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Effect of Ubrogepant vs Placebo on Pain and the Most Bothersome Associated Symptom in the Acute Treatment of Migraine
The ACHIEVE II Randomized Clinical Trial

Richard B. Lipton, MD; David W. Dodick, MD; Jessica Ailani, MD; Kaifeng Lu, PhD; Michelle Finnegan, MPH; Armin Szegedi, MD; Joel M. Trugman, MD

IMPORTANCE Ubrogepant is an oral calcitonin gene–related peptide receptor antagonist under investigation for acute treatment of migraine.

OBJECTIVE To evaluate the efficacy and tolerability of ubrogepant compared with placebo for acute treatment of a single migraine attack.

DESIGN, SETTING, AND PARTICIPANTS Phase 3, multicenter, randomized, double-blind, placebo-controlled, single-attack, clinical trial (ACHIEVE II) conducted in the United States (99 primary care and research clinics; August 26, 2016-February 26, 2018). Participants were adults with migraine with or without aura experiencing 2 to 8 migraine attacks per month.

INTERVENTIONS Ubrogepant 50 mg (n = 562), ubrogepant 25 mg (n = 561), or placebo (n = 563) for a migraine attack of moderate or severe pain intensity.

MAIN OUTCOMES AND MEASURES Co-primary efficacy outcomes were pain freedom and absence of the participant-designated most bothersome migraine-associated symptom (among photophobia, phonophobia, and nausea) at 2 hours after taking the medication.

RESULTS Among 1686 randomized participants, 1465 received study treatment (safety population; mean age, 41.5 years; 90% female); 1355 of 1465 (92.5%) were evaluable for efficacy. Pain freedom at 2 hours was reported by 101 of 464 participants (21.8%) in the ubrogepant 50-mg group, 90 of 435 (20.7%) in the ubrogepant 25-mg group, and 65 of 456 (14.3%) in the placebo group (absolute difference for 50 mg vs placebo, 7.5%; 95% CI, 2.6%-12.5%; *P* = .01; 25 mg vs placebo, 6.4%; 95% CI, 1.5%-11.5%; *P* = .03). Absence of the most bothersome associated symptom at 2 hours was reported by 180 of 463 participants (38.9%) in the ubrogepant 50-mg group, 148 of 434 (34.1%) in the ubrogepant 25-mg group, and 125 of 456 (27.4%) in the placebo group (absolute difference for 50 mg vs placebo, 11.5%; 95% CI, 5.4%-17.5%; *P* = .01; 25 mg vs placebo, 6.7%; 95% CI, 0.6%-12.7%; *P* = .07). The most common adverse events within 48 hours of any dose were nausea (50 mg, 10 of 488 [2.0%]; 25 mg, 12 of 478 [2.5%]; and placebo, 10 of 499 [2.0%]) and dizziness (50 mg, 7 of 488 [1.4%]; 25 mg, 10 of 478 [2.1%]; placebo, 8 of 499 [1.6%]).

CONCLUSIONS AND RELEVANCE Among adults with migraine, acute treatment with ubrogepant compared with placebo led to significantly greater rates of pain freedom at 2 hours with 50-mg and 25-mg doses, and absence of the most bothersome migraine-associated symptom at 2 hours only with the 50-mg dose. Further research is needed to assess the effectiveness of ubrogepant against other acute treatments for migraine and to evaluate the long-term safety of ubrogepant among unselected patient populations.

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Supplemental content

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Author Affiliations: Montefiore Headache Center, Albert Einstein College of Medicine, Bronx, New York (Lipton); Mayo Clinic, Phoenix, Arizona (Dodick); Medstar Georgetown University Hospital, Washington, DC (Ailani); Allergan plc, Madison, New Jersey (Lu, Finnegan, Szegedi, Trugman).

Corresponding Author: Richard B. Lipton, MD, Montefiore Headache Center, Albert Einstein College of Medicine, 1225 Morris Park Ave, Van Etten Bldg, Room 3c12c, Bronx, NY 10461 (richard.lipton@einstein.yu.edu).

