≥ 2 times the ULN.

Patients who meet the potential Hy's Law criteria from randomization to Visit 16 will be summarized. Supportive tabular displays also will be provided.

7.4 Subgroup Analyses

Subgroup analyses will be done for disposition, treatment exposure, and TEAEs for sex, age group (< 40 vs ≥ 40, and < 65 vs ≥ 65), race (white vs all other races), cardiovascular risk category, and renal function class.

[redacted]

7.6 Interim Analyses

The interim analysis for Study UBR-MD-04 will occur when at least 300 ubrogepant patients (with a minimum of 2 migraines treated with ubrogepant per month, on average) have been enrolled in Study UBR-MD-04 for 6 months and 200 ubrogepant patients (with a minimum of 2 migraines treated with ubrogepant per month, on average) have been enrolled in Study UBR-MD-04 for 1 year.

In regards to blinding, although this is an open-label study, randomization to the ubrogepant 50 mg or 100 mg arms is blinded. If and when an interim analysis occurs, Allergan staff will be unblinded to the ubrogepant doses; however, patients and sites will remain blinded. The interim analysis will include all analyses specified in the SAP except for efficacy analyses.

Details regarding the interim analysis are specified in the SAP.

8. Study Visit Schedule and Procedures

Table 1 presents the schedule of visits and procedures.

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the inclusion and exclusion criteria in Sections 4.3 and 4.4 who completed Study UBR-MD-01 or UBR-MD-02 will be considered for entry into this study.

8.1.2 Informed Consent and Patient Privacy

The study will be discussed with the patient and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization and other written documentation in accordance with local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each patient that provides informed consent will continue using the patient number assigned in the lead-in study for documentation throughout the study.

[redacted]

and [redacted]

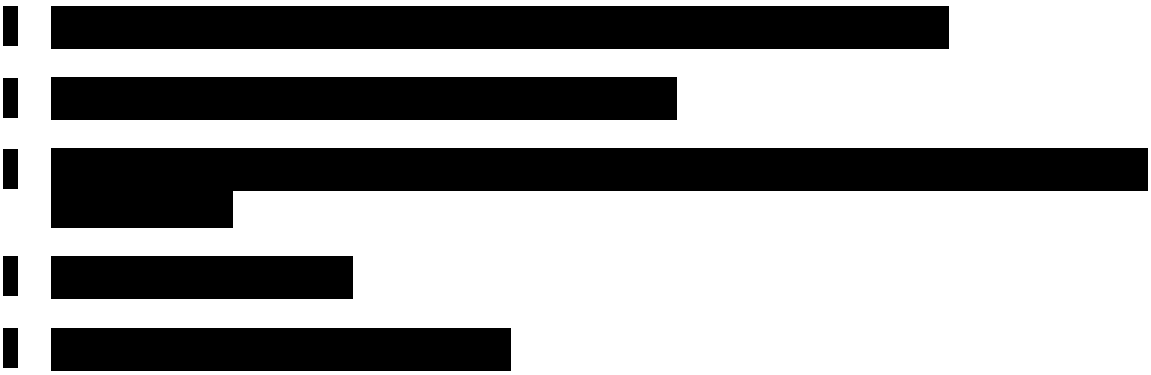
[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]



8.5 Instructions for the Patients

Section 4.5.3 provides diet and activity instructions for patients enrolled in the study.

All patients will be instructed to use an electronic diary (eDiary) to record details associated with their migraine attack. Training for the eDiary will be provided for qualified patients at Visit 2. Patients will be instructed to bring their eDiary to each clinic visit and for those who were dispensed ubrogepant, return their medication packs (used and unused).

8.6 Unscheduled Visits

Additional examinations and laboratory assessments may be performed as necessary to ensure the safety and well-being of the patients during the study period. Unscheduled visit eCRFs should be completed for each unscheduled visit. For all parameters not measured, indicate “not done”.

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 specified day. At each visit, the patient will be asked if he or she 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.

Patients will record the requested information regarding their migraine attack and ubrogepant taken in the eDiary. Ubrogepant compliance will be closely monitored by counting the number of tablets dispensed and returned. Every effort will be made to collect all unused ubrogepant.

8.8 Early Discontinuation of Patients

A premature discontinuation will occur when a patient who signed the informed consent form (ICF) and was randomized ceases participation in the study, regardless of circumstances, before completion of the study. Patients can be prematurely discontinued from the study for 1 of the following reasons:

- AE
- Protocol violation
- Noncompliance with ubrogepant
- Withdrawal of consent (a clear reason must be documented)
- Lost to follow-up (every effort must be made to contact the patient; a certified/traceable letter must be sent)
- Lack of qualifying event (a qualifying migraine is not treated within 6 months)
- Pregnancy
- Other reasons

Patients may voluntarily withdraw from the study at any time. Notification of early patient discontinuation from the study and the reason for discontinuation will be made to Allergan and will be clearly documented on the appropriate eCRF. All randomized patients who prematurely discontinue from the study, regardless of cause, should be seen for a final assessment. A final assessment will be defined as completion of the evaluations scheduled for Visit 15/ ET. If the patient discontinues prematurely, the patient is expected to return for a Safety Follow-up visit 4 weeks after Visit 15/ET.

8.9 Withdrawal Criteria

Women who become pregnant will be withdrawn from the study (see Section 4.5.1.2) and should refrain from taking ubrogepant. The patient should return to the clinic for Visit 15/ET procedures.

Patients who meet IP discontinuation criteria related to abnormal liver function tests (Section 9.5) and who are advised not to be re-challenged will be withdrawn from the study.

Patients 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 should not receive any further

ubrogepant, must be withdrawn from the study, and should receive appropriate follow-up as in routine clinical practice, including the Safety Follow-up visit (Visit 16) if ubrogepant was taken.

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

8.10 Study Termination

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

9. Adverse Events

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

9.1 Definitions

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, during the screening period, AEs will be assessed regardless of the administration of a pharmaceutical product.

Note: AEs must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and/or lack of efficacy, should NOT be reported as AEs unless the disease progression is greater than anticipated in the natural course of the disease.

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 patient a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported AEs will be documented on the appropriate case report form.

9.1.2 Serious Adverse Event

An SAE is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient, or the patient may require medical or surgical intervention to prevent one of the outcomes listed in this definition. See Section 9.3 for procedures for reporting an SAE.

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

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

Any preplanned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as an SAE and reported to Allergan.

9.1.3 Severity

A clinical determination will be made of the intensity of an AE. The severity assessment for a clinical AE must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity

9.1.4 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an AE and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any AE must be recorded on the appropriate eCRF.

All SAEs that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing Institutional Review Board/Independent Ethics Committee (IRB/IEC) as required by the IRB/IEC, local regulations, and the governing health authorities. Any AE that is marked “ongoing” at the exit visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any SAE occurring during the study period (beginning with informed consent) and for at least 30 days after the last dose of study drug must be immediately reported no later than 24 hours after learning of an SAE. SAEs must be reported to Allergan or Agent of Allergan (eg, contract research organization [CRO]) and recorded on the SAE form. All patients with an SAE must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of an SAE, the investigator must:

1. Notify Allergan immediately by fax or email using the SAE form (contact details can be found on page 1 of the SAE form); the fax number is on the front page of this protocol, and phone numbers and relevant Allergan personnel contacts are also on the study contacts page.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the AE(s) on the SAE form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the AE(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant

clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IRB/IEC of the SAE as required by the IRB/IEC, local regulations, and the governing health authorities.

