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Study ID: UBR-MD-01

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Single Attack Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogapant in the Acute Treatment of Migraine

Protocol Amendment 3 Date: 19 May 2017

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A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO- CONTROLLED SINGLE ATTACK STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF ORAL UBROGEPANT IN THE ACUTE TREATMENT OF MIGRAINE

Protocol Number: UBR-MD-01 Amendment 3

Phase: 3

Name of Investigational Product: Ubrogепant

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Serious Adverse Event Reporting Fax Number: [REDACTED]

Allergan Medical Monitor Contact Information: Please see Study Contacts Sheet

Allergan Signatory: [REDACTED]

Original Protocol Date: 29 Apr 2016

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Protocol Amendment 3 Date: 19 May 2017

The following information can be found on FDA Form 1572 and/or study contacts page: 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

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Protocol Summary

Study Compound(s): Ubrogепant

Phase: 3

Study Objective: To evaluate the efficacy, safety, and tolerability of 2 doses of ubrogепant (50 mg and 100 mg) compared to placebo for the acute treatment of a single migraine attack

Clinical Hypotheses:

1. At least 1 ubrogепant dose is superior to placebo in the acute treatment of migraine.
2. Ubrogепant is safe and tolerable.

Study Design

Structure: Multicenter, randomized, double-blind, placebo-controlled, parallel-group, single attack study; randomization to placebo, ubrogепant 50 mg, or ubrogепant 100 mg.

Duration: The study includes a screening period of up to 14 days prior to randomization, a 60-day period in which to treat a single migraine attack, and a 4-week follow-up period.

Study Treatment Groups: Ubrogепant 50 mg, ubrogепant 100 mg

Controls: Ubrogепant placebo

Dosage/Dose Regimen: Study participants will have up to 60 days to treat a single qualifying migraine attack of moderate or severe headache pain intensity at home. Patients have the option to take a second dose of investigational product (IP) or rescue medication if the patient has either a nonresponding migraine or a migraine recurrence.

[REDACTED]

[REDACTED]

[REDACTED]

Study Population Characteristics

Number of Patients: Approximately 1650 patients will be randomized (550 per treatment arm)

Condition/Disease: Migraine with or without aura

Key Inclusion Criteria: To be eligible for study participation, patients must be 18 to 75 years of age (inclusive), have a history of migraine with or without aura for at least 1 year consistent with a diagnosis according to the International Classification of Headache Disorders criteria, 3rd edition, beta version (ICHD-3 beta, 2013) and experience between 2 to 8 migraine attacks with moderate to severe headache pain in each of the 3 months prior to Screening (Visit 1).

Key Exclusion Criteria: [REDACTED]

Response Measures

Efficacy: Rating of headache severity, absence or presence of migraine-associated symptoms, use of rescue medication, use of optional second dose, and recurrence of headache pain

[REDACTED]

General Statistical Methods and Types of Analyses: The efficacy analyses will be based on the Modified Intent-to-treat (mITT) Population. The last observation carried forward (LOCF) approach will be used to impute missing posttreatment values. Baseline for efficacy is defined as the last nonmissing efficacy assessment before the initial dose of study treatment. For each primary variable, the observed response proportions will be provided by treatment group. The primary efficacy variable of pain freedom at 2 hours after the initial dose will be analyzed using a logistic regression model with categorical terms for treatment group, historical triptan response (triptan responder, triptan insufficient responder, or triptan naïve), use of medication for migraine prevention (yes/no), and baseline headache severity (moderate or severe). The primary efficacy variable of absence of the most bothersome symptom at 2 hours after the initial dose will be analyzed using a similar logistic regression model with an additional categorical term for the underlying symptom that was identified as the most bothersome. The respective comparisons of the ubrogepant doses versus placebo, which are the formal tests of the efficacy hypotheses, will be conducted using the appropriate pairwise contrasts within the logistic regression model. For secondary and other efficacy endpoints related to migraine headache pain severity and/or recurrence, migraine-associated symptoms, or use of rescue medication (including the second dose of IP), the observed response proportions will be analyzed using the same methods used to analyze the primary efficacy variables. For secondary efficacy endpoints on migraine-associated symptoms, baseline presence/absence of the symptom will be included as an additional covariate for the logistic regression model. The proportion of patients reporting satisfaction with study medication at 2 and 24 hours after the initial dose, the proportion of patients able to function normally at 1, 2, 4, and 8 hours after the initial dose, and the proportion of patients assessed by the PGIC as “much better” or “very much better” at 2 hours after the initial dose will be analyzed using the same methods used to analyze the primary efficacy variables. The baseline functional disability score will also be included as a covariate for the analysis of the proportion of patients able to function normally. For the change from baseline in EQ-5D-5L index value at 24 hours after the initial dose, treatment comparisons of ubrogepant dose groups versus placebo will be performed using an analysis of covariance (ANCOVA) model with categorical terms for treatment group, baseline severity, historical triptan response, and use of medication for migraine prevention, and with the baseline EQ-5D-5L index value as a covariate. Descriptive statistics will be provided for the change from baseline in the EQ VAS score at 24 hours after the initial dose by treatment group.

[REDACTED]

