Title Page

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine When Administered During the Prodrome

Protocol Number: 3110-304-002

Compound: Ubrogepant

Study Phase: 3

Short Title: Study to Evaluate Oral Ubrogepant in the Acute Treatment of Migraine During the Prodrome

Acronym: PRODROME

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine When Administered During the Prodrome

Short Title: Study to Evaluate Oral Ubrogepant in the Acute Treatment of Migraine During the Prodrome

Rationale:

Treating migraine during the prodrome has the potential to transform the current treatment paradigm and may prove to be the optimal way to treat migraine in those who can identify their prodrome symptoms ahead of a headache. The ability to administer a treatment at the beginning of the migraine (ie, preheadache) and potentially prevent or attenuate the headache phase has the potential to improve patient outcomes (ie, symptoms and functional impairment of migraine) for these patients. Ubrogepant's mechanism of action as a CGRP-RA, with favorable tolerability make it particularly well-suited to be tested for the acute treatment of migraine when administered during the prodrome.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on attenuation of the headache phase	Absence of a headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome
Secondary	
1: To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on attenuation of the headache phase	1: Absence of a headache of moderate or severe intensity within 48 hours after taking double-blind study intervention during the prodrome
2: To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on ability to function normally	2: Ability to function normally over 24 hours after taking double-blind study intervention during the prodrome

Objectives	Endpoints
3: To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on prevention of the headache phase	3: Absence of a headache of any intensity within 24 hours after taking double-blind study intervention during the prodrome

Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, crossover study to compare the efficacy, safety, and tolerability of ubrogepant 100 mg to placebo in the acute treatment of migraine when administered during the prodrome.

To be eligible for study participation, participants must be 18 to 75 years of age (inclusive) at Visit 1, have at least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders criteria, 3rd edition (ICHD-3) (2018), and experience 2 to 8 migraine attacks with moderate to severe headache per month by history in each of the 3 months prior to the Screening Visit (Visit 1). Participants must be able to identify their prodrome symptom(s) and demonstrate that they reliably experience headache after experiencing prodrome symptom(s).

The study includes a 60-day screening period (between Visit 1 and Visit 2) during which participants will demonstrate that they reliably develop headache after experiencing qualifying prodrome events. After meeting eligibility criteria, participants will be randomized at Visit 2 and dispensed double-blind study intervention to treat their first qualifying prodrome event. Four days after taking double-blind study intervention for their first qualifying prodrome event, participants will have Visit 3 at which time double-blind study intervention will be provided to treat a second qualifying prodrome event. Visit 4 will occur 4 days after taking double-blind study intervention for their second qualifying prodrome event. In summary, participants will have up to 60 days (double-blind treatment period between Visit 2 and Visit 4) to treat a total of 2 qualifying prodrome events with study intervention.

Disclosure Statement: This is a crossover treatment study with 2 sequences that is participant and investigator blinded.

Number of Participants: Approximately 516 participants will be randomized (258 participants per sequence). Section 9.2 describes the sample size determination.

Intervention Groups and Duration:

Approximately 516 eligible participants will be randomized (1:1) to treatment sequences A or B in this crossover study. Participants randomized to Treatment Sequence A will receive placebo to treat their first qualifying prodrome event and ubrogepant 100 mg to treat their second qualifying prodrome event. For those randomized to Treatment Sequence B, they will receive the reverse: ubrogepant 100 mg to treat their first qualifying prodrome event and placebo to treat their second qualifying prodrome event.

For each qualifying prodrome event, a single dose (2 tablets) of double-blind study intervention will be taken at the time the prodrome event qualifies to be treated.

The study duration will be approximately 4 months: 60 days for the screening period, and up to 60 days for double-blind treatment period.

Data Monitoring Committee: No

1.2. Schema

Please refer to the figures provided in Section 4.1.

1.3. Schedule of Activities (SoA)

Table 1-1 Schedule of Activities

Study Period	**Screening Period (60 days)**			**Double-blind Treatment Period (up to 60 days)**			
Visit	**Visit 1 Screening**	**Phone Call[a]**	**Visit 2 Randomization**	**First Qualifying Prodrome Event Treatment Day**	**Visit 3 Posttreatment**	**Second Qualifying Prodrome Event Treatment Day**	**Visit 4 Posttreatment/ ET[b]**
Scheduled day/week		30 days after Visit 1	60 days after Visit 1		4 days after dose of study intervention[c]	≥7 days after taking study intervention for first qualifying prodrome event	4 days after dose of study intervention[c]
Scheduling window		*± 7 days*	*+ 7 days*		*-2/+4 days*		*-2/+4 days*
Informed consent	X						
Access IWRS	X		X		X		X
Demographic information	X						
Duplicate Participation Identification consent and verification	X						
Inclusion and exclusion criteria	X		X				
Medical history (including CV disease and risk factors)	X						
Conduct comprehensive structured interview to confirm migraine diagnosis and assess prodrome symptoms[d]	X						
Prior medication[e]	X						

Study Period	**Screening Period (60 days)**			**Double-blind Treatment Period (up to 60 days)**			
Visit	**Visit 1 Screening**	**Phone Call[a]**	**Visit 2 Randomization**	**First Qualifying Prodrome Event Treatment Day**	**Visit 3 Posttreatment**	**Second Qualifying Prodrome Event Treatment Day**	**Visit 4 Posttreatment/ ET[b]**
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Scheduling window		*± 7 days*	*+ 7 days*		*-2/+4 days*		*-2/+4 days*
Concomitant medication	X	X	X		X		X
Migraine treatment history (eg, prior migraine preventative medication response and historical triptan response)			X				
Vital sign measurements[f]	X		X		X		X
ECG[g]	X		X				X
Physical examination	X						X
Clinical laboratory determinations[h]	X		X				X
Urine pregnancy test[i]	X		X		X		X
Drug screen	X						
C-SSRS[j]	X		X		X		X
Allodynia (ASC-12) questionnaire			X				
eDiary training	X		X				

Study Period	**Screening Period (60 days)**			**Double-blind Treatment Period (up to 60 days)**			
Visit	**Visit 1 Screening**	**Phone Call[a]**	**Visit 2 Randomization**	**First Qualifying Prodrome Event Treatment Day**	**Visit 3 Posttreatment**	**Second Qualifying Prodrome Event Treatment Day**	**Visit 4 Posttreatment/ ET[b]**
Scheduled day/week		30 days after Visit 1	60 days after Visit 1		4 days after dose of study intervention[c]	≥7 days after taking study intervention for first qualifying prodrome event	4 days after dose of study intervention[c]
Scheduling window		*± 7 days*	*+ 7 days*		*-2/+4 days*		*-2/+4 days*
Dispense eDiary to participant[k]	X						
Randomization			X				
Dispense study intervention; review dosing instructions			X		X		
Provide side-effects diary to participant			X[l]		X[l]		
Participant takes study intervention				X[m]		X[m]	
Participant completes assessments in eDiary	←---------- X[n,o] ----------→ (during the screening period)			X[o,p]		X[o,p]	
Collect study intervention and review compliance					X		X
Review eDiary data and compliance		X	X[q]		X		X
Collect eDiary from participant							X
Review and assess AEs	X						

Study Period	**Screening Period (60 days)**			**Double-blind Treatment Period (up to 60 days)**			
Visit	**Visit 1 Screening**	**Phone Call[a]**	**Visit 2 Randomization**	**First Qualifying Prodrome Event Treatment Day**	**Visit 3 Posttreatment**	**Second Qualifying Prodrome Event Treatment Day**	**Visit 4 Posttreatment/ ET[b]**
Scheduled day/week		30 days after Visit 1	60 days after Visit 1		4 days after dose of study intervention[c]	≥7 days after taking study intervention for first qualifying prodrome event	4 days after dose of study intervention[c]
Scheduling window		*± 7 days*	*+ 7 days*		*-2/+4 days*		*-2/+4 days*
For Participants Who Consent to Participating in Optional PK Substudy							
Obtain informed consent for optional PK substudy	X						
Provide DBS training			X				
Participant collects DBS sample to ensure comprehension of process			X[r]				
Provide participant with supplies for PK sample collection[s]			X		X		
Participant collects DBS samples and records date and time in eDiary				X[t]		X[t]	
Collect DBS samples from participant					X		X

[a] The follow-up check-in phone call is required 30 days after the Screening Visit (Visit 1). The site must check in with the participant via telephone call to review concomitant medications, assess any AEs, and review the data collected in the eDiary, including compliance in answering all questions.

[b] Randomized participants who are withdrawn or prematurely discontinue from the study, regardless of whether or not they took study intervention, will complete the assessments for the Visit 4/ET Visit.

[c] Participants will return to the clinic for Visit 3 after treating their first qualifying prodrome event as soon as possible after completing their assessments (the last assessment will be at the 48-hour timepoint). Similarly, participants will return to the clinic for Visit 4 after treating their second qualifying prodrome event as soon as possible after completing their assessments.

[d] A detailed comprehensive structured interview will be conducted to confirm diagnosis of migraine and collect migraine history. In addition, collect information such as participant's individual prodrome symptom(s) and the reliability of a headache following these symptom(s). Please use the guide/worksheet provided.

[e] Review of prior medications includes all migraine medications taken in the past, including any medications for the prevention of migraine.

[f] Collection of vital signs includes sitting and standing systolic and diastolic blood pressure, sitting and standing pulse rate, respiration rate, temperature, height (only at Visit 1), and weight (Section 8.2.2).

[g] Only one ECG is required for each assessment at each specified visit. If multiple ECGs are completed, all ECGs (readable and unreadable) must be transmitted to the central ECG vendor (Section 8.2.3).

[h] Clinical laboratory tests include chemistry, hematology, and urinalysis; coagulation are performed at Visit 1 only (Section 8.2.4).

[i] For WOCBP only.

[j] At Visit 1, the *Screening/baseline* assessment of the C-SSRS will be completed. At all other visits, the *Since the Last Visit* C-SSRS will be completed (Section 8.2.5).

[k] After being dispensed an eDiary device, participants should bring the eDiary to all visits and review with study site personnel. For participants who terminate prematurely after the eDiary is dispensed, the eDiary should be collected at the next visit. eDiary will need to be collected from those who discontinue the study as well as screen failure participants.

[l] Participant records side effects (if any) within 48 hours of taking study intervention in side-effects diary (paper diary). Side-effects diary should be collected at the following visits and reviewed with the participant per Section 8.

[m] Participant will take study intervention to treat 2 qualifying prodrome events during the double-blind treatment period (between Visit 2 and Visit 4) (up to 60 days). It is recommended to treat qualifying prodrome events that occur in the morning or early afternoon so that assessments can be collected in the eDiary during waking hours.

[n] During the 60-day screening period (between Visit 1 and Visit 2) participants will record their qualifying prodrome events and any headache (if it develops) in the eDiary.

[o] HEOR assessments will be completed by the participant in the eDiary during the screening period and double-blind treatment period as outlined in Section 8.10.

[p] During the double-blind treatment period (between Visit 2 and Visit 4) (up to 60 days), the participant will record in the eDiary 2 qualifying prodrome events and any headache (if it develops).

[q] Data collected on the eDiary during the screening period must be reviewed to determine if participant meets eligibility to be randomized. See inclusion criteria 2.06 and 2.07 (Section 5.1).

[r] If DBS sample collection unsuccessful during the training, the participant may not participate in the optional PK substudy.

[s] Review collection timing, handling, and storage of DBS samples that will be collected at home before providing the participant with the supplies for PK sample collection.

[t] Participants will collect 3 DBS samples at home after treating each qualifying prodrome event and record the date and time in their eDiary. Collection times are outlined in Section 8.5.

2. Introduction

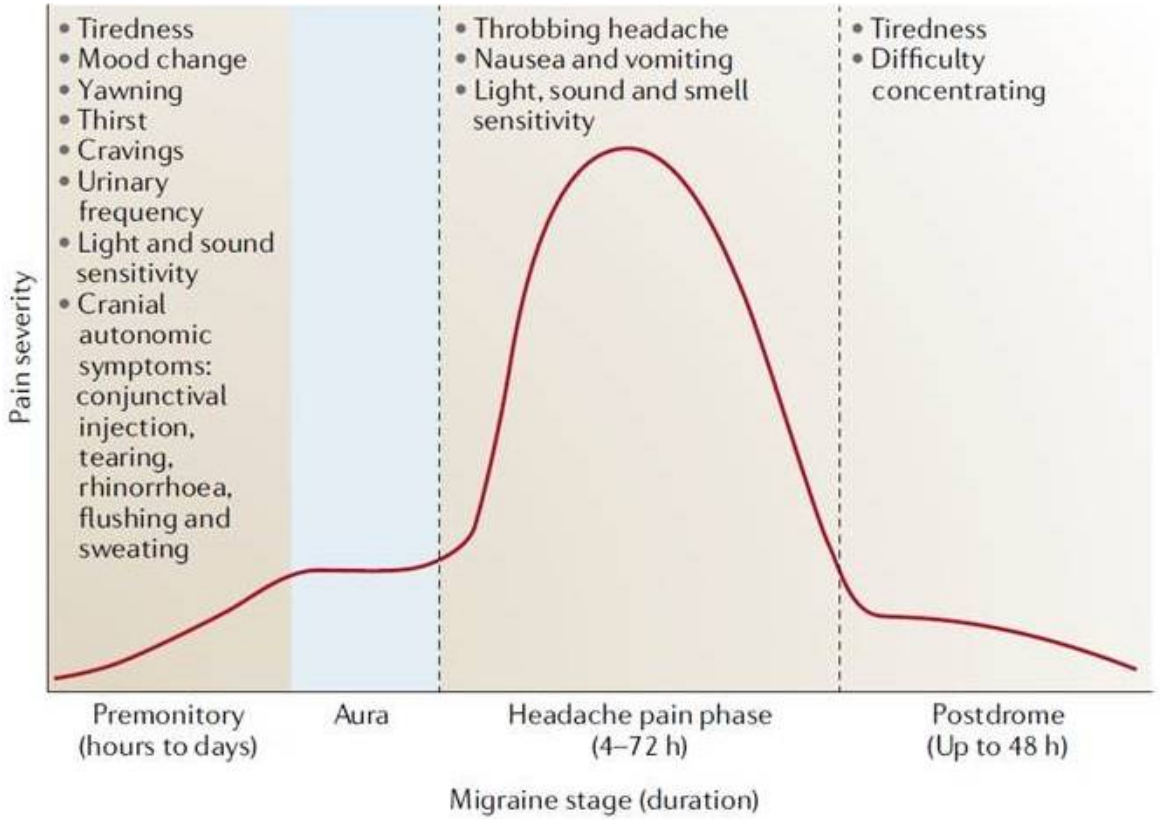
Ubrogepant (Ubrelvy™) is a CGRP receptor antagonist approved for the acute treatment of migraine with or without aura in adults. The recommended dose is 50 mg or 100 mg, taken orally, with a second dose available to be taken, at least 2 hours later, if needed. Pivotal studies demonstrated the efficacy of ubrogepant for the treatment of moderate or severe headache and nonheadache migraine symptoms (Dodick 2019; Lipton 2019).