9.4 Exposure to Investigational Product During Pregnancy

Study center personnel must report every pregnancy (from the time the patient signs the ICF for the trial until 30 days after the last dose of ubrogepant), on the Pregnancy Form as soon as possible (within 24 hours of learning of the pregnancy) to the SAE/pregnancy fax number, [redacted] even if no AE has occurred. Pregnancies in female partners of male patients must also be reported. The pregnancy must be followed to term, and the outcome reported by completing a follow-up Pregnancy Form. If, however, the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), in addition to the Pregnancy Form, a separate SAE Form must be filed as described in Section 9.3 with the appropriate serious criterion (eg, hospitalization) indicated.

9.5 ALT or AST Elevations

A post-treatment event of ALT or AST ≥ 3 times the ULN is considered an Event of Clinical Interest. Any patient with this laboratory result after ubrogepant was taken should have repeat testing within 48 to 72 hours to confirm the abnormality. For this repeat testing, the following tests should be performed: hematology and chemistry panels, international normalized ratio (INR), and a toxicology screen for acetaminophen. In addition, the investigator should perform a complete history and examination to evaluate for possible liver disease.

All ALT or AST elevations ≥ 3 times the ULN must be reported to Allergan using the AE of Interest Form and submitted within 24 hours of the time the investigator becomes aware of the event. All new elements of history, physical examination, diagnostic testing results, and other relevant medical reports are to be reported for each event.

If an ALT or AST elevation ≥ 3 times the ULN is confirmed and the patient meets any of the following criteria, close medical follow-up is required:

- Patients with ALT or AST ≥ 3 times ULN and ≤ 5 times the ULN and who are asymptomatic with regard to possible liver disease (ie, no fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia [> 5%])

- Patients with ALT or AST ≥ 3 times ULN and ≤ 5 times the ULN and (total bilirubin < 2 times the ULN and INR < 1.5)

Patients who meet these criteria should be followed clinically, and further medical evaluation should be performed per the judgment of the investigator and in conjunction with medical personnel at Allergan. The chemistry panel should be repeated 1 to 2 times per week to follow the course of ALT/AST elevation. An extra blood sample should be collected and sent to the central laboratory for further diagnostic testing at a later date if needed.

If an ALT or AST elevation ≥ 3 times the ULN is confirmed and the patient meets any of the following criteria, close medical follow-up is required:

- ALT or AST ≥ 3 times the ULN and the patient is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
- ALT or AST ≥ 3 times the ULN **and** total bilirubin > 2 times the ULN or INR > 1.5
- ALT or AST ≥ 5 times the ULN

In addition, for these patients, possible etiologies for acute hepatic injury should be excluded. The following laboratory tests should 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 (PCR), anti-hepatitis E IgM. An extra blood sample should be collected and sent to the central laboratory for further diagnostic testing at a later date if needed. The patient should be followed clinically, and further medical evaluation should be done per the judgment of the investigator and in conjunction with medical personnel at Allergan. In general, the chemistry panel should be repeated 1 to 2 times per week to follow the course of ALT/AST elevation. For procedural details on the medical evaluation of liver disease, please see the Study Reference Manual.

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

Study drug should be discontinued if any of the following criteria are met:

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

- ALT or AST ≥ 5 times the ULN for more than 2 weeks
- ALT or AST ≥ 8 times the ULN

The patient may be rechallenged with ubrogepant upon consultation with the Allergan Medical Monitor. If a patient is not rechallenged with IP, the patient must be discontinued from the study and complete the ET Visit 15 and Safety Follow-Up Visit 16. Patients should receive appropriate follow-up as per standard of care.

9.6 Potential Hy's Law Cases

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

- ALT or AST ≥ 3 times the ULN, AND
- Total bilirubin ≥ 2 times the ULN, AND
- Alkaline phosphatase < 2 times the ULN

A laboratory alert for potential Hy's laws cases will be in place, and the investigators and Allergan will be notified immediately when the above criteria have been met. Any potential Hy's law case should be considered an SAE and also reported as an AE of Special Interest.

Both the SAE and AE of Interest Forms must be completed as soon as possible (within 24 hours of learning of the potential Hy's law) and faxed to the SAE/Pregnancy fax number [redacted]. The eCRF pages associated with potential Hy's law cases should be completed within 7 calendar days. Every effort to determine the cause of the liver abnormalities must be made, and close monitoring should be initiated in conjunction with the Allergan Medical Monitor and in accordance with the FDA "Guidance for Industry: Drug Induced Liver Injury - Pre-Marketing Clinical Evaluation," dated July 2009 (FDA Guidance UCM174090, 2009). For specific instructions, please refer to the Study Reference Manual.

9.7 Procedures for Unmasking of Investigational Product

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, the Allergan Medical Monitor should be notified prior to unmasking ubrogepant. The investigator should inform the Allergan Medical Monitor of the unmasking if there is no notification prior to the unmasking.

The treatment assignment for the patient can be determined by designated site personnel logging into the IWRS via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

10. Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) Guideline on GCP.

10.1 Protection of Human Patients

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 patient prior to any study-related activities or procedures in the study, and/or from the patient's legally authorized representative.

10.1.2 Compliance with IRB or IEC Regulations

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

10.1.3 Compliance with Good Clinical Practice

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

10.1.4 Compliance with Electronic Records; Electronic Signatures

10.1.4.1 Regulations (US 21CFR Part 11)

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

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes to the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

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

10.3.1 Patient Privacy

Written authorization and other documentation in accordance with the local privacy requirements (where applicable) is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information [HIPAA]).

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

10.4 Documentation

10.4.1 Source Documents

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

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

- Patient's name

- Patient's contact information
- The date that the patient entered the study, patient number, and patient randomization (or medication kit) number
- The study title and/or the protocol number of the study and the name of Allergan
- A statement that informed consent was obtained (including the date); a statement that written authorization or other local patient privacy required documentation for this study has been obtained (including the date)
- Dates of all patient visits
- All concurrent medications (list all prescription and nonprescription medications being taken at the time of enrollment; at each subsequent visit, changes to the list of medications should be recorded)
- Occurrence and status of any AEs
- The date the patient exited the study, and a notation as to whether the patient 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, Good Clinical Practice: Consolidated Guidance and ALCOA, ie, records must be attributable, legible, contemporaneous, original, and accurate.

10.4.2 Case Report Form Completion

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

10.4.3 Study Summary

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

10.4.4 Retention of Documentation

All study related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all IPs, and copies of case report forms should be maintained on file.

For countries falling within the scope of the ICH guidelines, Allergan-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. 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.

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

10.5 Labeling, Packaging, and Return or Disposal of Investigational Products/Treatments

10.5.1 Labeling/Packaging

Ubrogepant will be supplied in blister cards and will be labeled with the protocol number, storage information, warning language, and instructions to take the tablets as directed. The card will also include the medication number. Immediately before dispensing the blister card, the principal investigator or designee will write the study center number, patient’s initials and identification number, and date on the card.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units received from Allergan, dispensed or administered to the patients, the number of units returned to the investigator by the patient (if applicable), and the number of units returned to Allergan during and at the completion of the study. A detailed inventory must be completed for all used and unused ubrogepant and packaging. Ubrogepant must be dispensed or administered only by an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol.

10.5.3 Return or Disposal of Investigational Products/Treatments and/or Supplies

All ubrogepant packaging, either empty or containing unused ubrogepant, must be returned to the site. All clinical IPs/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

10.6 Monitoring by Allergan

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

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

10.7 Handling of Biological Specimens/Samples

All urine pregnancy testing will be performed on site. Refer to your local laboratory manual for handling procedures.

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

10.8 Publications

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

10.9 Coordinating Investigator

A signatory coordinating investigator will be designated prior to the writing of the clinical study report.

