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## Research Submission

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# Long-Term Safety Evaluation of Ubrogepant for the Acute Treatment of Migraine: Phase 3, Randomized, 52-Week Extension Trial

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**Objective.**—To evaluate the long-term safety and tolerability of ubrogepant for the acute treatment of migraine.

**Background.**—Ubrogepant is an oral, calcitonin gene-related receptor antagonist in development for the acute treatment of migraine. The efficacy of ubrogepant was demonstrated in 2 phase 3 trials in which a significant improvement was observed in migraine headache pain, migraine-associated symptoms, and ability to function.

**Methods.**—This was a phase 3, multicenter, randomized, open-label, 52-week extension trial. Adults with migraine with or without aura entered the trial after completing one of 2 phase 3 lead-in trials and were re-randomized 1:1:1 to usual care, ubrogepant 50 mg, or ubrogepant 100 mg. Randomization to ubrogepant dose was blinded. Those randomized to usual care continued to treat migraine attacks with their own medication. The usual care arm was included in this trial to capture background rates of hepatic laboratory parameters and contextualize hepatic safety assessments. Safety and tolerability were the primary outcome measures. The safety population for the ubrogepant arms included all randomized participants who received at least 1 dose of treatment. All cases of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations of  $\geq 3$  times the upper limit of normal were adjudicated by an independent panel of liver experts who were blinded to dose.

**Results.**—The safety population included 1230 participants (404 in the ubrogepant 50-mg group, 409 in the ubrogepant 100-mg group, and 417 in the usual care group). Participants were on average 42 years of age, 90% (1106/1230) female and 85% (1043/1230) white, with an average BMI of 30 kg/m<sup>2</sup>. Throughout the trial, 21,454 migraine attacks were treated with 31,968 doses of ubrogepant. Treatment-emergent adverse events (TEAEs) were reported by 268/404 (66%) participants receiving ubrogepant 50 mg and 297/409 (73%) receiving ubrogepant 100 mg. The most commonly reported TEAE was upper respiratory tract infection (<12%); findings were similar across dose groups. Treatment-related TEAEs were reported by 42/404 (10%) participants in the ubrogepant 50-mg group and 43/409 (11%) in the ubrogepant 100-mg group. Serious adverse events (SAEs) were reported by 9/404 (2%) participants in the ubrogepant 50-mg group and 12/409 (3%) participants in the ubrogepant 100-mg group. Twenty cases of ALT/AST levels of  $\geq 3$  times the upper limit of normal were reported and reviewed by an independent clinical adjudication committee of liver experts. There were no cases of Hy's Law.

**Conclusions.**—Long-term intermittent use of ubrogepant 50 and 100 mg given as 1 or 2 doses per attack for the acute treatment of migraine was safe and well tolerated, as indicated by a low incidence of treatment-related TEAEs and SAEs and discontinuations due to adverse events in this 1-year trial.

**Key words:** migraine, acute treatment, calcitonin gene-related peptide, safety

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**Abbreviations:** ALT alanine aminotransferase, AST aspartate aminotransferase, CGRP calcitonin gene-related peptide, ECG electrocardiogram, IWRS interactive Web response system, NSAIDs non-steroidal anti-inflammatory drugs, SAE serious adverse event, TEAE treatment-emergent adverse event

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## INTRODUCTION

Migraine is a highly prevalent and burdensome chronic disease with attacks characterized by 1-sided pulsatile pain associated with sensitivity to light and sound, and nausea in various combinations.<sup>1</sup> Based on the recent Global Burden of Disease study, migraine ranks second among the leading causes of years lived with disability,<sup>2,3</sup> impacting not only a person's daily living activities but having a negative effect on their families as well.<sup>4-9</sup> Effective and safe treatment options are needed to help reduce the burden of migraine.

Several acute treatment options are currently available, including analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), ergot derivatives, and triptans.<sup>10-12</sup> Even with the number of acute treatments available, approximately 50% of those with migraine are not satisfied with their acute treatment for migraine and most have significant unmet treatment needs.<sup>13</sup> In the Migraine in America Symptoms and Treatment study,<sup>14</sup> of the 15,133 adults with migraine, only 15% were using a triptan and 95.8% had at least 1 unmet treatment need.<sup>15</sup> Among migraine-specific

acute medications, ergot derivatives and triptans, though effective, are associated with safety and tolerability issues as well as contraindications.<sup>11,16</sup> This supports the need for additional migraine-specific treatment options with desirable efficacy and safety profiles.

Calcitonin gene-related peptide (CGRP) plays an important role in migraine pathophysiology and as a result, small molecule CGRP receptor antagonists, known as *gepants*, are being studied for their efficacy in treating migraine.<sup>17,18</sup> Ubrogepant is an oral *gepant* in development for the acute treatment of migraine. The efficacy and safety of ubrogepant have been shown in proof-of-concept and large, placebo-controlled trials.<sup>19-21</sup> The phase 3 ACHIEVE I and II single-attack trials met their co-primary endpoints for the 50- and 100-mg doses, thereby establishing ubrogepant's efficacy. Rates of headache pain freedom 2 hours post-dose were significantly superior to placebo with ubrogepant 25, 50, and 100 mg ( $P \leq .01$ ).<sup>20,21</sup> In addition, the rates of absence of the most bothersome migraine-associated symptom (photophobia, phonophobia, or nausea)

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at 2 hours were significantly greater with ubrogepant 50 and 100 mg than placebo ( $P \leq .01$ ), but not with ubrogepant 25 mg.