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Migraine is a burdensome and prevalent neurological disease affecting approximately 1 billion people worldwide.[1,2] Characteristic symptoms of migraine include headache lasting 4 to 72 hours, nausea, and sensitivity to external stimuli (photophobia and phonophobia).[3] The disabling symptoms of migraine are associated with negative effects on all aspects of life, including physical and mental health, relationships, career, and financial well-being.[4-6] Several medications are available for acute treatment of migraine (eg, triptans, nonsteroidal anti-inflammatory drugs [NSAIDs], combination analgesics).[7] Many patients have contraindications to available acute treatments while others are dissatisfied because of adverse effects or suboptimal treatment effectiveness.[8,9] Inadequately treated migraine attacks may lead to medication overuse, potentially resulting in increasing attack frequency or medication overuse headache.[10,11]

Multiple lines of evidence support a role for calcitonin gene–related peptide (CGRP) in the pathogenesis of migraine.[12] Small-molecule, CGRP receptor antagonists, known as *gepants*, are under development and have shown efficacy for the acute treatment of migraine.[13,14] Ubrogepant is an oral gepant being developed for the acute treatment of migraine that was superior to placebo for achieving 2-hour pain freedom for 25-mg, 50-mg, and 100-mg doses in a phase 2b dose-ranging study.[15]

The present phase 3 ACHIEVE II trial was performed to evaluate the efficacy and tolerability of ubrogepant 25 mg and 50 mg for the acute treatment of migraine.

Key Points

Question Is ubrogepant, an oral calcitonin gene–related peptide receptor antagonist, effective in the acute treatment of migraine?

Findings In this randomized clinical trial that included 1686 participants, rates of pain freedom at 2 hours were significantly greater with ubrogepant 50 mg (21.8%) or 25 mg (20.7%) than with placebo (14.3%). Rates of freedom from the most bothersome migraine-associated symptom at 2 hours were significantly greater with the 50-mg (38.9%) dose but not the 25-mg (34.1%) dose vs placebo (27.4%).

Meaning Acute treatment of migraine with ubrogepant compared with placebo led to significantly greater rates of pain freedom at 2 hours with both the 50-mg and 25-mg doses, and freedom from the most bothersome migraine-associated symptom at 2 hours only with the 50-mg dose.

Methods

Ethical Considerations

The protocol and all amendments were approved by a central institutional review board (Advarra, previously named Schulman Associates Institutional Review Board, Inc) or by the individual research center's institutional review board. All participants provided written informed consent before initiation of study procedures and could be compensated for participation at the discretion and with the approval of their clinical sites. The trial protocol and statistical analysis plan are in Supplement 1.

Study Population

To be eligible for the trial, participants had to be 18 to 75 years of age, have a history of migraine with or without aura for at least 1 year consistent with a diagnosis according to the *International Classification of Headache Disorders Criteria, 3rd edition (beta version)* (*ICHD-3-beta*),[16] and have experienced between 2 and 8 migraine attacks with moderate to severe headache pain in each of the 3 months before screening. Participants were also required to have migraine onset before age 50 years, history of migraine typically lasting 4 to 72 hours if untreated or treated unsuccessfully, and migraine episodes separated by at least 48 hours of headache pain freedom.

Key exclusion criteria included difficulty distinguishing migraine from tension-type or other headaches; current diagnosis of chronic migraine as defined by the *ICHD-3-beta*[16] (participants with a previous diagnosis of chronic migraine who were currently having fewer than 15 headache days per month while taking concomitant preventive treatment were allowed in the study); taking medication for treatment of migraine attacks on 10 or more days per month in any of the previous 3 months; clinically significant hematologic, endocrine, cardiovascular, cerebrovascular, pulmonary, renal, hepatic, gastrointestinal, or neurologic disease; and a history of 15 or more headache days per month on average in the previous 6 months. Participants self-reported race/ethnicity based on fixed categories. Race/ethnicity data were collected to provide insight into the demographic characteristics of the trial population and for potential future subgroup analyses.