11. References

Cady RK, McAllister PJ, Spierings ELH, Messina J, Carothers J, Djupesland PG, et al. A randomized, double-blind, placebo-controlled study of breath powered nasal delivery of sumatriptan powder (AVP-825) in the treatment of acute migraine (The TARGET Study). Headache 2015;55:88–100.

Connor KM, Shapiro RE, Diener HC, Lucas S, Kost J, Fan X, et al. Randomized, controlled trial of telcagepant for the acute treatment of migraine. Neurology. 2009 Sep 22;73(12):970-977.

Food and Drug Administration Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation (UCM174090) July, 2009. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol. 1993;33(1):48–56.

Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. J Am Coll of Cardiology. 2004;44:720–732.

Hartmaier SL, Santanello NC, Epstein RS, Silberstein SD. Development of a brief 24-hour migraine - specific quality of life questionnaire. Headache. 1995;35:320–329.

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

Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629–808. http://www.ihs-classification.org/_downloads/mixed/InternationalHeadache-Classification-III-ICHD-III-2013-Beta.pdf.

Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. Curr Pain Headache Rep. 2012;16(1):86–92.

Lipton RB, Bigal ME, Diamond M, Freitag F, Reed MI, Stewart WF, on behalf of the AMPP advisory group. Migraine prevalence, disease burden, and the need for preventive therapy. Neurol. 2007;68(5):343–349.

National Cholesterol Education Program Adult Treatment Panel III Guidelines. NIH Publication No. 01-3670, May 2001. http://www.scymed.com/en/smnxdj/edzr/edzr9610.htm.

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(11):1104–1110.

Olesen J, Bousser MG, Diener HC, Dodick D, First M, Goadsby PJ, et al. Headache Classification Committee. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006;26(6):742–746.

Santanello NC, Hartmaier SL, Epstein RS, Silberstein SD. Validation of a new quality of life questionnaire for acute migraine headache. Headache.1995;35:330–337.

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

Tepper SJ, Cady RK, Silberstein S, Messina J, Mahmoud RA, Djupesland PG, et al. AVP 825 breath-powered intranasal delivery system containing 22 mg sumatriptan powder vs 100 mg oral sumatriptan in the acute treatment of migraines (The COMPASS study): a comparative randomized clinical trial across multiple attacks. Headache. 2015;55(5):621-635.

12. Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques

12.1.1 International Classification of Headache Disorders, 3rd Edition, Beta Version

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
      1.2.3.1.2 Familial hemiplegic migraine type 2
      1.2.3.1.3 Familial hemiplegic migraine type 3
      1.2.3.1.4 Familial hemiplegic migraine, other loci
    1.2.3.2 Sporadic hemiplegic migraine
  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 headache attributed to that disorder.

General comment

Primary or secondary headache or both?

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

Introduction

Migraine is a common disabling primary headache disorder. Epidemiological studies have documented its high prevalence and high socio-economic and personal impacts. In the *Global Burden of Disease Survey 2010*, it was ranked as the third most prevalent disorder and seventh-highest specific cause of disability worldwide.

Migraine has two major subtypes. 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 premonitory phase, occurring hours or days before the headache, and a headache resolution phase. Premonitory and resolution symptoms include hyperactivity, hypoactivity, depression, cravings for particular foods, repetitive yawning, fatigue and neck stiffness and/or pain.

When a patient fulfils criteria for more than one subtype of migraine, all subtypes 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*. Attacks of either type are included in the diagnostic criteria for 1.3 *Chronic 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 (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 2 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. In young children, photophobia and phonophobia may be inferred from their behaviour. Migraine attacks can be associated with cranial autonomic symptoms and symptoms of cutaneous allodynia.

Migraine without aura often has a menstrual relationship. ICHD-3 beta offers criteria for A1.1.1 *Pure menstrual migraine* and A1.1.2 *Menstrually related migraine*, but in the Appendix because of uncertainty over whether they should be regarded as separate entities.

Very frequent migraine attacks are now distinguished as 1.3 *Chronic migraine*. When there is associated medication overuse, both 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 migraine without aura, although blood flow changes may occur in the brainstem, as may cortical changes secondary to pain activation. This contrasts with the pathognomonic spreading oligaemia of migraine with aura. Although the bulk of the literature suggests that CSD does not occur in migraine without aura, some recent studies disagree. Furthermore, it has been suggested that glial waves or other cortical phenomena may be involved in migraine without aura. The messenger molecules nitric oxide (NO), 5-hydroxytryptamine (5-HT) and calcitonin gene-related peptide (CGRP) are involved. Although the disease was previously regarded as primarily vascular, the importance of sensitization of pain pathways, and the possibility that attacks may originate in the central nervous system, have gained increasing attention over recent 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, the central mesencephalic grey and the thalamus, have been recognized. New highly receptor-specific acute medications such as the triptans, which are $5HT_{1B/D}$ receptor agonists, $5\text{-}HT_{1F}$ receptor agonists and CGRP receptor antagonists have demonstrated efficacy in the acute treatment of attacks. Because of their high receptor-specificity, their mechanism of action provides new insight into migraine mechanisms. It is now clear that migraine without aura is a neurobiological disorder; clinical as well as basic neuroscience has advanced our knowledge of migraine mechanisms, and continues to do so.

1.2 Migraine with aura

Previously used terms:

Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnée; 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 two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes[1]
   3. at least one aura symptom is unilateral[2]
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

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

Comments:
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 pain phase has commenced, or continue into the headache phase.

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

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

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

When the aura includes motor weakness, the disorder should be coded as 1.2.3 *Hemiplegic migraine* or one of its subforms.

Aura symptoms of these different types 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 1 hour, but motor symptoms are often longer lasting.

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.

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*.

Premonitory symptoms may begin hours or a day or two before the other symptoms of a migraine attack (with or without aura). They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light and/or sound, nausea, blurred vision, yawning and pallor. The terms 'prodrome' and 'warning symptoms' are best avoided, because they are often mistakenly used to include aura.

Migraine aura is sometimes associated with a headache that does not fulfil 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 1 to

several hours, gradual transition into hyperaemia occurs in the same region. Cortical spreading depression of Leão is the likely underlying mechanism.

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 is not recognized in this classification. They are all coded as 1.2.1 *Migraine with typical aura*. Patients with aura symptoms arising from the brainstem are coded as 1.2.2 *Migraine with brainstem aura*, but they almost always have additional typical aura symptoms. Patients with 1.2.3 *Hemiplegic migraine* have motor weakness, and this is classified as a separate subform because of genetic and pathophysiological differences from migraine with typical aura. Such patients often have brainstem symptoms in addition.

The previously defined syndromes, *migraine with prolonged aura* and *migraine with acute-onset aura*, have been abandoned. The great majority of patients with such attacks have other attacks that fulfil criteria for one of the recognized subforms of 1.2 *Migraine with aura*, and should be coded to that diagnosis. The rest should be coded to 1.5.2 *Probable migraine with aura*, specifying the atypical feature (prolonged 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.

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 1 hour, a mix of positive and negative features and complete reversibility.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor, brainstem or retinal symptoms
C. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes[1]
   3. at least one aura symptom is unilateral[2]
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

1. When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes.
2. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

1.2.1.1 Typical aura with headache

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

Diagnostic criteria:

A. Fulfils criteria for 1.2.1 *Migraine with typical aura*
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. Fulfils criteria for 1.2.1 *Migraine with typical aura*
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 without headache*.