The primary objective of this phase 3, multicenter, randomized, 52-week extension trial was to evaluate the long-term safety and tolerability of intermittent treatment with ubrogepant for the acute treatment of migraine over 1 year. Treatment groups included ubrogepant 50 mg, ubrogepant 100 mg, and a usual care arm. The usual care arm was included to contextualize any hepatic safety findings over the course of this trial. Many treatments were included in the usual care arm, often treatments the patients were already using; therefore, non-laboratory adverse events (AEs) were not captured in relation to treatment in this arm.

## METHODS

**Trial Design.**—This was a phase 3, multicenter, randomized, open-label, 52-week extension trial conducted at 161 centers in the United States. The trial protocol and all amendments were approved by properly constituted local and central institutional review boards. All participants provided written informed consent before initiation of any trial-specific procedures. The trial was sponsored by Allergan plc, which included provision of trial treatment for those randomized to ubrogepant treatment arms. Changes to the original protocol are in Supplementary S1.

The first participant was enrolled September 13, 2016 and the last participant completed August 2, 2018. Participants were identified by the trial investigator and entered the trial after completing one of 2 randomized, double-blind, placebo-controlled, single-attack, phase 3 lead-in trials (ACHIEVE I, NCT02828020; ACHIEVE II, NCT02867709) and were re-randomized 1:1:1 to usual care, ubrogepant 50 mg, or ubrogepant 100 mg.

Participants who were on a stable dose of migraine preventive medication were allowed to continue on their medication. Those with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level  $\geq 1.5$  times the upper limit of normal (ULN) or bilirubin  $> 1.5$  mg/dL at screening were not included. Participants could not have any clinically significant abnormalities in their electrocardiogram (ECG), physical examination, or laboratory

test and could not have uncontrolled hypertension. Those with clinically significant cardiovascular or cerebrovascular disease or myocardial infarction, transient ischemic attack, or stroke within 6 months prior to Visit 1 were excluded from the trial. Use of moderate to strong CYP3A4 inhibitors and inducers was prohibited during the trial.

Although this was an open-label trial, randomization to the ubrogepant dose was blinded. Participants randomized to ubrogepant took 2 tablets to treat each migraine attack. Participants in the ubrogepant 100-mg arm took two 50-mg ubrogepant tablets, whereas participants in the ubrogepant 50-mg arm took 1 ubrogepant 50-mg tablet and 1 placebo tablet. Participants randomized to ubrogepant could treat up to 8 migraine attacks per 4-week interval during the 1-year trial period. If participants returned to the site and received study medication prior to the end of a designated 4-week interval, they could treat more than 8 migraine attacks in a 4-week interval. Participants could treat headache pain of any severity (ie, mild, moderate, or severe). A qualifying migraine attack must have met all of the following conditions: at least 48 hours had passed since the last dose of ubrogepant, the participant had at least 48 hours of pain freedom, less than 4 hours had passed since the headache started, the headache was not resolving on its own, and prohibited medications were not taken.

An optional second dose of ubrogepant or rescue medication, which could include analgesics (eg, acetaminophen, NSAIDs, opioids), anti-emetics, or triptans, was allowed at least 2 hours after the initial dose if the participant had a nonresponding migraine or migraine recurrence. The second dose of ubrogepant was the same as the first dose and could be taken 2–48 hours after the initial ubrogepant dose. If a second dose was taken, the participant was not allowed to take rescue medication for at least 2 hours after the second dose. If the participant opted to take rescue medication instead, an optional second dose of ubrogepant was not allowed. Participants randomized to the usual care arm continued to treat their migraine attacks with medication that they had been taking historically. Their usual care medications were identified at Visit 1 and any changes were recorded in the electronic case report form.

After screening and randomization, visits occurred every 4 weeks for 1 year. The clinic visits for safety assessments were at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 weeks relative to the randomization visit. A safety follow-up visit occurred 4 weeks after the 52-week visit or after early termination. Participants who did not treat a single migraine attack in the first 6 months of the trial were discontinued.

An automated interactive Web response system (IWRS) was used to manage the randomization and treatment assignment. The sponsor's biostatistician prepared the randomization codes. Investigational product was labeled with medication kit numbers. The IWRS provided the site with the specific medication kit number for each randomized participant in the ubrogepant arms at the time of randomization. Randomization was stratified by the participant's historical triptan response and current preventive concomitant medication use, as determined in the lead-in trials. All participants, site personnel, and trial sponsor personnel were blinded to ubrogepant dose in this open-label trial.