Optimizing the treatment of acute migraine has been a goal of the medical community for many years and one way to do this would be to treat early, ideally before the headache begins. The CGRP receptor antagonist mechanism, a mechanism that is intrinsically preventive, suggests that ubrogepant may be a good candidate to study when administered during the prodrome, the earliest clinical manifestation of the acute migraine attack. This study is designed to examine the potential of ubrogepant, when administered during the prodrome, to prevent or attenuate the headache phase.

2.1. Study Rationale

Migraine is a multiphasic, episodic disease of the nervous system with 4 generally recognized phases: prodrome/premonitory phase, aura phase, headache phase, and postdrome/postheadache phase (Karsan 2018; Figure 2-1). Per the recently updated ICHD-3 (2018), the term *prodrome* has replaced *premonitory phase* as the preferred terminology.

Figure 2-1 Phases of Migraine



Source: Karsan 2018

Although demonstration of efficacy for the treatment of a migraine headache of moderate to severe intensity is necessary for regulatory approval, this treatment paradigm is not optimal from the patient perspective. The FDA guidance acknowledges this and specifically states that *drug administration as early as practicable during the course of acute migraine is recommended by migraine experts* and *additional trials assessing drug response after treatment of acute migraine at the mild pain stage can be conducted and described in the label* (FDA Guidance 2018). Support for early treatment can also be found in the current treatment guidelines from the American Headache Society which recommend treating acute migraine as early as possible after the onset of headache pain, as delayed treatment may increase pain severity and disability (Marmura 2015). Early treatment of a migraine headache has been shown to improve rates of pain freedom and pain relief, and to reduce headache recurrence and rescue medication use when compared with treatment of a moderate to severe migraine headache (Dowson 2006).

Although treating a migraine at the beginning of the headache phase has advantages over delaying treatment until the headache is moderate to severe, this may still be suboptimal. Ideally, treatment should be initiated at the beginning of the migraine, before the headache starts, with the goal of either preventing or attenuating the headache phase and reducing nonheadache migraine symptoms. The possibility of treating a migraine attack with a triptan in the preheadache phases (ie, prodrome or aura) has been investigated previously with mixed results (Aurora 2009, Bates 1994, Dowson 1996, Luciani 2000, Olesen 2004). It is difficult to draw any definitive conclusions regarding the efficacy of triptans when administered during the prodrome

or aura because of significant design limitations with these studies (eg, small sample sizes, open-label design, and short timeframe from aura to headache).

The prodrome is the earliest clinical manifestation of a migraine attack. Therefore, treating during the prodrome is an attractive therapeutic option. Prodrome symptoms can be broadly grouped into 4 categories: cognitive and mood changes (eg, concentration change, difficulties reading, memory complaints, confusion, disorientation, and mood changes); homeostatic and hormonal changes (eg, food cravings, thirst, polyuria, yawning, altered sleep-wake cycle, and changes in alertness); migrainous and sensory sensitivities (mild head discomfort, photophobia, phonophobia, osmophobia, neck discomfort, allodynia, and nausea); and cranial autonomic symptoms (lacrimation, nasal stuffiness, rhinorrhea, aural fullness, abnormal taste, and sensation of throat swelling) (Karsan 2018).

How common are prodrome symptoms? Historically, a handful of small studies have attempted to quantify the proportion of patients with migraine who experience a clinically identifiable prodrome. These studies reported widely varying estimates from 8% to 87% of the adult population with migraine. Recently a large, cross-sectional study was conducted with approximately 2700 patients with migraine to specifically address this question. Among patients diagnosed with migraine, 77% reported a clinically identifiable prodrome (Laurell 2016). This proportion is consistent with feedback that the sponsor received from clinical migraine experts during consultation for this study. These experts noted that patients often do not spontaneously report prodromal symptoms and physicians often do not ask about these symptoms. However, when patients are educated about the prodrome and then asked directly if they experience these symptoms, it was estimated that approximately 70% to 80% of patients experience a clinically identifiable prodrome and can describe it in detail.

The prodrome represents the beginning of a migraine attack and there is evidence for alterations in hypothalamic and brainstem function during the prodrome, which can be demonstrated by functional imaging and electrophysiological methods (Karsan 2018). The headache phase is due to activation of trigeminal sensory neurons, many of which express CGRP, that innervate pain sensitive intracranial structures including the eye, dura, meningeal vessels, and dural venous sinuses. During the headache phase, CGRP is released pathologically from these sensory nerves in the meninges and from their central projections to the spinal trigeminal nucleus, and this can be detected as increased levels of CGRP in the cranial venous outflow (Goadsby 2017, Messlinger 2018).

The goal of this study is to administer ubrogepant during the prodrome so that it is 'on board' as the headache phase pathophysiology emerges, with the ultimate objective of preventing or ameliorating the headache phase. The pharmacokinetics of ubrogepant are well suited to do this. Ubrogepant is rapidly absorbed and long-acting. Based on an EC_{90} of 13 ng/mL for the inhibition of capsaicin-induced dermal blood flow (a pharmacodynamic measure of CGRP blockade), potentially effective concentrations of ubrogepant are achieved within 15 minutes and last 15 hours after a single dose of ubrogepant 100 mg (AHS poster presentation, Dodick 2019).

Treating a migraine during the prodrome may also be optimal from a practical perspective, as prodromal symptoms start well before the headache phase, thus providing patients with ample time to identify these symptoms and administer treatment, while also allowing the treatment sufficient time to act to reverse the neurobiological mechanisms that cause migraine. Ubrogepant

may be particularly well suited for administration during the prodrome for reasons including the unique role of CGRP in migraine pathophysiology, favorable tolerability profile, and no defined risk for medication overuse.

Tolerability is important when considering drug administration before the headache begins. Whereas patients may not be willing to take an acute treatment with significant side effects until a headache begins, ubrogepant has been shown to be extremely well tolerated and is a good candidate to be used in the preheadache phase. In addition, there is a concern that treatment during the prodrome phase may increase overall acute medication use and lead to medication overuse headache (Marmura 2015). While medication overuse headache is a recognized complication of excessive triptan use, ubrogepant does not share this risk given its mechanism of action.

In summary, treating migraine during the prodrome has the potential to transform the current treatment paradigm and may prove to be the optimal way to treat migraine in some patients. The ability to administer a treatment at the beginning of the migraine and potentially prevent or attenuate the headache phase has the potential to vastly improve patient outcomes (ie, symptoms and functional impairment of migraine). Ubrogepant's mechanism of action as a CGRP-RA, excellent tolerability, and low risk for the negative consequences of medication overuse make it particularly well-suited for the acute treatment of migraine when administered during the prodrome.

2.2. Background

Migraine affects 18% of women and 6% of men in the United States with peak prevalence between the ages of 25 to 55 years. Approximately one-third of those with migraine have 3 or more migraines per month, and over half report severe impairment or the need for bed rest during an attack (Lipton 2007). In the United States, work loss due to migraine is estimated to cost ~ $13 billion annually (Hu 1999). Prevalence is similar in Europe, with migraine affecting 17.6% of women and 8% of men (Stovner 2010). The Global Burden of Disease Survey (Vos 2012) estimated the global prevalence of migraine to be 14.7%, making it the third most common disease in the world in both males and females. According to the 2016 Global Burden of Disease study, migraine ranked second only to low back pain as the leading cause of years lived with disability (GBD 2016).

Migraine is typically characterized by attacks of throbbing, headache of moderate or severe pain intensity, associated with nausea, vomiting, and/or sensitivity to light (photophobia) and sound (phonophobia). In about 25% of individuals, the headache phase of migraine may be preceded by focal cerebral dysfunction (aura). Improving the diagnosis and optimizing treatments for migraine have been recognized as critically important to reduce the global burden of migraine (Katsarava 2012).

Because there are no biological markers for migraine, diagnosis is based on clinical history, exam, and the exclusion of other headache disorders. Physicians apply clinical criteria to guide diagnosis and 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 an ICHD-3 diagnosis (2018) applied to a subset of patients with ≥ 15 headache days per month (Katsarava 2012, Olesen 2006).

2.3. Benefit/Risk Assessment

Ubrogepant is FDA-approved for the acute treatment of migraine with or without aura in adults. Efficacy has been demonstrated for the acute treatment of migraine headache of moderate/severe intensity as well as for nonheadache migraine symptoms (ie, photophobia, phonophobia, and nausea). Ubrogepant has been shown to be safe and well tolerated (Ubrelvy™ Package Insert-Prescribing Information).

This study will assess the efficacy and safety of ubrogepant 100 mg when administered during the prodrome phase of migraine. Treatment with ubrogepant during the prodrome is consistent with the Indications and Usage section of the FDA Prescribing Information; that is, the Prescribing Information allows for treatment of acute migraine with ubrogepant during the prodrome. In addition, the dosing schedule of ubrogepant in this study is consistent with the US Prescribing Information.

The ability to administer a treatment at the beginning of the migraine and potentially prevent or attenuate the headache phase has the potential to vastly improve patient outcomes (ie, symptoms and functional impairment of migraine).

Overall, the benefit/risk assessment supports the study of ubrogepant in this clinical trial.

More detailed information about the known and expected benefits and risks and reasonably expected adverse effects of ubrogepant may be found in the US Prescribing Information and the investigator's brochure.

3. Objectives and Endpoints

The overall study objective is to evaluate the efficacy, safety, and tolerability of ubrogepant 100 mg compared to placebo for the acute treatment of migraine when administered during the prodrome.

The clinical hypotheses are:

1. Ubrogepant 100 mg is superior to placebo in the acute treatment of migraine when administered during the prodrome.
2. Ubrogepant 100 mg is safe and tolerable.

Objectives	Endpoints
Efficacy Objectives and Endpoints	
Primary To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on attenuation of the headache phase	Absence of a headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome
Secondary 1: To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on attenuation of the headache phase	1: Absence of a headache of moderate or severe intensity within 48 hours after taking double-blind study intervention during the prodrome
2: To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on ability to function normally	2: Ability to function normally over 24 hours after taking double-blind study intervention during the prodrome
3: To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on prevention of the headache phase	3: Absence of a headache of any intensity within 24 hours after taking double-blind study intervention during the prodrome

Objectives	Endpoints
Additional Objectives and Endpoints	
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on attenuation of the headache phase	• Absence of headache of any intensity by timepoint (excluding the endpoints that are already captured as primary and secondary endpoints) • Absence of moderate/severe headache by timepoint (excluding the endpoints that are already captured as primary and secondary endpoints) • Absence of severe headache by timepoint • Time to development of headache of any intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis) • Time to development of headache of moderate/severe intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis) • Time to development of headache of severe intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis)

Objectives	Endpoints
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on prodrome symptoms, nonheadache migraine symptoms (photophobia, phonophobia, nausea, and dizziness), and aura	For each of the 5 most common individual prodrome symptoms: • Absence of any intensity at each timepoint • Absence of moderate/severe intensity at each timepoint • Absence of severe intensity at each timepoint • Time to absence of any intensity After a headache of any intensity is reported: • Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of any intensity at each timepoint • Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of moderate/severe intensity at each timepoint • Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of severe intensity at each timepoint Other: • Absence of aura at each timepoint
To evaluate the effect of a single dose of ubrogepant (100mg) versus placebo on use of rescue medication	• Rescue medication use within 24 and 48 hours after taking double-blind study intervention • Time to rescue medication use within 48 hours after taking double-blind study intervention (Kaplan-Meier analysis)

Objectives	Endpoints
Additional HEOR Objectives and Endpoints	
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on satisfaction with study medication	• Satisfaction with study medication at 8 and 24 hours after taking double-blind study intervention during the prodrome
To evaluate the effect of a single dose of ubrogepant (100 mg) versus placebo, administered during the prodrome, on Activity Limitation	• Activity Limitation over 24 hours after taking double-blind study intervention during the prodrome
Safety Objective and Endpoint	
To compare the safety of ubrogepant versus placebo in participants with migraine	• AEs, clinical laboratory tests, ECGs, vital signs, and the C-SSRS

4. Study Design

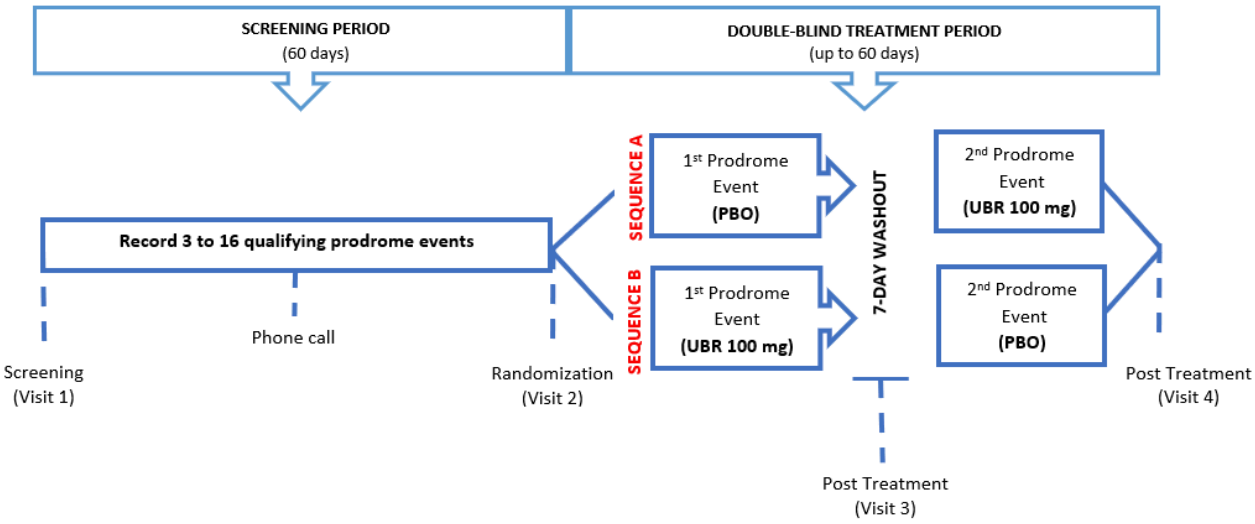
4.1. Overall Design

This multicenter, randomized, double-blind, placebo-controlled, crossover study will enroll approximately 516 participants from approximately 75 centers in the United States.

The study includes a 60-day screening period during which participants will demonstrate that they reliably develop headache after experiencing qualifying prodrome events. After meeting eligibility criteria, randomized participants will treat 2 qualifying prodrome events with study intervention during the double-blind treatment period (between Visit 2 and Visit 4) (up to 60 days), separated by a clinic visit (Visit 3) to ensure a minimum 7-day washout period. A posttreatment visit (Visit 4) will follow 4 days after the last treatment is taken.