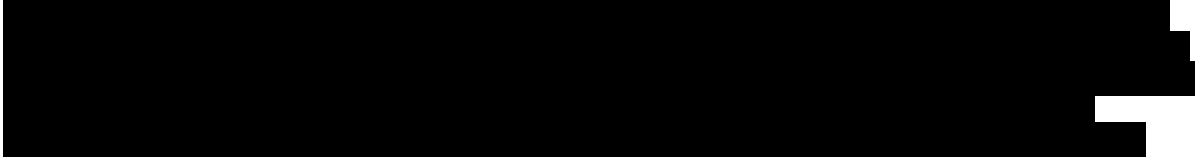
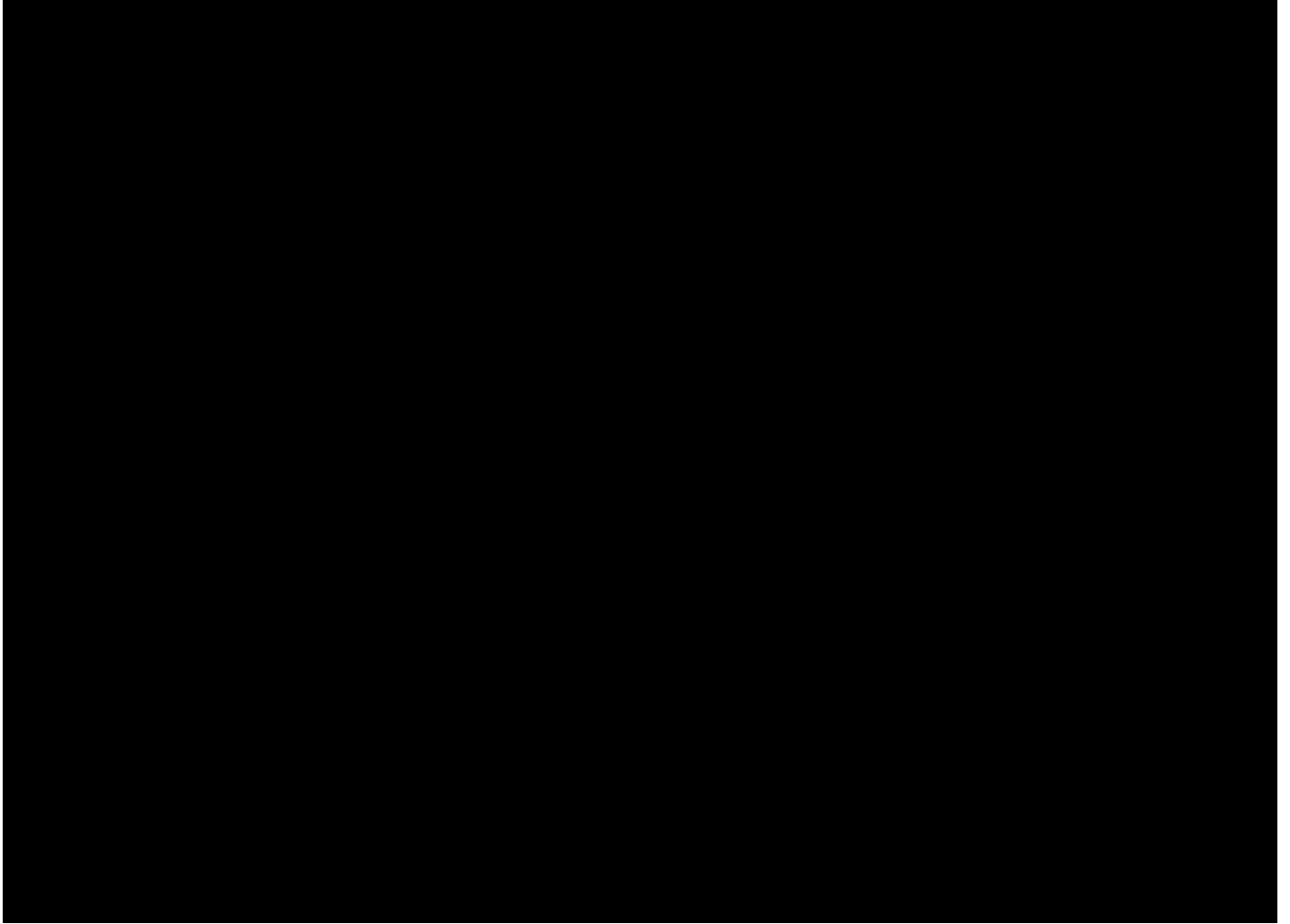
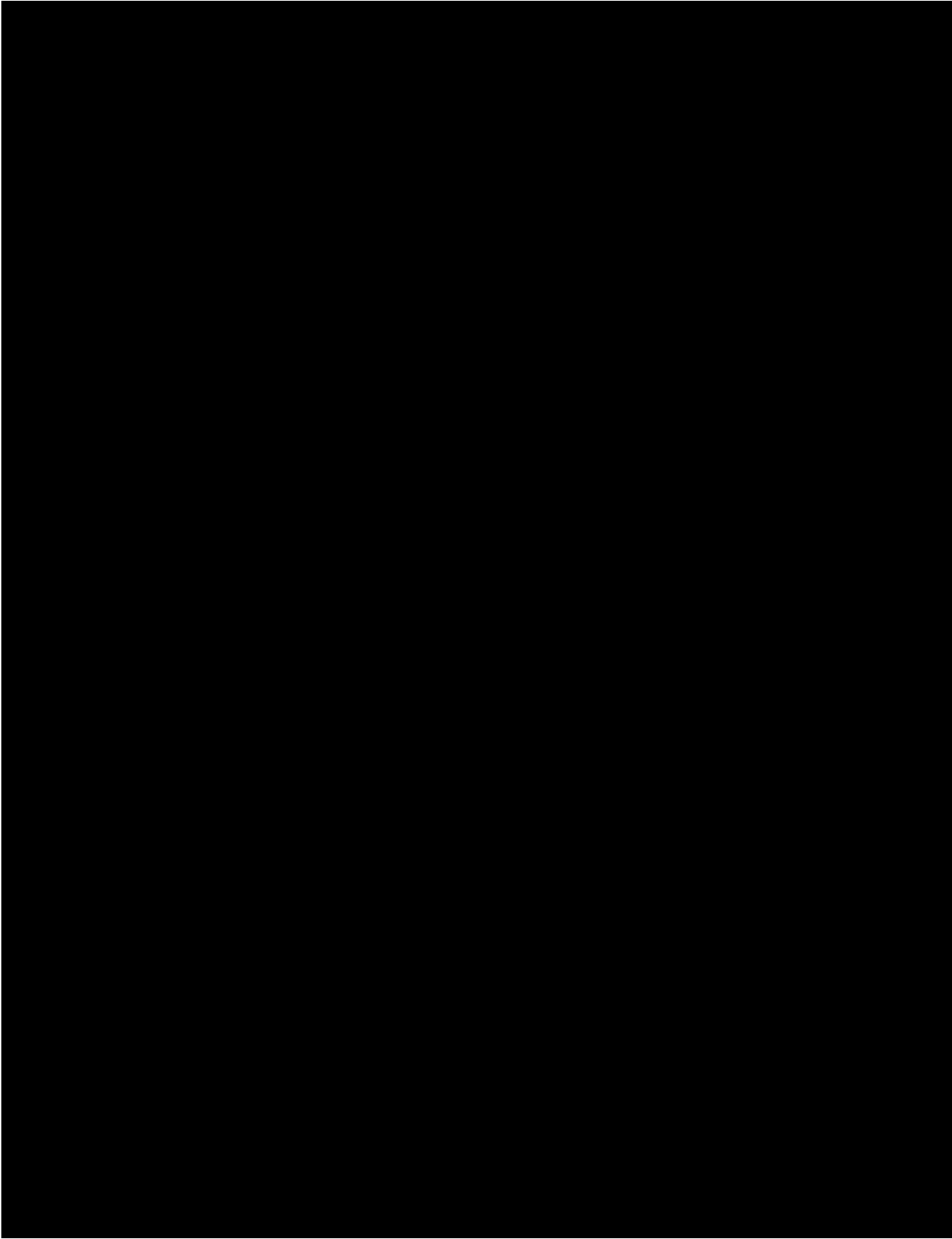