In the absence of headache fulfilling criteria for 1.1 *Migraine without aura*, the precise diagnosis of aura and its distinction from mimics that may signal serious

disease (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. At least two attacks fulfilling criteria B-D
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor[1] or retinal symptoms
C. At least two of the following brainstem symptoms:
   1. dysarthria
   2. vertigo
   3. tinnitus
   4. hypacusis
   5. diplopia
   6. ataxia
   7. decreased level of consciousness
D. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual aura symptom lasts 5-60 minutes[2]
   3. at least one aura symptom is unilateral[3]
   4. the aura is accompanied, or followed within 60 minutes, by headache
E. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Notes:

1. When motor symptoms are present, code as 1.2.3 *Hemiplegic migraine*.
2. When for example three symptoms occur during an aura, the acceptable maximal duration is 3×60 minutes.
3. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

Comments:
Originally the terms *basilar artery migraine* or *basilar migraine* were used but, as 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 C may occur with anxiety and hyperventilation, and therefore are subject to misinterpretation.

1.2.3 Hemiplegic[1] migraine

Description:
Migraine with aura including motor weakness.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of both of the following:
   1. fully reversible motor weakness
   2. fully reversible visual, sensory and/or speech/language symptoms
C. At least two of the following four characteristics:
   1. at least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
   2. each individual non-motor aura symptom lasts 5 60 minutes, and motor symptoms last <72 hours[2]
   3. at least one aura symptom is unilateral[3]
   4. the aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack and stroke have been excluded.

Notes:

1. The term *plegic* means paralysis in most languages, but most attacks are characterized by motor weakness.
2. In some patients, motor weakness may last weeks.
3. Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

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

1.2.3.1 Familial hemiplegic migraine (FHM)

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

Diagnostic criteria:

A. Fulfils 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 (FHM)* than was possible previously. Specific genetic subtypes have been identified: in FHM1 there are mutations in the CACNA1A gene (coding for a calcium channel) on chromosome 19; in FHM2 there are mutations in the ATP1A2 gene (coding for a K/Na-ATPase) on chromosome 1; and in FHM3 there are mutations in the SCN1A gene (coding for a sodium channel) on chromosome 2. There may be other loci not yet identified. When genetic testing is done, the genetic subtype (if discovered) should be specified at the fifth digit.

It has been shown that 1.2.3.1 *Familial hemiplegic migraine (FHM)* 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 CSF pleocytosis can occur.

1.2.3.1 *Familial hemiplegic migraine (FHM)* may be mistaken for epilepsy and (unsuccessfully) treated 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. Fulfils criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. A causative mutation on the CACNA1A gene has been demonstrated.

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

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

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

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

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

A. Fulfils 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

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

Diagnostic criteria:

A. Fulfils 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. At least two attacks fulfilling criteria B and C
B. Aura consisting of 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:
   1. clinical visual field examination
   2. the patient's drawing (made after clear instruction) of a monocular field defect
C. At least two of the following three characteristics
   1. the aura spreads gradually over ≥5 minutes
   2. aura symptoms last 5-60 minutes
   3. the aura is accompanied, or followed within 60 minutes, by headache
D. 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 cannot be ascertained as the underlying aetiology.

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[1,2]

Description:
Headache occurring on 15 or more days per month for more than 3 months, which has the features of migraine headache on at least 8 days per month.

Diagnostic criteria:

A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months[2] 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 without aura* and/or criteria B and C for 1.2 *Migraine with aura*
C. On ≥8 days per month for >3 months, fulfilling any of the following[3]:
   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.

Notes:

1. The diagnosis of 1.3 *Chronic migraine* excludes the diagnosis of 2. *Tension-type headache* or its subtypes because tension-type-like headache is within the diagnostic criteria for 1.3 *Chronic migraine*.
2. The reason for singling out chronic from 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. It is extremely difficult to keep such patients medication-free in order to observe the natural history of the headache. In this situation, attacks with or without aura are both counted, as well as tension-type-like headaches. 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 subtype 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, and the diagnosis of 8.2 *Medication-overuse headache* may in a sense be inappropriate (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule, patients meeting criteria for 1.3 *Chronic migraine* and for 8.2 *Medication-overuse headache* should be given both diagnoses. After drug withdrawal, migraine will either revert to the episodic subtype or remain chronic, and be re-diagnosed accordingly; in the latter case, the diagnosis of 8.2 *Medication-overuse*

headache may be rescinded. In some countries, it is usual practice to diagnose 8.2 *Medication-overuse headache* only on discharge.
3. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month. Sample diaries are available at http://www.i-h-s.org.

1.4 Complications of migraine

Comment:
Code separately for both the migraine subtype 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 because of medication or sleep are accepted.
2. Milder cases, not meeting criterion C2, are coded 1.5.1 *Probable migraine without aura*.

Comments:
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 1.3 *Chronic migraine* and 8.2 *Medication-overuse headache* but not for 1.4.1 *Status migrainosus*. When overuse of medication is of shorter duration than 3 months, code for the appropriate migraine subtype(s) only.

1.4.2 Persistent aura without infarction

Description:
Aura symptoms persisting for 1 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 1-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 as a result of cerebral infarction of other causes. Attacks lasting more than 1 hour and less than 1 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 associated with an ischaemic brain lesion in the appropriate territory demonstrated by neuroimaging.

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
C. Neuroimaging demonstrates ischaemic infarction in a relevant area
D. Not better accounted for by another diagnosis.

Comments:
Ischaemic stroke in a migraine sufferer may be categorized as cerebral infarction of other cause coexisting with migraine, cerebral infarction of other cause presenting

with symptoms resembling migraine with aura, or cerebral infarction occurring during the course of a typical migraine with aura attack. 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 two-fold increased risk of ischaemic stroke in patients with migraine with aura patients 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 frequency of aura and the nature of aura symptoms denoting the increase in risk is unknown. Most studies have shown a lack of association between 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 1 hour after, an attack of migraine with aura
C. Not better accounted for by another diagnosis.

Comment:
Migraine and epilepsy are prototypical examples of paroxysmal brain disorders. Although migraine-like headaches are quite frequently seen in the epileptic postictal 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 for association with 1.1 *Migraine without aura* is still 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 subtype of migraine coded above, and not fulfilling criteria for another headache disorder.

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A-D for 1.1 *Migraine without aura*, or all but one of criteria A-C for 1.2 *Migraine with aura*
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

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

1.5.1 Probable migraine without aura

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A D for 1.1 *Migraine without aura*
B. Not fulfilling ICHD-3 criteria for any other headache disorder
C. Not better accounted for by another ICHD-3 diagnosis.

1.5.2 Probable migraine with aura

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A C for 1.2 *Migraine with aura* or any of its subforms
B. Not fulfilling ICHD-3 criteria for any other headache 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 recurring with predictable periodicity
C. All of the following:
   1. nausea and vomiting occur at least four times per hour
   2. attacks last ≥1 hour and 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 childhood, with periods of complete normality between episodes. The cyclic nature is the hallmark, and is predictable.

This disorder was not included as a childhood periodic syndrome in ICHD-I, but it was 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 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. During attacks, at least two of the following:
   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, if 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 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.

Note:

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.

Comments:
Posterior fossa tumours, seizures and vestibular disorders must be excluded.

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 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.

Notes:

1. Attacks tend to recur monthly.
2. Ataxia is more likely in older children within the affected age group.

Comments:
The child's head can be returned to the neutral position during attacks: some resistance may be encountered, but can be overcome.

The differential diagnosis includes gastro-oesophageal reflux, idiopathic torsional dystonia and complex partial seizure, but particular attention must be paid to

the posterior fossa and craniocervical junction where congenital or acquired lesions may produce torticollis. 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

1.1 Migraine in general

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

Diener HC and Silberstein SD. Medication overuse headache. In: Olesen J, Goadsby PJ, Ramadan NM, et al. (eds). *The Headaches, 3rd ed.* Philadelphia: Lippincott Williams & Wilkins 2006;971 979.

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

Goadsby PJ. Recent advances in the diagnosis and management of migraine. *BMJ* 2006; 332:25 29.