To be eligible for study participation, participants must be 18 to 75 years of age (inclusive) at Visit 1, have at least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3 (2018; Section 10.8), and experience 2 to 8 migraine attacks with moderate to severe headache per month by history in each of the 3 months prior to screening. The overall study design is displayed below in Figure 4-1.

Figure 4-1 Overall Study Design



PBO = placebo; UBR = ubrogepant

Screening Visit (Visit 1)

At the Screening Visit (Visit 1), as part of the eligibility assessment, the investigator will conduct a detailed medical history which includes a comprehensive structured interview with the potential participant inquiring about their migraines, including prodrome symptoms and headache. This interview will confirm, per the investigator's judgment and based on participant history, that the participant can identify and routinely experiences prodrome symptom(s) that are reliably followed by headache (of any intensity) within 1 to 6 hours after experiencing the

prodrome symptoms (at least 3 out of 4 times, or 75% of the time). In addition, a description of the course of the participant's typical migraine will be documented, including a list of specific prodrome symptom(s) that the participant experiences and the usual timeframe from onset of prodrome symptom(s) to onset of the headache.

Screening Period

Participants who meet all eligibility criteria at the Screening Visit (Visit 1) will be asked to objectively demonstrate that their prodrome symptoms are reliably followed by headache. An eDiary will be dispensed and the participant asked to record all qualifying prodrome events during the full 60 day screening period (between Visit 1 and Visit 2). For both the screening and double-blind treatment periods, a *qualifying prodrome event* is defined as an event in which the participant experiences a clinically identifiable prodrome with ALL the following conditions met:

Definition of a Qualifying Prodrome Event

- Headache is not currently present
- The participant has not had a headache in the previous 48 hours
- Treatments for acute headache (eg, ibuprofen, acetaminophen, triptan, Excedrin®) have not been taken in the previous 48 hours
- The participant is confident that a headache will inevitably follow within 1 to 6 hours after experiencing the qualifying prodrome event
- The participant is able to complete the eDiary for the next 8 hours

A follow-up check-in phone call is required 30 days after the Screening Visit (Visit 1). The site should check in with the participant via telephone call to review the qualifying prodrome events and headaches (if any) reported on their eDiary, review any changes to concomitant medications or AEs.

Criteria for Randomization

Participants must record 3 to 16 qualifying prodrome events during the screening period.

Each prodrome event will be categorized as positive or negative depending on whether or not a headache of any severity (mild, moderate, severe) is reported within 1 to 6 hours after the start of the qualifying prodrome event.

For participants who record only 3 qualifying prodrome events, all events must be categorized as positive to be eligible for randomization (ie, 3 out of 3 positive events).

For participants who record 4 to 16 qualifying prodrome events, at least 75% of events must be categorized as positive to be eligible for randomization.

Randomization Visit (Visit 2)

At Visit 2, participants who meet all eligibility criteria will be randomized (1:1) to 1 of 2 treatment sequences, A or B, in this crossover study. A full list of inclusion criteria can be found in Section 5.1 and exclusion criteria can be found in Section 5.2.

Double-Blind Treatment Period

During the double-blind treatment period (between Visit 2 and Visit 4), participants will have up to 60 days to treat 2 qualifying prodrome events, as defined above, with study intervention. Participants should treat as soon as they are confident that a headache will inevitably follow their prodrome symptoms.

eDiary Assessments

During both the screening and double-blind treatment periods, the participant will report information in the eDiary at the time of each qualifying prodrome event:

- Confirmation that the participant is experiencing a *qualifying prodrome event*
- Identification and intensity of individually specific prodrome symptom(s)
- Headache pain and intensity (if it occurs)
- Nonheadache symptoms (photophobia, phonophobia, nausea, dizziness) including intensity (mild, moderate, severe)
- Presence or absence of aura
- Health Outcomes assessments

Participants will be asked to complete their eDiary at prespecified timepoints (1, 2, 3, 4, 6, 8, 24, and 48 hours) and on an event-driven basis (ie, when a headache occurs). In addition, in the double-blind treatment period, the date and time of when double-blind study intervention is taken will be captured, as well as rescue medication use.

Visit Schedule

In addition to the Screening Visit (Visit 1) and Randomization Visit (Visit 2) described above, participants will return to the clinic for the Posttreatment Visit (Visit 3) after the first qualifying prodrome event is treated, 4 days after taking double-blind study intervention. The first and second qualifying prodrome events must be 2 separate and distinct events that are at least 7 days apart. Participants unable to treat 2 qualifying prodrome events during the double-blind treatment period will be discontinued from the study.

Participants will return to the clinic for Visit 4 after the second qualifying prodrome event is treated, 4 days after taking double-blind study intervention. Visit 4 will be conducted for randomized participants who prematurely discontinue during the double-blind treatment period, regardless of whether or not they took study intervention. For additional information on study visits and procedures, please see the SoA (Section 1.3). The sequence of events during the screening and double-blind treatment periods are displayed below in Figure 4-2.

Figure 4-2 Screening Period

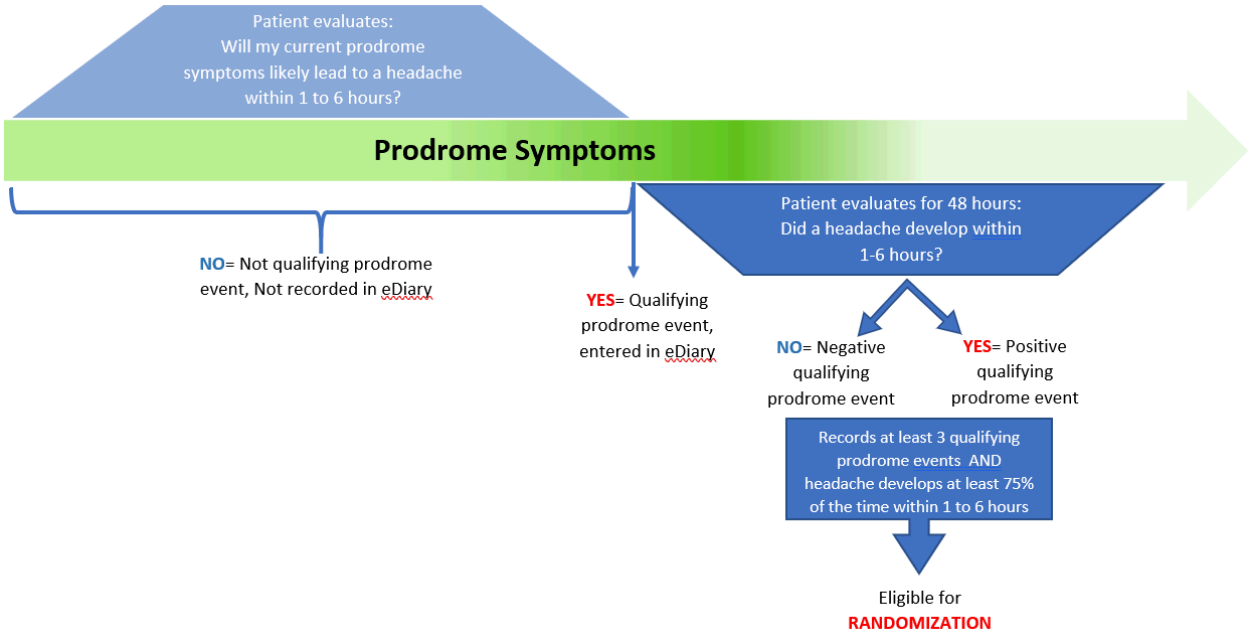
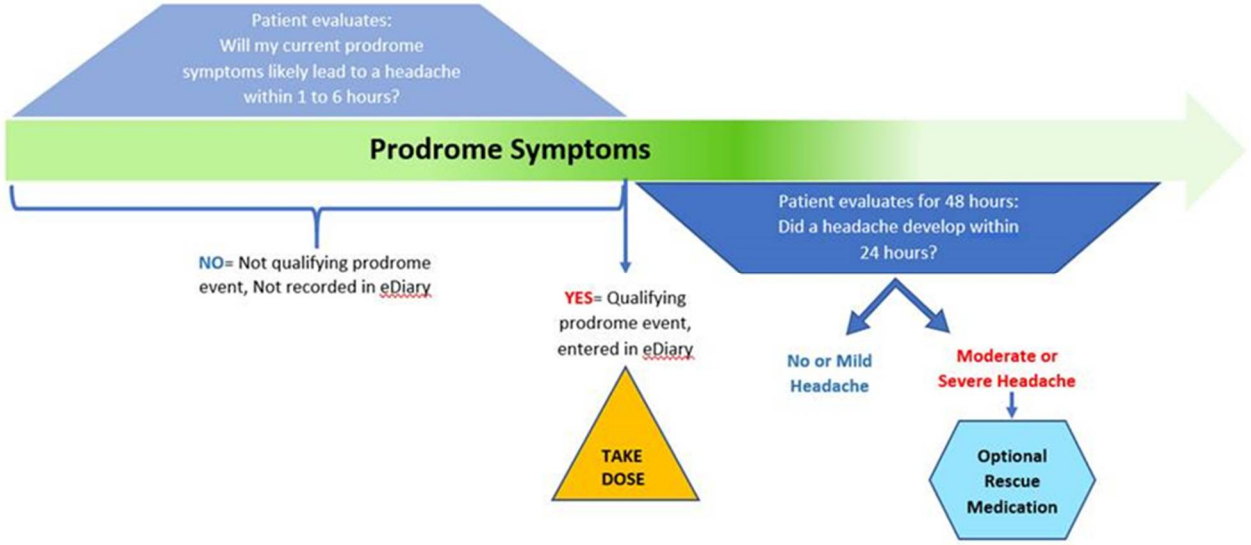


Figure 4-3 Double-blind Treatment Period



Efficacy, Safety, and Pharmacokinetic Assessments

The key efficacy assessments to be collected are ratings of prodrome symptom(s), headache, and nonheadache symptoms. A list and description of each efficacy assessment is in Section 8.1 and the efficacy analyses are presented in Section 9.4.1. The planned safety assessments are AEs, clinical laboratory tests, ECGs, vital signs, physical examination, and the C-SSRS. Details regarding safety assessments are described in Section 8.2 and the safety analyses are presented in Section 9.4.2.

A separate optional PK substudy will be conducted on a subset of participants who consent to participate in the optional PK substudy. These participants will undergo serial PK sample collection at home. PK samples will be collected using DBS methodology after taking the dose of double-blind study intervention (for details, please see Section 8.5).

4.2. Scientific Rationale for Study Design

The double-blind study design was adopted to minimize systematic bias resulting from the investigator, participant, and sponsor knowing the treatment being administered. Randomization is expected to minimize participant selection bias and increase baseline comparability among the treatment groups. Placebo was included as an ineffective agent against which to compare the response to ubrogepant. A crossover design was used to increase the efficiency for treatment comparisons.

The study was designed with a rigorous screening period to ensure that the appropriate participants who routinely have headaches after experiencing prodrome symptoms are selected to participate in the study. This select group of participants are required to test the hypothesis that ubrogepant is effective given at the beginning of the migraine before the participant develops a headache.

Treatment with the first dose is to test the efficacy of ubrogepant versus placebo in disrupting the usual course of the migraine and therefore attenuating the development of a headache. This design was implemented to reflect how ubrogepant could be utilized in practice.

4.3. Justification for Dose

This study will test 1 dose of ubrogepant versus placebo, with participants themselves also being the control, which was selected based on the safety and efficacy results in Phase 2b and Phase 3 studies. The highest tested dose in the Phase 3 pivotal studies, 100 mg, was selected because it was demonstrated to be the most efficacious dose and was well tolerated and without safety concerns.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has not been terminated early and has completed the study, including treating 2 qualifying prodrome events as well as the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study.

5. Study Population

Approximately 516 participants will be randomized (258 participants per sequence) from approximately 75 centers in the United States. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age and Sex**
1.01	Male or female participants ages 18 to 75 years, inclusive, at Visit 1
2.	**Type of Participant and Migraine Characteristics**
2.01	At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3 (2018; Section 10.8)
2.02	Migraine onset before age 50 years
2.03	By history, the participant'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.
2.04	History of 2 to 8 migraine attacks per month with moderate to severe headache in each of the 3 months prior to the Screening Visit (Visit 1)
2.05	By history and per investigator's judgment, the participant routinely experiences prodrome symptom(s) that are reliably followed (≥ 75% of the time) by a headache of any intensity within 1 to 6 hours after experiencing the prodrome symptoms.
2.06	Participant records ≥ 3 to ≤ 16 qualifying prodrome events in the eDiary during the screening period (Visit 1 to Visit 2).
2.07	Based on data collected during the screening period, demonstrated that the participant reliably experiences headache pain of any intensity within 1 to 6 hours following a qualifying prodrome event recorded in the eDiary. Participant may be eligible for randomization at Visit 2 if: • 3 qualifying prodrome events are recorded and headache develops within 1 to 6 hours following all three qualifying prodrome events (ie, headache develops after experiencing 100% of qualifying prodrome events). • 4 to 16 qualifying prodrome events are recorded and headache develops within 1 to 6 hours after at least 75% of qualifying prodrome events (eg, participant records 4 qualifying prodrome events in the eDiary and headache develops in 3 out of 4 qualifying prodrome events).