An interim analysis was planned for when at least 300 ubrogepant-treated participants who treated an average of  $\geq 2$  migraine attacks per month were enrolled in the trial for 6 months and 200 ubrogepant-treated participants who treated an average of  $\geq 2$  migraine attacks per month were enrolled for 1 year. At the time of the interim database lock, the ubrogepant dosing assignments were unblinded to the sponsor; participants and investigators remained blinded. A full data analysis was conducted after trial completion and the data from the final 1-year trial are reported here.

**Outcome Measures.**—The primary outcomes were safety and tolerability, which included collection of AEs, clinical laboratory determinations, ECGs, vital sign measurements, physical examinations, and the Columbia-Suicide Severity Rating Scale at each clinic visit. Investigators began each visit by querying for AEs by asking the participant a general, non-directed question such as “How have you been feeling since the last visit?” and then followed up with directed questioning, examination, and documentation, as appropriate. All AEs were coded using the Medical Dictionary for Regulatory Activities version 20.1 by the sponsor's med-

ical coding group. The investigators were required to provide an assessment of the severity, the likelihood of a causal relationship to the study medication, and seriousness of the event, document all actions taken with regard to the study medication, and detail any other treatment measures taken for the AE.

An independent clinical adjudication committee of liver experts was established for blinded adjudication of posttreatment elevations of ALT and/or AST  $\geq 3$  times the ULN. Potential Hy's Law cases were defined as an elevation of ALT or AST value  $\geq 3 \times$  the ULN and an elevated total bilirubin value  $\geq 2 \times$  ULN, and, at the same time, an alkaline phosphatase value  $< 2 \times$  ULN, all based on blood draws collected within a 24-hour period.<sup>22,23</sup> A data safety monitoring board monitored unblinded safety data. Exploratory efficacy assessments of headache severity, migraine-associated symptoms (photophobia, phonophobia, nausea, and vomiting), use of rescue medications, use of optional second dose, and recurrence of headache pain were collected for ubrogepant treatment arms only. This manuscript's focus is the safety outcomes; thus a comprehensive summary of efficacy findings will be reported separately.

**Statistical Analysis.**—The sample size was driven by regulatory safety requirements for duration of exposure and number of participants rather than statistical considerations. The expected randomization was 1200 participants with at least 70% completing 12 months of treatment and at least 50% expected to treat on average at least 2 migraine attacks per month.

The screened population included all screened participants who signed the informed consent. The intent-to-treat population included all randomized participants. The safety population included all randomized participants who took at least 1 dose of ubrogepant treatment and all participants randomized to the usual care arm.

AE data were analyzed by calculating the frequency and percentage of participants reporting the event in each treatment group. No formal statistical comparisons between treatment groups were planned or executed. The usual care population was included only to contextualize background rates of ALT/AST safety findings occurring in the ubrogepant-treated participants. Elevations of ALT/AST are often

asymptomatic; thus, the usual care arm provided within-study control of natural fluctuations in these evaluations within a migraine population. The usual care population included participants who had been on and had tolerated their medication prior to enrollment. The participants in the usual care arm selected their usual acute treatment for migraine based on their prior treatment experience; therefore, direct comparisons of AE rates between ubrogepant and the usual care arm cannot be made given this self-selection. Many of the usual care arm participants had a history of tolerating their selected medication; therefore, AE rates in the usual care arm would not have reflected the introduction of a new treatment, as they did in the ubrogepant arms. Because previous experience with the usual care drug could have reduced the probability of experiencing /reporting safety or tolerability AEs, AEs reported in the usual care arm were not assessed for relatedness to the usual care medication. To directly evaluate the safety and tolerability profiles of acute treatments, enrolled participants should be naïve to each treatment before randomization, after which AE profiles can be compared.

AEs occurring after the screening visit were summarized for treatment-emergent adverse events

(TEAEs), treatment-related TEAEs, serious adverse events (SAEs), and AEs leading to discontinuation. Treatment-related TEAEs were only determined for ubrogepant treatment arms.

Clinical laboratory assessments were summarized by treatment group. The adjudication committee findings were summarized by treatment group for participants with ALT or AST elevations  $\geq 3$  times the ULN.

Statistical analyses were conducted using SAS Version 9.4 or later (Cary, NC).

## RESULTS

**Participants and Extent of Exposure.**—In this trial, 1310 participants were screened, 1254 randomized, and 1230 included in the safety population (Fig. 1). Of the safety population, 665 participants were from the ACHIEVE I lead-in trial and 565 from the ACHIEVE II lead-in trial. In the ubrogepant 50-mg group, 404 participants treated 10,323 migraine attacks with 1 or more doses of ubrogepant for a total of 15,536 doses. In the ubrogepant 100-mg group, 409 participants treated 11,131 migraine attacks with 1 or more doses of ubrogepant for a total of 16,432 doses. Over the course of the trial, an average of 13.2 and 14.8 migraine attacks were treated with 1 dose of ubrogepant