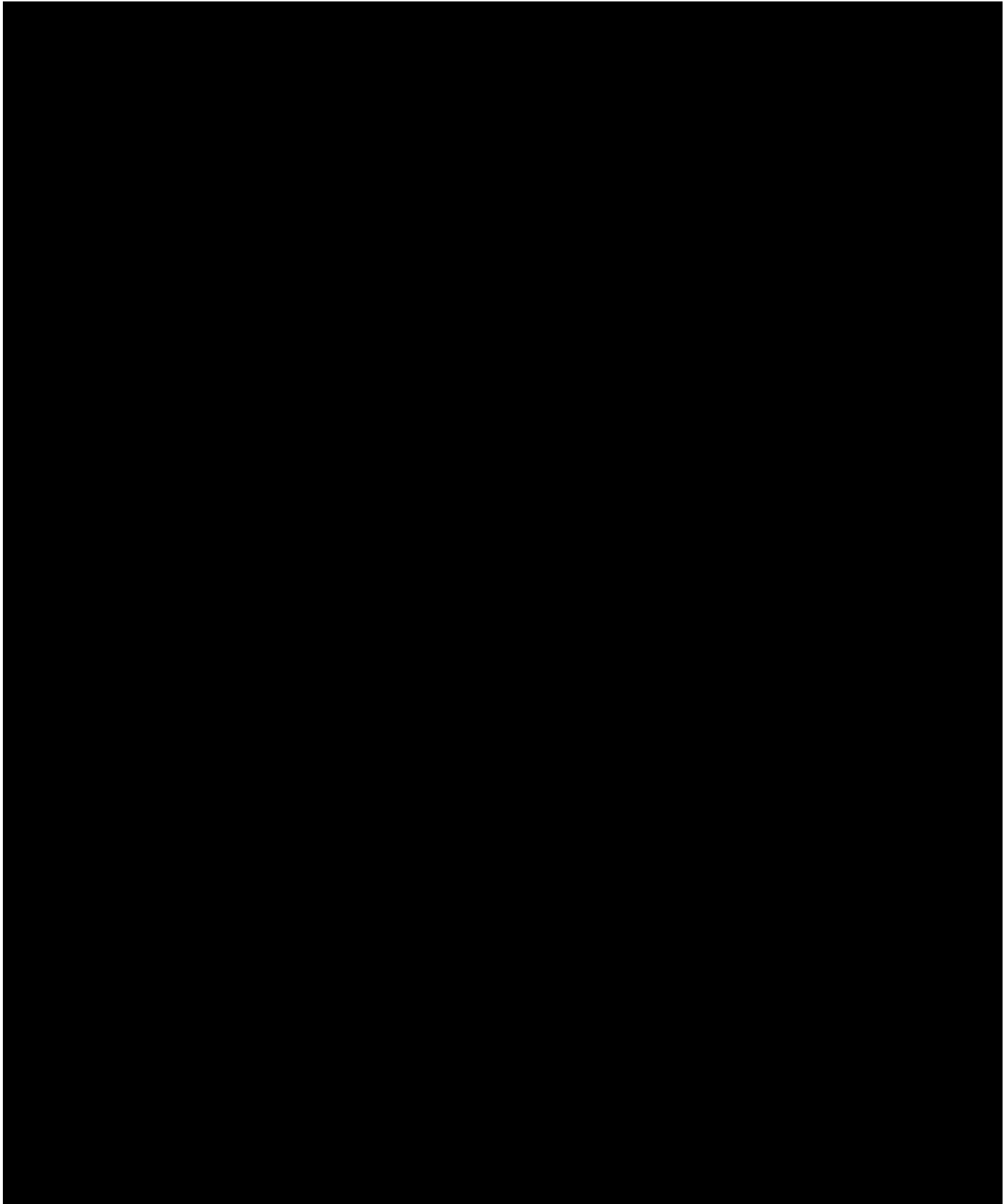
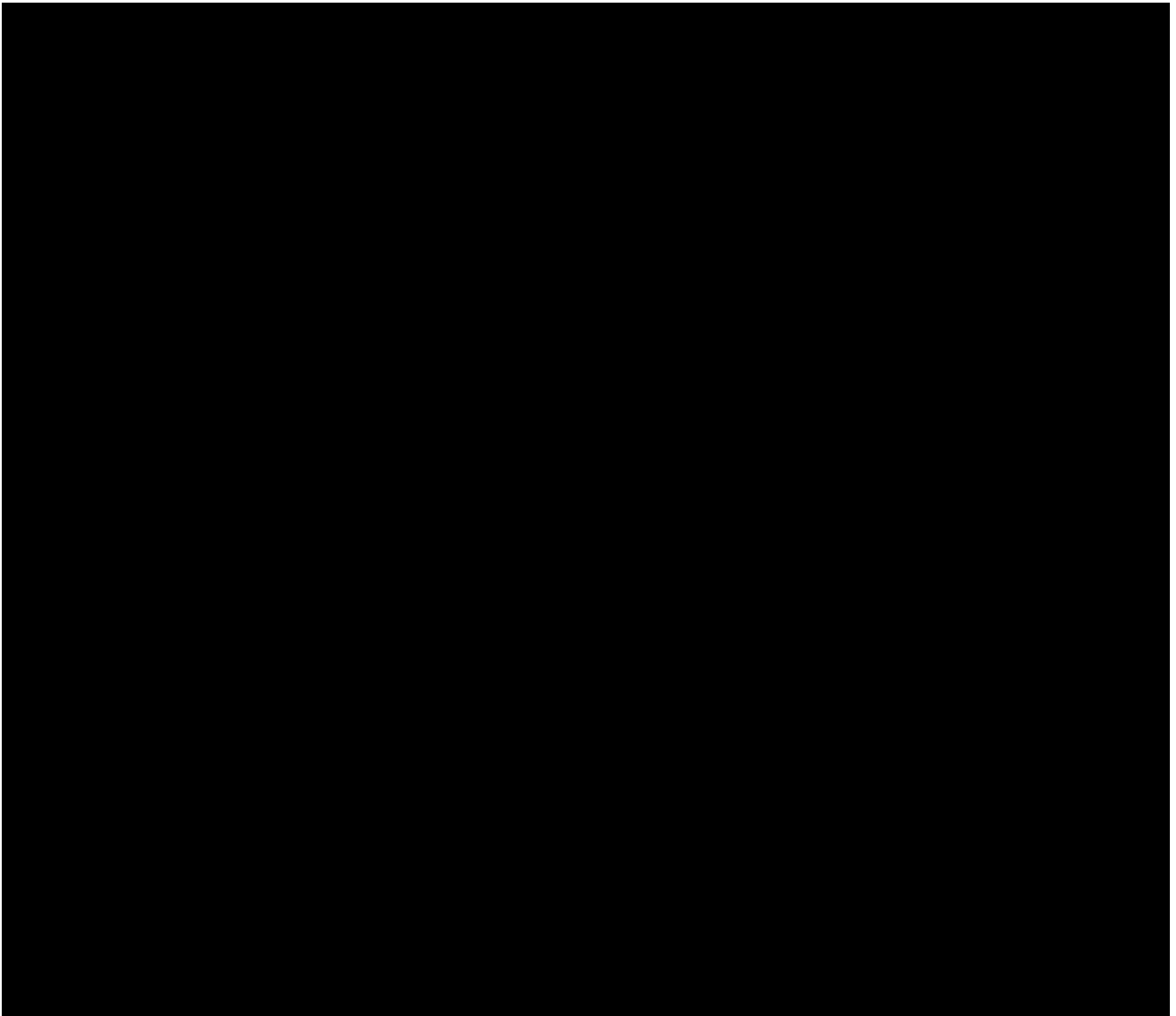