2.08	Current or past use of at least one prescription medication for the acute treatment of migraine (eg, triptan, opioid, prescription NSAID, barbiturate combination) or a prescription medication for preventive medication for migraine (eg, topiramate, amitriptyline, onabotuliumtoxin A)
3.	**Weight and Body Mass Index**
3.01	BMI $\leq$ 40 kg/m^2 at Visit 1 and Visit 2
4.	**Contraceptives**
4.01	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period. A female participant is eligible to participate if she is not pregnant (ie, has a negative urine pregnancy result at the Screening Visit [Visit 1] and Randomization Visit [Visit 2]; see Section 1.3), is not breastfeeding, and fulfills at least one of the following conditions: • Not a woman of child bearing potential as defined in Section 10.7. • OR A woman of child bearing potential who agrees to follow the contraceptive guidance in Section 10.7 for the duration of the study
4.02	Male participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period. A male participant must agree to use contraception as detailed in Section 10.7 of this protocol for the duration of the study and refrain from donating sperm during the course of the study.
5.	**Informed Consent**
5.01	Written informed consent and participant privacy information (eg, Written Authorization for Use and Release of Health and Research Study Information) obtained from the participant prior to initiation of any study-specific procedures.
6.	**Other**
6.01	Be able to read, understand and complete the study questionnaires and eDiary.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Any clinically significant hematologic, endocrine, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease. • If there is a history of such disease, but the condition has been stable for more than 1 year prior to Visit 1 and is judged by the investigator as not likely to interfere with the participant's participation in the study, the participant may be included. o Participants on dialysis for renal failure are excluded.
1.02	In the opinion of the investigator, other confounding pain syndromes, confounding psychiatric conditions, dementia, epilepsy or other significant neurological disorders other than migraine
1.03	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
1.04	History of any prior gastrointestinal conditions (eg, diarrhea syndromes, inflammatory bowel disease) that, per investigator judgment, may affect the absorption or metabolism of the study intervention; participants with prior gastric bariatric interventions (eg, Lap Band) which have been reversed are not excluded
1.05	Clinically significant cardiovascular or cerebrovascular disease per the investigator's opinion including, but not limited to: • Clinically significant ischemic heart disease (eg, unstable angina pectoris) • Clinically significant cardiac rhythm or conduction abnormalities (eg, atrial fibrillation, second- or third-degree heart block) or risk factors for Torsade de Pointes (eg, heart failure, hypokalemia, bradycardia) • Myocardial infarction, transient ischemic attack, or stroke within 6 months prior to Visit 1 • Heart failure defined as New York Heart Association functional classification system, Class III or IV
1.06	Significant risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator; participants must be excluded if they report suicidal ideation with intent, with or without a plan, (ie, Type 4 or 5 on the C-SSRS) in the past 6 months or report suicidal behavior in the last 6 months prior to Visit 1 or Visit 2 assessments (see Section 9.4.2.5 for details)
1.07	At Visit 1, current alcohol or drug abuse or dependence per investigator's judgment

2.	**Migraine Characteristics**
2.01	A current diagnosis of chronic migraine as defined by ICHD-3 (2018; Section 10.8), or a history of 15 or more headache days per month on average in the 6 months prior to Visit 1 in the investigator's judgment. A headache day is defined as a day in which there was any occurrence of a headache of a minimum duration of 2 hours or a headache of any duration for which acute medication was taken. • Participants with a diagnosis of chronic migraine who, in the opinion of the investigator, currently have fewer than 15 headache days per month due to concomitant prophylactic treatment are allowed in the study.
2.02	Participants who overuse medication for migraine defined as use of opioids or barbiturates > 2 days/month**,** triptans or ergots ≥ 10 days/month, or simple analgesics (eg, aspirin, NSAIDs, acetaminophen) ≥ 15 days/month in the 3 months prior to Visit 1 per investigator's judgment
2.03	Difficulty distinguishing migraine headache from tension-type or other headaches
2.04	Has a history of migraine aura with diplopia or impairment of level of consciousness, hemiplegic migraine, or retinal migraine as defined by ICHD-3 (2018; Section 10.8).
2.05	Has a current diagnosis of new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3 (2018; Section 10.8).
2.06	Required hospital treatment of a migraine attack 3 or more times in the 6 months prior to Visit 1.
3.	**Prior/Concomitant Therapy**
3.01	Requirement for any medication (eg, barbiturates) or diet (eg, grapefruit juice) that is on the list of prohibited concomitant medications (see Section 6.5.1 and Section 5.3.1) that cannot be discontinued or switched to an allowable, alternative medication before entering the double-blind treatment portion of this study. • Certain medications require stable dosing throughout the study; for these medications and requirements, please refer to Section 6.5.2. Examples of prohibited medications and allowed medications with restrictions are listed in Section 10.9.
3.02	Has a chronic nonheadache pain condition requiring daily pain medication (with the exception of pregabalin).
3.03	Previous exposure to: • Injectable monoclonal antibodies blocking the CGRP pathway within the last 3 months (eg, Aimovig™, Emgality™, Ajovy®)
3.04	History of hypersensitivity or clinically significant adverse reaction to a CGRP-RA
4.	**Prior/Concurrent Clinical Study Experience**
4.01	Currently participating or has participated in a study with an investigational compound or device within 30 days prior to Visit 1 (this includes studies using marketed compounds or devices).

5.	**Diagnostic Assessments**
5.01	Hypertension as defined by sitting systolic blood pressure > 160 mm Hg or sitting diastolic blood pressure > 100 mm Hg at Visits 1 or 2. Vital sign measurements that exceed these limits may be repeated only once.
5.02	Abnormal ECG results thought to be potentially clinically significant according to the investigator or designee
5.03	Clinically significant abnormalities (as determined by the investigator) in clinical laboratory safety test(s) or physical examination at Visit 1
5.04	Clinical laboratory results at Visit 1 (or before randomization) with the following: • ALT or AST > 1.5 × ULN OR • Total bilirubin > 1.5 mg/dL (except for participants with a diagnosis of Gilbert's disease) OR • Serum albumin < 2.8 g/dL
5.05	Positive result on the urine drug screen at Visit 1 unless explained by concomitant medication use (eg, opioids prescribed for migraine pain) • A positive urine drug screen for cannabinoids will exclude the participant from the study however one repeat urine drug screen will be allowed.
5.06	History of acute hepatitis within 6 months of the Screening Visit (Visit 1) or chronic hepatitis (including nonalcoholic steatohepatitis). Participants with severe hepatic impairment (ie, Child-Pugh C) are excluded from participation.
6.	**Other**
6.01	Employed by or is an immediate family member (parents, spouses, siblings, or children) of one of the investigators, study staff, or the sponsor.
6.02	Any medical or other reasons (eg, unlikely to adhere to the study procedures, keep appointments, or is planning to relocate during the study) that, in the investigator's opinion, might indicate that the participant is unsuitable for the study

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants must refrain from consuming grapefruit or grapefruit juice during the double-blind treatment period of the study (Visit 2 through Visit 4).

5.3.2. Alcohol

Alcohol intake should be limited to no more than 1 drink 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.

5.3.3. Activity

Maintaining a consistent lifestyle when participating in a clinical study is vital. Participants must refrain from implementing drastic changes in their diet or starting a new diet during the study.

Participants should not engage in intense exercise (eg, running a marathon) or start an intense exercise regimen during the course of the study.

After taking double-blind study intervention, participants should refrain from sleeping for at least 8 hours to ensure the eDiary assessments are completed.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention/entered in the study.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes indicating screen failure as reason for ending the study, demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened with permission from the sponsor. A participant who is rescreened will be screened again in the IWRS and given a new participant number.

6. Study Intervention

Study intervention is defined as any investigational intervention(s) or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 6-1 Study Interventions

Study Intervention Name	Ubrogepant 100 mg	Placebo
Dose Formulation	Compressed tablets containing 50 mg of ubrogepant	Compressed tablets containing placebo
Route of Administration	oral	oral
Dosing Instructions	For each qualifying prodrome event, 2 tablets will be taken as soon as the participant is confident that a headache will inevitably follow within 1 to 6 hours. Study intervention can be taken with or without food.	For each qualifying prodrome event, 2 tablets will be taken as soon as the participant is confident that a headache will inevitably follow within 1 to 6 hours. Study intervention can be taken with or without food.
Packaging and Labeling	Study intervention will be provided in blister cards. Each blister card will contain a total of 2 tablets to treat 1 qualifying prodrome event. The cards will be labeled as required per country requirement.	Study intervention will be provided in blister cards. Each blister card will contain a total of 2 tablets to treat 1 qualifying prodrome event. The cards will be labeled as required per country requirement.
Manufacturer	Allergan	Allergan

Immediately before dispensing the double-blind study intervention, the investigator (or appropriately trained designee) will write the participant's identification number and the date on the label.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants randomized in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual or other specified location.

6.3. Measures to Minimize Bias: Randomization and Blinding

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

An automated IWRS will be used to manage the randomization and assignment to study intervention. Before the study is initiated, log-in information and directions for the IWRS will be provided to each site. Study intervention will be dispensed at Visit 2 (one blister card) and Visit 3 (one blister card) as summarized in the SoA (Section 1.3).

At the time of randomization (Visit 2), eligible participants will be randomly assigned either Treatment Sequence A or B in a 1:1 ratio in this crossover study. All participants will be instructed to take 2 tablets for each dose of study intervention regardless of the treatment sequence they are assigned. As this is a crossover study, the study intervention for the first and second qualifying prodrome event will be the reverse for the two treatment sequences. Table 6-2 below outlines the study intervention administered for each treatment sequence.

Table 6-2 Study Interventions Administered for Each Treatment Sequence

Treatment Sequence	First Qualifying Prodrome Event	Second Qualifying Prodrome Event
	Single Dose (2 tablets)	Single Dose (2 tablets)
Treatment Sequence A	placebo/ placebo	ubrogepant 50 mg/ ubrogepant 50 mg
Treatment Sequence B	ubrogepant 50 mg/ ubrogepant 50 mg	placebo/ placebo

The sponsor's biostatistics (randomization programmer) will prepare the randomization codes.

Each blister card containing study intervention will be labeled with medication kit numbers. IWRS will provide the site with the specific medication kit number(s) for each randomized participant at the time of randomization (Visit 2) and at Visit 3. Sites will dispense study intervention according to the IWRS instructions at these 2 visits. Sites will receive the IWRS confirmation notifications for each transaction. All notifications are to be maintained with the study source documents.

All study interventions 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.

Once a randomization number has been assigned, it must not be reassigned. Withdrawn study participants will not be replaced. Returned study intervention should not be redispensed to the participants.

6.3.1. Qualifying Prodrome Event

For both the screening and double-blind treatment periods, a *qualifying prodrome event* is defined as an event in which the participant experiences a clinically identifiable prodrome with all the following conditions met:

- Headache is not currently present
- The participant has not had a headache in the previous 48 hours
- Treatments for acute headache (eg, ibuprofen, acetaminophen, triptan, Excedrin®) have not been taken in the previous 48 hours
- The participant is confident that a headache will inevitably follow within 1 to 6 hours after experiencing the qualifying prodrome event
- The participant is able to complete the eDiary for the next 8 hours

Participants who meet all of the initial study entry criteria at the Screening Visit (Visit 1) will be dispensed an eDiary to record their qualifying prodrome events within 60 days. At Visit 2, if they qualify, participants will be randomized, provided with double-blind study intervention to treat the first qualifying prodrome event, and redispensed the eDiary to record the first qualifying prodrome event. At Visit 3, participants will be provided with double-blind study intervention to treat the second qualifying prodrome event and redispensed the eDiary to record the second qualifying prodrome event.

For the double-blind treatment period, it is recommended to treat qualifying prodrome events that occur in the morning or early afternoon so that assessments can be collected in the eDiary during waking hours.

Study participants will have up to 60 days to treat 2 qualifying prodrome events at home with study intervention during the double-blind treatment period (between Visit 2 and Visit 4). Participants unable to treat 2 qualifying prodrome events within this time will be discontinued from the study.

Please refer to Section 6.5.3 for details regarding rescue medication use.

6.3.2. Breaking the Blind

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's study intervention assignment unless this could delay emergency treatment of the participant. If a participant's study intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

6.4. Study Intervention Compliance

At the clinic visits, study intervention compliance will be closely monitored by counting the number of tablets dispensed and returned. Before dispensing new study intervention at the study visits, study center personnel will make every effort to collect all unused study intervention and empty blister cards. Participants will be instructed to record in their eDiaries the date and time study intervention was taken.

The study center will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter, prescription medicines, vitamins, and herbal supplements) that the participant is receiving at the time of enrollment or takes during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

At every visit and phone call, study center staff will question each participant specifically on the use of concomitant medications. Participants who admit to using prohibited concomitant medications may be discontinued from the study at the discretion of the investigator or the sponsor.

6.5.1. Prohibited Interventions and Washout Before Study

The following classes of medications below are not allowed to be taken during the double-blind treatment period only, between Visit 2 and Visit 4/ET. Participants taking these medications at the Screening Visit (Visit 1) will need to discontinue them prior to randomization at Visit 2. Participants who cannot or should not be taken off these medications should not be enrolled. If a participant requires concomitant treatment with these medications at any time during the study, the participant must be discontinued. An extended list of examples of prohibited medications are displayed in Section 10.9.

- Strong/moderate CYP3A4 inducers, including but not limited to: **barbiturates** (eg, phenobarbital and primidone), systemic (oral/intravenous) glucocorticoids (eg, **methylprednisolone, prednisolone, prednisone**), nevirapine, efavirenz, pioglitazone, carbamazepine, phenytoin, rifampin, rifabutin, and St. John's wort
- Strong/moderate CYP3A4 inhibitors, including but not limited to: systemic (oral/intravenous) itraconazole, ketoconazole, **fluconazole**; erythromycin, clarithromycin, telithromycin; diltiazem, **verapamil**; aprepitant; cyclosporine (oral/intravenous only); nefazodone; cimetidine; quinine; and HIV protease inhibitors.
- Inhibitors of the BCRP transporter (eg, rifampicin)

The following medications are prohibited for the entire duration of the study (Visit 1 through Visit 4).

- Oral gepants (eg, Ubrelvy™ [ubrogepant], Nurtec™ [rimegepant])
- All injectable migraine prophylactic medications like botulinum toxin (Botox®) and injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®)
- Cannabinoids (ie, marijuana), CBD oil (systemically used)

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

6.5.2. Permitted Interventions

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

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 study intervention:

- any triptan or ditan
- any ergot derivative
- any opioid
- any NSAID
- any other form of analgesic (including acetaminophen and Excedrin®)
- any antiemetic agent

In regard to the permissibility of these medications after taking study intervention, please refer to the following section below on rescue medication use.

Examples of allowed but restricted medications listed above are displayed in Section 10.9.

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

SSRI or SNRI use will be permitted provided that treatment is stable at the Screening Visit (Visit 1) and continues without change in dose/frequency throughout the study. SSRIs and SNRIs may not be started during the study.

Standard oral migraine prophylactic medications (eg, amitriptyline, topiramate, propranolol, valproic acid) and nondrug therapies (eg, acupuncture, TENS, cranial traction, nociceptive trigeminal inhibition, occipital nerve block) will be permitted provided that the treatment is stable at the Screening Visit (Visit 1) and continues without change in dose/frequency throughout the study. New prophylactic medications may not be started during the study.

Any medication taken 6 months prior to Visit 1 and during the study between Visit 1 and the date of the EOS visit will be recorded in the eCRF. For medications taken for migraine, all past and current medications will be recorded in the eCRF. Any medication started after the EOS visit will not be considered a concomitant medication and should not be captured in the eCRF.

6.5.3. Rescue Medicine

Rescue medication refers to the participants' own medications used for the acute treatment of migraine headache. Rescue medications may include NSAIDs, acetaminophen, triptans, ditans,

ergotamines, analgesic or combination analgesics (eg, Excedrin®), opioids, or antiemetics; these may be taken during the study within the parameters noted in Section 6.5.2.

Screening Period:

- If a headache of any intensity develops following a qualifying prodrome event, then rescue medication can be taken to treat the headache.