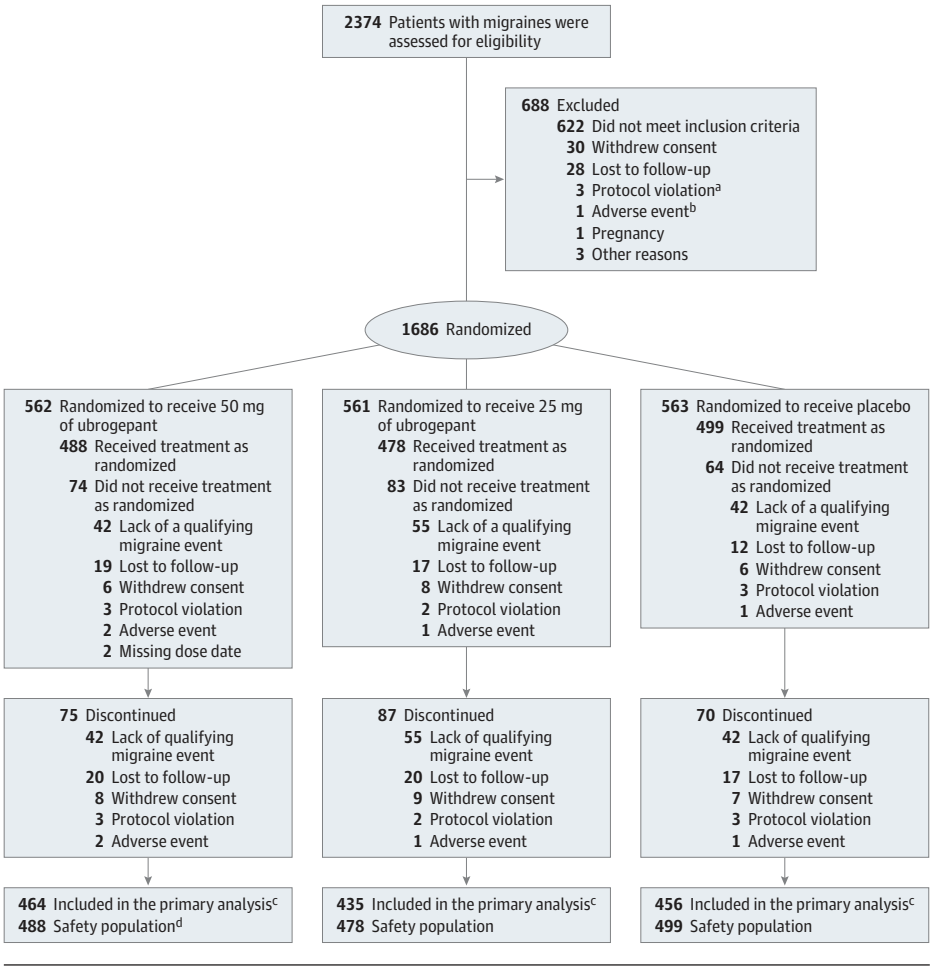
Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, single-attack, phase 3 trial, with 99 study centers (primary care and research clinics) in the United States randomizing at least 1 participant to treatment. The first participant was enrolled on August 26, 2016, and the last participant exited the trial on February 26, 2018. Participants were randomized 1:1:1 to placebo, 25 mg of ubrogepant, or 50 mg of ubrogepant (**Figure 1**). Randomization was stratified by previous response to triptans and current use of concomitant preventive medication for migraine. The randomization schedule was computer generated using a block size of 6 and managed using an automated interactive web-response system.

The trial included 4 clinic visits and 1 follow-up phone call: screening (visit 1), randomization (visit 2), return to clinic after treating qualifying migraine (visit 3), follow-up phone call 14 days after migraine treatment, and a safety follow-up (visit 4) conducted 4 weeks after visit 3.

Participants took 1 tablet of study medication (placebo, 25 mg of ubrogepant, or 50 mg of ubrogepant) as soon as possible within 4 hours of the onset of a qualifying migraine attack. Patients qualified if they met all of the following conditions: had moderate or severe migraine headache severity; had at least 1 migraine-associated symptom of photophobia, phonophobia, or nausea; had taken study medication within 4 hours of migraine headache onset; had not taken any of the prohibited medication (eg, triptan, ergot derivative, opioid, NSAID, any analgesic, antiemetic agent, or proton pump inhibitor); had

Figure 1. Flow Through the ACHIEVE II Randomized Trial of Ubrogepant vs Placebo for Treating Patients With Migraine Headaches



[a] One participant was a protocol deviation as a duplicate subject and 2 participants were protocol deviations because staff were unable to collect adequate blood work due to small veins or vein collapse.