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

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.

Vos T, Flaxman AD, Naghavi M, Lozano R, et al. Years lived with disability (YLD) for 1160 sequelae of 289 diseases 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, Weisskoff 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.

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 headache 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 differences 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 cerebral cortex. *J Neurophysiol* 1944; 7:359 390.

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.

Vibeke U, 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.

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.

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.

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.

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. Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 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. *Human 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 Psychiat* 2012; 83:205 212.
Jurkat-Rott K, Freilinger T, Dreier JP, et al. Variability of familial hemiplegic migraine with novel A1A2 Na+/K+-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, Roemer 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 Human 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.
Hedges TR. Isolated ophthalmic migraine in the differential diagnosis of cerebro-ocular ischemia. *Stroke* 1976; 7: 379 381.
Grosberg BM, Solomon S, Friedman DI and Lipton RB. Retinal migraine reappraised. *Cephalalgia* 2006; 26:1275 1286.
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, editors. *Wolff's Headache and Other Head Pain*. New York: Oxford University Press 2001; 459 474.
Troost T and Zagami AS. Ophthalmoplegic migraine and retinal migraine. In Olesen J, Tfelt-Hansen P and Welch KMA, editors. *The Headaches*. Philadelphia: Lippincott Williams & Wilkins 2000; 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 and Lipton RB. 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 healthcare 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 Quart* 2000; 11: 177.
Mathew NT, Stubits E and Nigam MR. Transformation of migraine into daily headache: Analysis of factors. *Headache* 1982; 22:66 68.
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 and Lipton RB. Prevalence of frequent headache in a population sample. *Headache* 1998; 38: 497 506.
Scher AI, Stewart WF, Ricci JA and Lipton RB. 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 and Mathew NT. 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.
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 appendix 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.
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 and Wang SJ. 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 and Ferrari MD. Acetazolamide treatment for migraine aura status. *Neurology* 2000; 55:1588 1589.
Haas DC. Prolonged migraine aura status. *Ann Neurol* 1982; 11:197 199.
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 Zermeño 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 prolonged aura. *Neurology* 2002; 58:1308 1310.
Wang YF, Fuh JL, Chen WT and Wang SJ. 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 and Clerici AM. 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 31P-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.
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 Trenité DG, et al. Migralepsy, hemicrania epileptica, post-ictal 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, Ruffatti 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 and Gigli GL. Seizures with prolonged EEG abnormalities during an attack of migraine without aura. *Headache* 2007; 47:919 922.
Parisi P and Kasteleijn-Nolst Trenitè 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 nondominant 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: Interobserver reliability in the diagnosis of primary headaches. *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 practice. *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 syndrome and new insights. *Semin Pediatr Neurol* 2001; 8: 13 21.
Li BUK, Lefevre F, Chelimsky GG, et al. NASPGHAN Consensus Statement on the Diagnosis and Management of CVS. *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 (Netherlands)* 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, Paolini J. 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

Prohibited Medications

The following medications are prohibited 30 days prior to Screening and throughout the study period for patients taking ubrogepant. Note that for patients assigned to the usual-care arm, these restrictions do not apply.

	Strong/Moderate CYP3A4 Inducers	Strong/Moderate CYP3A4 Inhibitors
Antidepressant/ Antianxiety	Barbiturates • Amobarbital (Amytal®) • Aprobarbital (Alurate®) • Butalbital (Fiorinal®, Fioricet®) • Butabarbital (Busodium®, Butisol®) • Mephobarbital (Mebaral®) • Pentobarbital (Nembutal®) • Phenobarbital (Luminal®, Solfoton®) • Secobarbital (Seconal®)	Nefazodone (Serzone®)
Antiseizure	Carbamazepine (Atretol®, Carbatrol®, Epitol®, Equetro®, Tegretol®) Oxcarbazepine (Trileptal®) Phenytoin (Dilantin®, Phenytek®) Primidone (Myidone®, Mysoline®)	
Diabetes	Pioglitazone (Actos®) Troglitazone (Rezulin®, Resulin®)	
Antiemetic		Aprepitant (Emend®)
Antihypertension		Diltiazem (Cardizem®) Verapamil (Calan®, Calan SR®)
Glucocorticoid (Systemic)	Betamethasone (Celestone®) Dexamethasone (Baycadron®, DexPak®) Hydrocortisone (Cortef®) Methylprednisolone (Medrol®) Prednisolone (Prelone®) Prednisone (Deltasone®) Triamcinolone (Kenalog®)	
Antibiotics	Rifabutin (Mycobutin®) Rifampicin/Rifampin (Rifadin®, Rifater®, Rimactane®)	Erythromycin (Benzamycin®, EryTab®) Clarithromycin (Biaxin®) Telithromycin (Ketek®)
Antifungal		Fluconazole (Diflucan®, Trican®) Itraconazole (Sporanox®) Ketoconazole (Nizoral®)

	Strong/Moderate CYP3A4 Inducers	Strong/Moderate CYP3A4 Inhibitors
Anti-HIV	Efavirenz (Stocrin®, Sustiva®) Nevirapine (Viramune®)	Indinavir (Crixivan®) Nelfinavir (Viracept®) Ritonavir (Norvir®) Saquinavir (Fortovase®, Invirase®)
Immunosuppressant		Cyclosporine - oral/intravenous only (Neoral®, Sandimmune®)
Other	St John's wort Enzalutamide (Xtandi®) Modafinil (Provigil®)	Buprenorphine (Cizol®, Subutex®, Suboxone®) Quinine, armodafinil (Nuvigil ™)

Drugs with Narrow Therapeutic Margins	Warfarin (Coumadin®) Digoxin (Digitek®, Lanoxin®, Digox®) Cisapride (Prepulsid®, Propulsid®) Pimozide (Orap®)

The following medications are allowed during the study; however, they are prohibited within 48 hours prior to taking ubrogepant:

Triptan	Almotriptan (Axert®) Eletriptan (Relpax®) Frovatriptan (Frova®) Naratriptan (Amerge®) Rizatriptan (Maxalt®) Sumatriptan (Imitrex®) Zolmitriptan (Zomig®)
Ergot Derivative	Dihydroergotamine (DHE 45®, Migranal®) Ergotamine (Cafergot®, Ergomar®, Wigraine®)
Opioid	Tramadol (eg, Ultracet®, Ultram®) Butorphanol (Stadol®) Codeine-containing analgesics (eg, Tylenol with Codeine #3®) Hydrocodone (Zohydro ER™)/Hydrocodone-containing analgesics (eg, Vicodin®) Oxycodone (Oxycontin®, Roxicodone®)/Oxycodone-containing analgesics (eg, Percocet®) Morphine (MS Contin®)
NSAID	Aspirin Combination medicines with NSAIDS (eg, Excedrin®) Diclofenac (Arthrotec®, Cataflam®, Voltaren®) Ibuprofen (eg, Advil®, Excedrin IB®, Motrin®) Ketoprofen (eg, Orudis®) Naproxen (eg, Aleve®, Naprosyn®)
Analgesic	Acetaminophen (eg, Tylenol® or any combination drug Tylenol®)

Antiemetic agent	Chlorpromazine (Thorazine®) Hydroxyzine (Vistaril®) Metoclopramide (Reglan®) Ondansetron (Zofran®) Prochlorperazine (Compazine®) Promethazine (Phenergan®, Mepergan®)
Proton Pump Inhibitor	Esomeprazole (Nexium®) Lansoprazole (Prevacid®, Zoton®) Omeprazole (Losec®, Prilosec®, Zegerid®) Pantoprazole (Pantoloc®, Pantozol®, Protonix®, Somac®, Zurcal®) Rabeprazole (Aciphex®, Pariet®, Rabecid®)