Double-blind Treatment Period:

- If a moderate or severe headache develops following a qualifying prodrome event, rescue medication can be taken at any time.
- If a mild headache develops following a qualifying prodrome event, rescue medication cannot be taken within 24 hours after taking the dose of double-blind study intervention.

Rescue medication will not be supplied by the sponsor. Use of rescue medication, and all allowable medication, must conform to the prescribing information of the product and the restrictions of this protocol.

6.5.4. Prohibited Interventions During the Study

Refer to Section 10.9 for examples of prohibited medications and allowed medications (with restrictions). Refer to Section 6.5.1 for examples of prohibited medications and washout before study.

6.6. Dose Modification

This protocol does not allow for any modification from the currently outlined dosing schedule as this is an event-driven study.

6.7. Intervention after the End of the Study

There is no intervention following the end of the study or optional PK substudy.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and has been randomized to receive study intervention ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Participants may voluntarily withdraw from the study at any time.

Notification of early discontinuation from the study and the reason for discontinuation will be clearly documented on the appropriate eCRF. All randomized participants 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 4/ET. If no study intervention is taken, Visit 4/ET will be the last study visit.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used or other acceptable terms:

- Adverse event
- Completed
- Lack of efficacy
- Lost to follow-up
- Non-compliance with study drug
- Other
- Pregnancy
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by subject
- Lack of qualifying events

7.1. Discontinuation of Study Intervention

A participant with a condition and/or a situation that, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study may be withdrawn from receiving study intervention. Discontinuation of study intervention also requires discontinuation from the study. Please see previous section above regarding final assessments to be completed for discontinuation from study.

The following conditions require participants to be withdrawn from study:

- Women who become pregnant will be withdrawn from the study and should refrain from taking further study intervention. The participant should return to the clinic for ET Visit study procedures (Visit 4/ET Visit) if the participant has been randomized.
- Participants who reply with yes to questions 4 or 5 in the suicidal ideation section indicating having suicidal ideation with intent (with or without plan) or yes to any question in the suicidal behavior section of the C-SSRS should receive appropriate follow-up as in routine clinical practice. The participant should return to the clinic for ET Visit study procedures (Visit 4/ET Visit) if the participant has been randomized.
- Posttreatment ALT/AST values meeting the following criteria:
    - ALT or AST ≥ 3 × ULN and the participant is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
    - ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN
    - ALT or AST ≥ 3 × ULN and INR > 1.5
    - ALT or AST ≥ 5 × ULN for more than 2 weeks
    - ALT or AST ≥ 8 × ULN

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Criteria for Study Termination

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

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request (a clear reason must be documented), or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1 (Appendix 1).

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participant Entry Procedures

Prospective participants as defined by the inclusion criteria in Section 5.1 and exclusion criteria in Section 5.2 will be considered for entry into this study. At the Screening Visit (Visit 1) and Randomization Visit (Visit 2), participants must meet all of the inclusion criteria and must not meet any of the exclusion criteria. Rescreening of participants may be considered with permission from the sponsor.

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

Each participant that provides informed consent will be assigned a participant number that will be used on participant documentation throughout the study.

The investigator or qualified designee will explain the PK substudy consent to the participant and answer all of his/her questions. If the participant would like to participate in this optional PK substudy, participants will sign a separate consent form before performing any procedure related to the substudy.

Procedures for Duplicate Participant Identification

A central vendor will be used to verify participants' current and past research study status in order to mitigate safety concerns associated with duplicate enrollment and protocol deviations associated with multiple trial enrollment. The procedure for identifying duplicate participants is mandatory. Following proper informed consent and after issuing a participant number, each participant will be checked for duplicate participation (see the SoA; Section 1.3). Partial identifiers will be utilized. Participants who are identified as verified duplicates must not be enrolled without documented approval from the sponsor.

Visits and Associated Procedures

This study will include 4 clinic visits and 1 phone call: Screening Visit (Visit 1), a phone call during the screening period, a Randomization Visit (Visit 2), a Posttreatment Visit (Visit 3) after

treating the first qualifying prodrome event, and a Posttreatment/ET Visit (Visit 4) after treating the second qualifying prodrome event.

Screening Visit (Visit 1)

The following study procedures will be carried out at the Screening Visit (Visit 1):

- Obtain informed consent and participant privacy
- Obtain informed consent for optional PK substudy (if participant wants to participate in the substudy)
- Duplicate Participation Identification consent and verification
- Register participant in IWRS
- Collect demographic information
- Assess inclusion/exclusion criteria
- Collect medical history (including CV disease and risk factors, as outlined in the Study Reference Manual)
- Collect migraine history and confirm diagnosis
- Conduct comprehensive structured interview (see additional detail following this list)
- Review prior medications (both prescription and over-the-counter), including prophylactic medication use (taken in the past 6 months for all medications and all past medications for migraine taken during the participants' lifetime) and concomitant medication.
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, height, and weight)
- Perform ECG
- Perform physical examination
- Collect blood and urine samples for clinical laboratory tests (chemistry, hematology, urinalysis, and coagulation)
- Perform urine pregnancy test (for WOCBP only)
- Collect urine sample for drug screen
- Assess C-SSRS on eTablet (the *Screening/baseline* assessment of the C-SSRS will be completed)
- Conduct eDiary training and dispense eDiary to participant
- Review and assess AEs (from time of informed consent)

At the Screening Visit (Visit 1), the investigator or medically qualified subinvestigator, familiar with diagnosing migraine, will collect a detailed medical history, including migraine diagnosis and migraine history. As part of this assessment, a comprehensive structured interview with the participant must be conducted to examine all aspects of the participant's migraine, including the prodrome phase and headache phase, treatments, and to record the following:

- Specific prodrome symptom(s) that the participant experiences
- Usual timeframe from onset of prodrome symptom(s) to onset of headache
- Establish that the participant routinely experiences prodrome symptom(s) that are reliably followed by headache pain of any intensity within 1 to 6 hours after experiencing the prodrome symptoms (at least 3 of 4 times, or 75% of the time). The investigator must document confirmation.

A worksheet will be provided to investigational sites to guide the interview and document confirmation.

Participants who meet initial eligibility requirements at the Screening Visit (Visit 1) will be trained on the use of the eDiary and instructed on recording their qualifying prodrome events and their headache (if it occurs), nonheadache symptoms as well as all the assessments to complete on the device. In addition, the site will review the timing of the reminders and assessments as well as qualifications for a prodrome event that requires recording on the eDiary. Refer to Section 6.3.1 for the definition of a qualifying prodrome event to be recorded in the eDiary.

Participants can use rescue medication during the screening period as outlined in Section 6.5.3. Once site staff are confident that the participant understands their responsibility, a patient-specific eDiary with the participant's own prodrome symptoms preprogrammed can be dispensed to the participant. The site will instruct the participant to return with the eDiary to each future visit as the same device will be used for the duration of study participation.

During Screening Period (between Visit 1 and Visit 2)

During the screening period (between Visit 1 and Visit 2), participants will have 60 days to demonstrate the reliability of developing a headache after experiencing a qualifying prodrome event. Participants will be instructed to record their qualifying prodrome events and headaches in the eDiary. Participants who record less than 3 qualifying prodrome events in the screening period (60 days) (ie, 1 or 2 events) will be screen failed (for failure to meet inclusion criterion 2.06).

Phone Call

A phone call will be made 30 days (± 7 days) after Visit 1 to check in with the participants to ensure there are no issues with their eDiary and recording of the participants' responses. Review the data collected in the eDiary including compliance in answering all questions. A review of concomitant medications and review and assessment of AEs will also be conducted.

Randomization Visit (Visit 2)

Review eDiary data collected during the screening period (between Visit 1 and Visit 2) to confirm that inclusion criteria 2.06 and 2.07 (Section 5.1) are met.

Confirm that the participant has met the following criteria to be randomized:

- 3 to 16 qualifying prodrome events have been recorded during the screening period
    - For participants who record only 3 qualifying prodrome events, all events (100%) must be followed by a headache within 1 to 6 hours.
    - For participants who record 4 to 16 qualifying prodrome events, at least 75% of events must be followed by a headache within 1 to 6 hours.

If eligible to continue, the remaining study procedures will be carried out at the Randomization Visit (Visit 2):

- Collect vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, and weight)
- Perform urine pregnancy test (for WOCBP only)
- Assess C-SSRS on eTablet (the *Since the Last Visit* assessment of the C-SSRS will be completed)
- Perform ECG
- Review concomitant medication
- Collect migraine treatment history (eg, prior migraine preventative medication response and historical triptan response), as outlined in the Study Reference Manual
- Review and assess AEs
- Collect blood and urine samples for clinical laboratory tests (chemistry, hematology, urinalysis)
- Participant completes ASC-12 (allodynia questionnaire)
- Register the participant's visit in IWRS and obtain the kit number for study intervention. If the participant does not qualify for the study, then the study site must enter the participant into the IWRS as a screen failure.
- Review dosing with the participant, including the qualifying prodrome events that need to occur before taking double-blind study intervention, prohibited medications, and rescue medication use (see Section 6.3.1, Section 6.5.1, and Section 6.5.3). Remind participants of the importance of completing all the assessments in the eDiary. To improve compliance, remind participants to treat qualifying prodrome events that occur in the morning or early afternoon so that assessments can be collected in the eDiary during waking hours. If participant understands their responsibilities and has successfully completed their eDiary training, dispense double-blind study intervention to treat 1 qualifying prodrome event.
- Provide the participant the side effects diary to list the date and time of any side effects the participant experiences after taking double-blind study intervention.

- For participants who have consented and are participating in the optional PK substudy:
    - Train participants on the collection of DBS samples
    - A DBS sample will be collected at this visit by the participant to ensure participant comprehension of the process. The sample can then be destroyed.
    - If DBS sample collection is unsuccessful during the training, the participant may not participate in the optional PK substudy.
    - Review collection timing, handling, and storage of DBS samples that will be collected at home, as well as recording the information in the eDiary, before providing the participant with the supplies for PK sample collection.

Treatment of First and Second Qualifying Prodrome Events (between Visit 2 and Visit 4)

During the double-blind treatment period (between Visit 2 and Visit 4), participants will have up to 60 days from the Randomization Visit (Visit 2) to treat 2 qualifying prodrome events at home with double-blind study intervention at the earliest time the participant is confident that a headache will inevitably follow within 1 to 6 hours of each qualifying prodrome event. The treatment of these 2 qualifying prodrome events will be separated by Visit 3 to ensure a minimum 7-day washout period.

The participant will report information in the eDiary at the time of each qualifying prodrome event:

- Confirmation that the participant is experiencing a qualifying prodrome event
- Identification and intensity of individually specific prodrome symptom(s)
- Headache pain and intensity (if it occurs)
- Nonheadache symptoms (photophobia, phonophobia, nausea, dizziness) including intensity (mild, moderate, severe)
- Presence or absence of aura
- Health Outcomes assessments

Participants will be asked to complete their eDiary at prespecified timepoints (1, 2, 3, 4, 6, 8, 24, and 48 hours). In addition, the date and time of when the dose of double-blind study intervention is taken will be captured, as well as rescue medication use. After recording a qualifying prodrome event, it is very important that the participant captures the development of a headache (if it happens) and completes all questions at every timepoint. To ensure maximum compliance, the participant can be contacted to be reminded to complete all assessments.

A side-effects diary (paper diary, not eDiary) will be kept by the participant to record any side effects experienced within 48 hours of taking double-blind study intervention.

Posttreatment Visit (Visit 3) After Treatment of First Qualifying Prodrome Event

This visit will occur 4 days (-2/+4 days) after double-blind study intervention is taken for the first qualifying prodrome event. It can occur as early as 2 days after taking double-blind study intervention (after the 48 hour assessment has been completed) and as late as 8 days after taking

double-blind study intervention; however, participants should be encouraged to come in for this visit as soon as possible after completing their 48 hour assessments.

The following study procedures will be carried out at the Posttreatment Visit (Visit 3):

- Register the participant's visit in the IWRS
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, and weight)
- Review concomitant medication
- Review and assess AEs
- Assess C-SSRS on eTablet (the *Since the Last Visit* assessment of the C-SSRS will be completed)
- Perform urine pregnancy test (for WOCBP only)
- Review eDiary entries and ensure all questions and assessments were completed. Ensure the eDiary is functioning appropriately, sending data as programmed, and the participant continues to understand how to use the eDiary. Complete retraining if needed. Redispense the eDiary back to the participant.
- Collect side effects diary. Review the side effects listed on the diary and enter identified AEs in EDC. Provide participant with new side effects diary.
- Collect study intervention blister package; review compliance against the information collected in the eDiary.
- Obtain the kit number for study intervention in IWRS and dispense a blister card with the study intervention for the second qualifying prodrome event. Review dosing instructions with the participant again if needed.

For those participants participating in the optional PK substudy:

- Collect the DBS samples that the participant collected at home and ensure that the collection dates and times are recorded in the eDiary
- Review collection timing, handling, and storage of DBS samples that will be collected at home after the second qualifying prodrome event. Provide the participant with the supplies for PK sample collection.

The first and second qualifying prodrome events must be 2 separate and distinct events that are at least 7 days apart.

Posttreatment Visit (Visit 4) After Treatment of Second Qualifying Prodrome Event/ ET Visit

This visit will occur 4 days (-2/+4 days) after double-blind study intervention is taken for the second qualifying prodrome event. It can occur as early as 2 days after taking double-blind study intervention (after the 48 hour assessment has been completed) and as late as 8 days after taking double-blind study intervention; however, participants should be encouraged to come in for this visit as soon as possible after completing their 48 hour assessments.

If none or 1 qualifying prodrome event has been treated during the double-blind treatment period and the 60-day time period has ended, the site will call the participant to schedule an ET Visit.

Randomized participants who exit the study early for any reason, whether or not they have taken study intervention, should also receive these evaluations. The following study procedures will be carried out at the Posttreatment/ET Visit (Visit 4):

- Register the participant's visit in the IWRS
- Collect vital sign measurements (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, and weight)
- Review concomitant medication
- Review and assess AEs
- Assess C-SSRS on eTablet (the *Since the Last Visit* assessment of the C-SSRS will be completed)
- Perform ECG
- Perform physical examination
- Collect blood and urine samples for clinical laboratory tests (chemistry, hematology, and urinalysis)
- Perform urine pregnancy test (for WOCBP only)
- Collect eDiary and ensure all recorded data has been sent
- Review eDiary entries and ensure all questions and assessments were completed
- Collect side effects diary. Review the side effects listed on the diary and enter identified AEs in EDC.
- Collect study intervention blister package; review compliance against the information collected in the eDiary

For those participants participating in the optional PK substudy:

- Collect the DBS samples that the participant collected at home and ensure that the collection dates and times are recorded in the eDiary

Unscheduled Visits

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

Instructions for Participants

Section 5.3.1, Section 5.3.2, and Section 5.3.3 list dietary restrictions and activity instructions for participants enrolled in the study.