[b] One participant discontinued before randomization due to a serious adverse event of renal vein thrombosis.

[c] The primary analysis set used for efficacy analyses included all randomized participants who received at least 1 dose of the study medication, recorded baseline migraine headache severity, and reported at least 1 postdose migraine headache severity rating or migraine-associated symptom outcome at or before 2 hours after the initial dose.

[d] Another 2 participants who took the study medication but had missing or partial data for the dosing date were excluded from the safety population.

a new migraine headache (ie, no other headache had occurred within 48 hours, and the headache was not a recurrence of a previous migraine headache); and had a migraine headache that was not already resolving.

An optional second dose or rescue medication was allowed for the treatment of moderate or severe headache starting from 2 to 48 hours after the initial dose. Redosing with study medication and use of rescue medication are considered sequentially: For those who opted to take the optional second dose, participants in the ubrogepant groups were randomized either to receive placebo or to repeat the previous dose of ubrogepant. All participants in the placebo group received placebo for the optional second dose. Participants who opted not to take the second dose could take rescue medication to treat their moderate or severe migraine headache beginning 2 hours after initial treatment. Rescue medication was defined as a treatment not provided as part of the study taken at the participant's option if study medication did not bring relief. Rescue medication options included acetaminophen, NSAIDs, opioids, antiemetics, or triptans. Once participants had taken rescue medication, they could not take an optional second dose. Rescue medication could be taken if needed 2 hours after the optional second dose of the study medication. An additional dose of ubrogepant study medication was administered at visit 3 for pharmacokinetic analysis.

Study medication was provided in identical blister cards by the trial sponsor and labeled and dispensed using the interactive web-response system.

Efficacy Assessments and Outcomes

Participants completed efficacy assessments in an electronic diary. Headache pain severity (ie, none, mild, moderate, or severe) and absence or presence of migraine-associated symptoms (ie, photophobia, phonophobia, nausea, and vomiting) were recorded before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours after the initial dose and, if the optional second dose was taken, at the time of the second dose and 2 hours after the second dose. Use of rescue medication or the optional second dose of the study medication and the incidence of headache recurrence in participants who had pain relief and pain freedom at 2 hours after the initial dose was documented.

Two co-primary efficacy outcomes were evaluated at 2 hours after the initial dose: pain freedom and absence of the most bothersome migraine-associated symptom. Pain freedom

was defined as reduction in headache severity from moderate or severe pain at baseline to no pain. Participants identified the most bothersome migraine-associated symptom (among photophobia, phonophobia, and nausea) at the time of the qualifying migraine attack. The primary efficacy outcomes were absence of what a participant had selected as the most bothersome associated symptom 2 hours after dosing. The study was to be considered a success if at least 1 ubrogepant dose was more effective than placebo for both co-primary outcomes after multiplicity adjustment.

Secondary efficacy outcomes included pain relief at 2 hours, sustained pain relief from 2 to 24 hours, sustained pain freedom from 2 to 24 hours, and absence of each migraine-associated symptom (photophobia, phonophobia, nausea) at 2 hours. Pain relief was defined as reduction of headache pain severity from moderate or severe to mild or none. Sustained pain relief (freedom) from 2 to 24 hours was defined as pain relief (freedom) without administration of a second dose of study medication or rescue medication and with no occurrence thereafter of a moderate or severe (mild, moderate, or severe) headache during 2 to 24 hours after taking the dose.

The Functional Disability Scale, a single item used to measure participants' ability to function normally,[17] was completed before dosing and at 1, 2, 4, and 8 hours after the initial dose. The response options range from 0 (no disability, able to function normally) to 3 (severely impaired, cannot do all or most things, bed rest may be necessary).