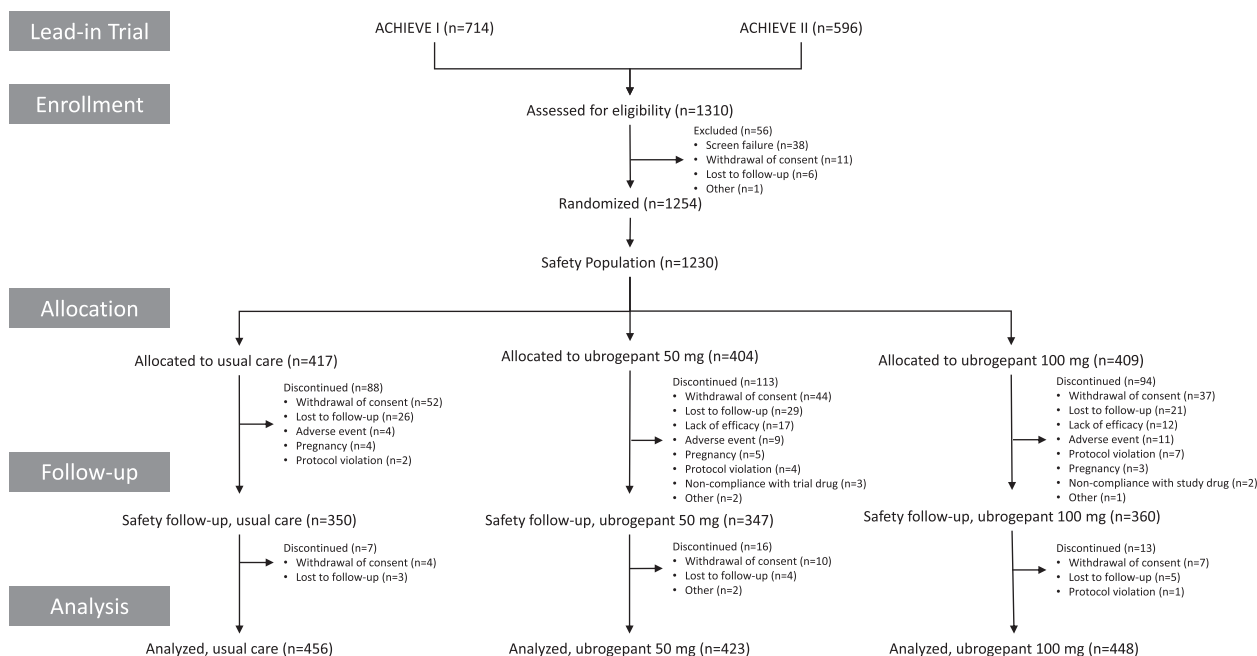


Fig. 1.—Participant disposition.

50 and 100 mg, respectively, and an average of 12.3 and 12.4 migraine attacks were treated with 2 or more doses of ubrogepant 50 and 100 mg, respectively. The average number of doses taken per participant over the 1-year trial period was 38.5 doses for ubrogepant 50 mg and 40.2 doses for ubrogepant 100 mg.

Considering the maximum number of treated attacks in any given month, a total of 233 (29%) ubrogepant-treated participants treated 6 or more migraine attacks during at least 1 month in the trial (109 participants in the ubrogepant 50-mg group and 124 participants in the ubrogepant 100-mg group). Of these, a total of 72 (9%) participants treated 8 or more migraine attacks in at least 1 month (30 participants in the ubrogepant 50-mg group and 42 in the ubrogepant 100-mg group). Cumulatively, participants treated 6 or more migraines in a month in 740 months (334 months for those who took ubrogepant 50 mg and 406 months for those who took ubrogepant 100 mg). Participants treated 8 or more migraine attacks in a month for a total of 144 months (55 months for those who took ubrogepant 50 mg and 89 months for those who took 100 mg).

**Demographics and Clinical Characteristics.**—In the safety population, participants were on average 41.8 years of age (SD = 11.7), predominantly female (N = 1106/1230, 90%) and white (N = 1043/1230, 85%), with an average BMI of 29.9 kg/m<sup>2</sup> (SD = 7.7). At the time of randomization, 306 (24.9%) participants in the safety population were on a preventive treatment for migraine (eg, topiramate, onabotulinumtoxinA, propranolol, amitriptyline), and use of preventive treatment was evenly distributed across treatment groups (n = 102 [25%] in each group). In the safety population, nearly all participants (99.5%) took at least 1 concomitant medication during the treatment period. The most common were ibuprofen (54.5%), combination aspirin-acetaminophen-caffeine (36.4%), sumatriptan (27.6%), and acetaminophen (25.6%). Overall, participant demographics and clinical characteristics were similar in the ubrogepant and usual care arms.

**Ubrogepant Adverse Events.**—TEAEs occurred in 268 (66%) participants in the ubrogepant 50-mg group and in 297 (73%) participants in the ubrogepant 100-mg group (Table 1). Most commonly reported TEAEs (≥2% of participants in any treatment group;

**Table 1.—Overall Summary of Adverse Events (Safety Population)**

	Ubrogepant 50 mg n = 404 n (%)	Ubrogepant 100 mg n = 409 n (%)
TEAEs†	268 (66.3)	297 (72.6)
Treatment-related TEAEs†	42 (10.4)	43 (10.5)
On therapy SAE‡,§	9 (2.2)	12 (2.9)
Deaths‡	0	0
AEs leading to discontinuation¶	9 (2.2)	11 (2.7)

†Treatment-emergent events were defined as those events that initially occurred or increased in intensity on or after the initial dose of treatment of the lead-in trial. An event that occurred after Visit 16 for participants with Visit 16 or more than 30 days after the last visit or last treatment, whichever was later, for participants without Visit 16 was not considered to be treatment emergent.