Participants will be provided with instructions on the use of the eDiary to complete when they experience qualifying prodrome events and they will be made aware of timepoints as to when

they are expected to enter data in the eDiary. A practice session with a hypothetical scenario should be administered to ensure the participants' comprehension of the questions and the information to be entered. In addition, criteria for qualifying prodrome events to be treated as well as prohibited medications should be reviewed with the participants. Participants should receive instructions on how to take the study intervention, the criteria for a qualifying prodrome event, and when participants are allowed to take rescue medication. Participants will be instructed to bring their eDiary at the next study visit and return their study intervention (used and unused).

For participants participating in the optional PK substudy, DBS sample collection training will be provided at Visit 2. For participants who have successfully completed the collection training, participants will be provided with the PK collection supplies and provided instructions on when the DBS samples must be collected and the dates and times recorded in the eDiary. Participants will collect 3 DBS samples at home after treating each qualifying prodrome event and record the date and time in their eDiary. Collection times are outlined in Section 8.5.

8.1. Efficacy Assessments

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

Absence/Presence of and Rating of Intensity of Prodrome Symptom(s)

After experiencing each qualifying prodrome event, the absence or presence of each identified prodrome symptom(s) will be followed (up to 48 hours) and the intensity subjectively rated (mild, moderate, or severe) for those that are present.

Absence/Presence of Headache and Rating of Headache Intensity

After the prodrome symptoms have started, the participant will be alerted to record the presence of a headache when it occurs or record the absence/presence at various timepoints (up to 48 hours) following the dose of double-blind study intervention (during the double-blind treatment period). If a headache is reported as present, the intensity will be subjectively rated (mild, moderate, or severe).

Absence/Presence of and Rating of Intensity of Nonheadache Symptoms

The participant will record whether nonheadache symptoms (photophobia, phonophobia, nausea, and/or dizziness) were absent or present as well as the intensity (mild, moderate, or severe) of the present nonheadache symptom (up to 48 hours).

Absence/Presence of Aura

The participant will record whether aura was present or absent (up to 48 hours).

Health outcomes assessments are described in Section 8.10.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A complete physical examination will be performed at the visits outlined in SoA (Section 1.3).

- A professionally trained physician or healthcare professional licensed to perform physical examinations will examine the participant for any detectable abnormalities of the following body systems: general appearance; neck (including thyroid); head, eyes, ears, nose, and throat; lungs; heart/cardiovascular; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; skin; and other.
- The neurologic examination should be conducted to detect the presence of any significant sensory/motor abnormalities.

8.2.2. Vital Signs

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

Sitting and standing BP and pulse rate will be determined as follows: BP and pulse measurements will be performed after the participant sits quietly for 5 minutes, followed by a second set of measurements taken after the participant stands for 3 minutes (but no longer than 10 minutes).

8.2.3. Electrocardiograms

A 12-lead ECG will be performed at the visits outlined in the SoA (Section 1.3). Only one ECG is required for each assessment at each specified visit. All ECGs should be performed after the participant has been supine for at least 5 minutes. A copy of the ECG will be saved as a source document. ECGs will be transmitted electronically to the central ECG laboratory for analysis according to the instructions provided by the laboratory to be read by a cardiologist. If multiple ECGs are completed, all ECGs (readable and unreadable) must be transmitted to the central ECG vendor. The overall interpretation of the clinical significance of the ECGs will be determined by the investigator and recorded in the source notes.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. Hematology, chemistry, urinalysis, and urine pregnancy tests will be conducted at the Screening Visit (Visit 1), Randomization Visit (Visit 2), and Posttreatment/ET Visit (Visit 4). Coagulation, and the urine drug screen will be conducted at the Screening Visit (Visit 1) only.
- The investigator or subinvestigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be screen failed or withdrawn from the study.

- Positive results on the urine drug screen (unless explained by previously reported concomitant medication use, such as opioids prescribed for migraine pain) will be excluded from the study.
- A positive pregnancy test at Visit 1 or Visit 2 will exclude the participant from participation in the study. Participants who are confirmed to be pregnant during the study will be withdrawn.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significant during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3) or laboratory manual.
    - If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded as an SAE or AE in the eCRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Ubrogepant is considered to be CNS active and participants being treated should be monitored appropriately and observed closely for suicidal ideation and behavior.

The C-SSRS is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [no plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

The C-SSRS will be completed at all study visits. At the Screening Visit (Visit 1) the C-SSRS will be completed for the participant's lifetime history and 6 months of suicidal ideation and suicidal behavior to assess eligibility. Based on this assessment and investigator judgment, if there is significant risk of self harm or harm to others, the participant must be excluded from the study. At all other visits, the C-SSRS will be completed for ideation and behavior since the previous visit.

The C-SSRS will be completed on the eTablet by the investigator or designee with current and valid training in administering the assessment. A participant should not be released from the study center until the results of C-SSRS are reviewed and it is confirmed that the participant is not considered to be at risk.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs from the signing of the ICF until 30 days after the last dose of study intervention will be collected at the timepoints specified in the SoA (see Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 (Appendix 3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 10.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3.

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

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies in female participants, and if indicated, female partners of male participants will be collected from the signing of the ICF and until completion of the study.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.7.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.3.6. Adverse Events of Special Interest

AESIs that warrant ongoing monitoring and rapid communication by the investigator to the sponsor are outlined in Section 10.3.

8.4. Treatment of Overdose

As the participant will only be provided with 1 dose of ubrogepant, the maximum amount of available ubrogepant for each participant will be at most 100 mg, an approved dose for the acute treatment of migraine.

8.5. Pharmacokinetics

PK samples will be collected using the DBS method from participants who specifically consented to provide PK samples for the purpose of obtaining ubrogepant PK data in individuals with prodrome symptoms. The PK component of the study is optional.

During the Randomization Visit (Visit 2), DBS sample collection training will be provided to the participants who consented to provide PK samples, and 1 DBS sample will be collected by the participant during the visit to ensure participant comprehension of DBS sample collection. This sample will be discarded.

Participants participating in the optional PK substudy will be instructed to collect a total of 6 DBS samples at home and record the date and time of DBS sample collection in their eDiary.

After treating the first qualifying prodrome event, the participant will collect:

- A DBS sample 15 minutes after taking double-blind study intervention
- A DBS sample 1 hour after taking double-blind study intervention
- A DBS sample anytime between 4 and 12 hours after taking double-blind study intervention

After treating the second qualifying prodrome event, the participant will collect:

- A DBS sample 30 minutes after taking double-blind study intervention
- A DBS sample 2 hours after taking double-blind study intervention
- A DBS sample anytime between 4 and 12 hours after taking double-blind study intervention

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Biomarkers are not evaluated in this study.

12-item Allodynia Symptom Checklist (ASC-12)

The ASC-12 is a patient-reported measure of how often pain or an unpleasant sensation in the skin during the most severe headache is experienced in the following scenarios: combing your hair, pulling your hair back (eg, ponytail), shaving your face, wearing eyeglasses, wearing contact lenses, wearing earrings, wearing a necklace, wearing tight clothing, taking a shower (when shower water hits your face), resting your face or head on a pillow, exposure to heat (eg, cooking, washing your face with hot water), and exposure to cold (eg, using an ice pack, washing your face with cold water). For each item, there are 5 response options ranging from does not apply to me to half the time or more, resulting in a total score that ranges from 0 (all items do not apply to me) to 24 (all items occur half the time or more). The total score can then be used to categorize each participant as having no cutaneous allodynia (0 to 2), mild (3 to 5), moderate (6 to 8), or severe (≥ 9). This measure will be conducted at Visit 2 in the eTablet.

8.9. Immunogenicity Assessments

Immunogenicity is not assessed in this study.

8.10. Health Economics Outcomes Assessments

Functional Disability Scale

The FDS is a single item used to measure the participant's level of functional disability (Cady 2015, Tepper 2015). Participants will be asked to rate the performance of daily activities using 4 response options ranging from 0 (no disability, able to function normally) to 3 (severely impaired, cannot do all or most things, bed rest may be necessary). The measure will be assessed at predose (baseline) and 1, 2, 3, 4, 6, 8, 24, and 48 hours after double-blind study intervention for treating the first and second qualifying prodrome events.

Satisfaction with Study Medication

Overall satisfaction with study medication for migraine will be assessed using a single item and 7-point rating scale ranging from extremely satisfied (0) to extremely dissatisfied (6). The question will be answered by the participants in their eDiary at 8 hours and 24 hours after taking double-blind study intervention for treating the first and second qualifying prodrome events.

Activity Limitation

A single-item measure assessing activity limitation based on a 24-hour recall will be administered as an additional health outcome measure. The measure will be used to evaluate activity limitation with a 5-level response ranging from "Not at all limited – I could do everything" to "Extremely limited." The measure will be administered at 24 hours after taking double-blind study intervention.

9. Statistical Considerations

9.1. Statistical Hypotheses

Primary null hypothesis: Ubrogepant 100 mg is the same as placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome.

Primary alternative hypothesis: Ubrogepant 100 mg is superior to placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome.

Secondary null hypothesis 1: Ubrogepant 100 mg is the same as placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of moderate/severe intensity within 48 hours after taking the double-blind study intervention during the prodrome.

Secondary alternative hypothesis 1: Ubrogepant 100 mg is superior to placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of moderate/severe intensity within 48 hours after taking the double-blind study intervention during the prodrome.

Secondary null hypothesis 2: Ubrogepant 100 mg is the same as placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who are able to function normally over 24 hours after taking the double-blind study intervention during the prodrome.

Secondary alternative hypothesis 2: Ubrogepant 100 mg is superior to placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who are able to function normally over 24 hours after taking the double-blind study intervention during the prodrome.

Secondary null hypothesis 3: Ubrogepant 100 mg is the same as placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of any intensity within 24 hours after taking the double-blind study intervention during the prodrome.

Secondary alternative hypothesis 3: Ubrogepant 100 mg is superior to placebo in the acute treatment of migraine when administered during the prodrome, as measured by the proportion of participants who do not develop headache of any intensity within 24 hours after taking the double-blind study intervention during the prodrome.

9.2. Sample Size Determination

The primary efficacy parameter is the absence of a headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome. Based on the assumption of a response rate of 64% for the placebo group and 80% for the ubrogepant 100 mg group, 240 participants in each study intervention will provide at least 95% power to detect the

above intervention difference at the 2-sided 5% significance level. The nQuery Advisor 7.0 was used for the power calculation.

A blinded sample size re-estimation has been performed as planned. Given that 7% of participants had no determinable primary endpoint as observed based on the data cut of July 5, 2021, approximately 516 participants will be randomized to maintain the effect sample size of 480 participants.

The actual power will be higher with the crossover design as some participants will contribute 2 qualifying prodrome events during the double-blind treatment period.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
ITT	All randomized participants. Participants will be summarized according to the randomized study/sequence intervention
Safety	All treated participants who take ≥ 1 administration of study intervention. Participants will be summarized according to the study intervention they actually received.
mITT	All randomized participants with ≥ 1 assessment of headache occurrence within 24 hours after taking double-blind study intervention for at least 1 qualifying prodrome event during the double-blind treatment period. Participants will be summarized according to the randomized study intervention.
PK	All participants who have evaluable PK parameters

9.4. Statistical Analyses

9.4.1. Efficacy Analyses

The efficacy analyses will be based on the mITT population. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All CIs will be 2-sided 95% CIs, unless stated otherwise.

9.4.1.1. Analysis Endpoints

The primary and secondary efficacy endpoints are listed below and analyses will be defined in the following sections. All analyses for other efficacy endpoints listed below will be defined in the SAP.

Primary efficacy endpoint:

- Absence of a headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome

Secondary efficacy endpoints:

- Absence of a headache of moderate or severe intensity within 48 hours after taking double-blind study intervention during the prodrome
- Ability to function normally over 24 hours after taking double-blind study intervention during the prodrome
- Absence of a headache of any intensity within 24 hours after taking double-blind study intervention during the prodrome

Additional endpoints:

- Absence of headache of any intensity by timepoint (excluding the endpoints that are already captured as primary and secondary endpoints)
- Absence of moderate/severe headache by timepoint (excluding the endpoints that are already captured as primary and secondary endpoints)
- Absence of severe headache by timepoint
- Time to development of headache of any intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis)
- Time to development of headache of moderate/severe intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis)
- Time to development of headache of severe intensity within 48 hours after taking double-blind study intervention during the prodrome (Kaplan-Meier analysis)
- For each of the 5 most common individual prodrome symptoms:
    - Absence of any intensity at each timepoint
    - Absence of moderate/severe intensity at each timepoint
    - Absence of severe intensity at each timepoint
    - Time to absence of any intensity
- After a headache of any intensity is reported:
    - Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) at each timepoint
    - Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of moderate/severe intensity at each timepoint
    - Absence of nonheadache migraine symptoms (photophobia, phonophobia, nausea, dizziness) of severe at each timepoint
- Absence of aura at each timepoint
- Rescue medication use within 24 and 48 hours after taking double-blind study intervention

- Time to rescue medication use within 48 hours after taking double-blind study intervention (Kaplan-Meier analysis)
- Satisfaction with study medication at 8 and 24 hours after taking double-blind study intervention during the prodrome
- Activity Limitation within 24 hours after taking double-blind study intervention during the prodrome

9.4.1.2. Primary Analyses

The primary efficacy endpoint for the absence of a headache of moderate/severe intensity within 24 hours after taking double-blind study intervention during the prodrome will be analyzed using a GLMM based on determinable data on the primary efficacy endpoint. Specifically, the status of absence of a headache of moderate/severe intensity within 24 hours should be decided based on all observed data including headache reported at a series of scheduled timepoints, reported event-driven, 24-hour recall headache, and whether a participant took rescue medication. If a participant did not report moderate/severe headache and has a missing 24-hour recall assessment, that participant will be counted as indeterminable. This GLMM model assumes a binary distribution for the response and uses a logit link. The analysis model will include period, and treatment as categorical fixed effects. An unstructured covariance matrix will be used for the covariance matrix of the residual effect for the repeated measurements (corresponding to the 2 qualifying prodrome events) within a participant. The treatment difference in terms of odds ratio between ubrogepant 100 mg and placebo will be estimated from the GLMM model.

The carryover effect will be tested although no or very minimum carryover effect is expected as the minimum 7-day washout period is much longer than the 5 times of half-life. A similar GLMM model will be fitted. The model includes period and treatment as categorical fixed effects, and period-by-treatment interaction. The carryover effect will be tested using the confounded period-by-treatment interaction. If the carryover effect is significant, the analysis should use first period only data. For sensitivity analysis purpose, first period only data analysis will be performed regardless of the significance level of the carryover effect.