Figure 1 Study Flow Diagram









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 et al, 2007). In the United States, work loss due to migraine is estimated to cost ~ \$13 billion annually (Hu et al, 1999). Prevalence is similar in Europe, with migraine headache affecting 17.6% of women and 8% of men (Stovner and Andree, 2010). It is currently ranked by the World Health Organization as 19th among causes of disability (Katsarava et al, 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 et al, 2012).

Because there are no biological markers for migraine, diagnosis is based on clinical history, exam, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnoses and subsequent treatment. Episodic migraine 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 et al, 2012; Olesen et al, 2006).

What is CGRP and What is its Relationship to Migraine?

CGRP (calcitonin gene-related peptide) 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 and Edvinsson, 1993) and exogenously administered CGRP has been shown to trigger migraine-like headache in migraineurs. The majority (80% to 90%) of trigeminal A δ 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 et al, 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 ([Connor et al, 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 Ubrogapant?

Ubrogapant, 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 ubrogapant have shown no evidence of hepatotoxicity.

A Phase 2b clinical study was conducted, which compared 1-, 10-, 25-, 50-, and 100-mg doses of ubrogapant to placebo in the acute treatment of migraine. Overall, all the ubrogapant doses tested were well tolerated and the adverse event (AE) profile of all ubrogapant doses did not differ significantly from placebo. For the primary efficacy endpoint of pain freedom at 2 hours, ubrogapant 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 ubrogapant doses differed from placebo, probably due to a high placebo response rate.

The absence of migraine-associated symptoms of photophobia, phonophobia, and nausea was assessed as key secondary endpoints. Ubrogapant 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 ubrogapant 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 sustained pain freedom and sustained pain relief) generally suggested that ubrogepant 50 mg and 100 mg were more effective than the 25-mg dose.

The purpose of this study will be to assess the safety and efficacy of 2 doses of ubrogepant, 50 and 100 mg, versus placebo in the acute treatment of migraine with or without aura, in a randomized, double-blind, placebo-controlled Phase 3 study.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To evaluate the efficacy, safety, and tolerability of 2 doses of ubrogepant (50 and 100 mg) compared to placebo for the acute treatment of a single migraine attack.

2.2 Clinical Hypotheses

1. At least 1 ubrogepant dose is superior to placebo in the acute treatment of migraine.
2. Ubrogepant is safe and tolerable.

3. Study Design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, single attack study will enroll approximately 1650 patients from approximately 100 centers in the United States. Patients will be randomized (1:1:1) to 1 of the following 3 treatment groups: placebo, ubrogepant 50 mg, or ubrogepant 100 mg.

Study participants will have up to 60 days to treat a single qualifying migraine attack of moderate or severe intensity at home. Patients unable to treat a qualifying migraine within this time will be discontinued from the study.

[REDACTED]

The planned efficacy assessments are rating of headache severity, absence or presence of migraine-associated symptoms, use of rescue medication, use of optional second dose, and

recurrence of headache pain. A list and description of each efficacy assessment is in [Section 6.1](#) and the efficacy analyses are presented in [Section 7.3.1](#).

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3.1 Adjudication Committee and Data Safety Monitoring Board

An Adjudication Charter will be established and will describe the process for the blinded surveillance, monitoring, and adjudication by the Clinical Adjudication Committee of events of posttreatment 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 related to ubrogepant.

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

Details of the DSMB memberships, standard operational procedures for data monitoring/review, frequency of review, and other pertinent details will be provided in a separate DSMB Charter.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 1650 patients will be randomized (550 patients per arm) from approximately 100 centers in the United States.

4.2 Study Population Characteristics

This study will include adult patients with migraine with or without aura.

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. Male or female patients ages 18 to 75 years, inclusive, at Visit 1
3. At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition, beta version ([ICHD-3 beta, 2013; Section 12.1.1](#))
4. Migraine onset before age 50
5. By history, the patient's migraines typically last between 4 and 72 hours if untreated or treated unsuccessfully and migraine episodes are separated by at least 48 hours of headache pain freedom
6. History of 2 to 8 migraine attacks per month with moderate to severe headache pain in each of the 3 months prior to Screening (Visit 1)

[REDACTED]

- 8. Be able to read, understand and complete the study questionnaires and eDiary.

4.4 Exclusion Criteria

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

[Redacted]

- 2. Difficulty distinguishing migraine headache from tension-type or other headaches.

[Redacted]

- 4. Has taken medication for acute treatment of headache (including acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], triptans, ergotamine, opioids, or combination analgesics) on 10 or more days per month in any of the 3 months prior to Visit 1.

- 5. Has a history of migraine aura with diplopia or impairment of level of consciousness, hemiplegic migraine, or retinal migraine as defined by ICHD-3 beta (Section 12.1.1)

- 6. Has a current diagnosis of new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3 beta (Section 12.1.1)

- 7. Required hospital treatment of a migraine attack 3 or more times in the 6 months prior to Visit 1.

[Redacted]

[REDACTED]

9. Has a chronic non-headache pain condition requiring daily pain medication (with the exception of pregabalin)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[Redacted]

[Redacted]

- 20. History of malignancy in the 5 years prior to Visit 1, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer
- 21. History of any prior gastrointestinal (GI) conditions (eg, diarrhea syndromes, inflammatory bowel disease) that may affect the absorption or metabolism of investigational product (IP); patients with prior gastric bariatric interventions (eg, Lap Band) which have been reversed are not excluded
- 22. History of acute hepatitis within 6 months of Screening (Visit 1) or chronic hepatitis (including nonalcoholic steatohepatitis) or a positive result on anti-hepatitis A immunoglobulin M (IgM) antibody, hepatitis B surface antigen, or anti-hepatitis C antibody testing at Screening (Visit 1)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]




4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Medications which are not specifically prohibited are allowed; however, there may be clarifications and restrictions with certain medications.

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

- any triptan
- any ergot derivative
- any opioid
- any 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 IP:

- any antacid
- any H₂ blocker

Examples of allowed but restricted medications listed above are displayed in [Attachment 12.2](#).

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

Daily use of pregabalin is allowed.

Selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) will be permitted provided that treatment is stable for at least 60 days prior to screening (Visit 1) and continues without change in dose throughout the study. SSRIs and SNRIs may not be started during the study.

Standard migraine prophylactic medications (eg, beta-blocker, tricyclic antidepressant, topiramate, valproic acid, botulinum toxin) will be permitted provided that the treatment is stable for at least 30 days prior to Visit 1, and continues without change in dose throughout the study. Prophylactic medications may not be started during the 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](#).

[REDACTED]

[REDACTED] For details regarding the requirements for treatment with rescue medication and optional second dose, please refer to [Section 5.6.3](#).

[REDACTED]

4.5.1.2 Definition of Females of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

For 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 women of childbearing potential 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: post-bilateral vasectomy, barrier contraception, or sexual abstinence. Male participants must also refrain from donating sperm during the course of the study.

The investigator and each patient will determine the appropriate method of contraception for the patient during the 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 exited 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 30 days prior to Visit 1 and throughout the study period:

- 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 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 BCRP (breast cancer resistance protein) transporter (eg, rifampicin)
- Drugs with narrow therapeutic margins (eg, digoxin, warfarin)

Examples of prohibited medications in the classes noted above are displayed in [Section 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 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 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.

5.2 Control Treatment

Ubrogepant placebo [REDACTED] tablets.

5.3 Methods for Masking/Blinding

All study treatments will be provided in identical blister cards to maintain masking of the study. Tablets of ubrogepant 50 mg and placebo will be identical in appearance.