‡On-therapy events were defined as those events that occurred between the treatment start date of the lead-in trial and Visit 16, or within 30 days after the last visit or last treatment, whichever was later, for participants without Visit 16.

§All SAEs reported, by preferred term, ubrogepant 50 mg: cholecystitis acute, cholelithiasis, pneumonia, device allergy (allergic reaction due to Essure® implant), gait disturbance, hypertensive crisis, intestinal obstruction, pelvic inflammatory disease, postprocedural infection, sinus tachycardia, substance-induced mood disorder; ubrogepant 100 mg: abortion, abortion spontaneous, acute respiratory failure, cholecystitis acute, cholelithiasis, colitis, diabetic ketoacidosis, ectopic pregnancy, gastroenteritis norovirus, hemiparesis, hiatus hernia, non-cardiac chest pain, pancreatitis acute, pneumonia, sepsis, subdural hematoma, suicidal ideation.

¶Includes events that occurred from screening to Visit 16, or within 30 days after the last visit or last treatment, whichever was later, for participants without Visit 16.

Only events that occurred on or after the randomization date are included except for AEs leading to discontinuation. Participants are counted only once within each category.

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 2) were upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, influenza, and nausea. No increase in the incidence of TEAEs was noted with an increase in number of attacks treated per month (Supplementary S2). The incidence of TEAEs was similar across age (Supplementary S3), sex (Supplementary S4), and race subgroups (Supplementary S5).

Of the participants who had TEAEs, approximately 10% were considered related to ubrogepant

**Table 2.—Common ( $\geq 2\%$ )† Treatment-Emergent Adverse Events by Preferred Term**

Preferred Term‡	Ubrogепant 50 mg n = 404 n (%)	Ubrogепant 100 mg n = 409 n (%)
	Nasopharyngitis	33 (8.2)
Upper respiratory tract infection	47 (11.6)	44 (10.8)
Sinusitis	28 (6.9)	26 (6.4)
Urinary tract infection	22 (5.4)	26 (6.4)
Influenza	17 (4.2)	25 (6.1)
Nausea	19 (4.7)	19 (4.6)
Bronchitis	13 (3.2)	18 (4.4)
Blood creatine phosphokinase increased	10 (2.5)	16 (3.9)
Alanine aminotransferase increased	9 (2.2)	15 (3.7)
Aspartate aminotransferase increased	7 (1.7)	14 (3.4)
Back pain	14 (3.5)	14 (3.4)
Nephrolithiasis	4 (1.0)	13 (3.2)
Dizziness	5 (1.2)	12 (2.9)
Anxiety	6 (1.5)	11 (2.7)
Cough	8 (2.0)	11 (2.7)
Diarrhea	10 (2.5)	11 (2.7)
Arthralgia	11 (2.7)	10 (2.4)
Gastroenteritis viral	7 (1.7)	10 (2.4)
Muscle strain	2 (0.5)	10 (2.4)
Depression	1 (3.2)	5 (1.2)
Migraine	6 (1.5)	4 (1.0)
Abdominal pain	4 (1.0)	2 (0.5)
Epididymitis§	1 (3.2)	0 (0)
Testicular pain§	1 (3.2)	0 (0)

†Only adverse events reported in  $\geq 2\%$  of participants (after rounding) in any treatment group are shown. Participants are counted only once within each preferred term.

‡Preferred terms were coded according to the Medical Dictionary of Regulatory Activity (MedDRA) Version 20.1.

§For sex-specific adverse events, percentages are relative to the number of participants of the appropriate sex.

treatment by the investigator. The most commonly reported treatment-related TEAEs ( $\geq 1\%$ ) in any ubrogепant dose group were nausea (1.5 and 1.7% with ubrogепant 50 and 100 mg, respectively), dizziness (0.5 and 1.5%), and somnolence (1.5 and 1.2%). ALT increases (0.7 and 1.0%) and AST increases (0.5 and 1.0%) also occurred with ubrogепant 50 and 100 mg.

Most TEAEs were mild or moderate in severity. Severe TEAEs were reported for 6.2 and 8.1% of participants in ubrogепant 50-mg and ubrogепant 100-mg groups, respectively. Severe TEAEs that were reported for 3 or more participants in the ubrogепant groups

were AST increase, cholelithiasis, nephrolithiasis, pneumonia, and sinusitis (each reported for 3 ubrogепant-treated participants); influenza, migraine, and nausea were each reported for 4 ubrogепant-treated participants.