Tolerability assessments included monitoring of adverse events occurring within 48 hours after taking the initial or optional second dose and within 30 days after taking any dose of the study medication; clinical laboratory test results; vital signs, electrocardiograms, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Potential Hy's law criteria (within a 24-hour window) were defined by a postbaseline elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values 3 or more times the upper limit of normal (ULN), along with total bilirubin values 2 or more times the ULN and alkaline phosphatase values less than 2 times the ULN, all based on blood draws collected within a 24-hour period.[18,19] Potential Hy's law criteria (without a time window) were defined by a maximum postbaseline elevation of ALT or AST 3 or more times the ULN, along with a maximum postbaseline elevation of total bilirubin 2 or more times the ULN.[18,19]

Statistical Analysis

A target sample size of 550 randomized participants per treatment group was established to provide at least 85% power to detect treatment differences between each of the 2 ubrogepant doses (assuming equal effectiveness) and placebo for the co-primary outcomes. The assumed response rates were 10% for placebo and 24% for ubrogepant for pain freedom at 2 hours and 26.7% for placebo and 37.7% for ubrogepant for absence of the most bothersome associated symptom at 2 hours based on the average response rates across previous phase 2b and phase 3 studies across the gepant class[20-22] and the phase 2b study of ubrogepant.[15] The target sample size would also provide at least 60% power to detect treatment differences for secondary efficacy outcomes.

The full analysis set included all randomized participants. The primary analysis set for efficacy analyses included all randomized participants who received at least 1 dose of the study medication, recorded a baseline migraine headache severity rating, and reported at least 1 postdose migraine headache severity rating or migraine-associated symptom outcome at or before 2 hours after the initial dose. The safety population comprised all participants who received at least 1 dose of the study medication.

The co-primary efficacy variables of pain freedom and absence of the most bothersome associated symptom at 2 hours after the initial dose were analyzed using a logistic regression model with categorical terms for treatment group, historical triptan response, use of medication for migraine prevention, and baseline headache severity. The analysis of the most bothersome associated symptom at 2 hours also included a categorical term for the type of the most bothersome migraine-associated symptom identified at baseline. Treatment comparisons were based on model-derived odds ratios (ORs) and their associated 95% CIs. Two-sided *P* values are reported. Absolute differences vs placebo and associated 95% CIs were based on the Miettinen-Nurminen method. The last observation carried forward approach was the primary imputation method for missing posttreatment values. A sensitivity analysis that imputed participants with missing data at 2 hours as nonresponders—provided that the participant had at least 1 postdose value before 2 hours after the initial dose—was conducted for the primary efficacy outcomes. Post hoc analyses, including trial site as a random effect in the model, were conducted for the primary and secondary efficacy variables.

Post hoc multiple imputation analysis used a full conditional specification logistic regression model to impute missing data of the primary efficacy outcomes at 0.5, 1, 1.5, and 2 hours after the initial dose by treatment group. For pain freedom, the imputation and analysis models included baseline covariates for historical triptan response, use of medication for migraine prevention, and baseline headache severity. For absence of the most bothersome symptom, a categorical term for the type of most bothersome migraine-associated symptom identified at baseline was also included in the imputation and analysis models.

In an exploratory analysis, Kaplan-Meier plots of time to pain freedom from 2 to 48 hours after the initial dose were constructed. The first of these time-to-event analyses included data collected after taking an optional second dose of the study or rescue medication. In order to examine the efficacy of the initial dose, a second Kaplan-Meier plot was generated that excluded any data collected after the use of a second dose of the study or rescue medication.

Secondary outcome measures of pain relief and absence of photophobia, phonophobia, and nausea were analyzed using the same logistic regression model used for the primary efficacy analysis. For secondary outcomes related to migraine-associated symptoms, baseline presence or absence of the symptom was included as an additional covariate. Primary analyses of sustained efficacy outcomes were conducted on the subpopulation of participants with available data.

The overall type I error rate for multiple comparisons across the ubrogepant doses and primary and secondary efficacy

outcomes was controlled at α = .05 using a graphical approach,[23] with the co-primary efficacy outcomes serving as gatekeepers for secondary outcomes (eFigure 1 in Supplement 2). Secondary outcomes were tested in the order in which they appear in the list of secondary outcomes, except for the 2 migraine-associated symptoms of photophobia and phonophobia, which were tested at the same level to allow the recycling of weights among the 2 symptom outcomes. Recycling of weights between the 2 doses from nausea to pain freedom was also allowed.