A modified double-dummy design will be utilized to maintain the study blind. All patients will be instructed to take 2 tablets to treat their migraine attack regardless of the dose group to which they are assigned. The treatments to be used in this study are outlined in [Table 2](#).

5.4 Treatment Allocation Ratio [REDACTED]

Patients who meet all of the study entry criteria will be randomized and provided with IP to treat 1 migraine attack on an outpatient basis. Patients will be assigned randomly in a 1:1:1 ratio to 1 of the following 3 treatment groups: placebo, ubrogepant 50 mg, or ubrogepant 100 mg.

[REDACTED]

[REDACTED]

[REDACTED]

- | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]

- | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]
 - | [REDACTED]

| [REDACTED]

**5.5 Method for Assignment to Treatment
Groups/Randomization/[REDACTED]**

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.

An automated interactive web response system (IWRS) will be used to manage the randomization and treatment assignment. At the time of randomization (Visit 2), eligible patients will be randomly assigned to 1 of 3 treatment arms in a 1:1:1 ratio to placebo, ubrogepant 50 mg, or ubrogepant 100 mg [REDACTED]

Allergan Biostatistics (randomization programmer) will prepare the randomization codes.

IP will be labeled with medication kit numbers. The IWRS will provide the site with the specific medication kit number(s) for each randomized patient 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 are to be maintained with the study source documents.

5.6 Treatment Regimen and Dosing

5.6.1 Treatment Administration

Table 2 presents the treatments that will be administered in this study. All patients will be instructed to take 2 tablets for their initial dose to treat their migraine attack regardless of the dose group to which they are assigned. If taking the optional second dose, patients will also be instructed to take 2 tablets. [REDACTED]

Table 2 Treatments Administered for Initial and Optional Second Dose

Drug/Dose	Route of Administration	Investigational Product Administered for Initial Dose	[REDACTED]	[REDACTED]
Placebo	Oral (tablet)	50 mg placebo/ 50 mg placebo	[REDACTED]	[REDACTED]
Ubrogepant 50 mg	Oral (tablet)	Ubrogepant 50 mg/ 50 mg placebo	[REDACTED]	[REDACTED]
Ubrogepant 100 mg	Oral (tablet)	Ubrogepant 50 mg/ ubrogepant 50 mg	[REDACTED]	[REDACTED]

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5.6.3 Optional Second Dose and Rescue Medication

Two hours after initial treatment with IP, patients who did not adequately respond may take a blinded optional second dose, active treatment or placebo, as assigned at the Randomization Visit (Visit 2) or patients' own rescue medication, or may elect to take no further medication. Inadequate response to the initial dose of IP is defined as meeting 1 of the following:

- Continues to have a headache that is either moderate or severe; OR
- After initial pain relief at 2 hours (defined as a headache severity rating of no pain or mild pain), moderate or severe headache returns within 2 to 48 hours after the initial dose

[REDACTED]

[REDACTED]

[REDACTED]



5.7 Storage of Investigational Products/Treatments

IP 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

6.1 Efficacy Measures

Efficacy measurement assessments are based on information recorded by the patient in an eDiary.

Rating of Headache Severity

Headache severity will be subjectively rated by the patient at predefined timepoints (predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours after the initial dose) on a scale from no pain to severe pain:

- No pain
- Mild pain
- Moderate pain
- Severe pain

Migraine Associated Symptoms

The patient will record whether the following associated symptoms were present or absent at predefined timepoints (predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours after the initial dose):

- Photophobia
- Phonophobia
- Nausea
- Vomiting

Use of Rescue Medication

Patients will record in their eDiary any rescue medication taken within 48 hours after treating their migraine attack with IP, in addition documenting the date and time that the rescue medication was taken.

Use of Optional Second Dose and Recurrence of Headache Pain

Patients will record in their eDiary use of the optional second dose of IP due to inadequate response to their initial dose of IP. Date and time of the second dose will be reported, as well as pain severity and absence or presence of migraine-associated symptoms at the time the second dose is taken and 2 hours after taking the second dose. The incidence of recurrence in patients who had pain relief and pain freedom at 2 hours after the initial dose will be collected.

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6.6 Other Study Supplies

The following will be provided by Allergan:

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

6.7 Summary of Methods of Data Collection

An IWRS will be used to randomize patients and manage IP inventory. Data for this study will be collected using eCRFs via an electronic data capture system, eDiaries, and eTablets. 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 the respective laboratory manuals.

Patients will use an eDiary to record details associated with their migraine attack, including, but not limited to the date and time of dosing, efficacy assessments (eg, pain severity, absence or presence of migraine-associated symptoms), and other important study information at designated timepoints post-dose. Training for the eDiary will be provided for qualified patients during the Randomization Visit (Visit 2). For details regarding eDiary instructions to patients, see the eDiary manual.

The C-SSRS will be conducted as a clinical interview at each visit and recorded by qualified site staff 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 study treatment, recorded a baseline migraine headache severity measurement, and had at least 1 postdose migraine headache severity or migraine-associated symptom measurement at or before the 2-hour timepoint.

7.1.2 Safety Population

The Safety Population will consist of all randomized patients who received at least 1 dose of study treatment.

7.2 Collection and Derivation of Efficacy Assessments

7.2.1 Primary Efficacy Variables

The coprimary efficacy parameters for the United States are as follows:

- Pain freedom (PF) at 2 hours after the initial dose, defined as a reduction in headache severity from moderate/severe at baseline to no pain, at 2 hours after the initial dose
- Absence of the most bothersome migraine-associated symptom (the most bothersome migraine-associated symptom will be identified at baseline for each patient) at 2 hours after the initial dose.

[REDACTED]

■ [REDACTED]

7.2.2 Secondary Efficacy Variables

The secondary efficacy parameters for the United States are:

- Pain relief (PR) at 2 hours after the initial dose, defined as the reduction of a moderate/severe migraine headache to a mild headache or to no headache, at 2 hours after the initial dose
- Sustained pain relief (SPR) from 2 to 24 hours after the initial dose, defined as pain relief with no administration of either rescue medication or the second dose of IP, and with no occurrence thereafter of a moderate/severe headache during the relevant number of hours after dosing with the IP
- Sustained pain freedom (SPF) from 2 to 24 hours after the initial dose, defined as pain freedom with no administration of either rescue medication or the second dose of IP, and with no occurrence thereafter of a mild/moderate/severe headache during the relevant number of hours after dosing with the IP
- Absence of photophobia at 2 hours after the initial dose
- Absence of phonophobia at 2 hours after the initial dose
- Absence of nausea at 2 hours after the initial dose

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7.3 Hypothesis and Methods of Analysis

The efficacy analyses will be based on the mITT Population. The last-observation-carried-forward (LOCF) approach will be used to impute missing posttreatment values. Baseline for efficacy is defined as the last nonmissing efficacy assessment before the initial dose of study treatment. All statistical tests will be 2 sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

7.3.1 Efficacy Analyses

7.3.1.1 Primary Efficacy Analyses

For each primary variable, the observed response proportions will be provided by treatment group. The primary efficacy variable of pain freedom at 2 hours after the initial dose will be analyzed using a logistic regression model with categorical terms for treatment group, historical triptan response (triptan responder, triptan insufficient responder, or triptan naïve), use of medication for migraine prevention (yes/no), and baseline headache severity (moderate or severe). The primary efficacy variable of absence of the most bothersome symptom at 2 hours after the initial dose will be analyzed using a similar logistic regression model with an additional categorical term for the underlying symptom that was identified as the most bothersome. If the logistic regression model fails to converge due to complete or quasi-complete separation, Firth’s penalized likelihood method (Firth, 1993) will be used. The logistic regression model will be referred to as the primary model.