SAEs were reported for 9/404 (2%) participants in the ubrogепant 50-mg group and 12/409 (3%) participants in the ubrogепant 100-mg group (Table 1). Only 1 SAE was considered related to treatment by the investigator (sinus tachycardia), and this event occurred in a participant with a history of supraventricular tachycardia with ablation; the participant continued to take ubrogепant after this event without further complications. No deaths occurred during the trial. Discontinuations due to AEs were reported for 2–3% of the ubrogепant-treated participants. TEAEs leading to discontinuation assessed as related to treatment by the investigator were reported for 4 participants in the ubrogепant 50-mg group (nausea, thrombocytopenia, urticaria, and vomiting) and 4 in the ubrogепant 100-mg group (abnormal ECG and extrasystolic beats; nausea and palpitations; pruritus; ALT and AST increase). The event of thrombocytopenia was reported as *unknown* in terms of relatedness and imputed as *related*.

**Cardiovascular Safety.**—Frequency of cardiovascular TEAEs in predefined categories of cardiac arrhythmia, central nervous system (CNS) vascular disorders, embolic and thrombotic events, hypertension, and ischemic heart disease were generally balanced between ubrogепant treatment groups (Table 3). No cardiovascular TEAEs occurred at a rate  $>2\%$  in either ubrogепant treatment arm; few cardiovascular SAEs were reported. Two SAEs were reported in the category of CNS vascular disorders, both considered not related to study medication. One event was an SAE of hemiparesis; vascular etiology (ie, stroke) was ruled out and the investigator considered the event to be due to poorly controlled hypothyroidism (Supplementary S6). The other SAE was a traumatic subdural hematoma due to a head injury. One cardiovascular SAE was considered related to treatment by the investigator (sinus tachycardia, details presented in *Ubrogепant Adverse Events* section). No cardiovascular events related to myocardial infarction or stroke were reported in either ubrogепant treatment arm.

**Table 3.—Treatment-Emergent Cardiovascular Adverse Events of Special Interest**

TEAE Category† Preferred Term	Ubrogapant 50 mg n = 404	Ubrogapant 100 mg n = 409
	n (%)	n (%)
Cardiac arrhythmias	4 (1.0)	5 (1.2)
Arrhythmia	0	1 (0.2)
ECG QRS complex prolonged	0	1 (0.2)
Extrasystoles	0	1 (0.2)
Sinus tachycardia‡	1 (0.2)	1 (0.2)
Ventricular extrasystoles	0	1 (0.5)
Atrioventricular block first degree	1 (0.2)	0
Cardiac flutter	1 (0.2)	0
Sinus bradycardia	1 (0.2)	0
CNS vascular disorder/embolic and thrombotic events	0	2 (0.5)
Hemiparesis†,‡,§	0	1 (0.2)
Traumatic subdural hematoma‡	0	1 (0.2)
Hypertension	13 (3.2)	11 (2.7)
Hypertension	8 (2.0)	7 (1.7)
Blood pressure diastolic increased	1 (0.2)	2 (0.5)
Blood pressure increased	3 (0.7)	2 (0.5)
Hypertensive crisis‡	1 (0.2)	0
Prehypertension	1 (0.2)	0
Ischemic heart disease	2 (0.5)	2 (0.5)
Angina pectoris	2 (0.5)	2 (0.5)

†Each category is based on predefined standard groups of Preferred Terms (narrow Standard MedDRA Queries).

‡Reported as a serious adverse event.

§The participant with hemiparesis had negative imaging for any vascular events and stroke was ruled out as a possible cause. The investigator attributed the event to severe uncontrolled hypothyroidism.

CNS = central nervous system; TEAE = treatment-emergent adverse event.

**Hepatic Safety.**—The mean changes in ALT and AST from baseline to postbaseline visits were similar across the ubrogapant treatment groups and the usual care arm (Supplementary S7). Postbaseline hepatic laboratory values of clinical interest are presented in Table 4. There were no cases of confirmed Hy's Law. One participant, while hospitalized with recurrent acute cholecystitis due to gallstones seen in the common bile duct, had rapid rises in ALT/AST and bilirubin levels. Following gallbladder removal, enzymes returned to normal (Supplementary S8). As there was an underlying cause for these ALT/AST and bilirubin elevations, this case did not meet criteria for Hy's Law. Twenty cases of ALT or AST elevations of

$\geq 3 \times$  ULN were reported, as follows: 4/398 (1.0%) in the usual care arm, 5/399 (1.3%) in the ubrogapant 50 mg arm, and 11/406 (2.7%) in the ubrogapant 100 mg arm. All  $\geq 3 \times$  ULN ALT or AST cases were adjudicated by an independent panel of liver experts blinded to ubrogapant dose (Supplementary S8). Out of the 20 cases, 17 (4 usual care, 3 ubrogapant 50 mg, and 10 ubrogapant 100 mg) were judged *Unlikely Related* to study medication. Two cases (both ubrogapant 50 mg) were judged *Possibly Related* with confounding factors reported (increased alcohol and acetaminophen use; dilated bile duct). Only 1 case of ALT or AST elevations of  $\geq 3 \times$  ULN (ubrogapant 100 mg) was judged *Probably Related*; however, confounding factors were noted (prednisone use for exacerbation of psoriasis prior to rise in ALT/AST). All cases of ALT or AST elevation  $\geq 3 \times$  ULN resolved in those who continued ubrogapant dosing.