A sensitivity analysis will use multiple imputation approach to impute the missing headache occurrence or indeterminable status within 24 hours for each qualifying prodrome event. Specifically, for a participant who has not experienced headache of moderate/severity by time t_j (< 24 hours) after taking double-blind study intervention and has missing headache severity assessment at the next timepoint t_{j+1}, whether the participant will experience headache of moderate/severe intensity at t_{j+1} will be imputed based on other participants on the same treatment who have not experienced headache of moderate/severe intensity by time t_j but have observed headache severity assessment at t_{j+1} . So firstly, the missing headache severity assessment at time t_1 will be imputed. The missing headache at the following timepoints (2, 3, 4, 6, 8, 24, and 48 hours) will be imputed step by step similarly. The treatment difference between ubrogepant 100 mg and placebo will be estimated from the GLMM model for each imputed data set and combined across imputations to obtain the multiple imputation estimate using standard multiple imputation techniques.

Additional sensitivity analysis will impute participants with missing headache occurrence status within 24 hours as nonresponders for the qualifying prodrome event. For participants who go

through the 60-day double-blind treatment period with only 1 qualifying prodrome event due to lack of qualifying event or having an event but with no headache assessment, the missing data for the missing qualifying prodrome event will be considered as missing at random. For participants who discontinued the double-blind treatment period with only 1 qualifying prodrome event for other reasons, the missing data for the second qualifying prodrome event will be imputed based on the observed data for the second qualifying prodrome event from participants who use placebo to treat the second qualifying prodrome event. The treatment difference between ubrogepant 100 mg and placebo will be estimated from the GLMM model for each imputed data set and combined across imputations to obtain the multiple imputation estimate using standard multiple imputation techniques.

9.4.1.3. Secondary Analyses

The first and third secondary endpoints (ie, the absence of a headache of moderate or severe intensity within 48 hours after taking double-blind study intervention during the prodrome and absence of a headache of any intensity within 24 hours), will be analyzed using a GLMM model based on observed data similar to the one used for the analysis of the primary endpoint.

A sensitivity analysis will use multiple imputation approach described for the primary endpoint to impute the missing headache occurrence status within 24 hours/48 hours for the participant for each qualifying prodrome event with an unknown status of headache occurrence within 24 hours/48 hours after taking double-blind study intervention.

A sensitivity analysis will impute participants with missing headache occurrence or indeterminable status within 24 hours/48 hours as nonresponders. For participants who go through the 60-day double-blind treatment period with only 1 qualifying prodrome event due to lack of qualifying event or having an event but with no headache assessment, the missing data for the missing qualifying prodrome event will be considered as missing at random. For participants who discontinued the double-blind treatment period with only 1 qualifying prodrome event for other reasons, the missing data for the second qualifying prodrome event will be imputed based on the observed data for the second qualifying prodrome event from participants who use placebo to treat the second qualifying prodrome event. Analyses using only the first period data will also be performed as a sensitivity analysis.

The second secondary endpoint, ie, ability to function normally over 24 hours after taking double-blind study intervention during the prodrome, includes the repeated measures of dichotomized FDS response at each postdose timepoint over 24 hours. The dichotomized response takes value 1 if the participant records *no disability, able to function normally* on the FDS, and takes value 0 otherwise. The repeated binary responses will be analyzed using a GEE model with a logit link. The GEE model will include period, treatment, time, treatment-by-time interaction as categorical fixed effects, predose baseline FDS score for the period, and predose baseline-by-time interaction as covariates. An unstructured working correlation matrix will be used for the repeated measures within each participant. The treatment effect will be expressed in terms of the geometric mean of the odds ratios of ubrogepant 100 mg relative to placebo estimated at the scheduled timepoints within 24 hours after taking double-blind study intervention.

A serial gatekeeping procedure will be used to control the overall type I error rate at the 0.05 level for multiple comparisons across the primary and 3 secondary efficacy endpoints. The

primary endpoint will serve as the gatekeeper for the first secondary endpoint. The first secondary endpoint will serve as the gatekeeper for the second secondary endpoint, which, in turn, serves as the gatekeeper for the third secondary endpoint.

9.4.1.4. Other Efficacy Analyses

The absence of a headache of any intensity by each timepoint after taking double-blind study intervention will be analyzed using the same GLMM model as primary endpoint. Similar analyses will be performed for the absence of a headache of moderate/severe intensity and absence of severe headache by timepoint. Kaplan-Meier curves for time to development of any intensity headache (or rescue medication taken), time to development of moderate/severe headache, time to development of severe headache within 48 hours will be produced by treatment and compared between treatment using the log-rank test. Additional Kaplan-Meier curves will be generated treating rescue medication as an event for the time to development of moderate/severe intensity headache and time to development of severe headache.

For each of the 5 most common individual prodrome symptoms, the absence of any intensity, absence of moderate/severe intensity, absence of severe intensity at each timepoint will be analyzed using the same GLMM model as primary endpoint. Similar analyses will be performed for the absence of any intensity nonheadache migraine symptom, absence of moderate/severe nonheadache migraine symptom, absence of severe nonheadache migraine symptom at each timepoint, and absence of aura at each timepoint. Kaplan-Meier curves for time to absence of prodrome symptoms will be produced by treatment and compared between treatment using the log-rank test. Kaplan-Meier curves will also be generated censoring data collected after rescue medication.

The observed proportions of participants who used rescue medication within 24 and 48 hours after taking double-blind study intervention will be summarized and analyzed using the same GLMM model as primary endpoint. The treatment comparisons will be conducted using the primary model. Kaplan-Meier curves for time to rescue medication use within 48 hours after taking double-blind study intervention will also be produced by treatment and compared by log-rank test.

Analysis methods for the endpoints of satisfaction with study medication and Activity Limitation will be specified in the SAP.

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs, clinical laboratory tests, ECGs, vital signs, and the C-SSRS. For each of the clinical laboratory tests, vital signs, and ECG parameters, the last nonmissing safety assessment before the first dose of double-blind study intervention will be used as the baseline for all analyses of that safety parameter.

9.4.2.1. Adverse Events

An AE will be assigned to a study intervention if it occurred on or after the first dose of the study intervention and before the first dose of the next study intervention. An AE will be assigned to

the last study intervention of the treatment sequence if it occurred on or after the first dose of the last study intervention.

AEs will primarily be assessed through the analysis of AEs reported in the 48 hours following the administration of study intervention. A supportive analysis will include AEs reported within 30 days after the last dose of the study intervention (and before the first dose of the next intervention if any).

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of study intervention. However, an AE that occurs more than 30 days after the Period 1 study intervention and before the date of the Period 2 study intervention and an AE that occurs more than 30 days after the Period 2 study intervention will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

The number and percentage of participants with TEAEs in each study intervention will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity.

The number and percentage of participants with treatment-related TEAEs in each study intervention will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant on the same study treatment, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Section 10.3 (Appendix 3).

9.4.2.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline and changes from baseline at postdose assessment will be presented by study intervention for each clinical laboratory assessment.

The criteria for potentially clinically significant laboratory values will be detailed in the SAP. The number and percentage of participants who have potentially clinically significant postbaseline clinical laboratory values will be tabulated by study intervention. The assessment will be presented in the last study intervention the participant received. The percentages will be calculated relative to the number of participants who have available nonpotentially clinically significant baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 potentially clinically significant postbaseline value. A supportive listing of participants with potentially clinically significant postbaseline values will be provided for the safety population.

9.4.2.3. Vital Signs

Descriptive statistics for vital signs (sitting and standing systolic and diastolic BP, sitting and standing pulse rate, respiration rate, temperature, weight, and body mass index) at baseline and changes from baseline at postdose assessment will be presented by study intervention.

Vital signs values will be considered to be potentially clinically significant if they meet both the observed-value criteria and the change-from-baseline-value criteria that will be detailed in the SAP. The number and percentage of participants who have potentially clinically significant postbaseline vital sign values will be tabulated by study intervention. The assessment will be presented in the last study intervention the participant received. The percentages will be calculated relative to the number of participants who have available nonpotentially clinically significant baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 potentially clinically significant postbaseline value. A supportive listing of participants with potentially clinically significant postbaseline values will be provided for the safety population.

9.4.2.4. Electrocardiograms

Descriptive statistics for ECG parameters (heart rate, PR interval, QRS interval, RR interval, QT interval, QTcB, and QTcF) at baseline and changes from baseline values at postdose assessment will be presented by study intervention.

The criteria for potentially clinically significant ECG values will be detailed in the SAP. The number and percentage of participants who have potentially clinically significant postbaseline ECG values will be tabulated by study intervention. The assessment will be presented in the last study intervention the participant received. The percentages will be calculated relative to the number of participants who have available nonpotentially clinically significant baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 potentially clinically significant postbaseline value. A supportive listing of participants with potentially clinically significant postbaseline values will be provided for the safety population.

9.4.2.5. Suicidality Assessment

For the C-SSRS, the number of participants with suicidal ideation and suicidal behavior in lifetime history and after taking double-blind study intervention will be summarized by study intervention for the safety population. The assessment will be presented in the last study intervention the participant received. A supportive listing of participants with suicidal ideation or suicidal behavior will be provided for the safety population.

9.4.2.6. Potential Hy's Law

Potential Hy's Law criteria within a 24-hour window is defined by elevated ALT or AST laboratory value that is $\geq 3 \times$ ULN and an elevated total bilirubin laboratory value that is $\geq 2 \times$ ULN and, at the same time, an alkaline phosphatase laboratory value that is $< 2 \times$ ULN, all based on blood draws collected within a 24-hour period.

Potential Hy's Law criteria without time window (evaluation of drug-induced serious hepatotoxicity) is defined by maximum of postbaseline elevation of ALT or AST laboratory

value that is ≥ 3 × ULN, along with maximum of postbaseline total bilirubin laboratory value that is ≥ 2 × ULN.

Participants who meet the potential Hy's Law criteria after taking study intervention and to the end of study participation will be summarized. If participants have unscheduled laboratory results after Visit 4 that meet potential Hy's Law criteria, the participants will be included in analysis. Supportive tabular displays will also be provided.

Participants who meet the potential Hy's Law criteria will be summarized by study treatment. The assessment will be present in the last study treatment the participant received.

9.4.3. PK Analyses

9.4.3.1. PK Parameters

T_{max}, C_{max}, and $AUC_{0\text{-}last}$ of ubrogepant will be calculated for all participants in the optional PK substudy. In addition, estimates of $T_{1/2}$ and $AUC_{0\text{-}inf}$ will be calculated, if a sufficient portion of the terminal elimination phase has been captured until the last PK sample collection.

9.4.3.2. Statistical Analyses of PK Data

Details of the statistical analyses of PK data (both PK concentrations and PK parameters) will be described in a separate PK analysis plan, that will be finalized before database lock. Descriptive statistics will be provided for PK concentrations and PK parameters by participant for all participants in the PK population.

9.4.4. Other Analyses

Health outcomes exploratory analyses will be described in a SAP finalized before database lock.

9.4.4.1. Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint will be performed by current exposure (yes/no) to a migraine preventative medication with proven efficacy, and by allodynia status at randomization (absence/presence).

9.5. Interim Analyses

No unblinded interim analysis is planned for the study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the CIOMS International Ethical Guidelines
    - Applicable ICH/ISO GCP Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; any identifiable participant information will only be transferred in accordance with the signed Informed Consent provisions.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local privacy and data protection laws. The level of disclosure must also be explained to the participant who will be required to give consent for their personal data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Not applicable.

10.1.6. Dissemination of Clinical Study Data

- Study data and information may be published in nonpromotional, peer-reviewed publications either by or on behalf of the sponsor.
- Clinical study reports, safety updates, and annual reports will be provided to regulatory authorities as required.
- Company-sponsored study information and tabular study results will be posted on the US National Institutes of Health's website www.ClinicalTrials.gov and other publicly accessible sites.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records should be available.
- Definition of what constitutes source data can be found in the Study Reference Manual.

10.1.9. Study and Site Start and Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up. If a premature termination or suspension occurs, the sponsor shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of participants enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.10. Publication Policy

- The sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and sponsor personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with the sponsor.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.11. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 10-1 Protocol-required Clinical Laboratory Tests

Category	Parameter
Chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, lactate dehydrogenase, creatine kinase, total protein, albumin, calcium, phosphorus, uric acid, total cholesterol, high density lipoprotein, low density lipoprotein, total triglycerides. The estimated glomerular filtration rate will be calculated by the central laboratory.
Hematology	Hemoglobin; hematocrit; red blood cell count; red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration); white blood cell count, including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils); platelet count
Urinalysis	Urine dipstick for specific gravity, pH, protein, glucose, ketones, bilirubin, and blood; microscopic exam including red blood cells/high-power field, white blood cells/high-power field, and casts/low-power field.
Coagulation	At Visit 1 only: INR
Urine Drug Screen	Screening for drugs of abuse (eg, marijuana, cocaine, phencyclidine, amphetamines, benzodiazepines, barbiturates, opiates) will be conducted using a urine drug screen at Visit 1. Urine drug screens positive for recreational (including marijuana regardless of legality) or illicit drugs or nondisclosed concomitant medications are allowed to be repeated. Further urine drug screens may be repeated with permission from the sponsor; a negative result or an explanation of a positive result due to concomitant medication use (eg, opioids prescribed for migraine pain) will be required for randomization.

Refer to Section 10.3 for information regarding clinical laboratory tests for AESIs.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Adverse Event of Special Interest

An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study intervention or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESI(s) have been identified for the study intervention(s) in this protocol and will be closely monitored:

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

Responses to the C-SSRS that meet the above criterion will be captured in the eTablet and monitored by the sponsor. These AEs or events determined to be SAEs must be reported appropriately via the designated eCRFs and safety forms.

Serious AESIs should be reported to the sponsor within 24 hours via the SAE form. Nonserious AESIs should be recorded in a timely fashion on the appropriate page of the eCRF.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease); for example:
    - The test result is associated with accompanying symptoms, and/or
    - The test result requires additional diagnostic testing or medical/surgical intervention, and/or
    - The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
    - The test result is considered to be an AE by the investigator or sponsor.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

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

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities or daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE or as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor or Designee Within 24 Hours
• Contacts for SAE reporting can be found on the protocol title page. • Email is the preferred method to transmit SAE information. • Facsimile transmission of the SAE information is also acceptable. • In rare circumstances and in the absence of facsimile equipment, notification by telephone (see the study contact list) is acceptable with a copy of the SAE form, sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.