The following medications are allowed during the study; however, they are prohibited within 24 hours prior to taking ubrogepant:

Antacid	Aluminum Carbonate Gel (Basaljel®) Aluminum Hydroxide (AlternaGEL®, Amphojel®) Aluminum Hydroxide and magnesium hydroxide (Maalox®, Mylanta®) Bismuth Subsalicylate (Pepto-bismol®) Calcium Carbonate (Alcalak®, Quick-Eze®, Rennie®, Rolaids®, Titralac®, TUMS®) Hydrotalcite (Talcid®) Magaldrate plus Simethicone (Pepsil®) Magnesium Hydroxide (Phillips' Milk of Magnesia®) Sodium Bicarbonate (Alka-Seltzer®, Bicarbonate of Soda®)
H_2 Blocker	Famotidine (Pepcid®) Nizatidine (Axid®) Ranitidine (Zantac®) Cimetidine (Tagamet®)

12.3 Glossary of Abbreviations

Term/Abbreviation	Definition
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original, and accurate
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
CGRP	calcitonin gene-related peptide
CGRP RA	CGRP receptor antagonist
CHD	coronary heart disease
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
ECG	electrocardiogram
eCRF	electronic case report form
eDISH	evaluation of drug-induced serious hepatotoxicity
ET	early termination
[redacted]	[redacted]
GCP	Good Clinical Practices
HEOR	Health Economics and Outcomes Research
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
ICHD-3 beta	International Classification of Headache Disorders criteria, 3rd edition beta version
IEC	Independent Ethics Committee
INR	international normalized ratio (blood-clotting test)
IP	investigational product

IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LOCF	last observation carried forward
mITT	modified intent-to-treat
[redacted]	[redacted]
NCEP	National Cholesterol Education Program
NSAID	nonsteroidal anti-inflammatory drug
PCS	potentially clinically significant
PCR	polymerase chain reaction
PF	pain freedom
PR	pain relief
PR interval	the period from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (the onset of ventricular depolarization)
QoL	Quality-of-Life
QRS interval	part of ECG corresponding to the depolarization of the right and left ventricles of the human heart.
QT interval	time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles.
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RR interval	interval between R waves in ECG
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SNRI	serotonin norepinephrine reuptake inhibitors
SPF	sustained pain freedom
SSRI	selective serotonin reuptake inhibitors
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

US	United States
WOCBP	women of childbearing potential

12.4 Protocol Amendment 1 Summary

Title: A Multicenter, Randomized, Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine With or Without Aura

Protocol UBR-MD-04 Amendment 1

Date of Amendment: 15 Nov 2016

Amendment Summary

This summary includes changes made to Protocol UBR-MD-04 (02 May 2016). This protocol was amended to: 1) update health outcomes measures and efficacy variables; and 2) clarify Exclusion Criterion 2. Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Global Change	In reference to the Satisfaction With Study Medication assessment, instances of "migraine treatment" were changed to "study medication"	Based on input from patient qualitative interviews, expert panel suggested rephrasing "migraine treatment" to "study medication"
Global Change	Revised SAE/Pregnancy Reporting Fax Number	Administrative update
Global Change	[redacted]	[redacted]
Global Change	[redacted]	[redacted]
Protocol Title Page	Revised name of the Authorized US Agent from Allergan, Inc. to Allergan Sales, LLC	Administrative update
	[redacted]	Administrative update

Section	Revision	Rationale
Protocol Summary – General Statistical Methods and Types of Analyses	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 3.1, Section Title	Section title and in-text change updated to "Data ~~Drug~~ Safety Monitoring Board"	Clarification

Section	Revision	Rationale
Section 4.4, [redacted]	[redacted]	Clarification
Section 4.5.1, Permissible Medications/Treatments	Added text regarding prohibited and allowed medications for those assigned to the usual-care arm: Medications that are not specifically prohibited are allowed, with the following clarifications and restrictions for patients taking ubrogepant. Note that for patients assigned to the usual-care arm, these restrictions do not apply.	Clarification to note that restrictions on medications do not apply to patients in the usual-care arm
	Deleted "any proton pump inhibitor" from list of medications prohibited within 24 hours prior to taking IP and added it to list of medications prohibited within 48 hours prior to IP dosing	Amended per FDA request
Section 4.5.1.2, Definition of Females of Childbearing Potential and/or Acceptable Contraceptive Methods	Moved surgical sterilization from a method of contraception to defining WOCBP: For the purposes of this study, females 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 salpingectomy, bilateral oophorectomy or hysterectomy).	Clarification

Section	Revision	Rationale
Section 4.5.1.2, Definition of Females of Childbearing Potential and/or Acceptable Contraceptive Methods	Updated acceptable contraceptive methods: For WOCBP who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, vaginal ring, injection, implant), male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, ~~vaginal contraceptive ring,~~ intrauterine device, ~~surgical sterilization (bilateral tubal ligation, bilateral salpingectomy),~~ vasectomized partner, or sexual abstinence….. Male participants must also refrain from donating sperm during the course of the study.	Clarification
Section 4.5.2, Prohibited Medications/Treatments	Added text regarding prohibited medication: The following medications are prohibited throughout the study period for patients taking ubrogepant. Note that for patients assigned to the usual-care arm, these restrictions do not apply.	Clarification to note that restrictions on medications do not apply to patients in the usual-care arm

[redacted]

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 6.3, Other Study Supplies	Deleted Allergan-supplied thermometer from list of Allergan-provided supplies: • ~~ElPro Libero thermometer~~	Clarification to note that Allergan will not provide a thermometer
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
Section 8.8, Early Discontinuation of Patients	Revised text regarding prematurely discontinued patients: A final assessment will be defined as completion of the evaluations scheduled for Visit 15/ET. If the patient discontinues prematurely ~~after ubrogepant is taken,~~, the patient is expected to return for a safety follow-up visit 4 weeks ~~postdose~~ after Visit 15/ET.	Clarification to note that all patients, independent of randomization treatment arm, will need to return for a Safety Follow-up visit
Section 9.5, ALT or AST Elevations	Revised re-challenge text: If a patient is not rechallenged with IP, the patient must be discontinued from the study and complete the Early Termination Visit 15 and Safety Follow-Up Visit 16. Patients should receive appropriate follow-up as per standard of care.	Clarification regarding follow-up if the patient is not rechallenged with IP
Section 11, References	Added Cady and Tepper references	Administrative update

Section	Revision	Rationale
Section 12.2, Examples of Prohibited Medications	Revised introductory text: The following medications are prohibited 30 days prior to Screening and throughout the study period for patients taking ubrogepant. Note that for patients assigned to the usual-care arm, these restrictions do not apply.	Clarification to note that restrictions on medications do not apply to patients in the usual-care arm.
	Deleted the following Proton Pump Inhibitors from the list of medications prohibited within 24 hours prior to IP dosing and added them to the list of medications prohibited within 48 hours prior to IP dosing: Esomeprazole (Nexium®) Lansoprazole (Prevacid®, Zoton®) Omeprazole (Losec®, Prilosec®, Zegerid®) Pantoprazole (Pantoloc®, Pantozol®, Protonix®, Somac®, Zurcal®) Rabeprazole (Aciphex®, Pariet®, Rabecid®)	Amended per FDA request
	Added to "Others" category: armodafinil (Nuvigil™)	Clarification
Section 12.3, Glossary of Abbreviations	[redacted]	[redacted]

12.5 Protocol Amendment 2 Summary

Title: A Multicenter, Randomized, Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine With or Without Aura