**Usual Care Adverse Events.**—As noted, the usual care population was included to examine variability in hepatic laboratory parameters to help contextualize the hepatic safety data. The trial was not designed to specifically compare AEs between these groups due to the differences in the usual care and ubrogapant-treated populations, as outlined above. A total of 271/417 participants (65.0%) reported a TEAE; relatedness was not assessed for the usual care arm. The most common ( $\geq 2\%$  participants in any group; Supplementary S9) were upper respiratory tract infection (n = 48/417, 11.5%), nasopharyngitis (n = 33, 7.9%), sinusitis (n = 25, 6.0%), urinary tract infection (n = 23, 5.5%), and influenza (n = 21, 5.0%). Severe TEAEs were reported for 6.2% of participants. Serious AEs were reported by 17 participants (4.1%) (Supplementary S10). No deaths were reported and 4 participants (1.0%) reported TEAEs that led to discontinuation.

## DISCUSSION

This phase 3, long-term safety evaluation followed 813 participants treated intermittently with ubrogapant 50 or 100 mg over the course of 1 year. A total of 21,454 migraine attacks were treated with 31,968 doses of ubrogapant. Participants treated  $\geq 8$  migraine attacks with ubrogapant 50 or 100 mg in a total of 144 months. Overall, there was a low



Table 4.—Hepatic Laboratory Parameters: Postbaseline Values of Clinical Interest (Safety Population)

Preferred Term	Usual Care n = 417 n (%)	Ubrogepant 50 mg n = 404 n (%)	Ubrogepant 100 mg n = 409 n (%)
ALT (U/L)			
≥1 × ULN	114/397 (28.7)	117/399 (29.3)	122/406 (30.0)
≥1.5 × ULN	38/397 (9.6)	38/399 (9.5)	55/406 (13.5)
≥2 × ULN	16/397 (4.0)	14/399 (3.5)	33/406 (8.1)
≥3 × ULN	4/397 (1.0)	4/399 (1.0)	8/406 (2.0)
≥5 × ULN	1/397 (0.3)	2/399 (0.5)	4/406 (1.0)
≥10 × ULN	0/397	0/399	1/406 (0.2)
≥20 × ULN	0/397	0/399	0/406
AST (U/L)			
≥1 × ULN	60/397 (15.1)	55/399 (13.8)	70/406 (17.2)
≥1.5 × ULN	13/397 (3.3)	16/399 (4.0)	28/406 (6.9)
≥2 × ULN	5/397 (1.3)	9/399 (2.3)	10/406 (2.5)
≥3 × ULN	2/397 (0.5)	2/399 (0.5)	9/406 (2.2)
≥5 × ULN	1/397 (0.3)	1/399 (0.3)	4/406 (1.0)
≥10 × ULN	0/397	0/399	2/406 (0.5)
≥20 × ULN	0/397	0/399	1/406 (0.2)
ALT or AST (U/L)			
≥1 × ULN	123/397 (31.0)	124/399 (31.1)	134/406 (33.0)
≥1.5 × ULN	42/397 (10.6)	41/399 (10.3)	59/406 (14.5)
≥2 × ULN	19/397 (4.8)	20/399 (5.0)	35/406 (8.6)
≥3 × ULN	4/397 (1.0)	5/399 (1.3)	11/406 (2.7)
≥5 × ULN	1/397 (0.3)	2/399 (0.5)	6/406 (1.5)
≥10 × ULN	0/397	0/399	2/406 (0.5)
≥20 × ULN	0/397	0/399	1/406 (0.2)
Bilirubin total (μmol/L)			
≥1 × ULN	14/397 (3.5)	16/399 (4.0)	18/406 (4.4)
≥1.5 × ULN	3/397 (0.8)	5/399 (1.3)	2/406 (0.5)
≥2 × ULN	1/397 (0.3)	3/399 (0.8)	2/406 (0.5)
≥3 × ULN	0/397	1/399 (0.3)	1/406 (0.2)
≥5 × ULN	0/397	0/399	0/406
≥10 × ULN	0/397	0/399	0/406
≥20 × ULN	0/397	0/399	0/406
Alkaline phosphatase (U/L)			
≥1 × ULN	35/397 (8.8)	48/399 (12.0)	36/406 (8.9)
≥1.5 × ULN	3/397 (0.8)	1/399 (0.3)	1/406 (0.2)
≥2 × ULN	1/397 (0.3)	1/399 (0.3)	0/406
≥3 × ULN	0/397	0/399	0/406
≥5 × ULN	0/397	0/399	0/406
≥10 × ULN	0/397	0/399	0/406
≥20 × ULN	0/397	0/399	0/406
Concurrent elevations <sup>†</sup>			
ALT or AST ≥3× ULN and bilirubin total ≥1.5× ULN	0/397	0/399	1/406 (0.2)
ALT or AST ≥3× ULN and bilirubin total ≥2× ULN	0/397	0/399	1/406 (0.2)
Potential Hy's law <sup>‡</sup>			
ALT or AST ≥3× ULN and bilirubin total ≥2× ULN and ALP <2× ULN	0/397	0/399	1/406 (0.2)

<sup>†</sup>Concurrent elevations are from the same day.