The respective comparisons of the ubrogepant doses versus placebo, which are the formal tests of the efficacy hypotheses, will be conducted using the appropriate pairwise contrasts within the logistic regression model. Treatment comparisons will be based on the model-derived odds ratios and their associated 95% confidence intervals. Two-sided p-values will also be provided.

[REDACTED], the study will be considered a success if at least 1 ubrogepant dose is demonstrated to be superior to placebo on both coprimary variables after multiplicity adjustment.

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7.3.1.2 Secondary Efficacy Analyses

For each secondary efficacy endpoint, the observed response proportions will be analyzed using the same methods used to analyze the primary efficacy variables. The respective comparisons of the ubrogepant doses versus placebo will be conducted using model-derived odds ratios, 95% confidence intervals and p-values from the logistic regression model. For secondary efficacy endpoints on migraine-associated symptoms, baseline presence/absence of the symptom will be included as an additional covariate for the logistic regression model.

A graphical approach by Bretz et al (2009) will be used to control the overall type I error rate for multiple comparisons across the ubrogepant doses and the primary and secondary efficacy endpoints. The coprimary efficacy endpoints will serve as the gatekeepers of the secondary endpoints. The secondary endpoints will be tested in the same order as they appear in the list of secondary endpoints, except for the 3 migraine-associated symptoms which will be treated at the same level to allow the recycling of weights among the 3 symptom endpoints. Recycling of weights between the 2 doses is also allowed. The details of the multiple comparison procedure will be provided in the statistical analysis plan (SAP).

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Table 4 Assumed Response Rates and Estimated Power for Primary and Secondary Efficacy Endpoints

Endpoint	Assumed Response Rate for Placebo	Assumed Response Rate for Ubrogepant Groups	Power After Multiplicity Adjustment
PF 2h	10%	24%	>99%
Absence of the Most Bothersome Symptom 2h	26.7%	37.7%	88%
PR 2h	34%	56%	88%
SPR 2 to 24h	19%	38%	88%
SPF 2 to 24h	6.5%	14.5%	83%
Absence of Photophobia 2h	32%	44%	78%
Absence of Phonophobia 2h	43%	57%	81%
Absence of Nausea 2h	59%	70%	71%

; h = hours; PF = pain freedom; PR = pain relief; SPF = sustained pain freedom; SPR = sustained pain relief

7.6 Interim Analyses

No interim analysis is planned for this study.

8. 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](#) 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 be assigned a patient number that will be used on patient documentation throughout the study.

[REDACTED]

8.2 Washout Intervals/Run-In

This study will not include a washout period.

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8.5 Instructions for the Patients

[Section 4.5.3](#) provides diet and activity instructions for patients enrolled in the study.

Patients will be provided with instructions on the use of the eDiary to complete when they experience a qualifying migraine. A practice session with a hypothetical scenario should be administered to ensure the patients' comprehension of the questions and the information to be entered. In addition, criteria for a qualifying migraine to be treated as well as prohibited medications should be reviewed with the patients. Patients will be instructed to bring their eDiary at the next clinic visit and return their IP (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 the patient 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 the IP taken in the eDiary. IP compliance will be closely monitored by counting the number of tablets dispensed and returned. Every effort will be made to collect all unused IP.

8.8 Early Discontinuation of Patients

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

- Adverse event (AE)
- Protocol violation
- Noncompliance with IP
- 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 60 days from Randomization [Visit 2])
- 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 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 3/Early Termination [REDACTED]

[REDACTED]. If the patient discontinues after IP is taken, the patient is also expected to return for the Safety Follow-up Visit (Visit 4) 4 weeks postdose.

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 IP. The patient should return to the clinic for early termination procedures (Visit 3), including the safety follow-up visit (Visit 4) if IP was taken.

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 at Visit 3 [REDACTED] and should receive appropriate follow-up as in routine clinical practice, including the safety follow-up visit (Visit 4) if IP 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.

[REDACTED]

8.11 Study Termination

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

9. Adverse Events

Adverse events occurring during the study will be recorded on an adverse event eCRF. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event 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 adverse event 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, adverse events will be assessed regardless of the administration of a pharmaceutical product.

Note: Adverse events 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 adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events 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 adverse events 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 adverse events will be documented on the appropriate case report form.

9.1.2 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, 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 a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require

medical or surgical intervention to prevent one of the outcomes listed in this definition. (See [Section 9.3](#) for procedures for reporting a serious adverse event.)

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as a serious adverse event.

Preplanned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

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 a serious adverse event and reported to Allergan.

9.1.3 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event 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 adverse event 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 adverse event may have been caused by the drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate case report form.

All serious adverse events 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 adverse event that is marked "ongoing" at the exit visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event 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 but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan or Agent of Allergan (eg, contract research organization [CRO]) and recorded on the serious adverse event form. All patients with a serious adverse event 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 a serious adverse event, the investigator must:

1. Notify Allergan immediately by fax or email using the serious adverse event form (contact details can be found on page 1 of the serious adverse event form); phone numbers and relevant Allergan personnel contacts are also on the front page of protocol.
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 adverse event(s) on the serious adverse event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(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 serious adverse event 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 he or she signs the ICF for the trial until 30 days after the last dose of IP on the Pregnancy Form as soon as possible (within 24 hours of learning of the pregnancy to the SAE/Pregnancy fax number, [REDACTED] [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 a 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.

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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 IP. 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 on to 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 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 Regulations (US 21 CFR 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 of 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 patient's name will not be disclosed in these documents. The patient's name 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 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, 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 ECGs. The investigator's copy of the case report forms 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
- Patient's medical history
- Information regarding patient's diagnosis of migraine headache
- All concurrent medications (list all prescription and nonprescription medications being taken at the time of enrollment; at each subsequent visit, changes to the list of medications should be recorded)
- Occurrence and status of any adverse events
- 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 Electronic Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRF 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 eCRFs 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 investigational products, 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 investigational product. 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

IP will be supplied in blister cards and will be labelled with the protocol number, storage information, warning language, and instructions to take the tablets as directed. The card will also include the medication number. Immediately before dispensing the blister card, the investigator or designee will write the study center number, patient's initials and patient number, and date on the blister 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 of all used and unused IP and packaging. The IP 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 clinical IPs/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction.

10.6 Monitoring by the Sponsor

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

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

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

[REDACTED]

All samples will be returned to Allergan or Allergan’s designee for destruction. Allergan shall have full ownership rights to any biological specimens/samples derived from the study. For additional details regarding handling of biological samples please refer to the Laboratory Manual.

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.