Protocol UBR-MD-04 Amendment 2

Date of Amendment: 06 Dec 2017

Amendment Summary

This summary includes changes made to Protocol UBR-MD-04 (02 May 2016) and Protocol Amendment 1 (15 Nov 2016). This protocol was amended to: 1) add a new health outcomes measure and update variables; 2) update the definition of the safety population. Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Clarification

Section 7.1.2 Safety Population	Definition changed as follows: The Safety population will <u>will be defined separately for the ubrogepant arms and the usual-care arm.</u> <u>Ubrogepant arms: All randomized patients who received ≥ 1 dose of treatment</u> <u>Usual care arm: All randomized patients in the usual-care arm.</u> <u>The purpose of the usual care arm is to</u>	Definition of Safety population modified to include all randomized patients in the usual-care arm to better contextualize the safety findings for both arms.

	contextualize any safety findings that may occur in the ubrogepant treated patients over the course of 12 months. As such, data from all patients randomized to the usual care arm, regardless of whether the patient used medication to treat migraine, will be included in the safety analyses.	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 7.3.2.1 Adverse Events	Defined first dose of treatment in the lead-in study throughout section	Clarification
	AE redefined: An AE that occurs after Visit 16 for patients with Visit 16 or more than 30 days after the last ~~dose of treatment~~ visit for patients without Visit 16 will not be considered as a TEAE.	Clarification
	The number and percentage of patients reporting TEAEs after randomization in each treatment group will be tabulated by descending percentage in any group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study treatment.	Clarification
	An SAE that occurred between the date of the first dose of treatment in the lead-in study and Visit 16 for patients with Visit 16 or within 30 days after the last ~~dose of treatment~~ visit for patients without Visit 16, inclusive, will be considered an on-therapy SAE. The number and percentage of patients who have on-therapy SAEs after ~~the first dose of treatment~~ randomization will be summarized by preferred term and treatment group. In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term for each treatment group.	Clarification
Section 7.3.2.3 Clinical Laboratory Parameters	Text clarified as follows: Any post-treatment ALT and/or AST results that are ≥ 3 times the ULN are considered events of clinical interest in this study and are ~~patient~~ subject to blinded adjudication by the Clinical Adjudication Committee to determine whether the elevation is due to treatment or not,	Typo

	and to determine whether there is a confounding factor.	
Section 7.3.2.4 Vital Signs Measurements	Added BMI: Descriptive statistics for vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiratory rate, temperature, ~~and~~ weight, and BMI) and changes from baseline values at each visit and at the end of study will be presented by treatment group.	Administrative change
7.3.2.6 Suicidality Assessment	Timing of assessment amended as follows: For the C-SSRS, the number of patients with suicidal ideation and suicidal behavior in lifetime history, during the treatment period, and during the safety follow-up period ~~after the first dose of treatment~~ will be summarized by treatment group for the Safety population.	Clarification
Section 7.3.2.7 Potential Hy's Law	Timing of assessment amended as follows: Patients who meet the potential Hy's Law criteria from ~~the first dose of treatment~~ randomization to Visit 16 will be summarized. Supportive tabular displays also will be provided.	Clarification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 9.3 Procedures for Reporting a Serious Adverse Event	Notify Allergan immediately by fax or email using the ~~serious adverse event~~SAE form (contact details can be found on page 1 of the ~~serious adverse event~~ SAE form); the fax number is on the front page of this protocol, and phone numbers and relevant Allergan personnel contacts are also on the ~~front~~study contacts page ~~of protocol~~.	Changed to show correct location of study contact details

Section 9.5 ALT or AST Elevations	For this repeat testing, the following tests should be performed: hematology and chemistry panels, international normalized ratio (INR), and a ~~urine~~ toxicology screen for acetaminophen.	The toxicology screen for acetaminophen will not be tested from urine samples
Section 11 References	[redacted]	
	Santanello NC, Hartmaier SL, Epstein RS, Silberstein SD. Validation of a new quality of life questionnaire for acute migraine headache. Headache 1995;35:330-337.	
	O'Brien P. Procedures for comparing samples with multiple endpoints. Biometrics 1984;40:1079-1087.	Reference added to support Section 7.3.1 Efficacy Analyses
[redacted]		

12.6 Protocol Amendment 3 Summary

Title: A Multicenter, Randomized, Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine With or Without Aura