<sup>‡</sup>One participant met biochemical Hy's Law criteria due to an episode of acute cholecystitis; however, there were no confirmed Hy's Law cases.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal value.

incidence of TEAEs, which were mostly mild to moderate in severity with the majority considered unrelated to treatment by the investigator. There was no apparent relationship between TEAE incidence and the number of attacks treated per month. In addition, no hepatic or cardiovascular safety issues were noted. Additionally the rates of SAEs and discontinuations due to AEs were low, with less than 3% of participants treated with ubrogepant experiencing either. Based on these results, long-term, intermittent use of ubrogepant for the acute treatment of migraine appears to be safe and well tolerated.

Previously, the gepant class had been evaluated for their efficacy and safety in the acute treatment of migraine and showed promising efficacy, but safety concerns halted their development.<sup>24-27</sup> The results of 1 phase 2B<sup>19</sup> and 2 phase 3<sup>20,21</sup> clinical trials demonstrated that ubrogepant is well tolerated and effective for the acute treatment of migraine attacks. The most common ( $\geq 2\%$  of participants in any treatment group) TEAEs in the ACHIEVE I phase 3 trial were nausea, somnolence, and dry mouth and in the phase 3 ACHIEVE II trial were nausea and dizziness.<sup>20,21</sup> No serious AEs were reported within 48 hours postdose in either trial. No participants discontinued because of AEs and no hepatic safety signals were identified in either trial.

Overall, data from this trial further support the safety profile of ubrogepant. With regard to hepatic safety, 2% (16/805) of participants randomized to ubrogepant had increases in their ALT/AST  $\geq 3\times$  the ULN versus 1% (4/397) of participants in the usual care arm. There were no concerning hepatic safety findings and 13 of the 16 cases in the ubrogepant groups were adjudicated as *Unlikely Related* to trial treatment. Two cases were judged *Possibly Related* and 1 case was judged *Probably Related*; however, confounding factors were noted in each case (increased alcohol and acetaminophen use; dilated bile duct; and prednisone use). These findings, along with the observation that all aminotransferase elevations  $\geq 3\times$  ULN resolved in participants who continued ubrogepant dosing, indicate that there were no clinically meaningful hepatic safety signals for ubrogepant in this trial. These data also help to confirm findings from the dedicated hepatic safety trial in healthy volunteers, where ubrogepant was

found to be safe and well tolerated, with no hepatic safety signals noted following high-frequency dosing for 12 weeks.<sup>28</sup>

The efficacy of ubrogepant has been demonstrated in 2 phase 3, multicenter, randomized, double-blind, placebo-controlled single-attack trials (ACHIEVE I and II).<sup>20,21</sup> The percentage of participants reporting pain freedom 2 hours post-initial dose was significantly greater in the ubrogepant arms than the placebo arms of both trials. In addition, the proportion of participants reporting absence of the most bothersome migraine-associated symptom (photophobia, phonophobia, or nausea) at 2 hours was greater in the ubrogepant arms than the placebo arms of both trials. While the present trial was designed as a long-term safety trial, efficacy measures were collected for the ubrogepant treatment arms.<sup>29</sup> Participants reported pain freedom at 2 hours for an average of 23% of attacks treated with ubrogepant 50 mg and 25% of attacks treated with ubrogepant 100 mg. Pain relief at 2 hours was achieved for 65% of attacks treated with ubrogepant 50 mg and 68% treated with ubrogepant 100 mg. Efficacy was maintained over the 1-year trial period.

As with most trials, this trial does have some limitations that may impact the interpretation and generalizability of the data. First, exclusion of those with certain diseases, disease states, and clinically significant conditions as outlined in the methods section may limit these data from being reflective of real-world experience. However, inclusion of participants with ALT/AST elevations  $\leq 1.5\times$  the ULN and bilirubin  $< 1.5$  mg/dL increases the generalizability of the data. Second, differences in participant populations and trial designs limit the ability to compare safety profiles of different acute treatment options for migraine. In particular, headache pain of any severity was allowed to be treated in this trial, which may not be consistent with other reported trials. Third, commonly reported AEs of nausea and dizziness can be symptoms associated with a migraine attack, making it difficult to discern the causality of these AEs. Finally, the usual care arm was included to identify possible fluctuations in hepatic laboratory parameters to help contextualize the hepatic safety data. Interpretation of the AE data in the usual care arm, and comparison to the ubrogepant arms, is limited as the usual care arm consisted of

participants who had been on and had tolerated their medication; therefore, AE rates do not reflect the introduction of a new treatment. The usual care arm of the present study does, however, reflect similar AE rates observed in other long-term safety studies conducted on alternative acute treatments for migraines, in which overall AE rates ranged from 45 to 68% of patients for up to an 18-month period.<sup>30-32</sup>

## CONCLUSIONS

Long-term intermittent use of ubrogepant 50 and 100 mg given as 1 or 2 doses per attack for the acute treatment of migraine was safe and well tolerated, as indicated by a low incidence of TEAEs and low rate of SAEs and discontinuations due to AEs, in this 1-year trial.

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