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12. Attachments

12.1 Examination Procedures, Tests, Equipment, and Techniques

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

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Cephalalgia 33(9)

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 attacks¹ 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 oligoemia 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-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, hemiparesis, 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 minutes¹
 - 3. at least one aura symptom is unilateral²
 - 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 minutes¹
 3. at least one aura symptom is unilateral²
 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 motor¹ 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 minutes²
 3. at least one aura symptom is unilateral³
 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 Hemiplegic¹ 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 hours²
 3. at least one aura symptom is unilateral³
 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 months² 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 following³:
 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 hours¹
 2. pain and/or associated symptoms are debilitating²
- 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. Vertigo¹ 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 attacks¹ 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. ataxia²
 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.

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12.2 Examples of Prohibited Medications

Prohibited Medications

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

	Strong/Moderate CYP3A4 Inducers	Strong/Moderate CYP3A4 Inhibitors
Antidepressant/ Antianxiety	Barbiturates <ul style="list-style-type: none"> • Amobarbital (Amytal[®]) • Aprobarbital (Alurate[®]) • Butalbital (Fiorinal[®], Fioricet[®]) • Butobarbital (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 [®])
Anti-HIV	Efavirenz (Stocrin [®] , Sustiva [®]) Nevirapine (Viramune [®])	Indinavir (Crixivan [®]) Nelfinavir (Viracept [®]) Ritonavir (Norvir [®]) Saquinavir (Fortovase [®] , Invirase [®])
Immunosuppressant		Cyclosporine - oral/IV 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 [®])
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The following medications are allowed during the study; however, they are prohibited within 48 hours prior to taking IP:

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 IP:

Antacid	Aluminum Carbonate Gel (Basaljel [®]) Aluminium Hydroxide (AlternaGEL [®] , Amphojel [®]) Aluminium Hydroxide and magnesium hydroxide (Maalox [®] , Mylanta [®]) Bismuth Subsalicylate (Pepto-bismol [®]) Calcium Carbonate (Alcalak [®] , Quick-Eze [®] , Rennie [®] , Rolaid [®] , Titalac [®] , TUMS [®]) Hydrotalcite (Talcid [®]) Magaldrate plus Simethicone (Pepsil [®]) Magnesium Hydroxide (Phillips' Milk of Magnesia [®]) Sodium Bicarbonate (Alka-Seltzer [®] , Bicarbonate of Soda [®])
H₂ Blocker	Famotidine (Pepcid [®]) Nizatidine (Axiid [®]) 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
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BP	blood pressure
C2hr	plasma concentration at 2 hours postdose
CAP	College of American Pathology
CGRP	calcitonin gene-related peptide
CGRP RA	CGRP receptor antagonist
CHD	coronary heart disease
CLIA	Clinical Laboratory Improvement Amendments
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
CYP3A4	cytochrome P450 3A4
DBS	dry blood spot
DSMB	Data Safety Monitoring Board
EC ₅₀	half-maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
eDISH	evaluation of drug-induced serious hepatotoxicity
EMA	European Medicines Agency
E _{max}	maximum drug effect
eTablet	electronic tablet
EU	European Union
FDS	Functional Disability Scale
EQ-5D-5L	European Quality of Life – 5-Dimensional – 5-Level
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation

ICHD-3 beta	International Classification of Headache Disorders criteria, 3 rd edition (beta version, 2013)
IEC	Independent Ethics Committee
IETD	investigator emergency treatment disclosure
IgM	immunoglobulin M
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
NCEP	National Cholesterol Education Program
NSAID	nonsteroidal anti-inflammatory drug
PCS	potentially clinically significant
PF	pain freedom
PGIC	Patient Global Impression of Change
PR	pain relief
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR) ^{1/3})
■	■
SAE	serious adverse event
SAP	statistical analysis plan
SSRI	selective serotonin reuptake inhibitors
SNRI	serotonin norepinephrine reuptake inhibitors
SPF	sustained pain freedom
SPR	sustained pain relief
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
VAS	visual analogue scale

12.4 Protocol Amendment 1 Summary

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Single Attack Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine

Protocol UBR-MD-01 Amendment 1

Date of Amendment: 09 June 2016

Amendment Summary

This summary includes changes made to Protocol UBR-MD-01 (29 April 2016). This protocol was amended to: 1) revise title page, key responder definitions, health outcomes measures, and efficacy variables, and 2) clarify various study activities.

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
Protocol Title Page	Revised name of the Authorized US Agent from Allergan, Inc. to Allergan Sales, LLC	The name of Allergan in the US has changed
	Added Emergency Telephone Number	To remove need to consult the study contacts page
	Added "Protocol Amendment 1 Date" to the title page	To reflect the approval date of Amendment 1
	Deleted Name and contact information of Allergan study personnel and	To reflect change in study contacts page
Protocol Summary, [Redacted]	[Redacted]	[Redacted]
	[Redacted]	[Redacted]
	[Redacted]	[Redacted]

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
Section 3.1, Adjudication Committee and Drug Safety Monitoring Board	Added <u>Drug</u> to title and text for DSMB, and added that details of the DSMB will be provided in a separate Charter	Clarification
[REDACTED]	[REDACTED]	[REDACTED]
Section 4.5.1.2, Definition of Females of (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods Section 5.3, Methods for Masking/Blinding	Added to description of male contraception methods: <u>Male participants should also refrain from donating sperm during the course of the study.</u>	To clarify that since male study participants should use contraception during the study, they should also refrain from donating sperm per central IRB request
	Added to description of study treatments: <u>Tablets of ubrogepant 50 mg and placebo will be identical in appearance.</u>	To clarify that ubrogepant and placebo tablets will be indistinguishable to maintain blinding
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 7.4, Subgroup	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

12.5 Protocol Amendment 2 Summary

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Single Attack Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogепant in the Acute Treatment of Migraine

Protocol UBR-MD-01 Amendment 2

Date of Amendment: 04 Nov 2016

Amendment Summary

This summary includes changes made to Protocol UBR-MD-01 Amendment 1, (09 June 2016). This protocol was amended to: 1) update health outcomes measures and efficacy variables; and 2) clarify several exclusion criteria

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
Protocol Title Page	[REDACTED]	Administrative update
Protocol Summary – General Statistical Methods and Types of Analyses	Revised to note that PGIC will be completed 2 hours after the initial dose: ...the proportion of patients assessed by the PGIC as “much better” or “very much better” at <u>2</u> 24hours after the initial dose will be analyzed using the same methods used to analyze the primary efficacy variables.	Expert input recommended a change in PGIC assessment from 24 hours to 2 hours after the initial dose to increase the probability of differentiating between treatment and placebo
[REDACTED]	[REDACTED]	[REDACTED]

Section	Revision	Rationale
[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]
Section 3.1, Adjudication Committee and Data Safety Monitoring Board	Section title and in-text change updated to <u>Data Drug</u> Safety Monitoring Board	Clarification
Section 4.4, [Redacted]	[Redacted]	[Redacted]
Section 4.4, [Redacted]	[Redacted]	[Redacted]