10.4. Appendix 4: Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASC-12	12-item Allodynia Symptom Checklist
AST	aspartate aminotransferase
$AUC_{0\text{-inf}}$	area under the blood concentration versus time curve from time 0 to infinity
$AUC_{0\text{-last}}$	area under the blood concentration versus time curve from time 0 to time t, where t is the last quantifiable/collected timepoint
BCRP	breast cancer resistance protein
BMI	body mass index
BP	blood pressure
CBD	cannabidiol
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CGRP-RA	calcitonin gene-related peptide receptor antagonist
C_{max}	maximum blood concentrations
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
CYP3A4	cytochrome P450 3A4
DBS	dry blood spot
ECG	electrocardiogram
EC_{90}	90% maximal effective concentration
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
ET	early termination
eTablet	electronic tablet
FDA	Food and Drug Administration
FDS	Functional Disability Scale
FSH	follicle-stimulating hormone
GBD	Global Burden of Disease
GCP	Good Clinical Practice
GEE	generalized estimating equations
GLMM	generalized linear mixed model
HEOR	Health Economics Outcomes Research
HIV	Human immunodeficiency virus

Abbreviation	Definition
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD-3	International Classification of Headache Disorders criteria, 3rd Edition
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ISO	International Organization for Standardization
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IWRS	interactive web response system
mITT	modified intent-to-treat
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
PK	pharmacokinetic
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SNRI	serotonin norepinephrine reuptake inhibitor
SoA	schedule of activities
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	terminal elimination half life
TEAE	treatment-emergent adverse event
TENS	transcutaneous electrical nerve stimulation
TESAE	treatment-emergent serious adverse event
T_{max}	time to achieve maximum concentrations
ULN	upper limit of normal
WOCBP	women of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. CDISC terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any 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. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion, or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Progressive disease	A disease process that is increasing in extent or severity (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury. (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)

CDISC Submission Value	CDISC Definition
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy, Safety, and Tolerability of Oral Ubrogepant in the Acute Treatment of Migraine When Administered During the Prodrome
	Clinical Study Sponsor	AbbVie Inc
	Trial Phase Classification	Phase 3
	Trial Indication	Migraine
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	Approximately 4 months
	Planned Country of Investigational Sites	United States
	Planned Number of Subjects	Approximately 516 participants
	FDA-regulated Device Study	No
	FDA-regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18 years
	Planned Maximum Age of Subjects	75 years
	Sex of Participants	Both
	Stable Disease Minimum Duration	1 year
Treatments	Investigational Therapy or Treatment	Ubrogepant
	Intervention Type	Drug
	Dose per Administration	100 mg
	Dose Units	50 mg
	Dosing Frequency	One dose (100 mg) to treat a qualifying prodrome event. Placebo would be taken to treat second qualifying prodrome event.
	Route of Administration	Oral
Trial design	Study Type	Interventional
	Intervention Model	Crossover
	Planned Number of Arms	2 sequences
	Trial Is Randomized	Yes
	Trial Blinding Schema	Double blind
	Adaptive Design	No

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Male Participants

Nonvasectomized male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following for the duration of the study:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

- Agree to use a male condom with spermicide plus partner use of a contraceptive method with a failure rate of < 1% per year as described in Table 10-2 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

In addition, nonvasectomized male participants must refrain from donating sperm for the duration of the study.

Nonvasectomized male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration for the duration of the study.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective and acceptable method of contraception consistently and correctly as described in Table 10-2.

Table 10-2 Highly Effective and Acceptable Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • IUD • IUS • Etonogestrel implant (ie, Nexplanon®) • Bilateral tubal occlusion (eg, Essure®, bilateral tubal ligation) • Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

Acceptable Methods *Acceptable birth control methods that result in a failure of more than 1% per year include:*
• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cap, diaphragm, or sponge with spermicide • Nonhormonal intrauterine device A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test at the screening and randomization visits.
- Additional pregnancy testing will be performed at Visit 3 during the study intervention period and at Visit 4 after the last dose of study intervention.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.8. Appendix 8: International Classification of Headache Disorders, 3rd Edition, 2018

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

Coded elsewhere:

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

General comment

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

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

Introduction

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

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

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

1.1 Migraine without aura

Previously used terms: Common migraine; hemicrania simplex

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

Diagnostic criteria:

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

Notes:

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

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

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

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

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

migraine with aura, A1.2.0.2 *Menstrually related migraine with aura* and A1.2.0.3 *Non-menstrual migraine with aura* to encourage better characterization of these uncommon subforms if they are separate entities.

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

At the same time, the circuitry of migraine pain, the trigeminovascular system, and several aspects of its neurotransmission peripherally and in the trigeminal nucleus caudalis, central mesencephalic grey and thalamus, have been recognized. Highly receptor- specific acute medications including 5-$HT_{1B/D}$ receptor agonists (triptans), 5-HT_{1F} receptor agonists and CGRP receptor antagonists have demonstrated efficacy in the acute treatment of migraine attacks. Because of their high receptor-specificity, their mechanisms of action provide new insight into migraine mechanisms. It is now clear that 1.1 *Migraine without aura* is a neurobiological disorder, while clinical as well as basic neuroscience studies continue to advance our knowledge of migraine mechanisms.

1.2 Migraine with aura

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

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

Diagnostic criteria:

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

Notes:

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

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

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

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

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

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

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

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

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

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

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

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

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

The previously defined syndromes, *migraine with prolonged aura* and *migraine with acute-onset aura*, have been abandoned. It is not rare for aura to last more than one hour but, in most such cases, patients have at least two of the other characteristics of criterion C. Even when most of a patient's attacks do not fulfil criterion C, it is usual that other attacks fulfil criteria for one of the recognized subtypes or subforms of 1.2 *Migraine with aura*, and this should be the diagnosis. The few other cases should be coded to 1.5.2 *Probable migraine with aura*, specifying the atypical feature (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.

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

1.2.1 Migraine with typical aura

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

Diagnostic criteria:

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

1.2.1.1 Typical aura with headache

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

Diagnostic criteria:

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

1.2.1.2 Typical aura without headache

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

Diagnostic criteria:

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

Comments: In some patients, a typical aura is always followed by migraine headache, but many patients have, in addition, attacks with aura followed by a less distinct headache or even without headache. A number of patients have, exclusively, 1.2.1.2 *Typical aura 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. Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below
B. Aura with both of the following:
    1. at least two of the following fully reversible brainstem symptoms:
        a. dysarthria[1]
        b. vertigo[2]
        c. tinnitus
        d. hypacusis[3]
        e. diplopia[4]
        f. ataxia not attributable to sensory deficit
        g. decreased level of consciousness (GCS ≤13)[5]
    2. no motor[6] or retinal symptoms.

Notes:

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

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

There are typical aura symptoms in addition to the brainstem symptoms during most attacks. Many patients who have attacks with brainstem aura also report other attacks with typical aura and should be coded for both 1.2.1 *Migraine with typical aura* and 1.2.2 *Migraine with brainstem aura.*
Many of the symptoms listed under criterion B1 may occur with anxiety and hyperventilation, and are therefore subject to misinterpretation.

1.2.3 Hemiplegic[1] migraine

Description: Migraine with aura including motor weakness.

Diagnostic criteria:

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

Notes:

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

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

1.2.3.1 Familial hemiplegic migraine (FHM)

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

Diagnostic criteria:

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

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

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

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

1.2.3.1.1 Familial hemiplegic migraine type 1 (FHM1)

Diagnostic criteria:

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

1.2.3.1.2 Familial hemiplegic migraine type 2 (FHM2)

Diagnostic criteria:

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

1.2.3.1.3 Familial hemiplegic migraine type 3 (FHM3)

Diagnostic criteria:

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

1.2.3.1.4 Familial hemiplegic migraine, other loci

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*
B. Genetic testing has demonstrated no mutation on the *CACNA1A*, *ATP1A2* or *SCN1A* genes.

1.2.3.2 Sporadic hemiplegic migraine (SHM)

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

Diagnostic criteria:

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

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

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

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

1.2.4 Retinal migraine

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

Diagnostic criteria:

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

B. Aura characterized by both of the following:
   1. fully reversible, monocular, positive and/or negative visual phenomena (e.g., scintillations, scotomata or blindness) confirmed during an attack by either or both of the following:
      a. clinical visual field examination

b. the patient's drawing of a monocular field defect (made after clear instruction)

2. at least two of the following:
   a. spreading gradually over ≥5 minutes
   b. symptoms last 5–60 minutes
   c. accompanied, or followed within 60 minutes, by headache

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

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

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

1.3 Chronic migraine

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

Diagnostic criteria:

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

Notes:

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

1.4 Complications of migraine

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

1.4.1 Status migrainosus

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

Diagnostic criteria:

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

Notes:

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

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

1.4.2 Persistent aura without infarction

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

Diagnostic criteria:

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

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

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

1.4.3 Migrainous infarction

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

Diagnostic criteria:

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

Note:

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

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

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

1.4.4 Migraine aura-triggered seizure

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

Diagnostic criteria:

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

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

1.5 Probable migraine

Previously used term: Migrainous disorder.

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

Description: Migraine-like attacks missing one of the features required to fulfil all criteria for a type or 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 subtypes
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 for ≥1 hour, up to 10 days
    3. attacks occur ≥1 week apart
D. Complete freedom from symptoms between attacks
E. Not attributed to another disorder.[1]

Note:

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

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

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

1.6.1.2 Abdominal migraine

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

Diagnostic criteria:

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

Note:

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

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

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

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

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

1.6.2 Benign paroxysmal vertigo

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

Diagnostic criteria:

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

Notes:

1. Young children with vertigo may not be able to describe vertiginous symptoms. Parental observation of episodic periods of unsteadiness may be interpreted as vertigo in young children.

2. In particular, posterior fossa tumours, seizures and vestibular disorders have been excluded.

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

1.6.3 Benign paroxysmal torticollis

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

Diagnostic criteria:

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

Notes:

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

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

These observations need further validation by patient diaries, structured interviews and longitudinal data collection.

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

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1.6.2 Benign paroxysmal vertigo

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1.6.3 Benign paroxysmal torticollis

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10.9. Appendix 9: Examples of Prohibited Medications and Allowed Medications (with Restrictions)

Prohibited Medications: The following classes of medications below are not allowed to be taken during the double-blind treatment period, between Visit 2 and Visit 4/ET. Participants taking these medications at the Screening Visit (Visit 1) will need to discontinue them prior to randomization at Visit 2. Participants who cannot or should not be taken off these medications should not be enrolled. If a participant requires concomitant treatment with these medications at any time during the study, the participant must be discontinued.

	Strong/Moderate CYP3A4 Inducers	Strong/Moderate CYP3A4 Inhibitors
Antidepressant/ Antianxiety	Barbiturates • Amobarbital (Amytal®) • Aprobarbital (Alurate®) • Butalbital (Fiorinal®, Fioricet®) • Butabarbital (Busodium®, Butisol®) • Mephobarbital (Mebaral®) • Pentobarbital (Nembutal®) • Phenobarbital (Luminal®, Solfoton®) • Secobarbital (Seconal®)	Nefazodone (Serzone®)
Antiseizure	Carbamazepine (Atretol®, Carbatrol®, Epitol®, Equetro®, Tegretol®) Oxcarbazepine (Trileptal®) Phenytoin (Dilantin®, Phenytek®) Primidone (Myidone®, Mysoline®)	
Diabetes	Pioglitazone (Actos®) Troglitazone (Rezulin®, Resulin®)	
Antiemetic		Aprepitant (Emend®)
Antihypertension		Diltiazem (Cardizem®) Verapamil (Calan®, Calan SR®)
Glucocorticoid (systemic [oral/intravenous])	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®)

	Strong/Moderate CYP3A4 Inducers	Strong/Moderate CYP3A4 Inhibitors
Antifungal (systemic [oral/intravenous])		Fluconazole (Diflucan®, Trican®) Itraconazole (Sporanox®) Ketoconazole (Nizoral®)
HIV protease inhibitors	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™) Cimetidine (Tagamet®)
Inhibitors of the BCRP (breast cancer resistance protein) transporter (eg, rifampicin)		
Medications prohibited for the duration of the study (Visit 1-4)		
• Oral gepants (ie, Ubrelvy™, Nurtec™) • All injectable migraine prophylactic medications: botulinum toxin (Botox) and injectable monoclonal antibodies blocking the CGRP pathway (eg, Aimovig™, Emgality™, Ajovy®) • Cannabinoids (ie, marijuana), CBD oil (systemic use)		

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

Triptan or Ditan	Almotriptan (Axert®) Eletriptan (Relpax®) Frovatriptan (Frova®) Naratriptan (Amerge®) Rizatriptan (Maxalt®) Sumatriptan (Imitrex®) Zolmitriptan (Zomig®) Lasmitidan (Reyvow®)
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 with acetaminophen, Excedrin®)
Antiemetic agent	Chlorpromazine (Thorazine®) Hydroxyzine (Vistaril®) Metoclopramide (Reglan®) Ondansetron (Zofran®) Prochlorperazine (Compazine®) Promethazine (Phenergan®, Mepergan®)

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12. Protocol Amendment 2 Summary

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

Protocol 3110-304-002

Amendment Summary

This amendment includes changes made to Protocol 3110-304-002 Amendment 1, dated 01 Dec 2021. This protocol was amended to re-order the secondary endpoints.

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

Section	Revision	Rationale
As applicable	Changed sponsor name.	Changed sponsor from Allergan Sales, LLC to AbbVie Inc.
1.1 Synopsis	In the table presented in this section, objectives and endpoints are re-ordered.	The re-ordered first secondary is now better related, and in temporal continuation, to the primary endpoint assessment. The re-ordered second secondary endpoint now better reflects a meaningful clinical outcome.
3.0 Objectives and Endpoints	In the table presented in this section, objectives and endpoints are re-ordered.	Updated in line with re-ordering of secondary endpoints
9.1 Statistical Hypotheses	Updated the numbering of secondary null and alternative hypotheses.	Updated in line with re-ordering of secondary endpoints
9.1 Statistical Hypotheses	~~This sample size will provide approximately 75% power for the first secondary endpoint assuming a response rate of 36% for the placebo group and 48% for the ubrogepant 100 mg group.~~	Sentence no longer applicable as it described assumption based on previous first secondary endpoint.

Section	Revision	Rationale
9.4.1.1 Analyses Endpoints	Re-ordered secondary endpoints in bulleted list.	Updated in line with re-ordering of secondary endpoints
9.4.1.3 Secondary Analyses	The first and ~~second~~ **third** secondary endpoints (ie, the absence of a headache of moderate or severe intensity within 48 hours after taking double-blind study intervention during the prodrome **and absence of a headache of any intensity within 24 hours**), will be analyzed using a GLMM model based on observed data similar to the one used for the analysis of the primary endpoint. … The ~~third~~ **second** secondary endpoint, ie, ability to function normally over 24 hours after taking double-blind study intervention during the prodrome, includes the repeated measures of dichotomized FDS response at each postdose timepoint over 24 hours.	Updated in line with re-ordering of secondary endpoints
Global	Update additional efficacy endpoint to "Absence of aura at each timepoint"	Clarification