Protocol UBR-MD-04 Amendment 3

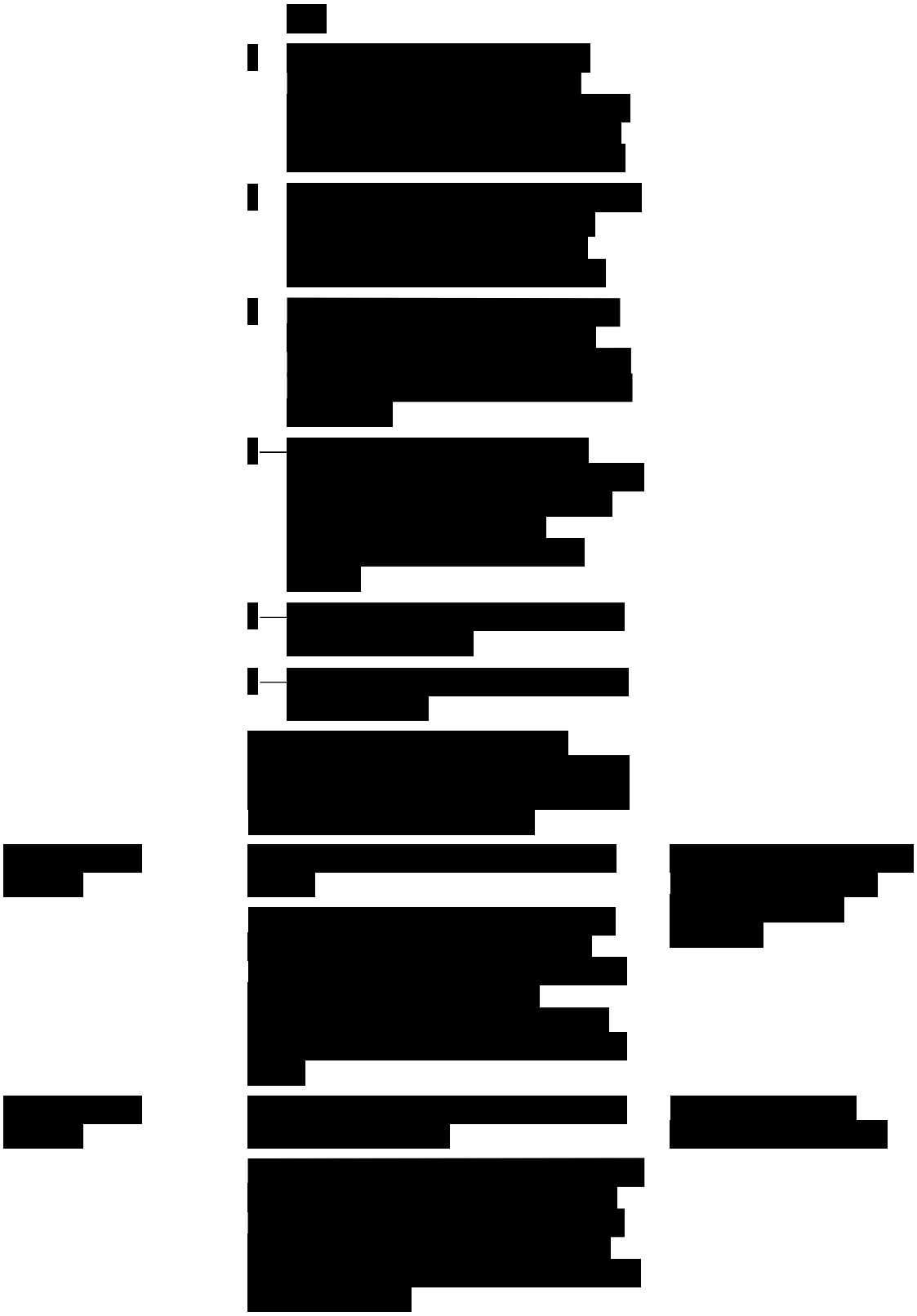
Date of Amendment: 11 Apr 2018

Amendment Summary

This summary includes changes made to Protocol UBR-MD-04 (02 May 2016), Protocol Amendment 1 (15 Nov 2016), and Protocol Amendment 2 (06 Dec 2017). This protocol was amended primarily to add information regarding an interim analysis, update efficacy endpoints, and add a subgroup analysis for safety. Following is a summary of content-oriented changes that were made to each relevant section of the protocol and a brief rationale for each of these changes. If needed to clarify revisions, added text is shown in bold italics and deleted text is shown with strikethroughs. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
Protocol Summary – Study Design	The following revision was made in the "Structure" section of the protocol summary: *Structure:* multicenter, randomized, open-label, 52-week extension study~~;~~ ~~randomization to the ubrogepant arms (50 and 100 mg) will be blinded~~	This information was removed to avoid redundancy.
Protocol Summary – General Statistical Methods and Types of Analyses	Changes made to this section are described below. [redacted] 3. The safety analyses information was revised as follows: The safety analyses will be performed using the Safety population and will include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, and the C-SSRS. For each of the clinical, laboratory, vital sign, and ECG parameters, the last nonmissing safety assessment before ~~the first dose of treatment~~ ***the first dose in the lead-in study*** will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by the number of patients and mean, SD, median, minimum, and maximum values. Categorical variables	[redacted] The safety analyses information was changed as a clarification.

	will be summarized by number and percentage of patients.	
Protocol Summary – General Statistical Methods and Types of Analyses	The following statement was removed from this section: "Summary statistics for the patient-specific monthly attack rates will be provided by treatment groups."	This information was removed because this analysis is no longer being performed for efficacy but will be summarized for the Safety Population.
Protocol Summary – General Statistical Methods and Types of Analyses	[redacted]	[redacted]
Section 3 – Study Design	The following revision was made in this section: This multicenter, randomized, open-label, 52-week extension study will enroll approximately 1200 patients from approximately 200 centers in the United States. Patients will be randomized (1:1:1) to 1 of the following 3 treatment groups: usual care, ubrogepant 50 mg, or ubrogepant 100 mg (400 patients per arm). The study is open-label; however, randomization to the ubrogepant arms (50 and 100 mg) will be blinded***. If and when an interim analysis occurs, the doses will be unblinded (see Section 7.6).***	The randomization to the ubrogepant arms has been blinded; however, this section was revised because after the interim analysis, if performed, Allergan will be unblinded to the ubrogepant doses. Sites and patients will remain blinded throughout the study. Details of the interim analysis and blinding are provided in Section 7.6.
Section 5.4 –Treatment Allocation Ratio and Stratification	The following revision was made in this section: Patients will be randomized (1:1:1) to 1 of the following 3 treatment groups: usual-care, ubrogepant 50 mg, or ubrogepant 100 mg. The study is open-label; however, randomization to the ubrogepant arms (50 and 100 mg) will be blinded***. If and when an interim analysis occurs, the doses will be unblinded (see Section 7.6).***	The randomization to the ubrogepant arms has been blinded; however, this section was revised because after the interim analysis, if performed, Allergan will be unblinded to the ubrogepant doses. Sites and patients will remain blinded throughout the study. Details of the interim analysis and blinding are provided in Section 7.6.
[redacted]	[redacted]	[redacted]



[redacted]

7.3.2 – Safety Analyses	The safety analyses information was revised as follows: The safety analyses will be performed using the Safety population. The safety parameters will include AEs, clinical laboratory evaluations, vital sign measurements, ECG parameters, and the C-SSRS. For each of the clinical, laboratory, vital sign, and ECG parameters, the last nonmissing safety assessment before the first dose ~~of treatment~~ in the lead-in study will be used as the baseline for all analyses of that safety parameter.	The safety analyses information was revised as a clarification.
7.3.2.1 – Adverse Events	The following revision was made regarding the definition of a TEAE: An AE that occurs after Visit 16 for patients with Visit 16***,*** or more than 30 days after the last visit ***or last treatment, whichever is later,*** for patients without Visit 16 will not be	This information was revised as a clarification.

	considered as a TEAE.	
7.3.2.1 – Adverse Events	The statement regarding tabulation of TEAEs was revised as follows: The number and percentage of patients reporting TEAEs after randomization in each treatment group will be tabulated by descending percentage in ~~any~~ ***the highest dose*** group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study treatment.	This information was revised as a clarification.
7.3.2.1 – Adverse Events	The following revisions were made regarding the definition of an SAE and the summarization of deaths: A SAE that occurred between the date of the first dose of treatment in the lead-in study and Visit 16 for patients with Visit 16***,*** or within 30 days after the last visit ***or last treatment, whichever is later,*** for patients without Visit 16, inclusive, will be considered an on-therapy SAE. The number and percentage of patients who have on-therapy SAEs after randomization will be summarized by preferred term and treatment group. ~~In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term for each treatment group~~.	The definition of SAE was revised as a clarification. The statement regarding summarization of death was removed because this information will not be presented in tabular format.

7.3.2.1 – Adverse Events	The following revisions were made regarding summarization of TEAEs of special interest: ***The number and percentage of patients with TEAEs of clinical interest will be summarized by preferred term and treatment group. TEAEs of clinical interest include triptan-associated TEAEs, abuse-related TEAEs, hepatic injury TEAEs, cardiac arrhythmias TEAEs, central nervous system TEAEs, vascular disorders TEAEs, embolic and thrombotic events TEAEs, hypertension TEAEs, ischemic heart disease TEAEs, and suicide/self-injury TEAEs.*** ~~The number and percentage of patients who had triptan-associated AEs also will be summarized by treatment group. The triptan-associated AE class consists of the following individual AEs: any chest pain, chest tightness, throat tightness, asthenia, paresthesia, dysesthesia, and hyperesthesia.~~	The paragraph regarding summarizations of TEAEs of special interest was revised because of a change in the way this information is being presented.
Section 7.4 – Subgroup Analyses	The following revision was made to this section: ***Subgroup analyses will be done for disposition, treatment exposure, and TEAEs for sex, age group (< 40 vs ≥ 40, and < 65 vs ≥ 65), race (white vs all other races), cardiovascular risk category, and renal function class.*** ~~No subgroup analysis is planned for this study.~~	This information was added because subgroup analyses are now planned for this study.
[redacted]	[redacted]	[redacted]
Section 7.6 – Interim Analysis	This section has been revised to include information regarding an interim analysis, as follows: ~~No interim analysis is planned for this study.~~ ***The interim analysis for Study UBR-MD-04 will occur when at least 300 ubrogepant patients (with a minimum of 2 migraines treated with ubrogepant per month, on average) have been enrolled in Study UBR-MD-04 for 6 months and 200 ubrogepant patients (with a minimum***	This new information was added because an interim analysis is now planned for this study if requirements are met.

of 2 migraines treated with ubrogepant per month, on average) have been enrolled in Study UBR-MD-04 for 1 year.

In regards to blinding, although this is an open-label study, randomization to the ubrogepant 50 mg or 100 mg arms is blinded. If and when an interim analysis occurs, Allergan staff will be unblinded to the ubrogepant doses; however, patients and sites will remain blinded. The interim analysis will include all analyses specified in the SAP except for efficacy analyses.

Details regarding the interim analysis are specified in the SAP.