Section	Revision	Rationale
Section 4.4, [REDACTED]	[REDACTED]	[REDACTED]
Section 4.4, Exclusion 21	History of gastric or small intestinal surgery (including gastric bypass surgery or banding), or has a disease that causes malabsorption (eg, Crohn's disease) any prior gastrointestinal (GI) conditions (eg, diarrhea syndromes, inflammatory bowel disease) that may affect the absorption or metabolism of investigational product (IP); patients with prior gastric bariatric interventions (eg, Lap Band) which have been reversed are not excluded	Clarification on excluded GI procedures and conditions including inclusion of patients with reversal of certain procedures.
Section 4.4, [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
Section 4.5.1 Permissible Medications/Treatments	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 (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods	Moved surgical sterilization from a method of contraception to defining women of childbearing potential: For 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, <u>bilateral salpingectomy</u> , <u>bilateral oophorectomy</u> or hysterectomy).	Clarification

Section	Revision	Rationale
Section 4.5.1.2 Definition of Females of (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods	Updated acceptable contraceptive methods: For women of childbearing potential who may participate in the study, the following methods of contraception, if properly used, are generally considered reliable: hormonal contraceptives (ie, oral, patch, <u>vaginal ring</u> , 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 should must also refrain from donating sperm during the course of the study.	Clarification
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Section	Revision	Rationale
[REDACTED]	[REDACTED]	[REDACTED]
Section 12.2 Examples of Prohibited Medications	Added “(Systemic)” to Glucocorticoid class Added to “Others” category: <u>armodafinil (Nuvigil™)</u> 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: <u>Esomeprazole (Nexium®)</u> <u>Lansoprazole (Prevacid®, Zoton®)</u> <u>Omeprazole (Losec®, Prilosec®, Zegerid®)</u> <u>Pantoprazole (Pantoloc®, Pantozol®, Protonix®, Somac®, Zurcal®)</u> <u>Rabeprazole (Aciphex®, Pariet®, Rabecid®)</u>	Clarification that only systemic glucocorticoids are excluded Clarification Amended per FDA request

12.6 Protocol Amendment 3 Summary

Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Single Attack Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine

Protocol UBR-MD-01 Amendment 3


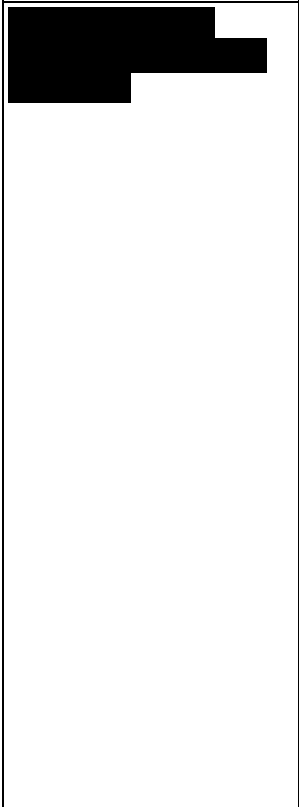
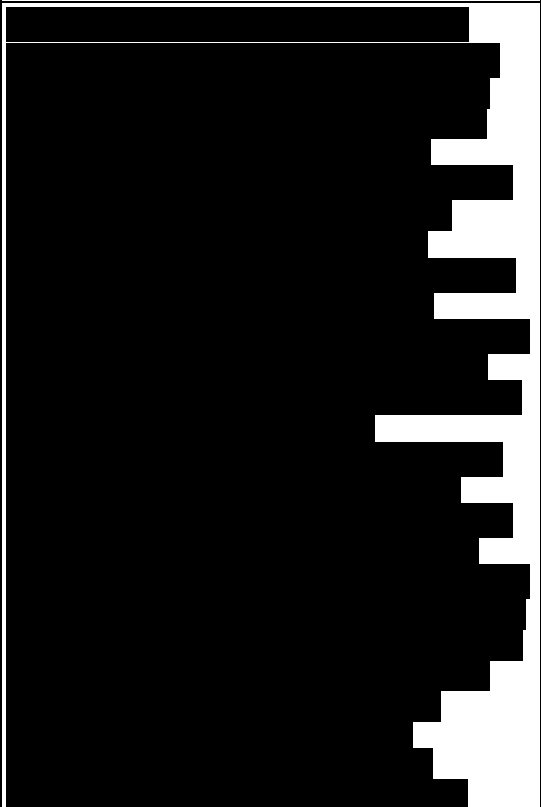

Date of Amendment: 19 May 2017


Amendment Summary

This summary includes changes made to Protocol UBR-MD-01 Amendment 2, (04 Nov 2016). This protocol was amended to: 1) increase sample size from 450 to 550 patients per arm; 2) revise statistical methods to include an additional categorical term to the logistic regression analysis for the primary efficacy variable of absence of the most bothersome symptom at 2 hours after the initial dose; 3) revise statistical methods to include an additional categorical term to the logistic regression analysis for the secondary efficacy endpoints on migraine-associated symptoms; 4) reorder the secondary endpoints, 5) [REDACTED] [REDACTED] [REDACTED] 6) remove the 35% triptan insufficient responder requirement.

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
Title Page	Replaced Emergency Telephone Number and Allergan Medical Monitor Contact Information with instructions to refer to Study Contacts Sheet.	Administrative update
Protocol Summary, Section 3 Study Design, Section 4.1 Number of Patients	Increased number of patients to be randomized to approximately 1650 (550 patients per treatment arm).	Sample size re-estimate based on updated assumptions
Section 5.5 Method for Assignment to Treatment Groups/Randomization/ [REDACTED]	[REDACTED]	[REDACTED]
Section 7.2.2 Secondary Efficacy Variable	Reordered the secondary efficacy parameters for both the US [REDACTED] so that SPF from 2 to 24 (48) hours is listed third, after PR at 2 hours and	The re-ordering of the secondary efficacy endpoints is based on new assumptions. The

Section	Revision	Rationale
	<p>SPR from 2 to 24 (48) hours. Removed satisfaction with study medication and ability to function normally at 2 hours from the secondary efficacy parameters.</p>	
<p>Protocol Summary, Section 7.3.1.1 Primary Efficacy Analyses</p>	<p>Revised logistic regression model as follows: For each primary variable, the observed response proportions will be provided by treatment group. <u>The primary efficacy variable of pain freedom at 2 hours after the initial dose will be analyzed using a logistic regression model with categorical terms for treatment group, historical triptan response (triptan responder, triptan insufficient responder, or triptan naïve), use of medication for migraine prevention (yes/no), and baseline headache severity (moderate or severe). The primary efficacy variable of absence of the most bothersome symptom at 2 hours after the initial dose will be analyzed using a similar logistic regression model with an additional categorical term for the underlying symptom that was identified as the most bothersome.</u></p>	<p>The treatment response on the most bothersome symptom varies according to which symptom is identified as the most bothersome</p>
<p>Protocol Summary, Section 7.3.1.2 Secondary Efficacy Analyses</p>	<p>Revised logistic regression model to include: <u>For secondary efficacy endpoints on migraine-associated symptoms, baseline presence/absence of the symptom will be included as an additional covariate for the logistic regression model.</u></p>	<p>The treatment response on migraine-associated symptoms is different depending on whether the patient had the symptom at predose baseline.</p>
		

Section	Revision	Rationale
	 The 'Revision' column contains two large blocks of text that have been completely redacted with black boxes. The first block is approximately 10 lines high, and the second block is approximately 5 lines high, separated by a small gap.	