The proportion of participants reporting "no disability, able to function normally" on the Functional Disability Scale (responder) was analyzed using the methods used for the primary efficacy analysis, with baseline functional disability score included as a covariate.

All statistical tests were 2-sided hypothesis tests performed at the 5% significance level; all CIs were 2-sided 95% CIs, unless stated otherwise.

Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc).

Results

Participant Characteristics

In total, 1686 participants were randomized: 563 to placebo, 561 to 25 mg of ubrogepant, and 562 to 50 mg of ubrogepant. Of those randomized, 1465 participants constituted the safety population, and 1355 constituted the primary analysis population (Figure 1). Eighty-six percent (1454 of 1686) of randomized participants completed the treatment period; the most common reason for discontinuation was lack of a qualifying migraine event (8%; 139 of 1686).

Participants in the safety population were a mean age of 41.5 years. Ninety percent were women; 82%, white; and 16%, black. Ninety-seven percent had taken acute treatments for migraine. In the primary analysis population, 24% of participants reported current use of a preventive migraine medication. Immediately before treating a qualifying migraine attack, 59% of participants rated their migraine headache pain as moderate and 41% rated it as severe. Ninety percent of participants reported the presence of photophobia at the time of the qualifying attack, while 81% reported phonophobia and 64% reported nausea at attack baseline. The most frequently reported most bothersome migraine-associated symptom was photophobia (57%), followed by phonophobia (26%), and nausea (17%). Treatment groups were similar with regard to demographics and baseline clinical characteristics (**Table 1**).

Efficacy Outcomes

The percentage of participants who reported pain freedom at 2 hours after taking the initial dose (co-primary outcome measure) was significantly greater in the 50-mg group (21.8% [101 of 464]; OR, 1.62 [95% CI, 1.14-2.29]; absolute difference, 7.5% [95% CI, 2.6%-12.5%]; adjusted P = .01) and in the 25-mg group (20.7% [90 of 435]; OR, 1.56 [95% CI, 1.09-2.22]; absolute difference, 6.4% [95% CI, 1.5%-11.5%]; adjusted P = .03) than in the placebo group (14.3% [65 of 456]) (**Table 2**; eFigure 2A in Supplement 2).

The percentage of participants reporting absence of the most bothersome migraine-associated symptom at 2 hours (co-primary outcome) was significantly greater in the 50-mg group (38.9% [180 of 463]; OR, 1.65 [95% CI, 1.25-2.20]; absolute difference, 11.5% [95% CI, 5.4%-17.5%]; adjusted P = .01) but not significantly greater in the 25-mg group (34.1% [148 of 434]; OR, 1.37 [95% CI, 1.02-1.83]; absolute difference, 6.7% [95% CI, 0.6%-12.7%]; adjusted P = .07) than in the placebo group (27.4% [125 of 456]) (Table 2; eFigure 2B in Supplement 2). The results of the sensitivity analysis—in which participants who were missing the 2-hour postdose headache pain severity assessment and nonheadache migraine symptom assessment were imputed as nonresponders—confirmed the robustness of the primary analysis results (Table 2). Results of an additional analysis using multiple imputation for missing data also confirmed the results of the primary analysis (eTable 1 in Supplement 2).

Time to pain freedom beyond the 2-hour time point, including data collected after use of an optional second dose of the study medication or rescue medication, is presented as a Kaplan-Meier plot in **Figure 2**A and B. Maximum efficacy and separation between the ubrogepant and placebo groups was observed from 3 to 8 hours after the initial dose, despite greater rates of rescue medication use in the placebo group. Treatment differences for pain-free rates for active drug minus placebo, including those who used an optional second dose of the study or rescue medication (Figure 2A), for the 25-mg dose were 6.4% (95% CI, 1.3%-11.6%) at 2 hours, 11.0% (95% CI, 4.9%-17.0%) at 3 hours, 15.1% (95% CI, 8.7%-21.6%) at 4 hours, 17.3% (95% CI, 10.8%-23.8%) at 6 hours, and 14.3% (95% CI, 7.9%-20.6%) at 8 hours after dosing. The pain-free rates for the 50-mg dose minus placebo were 7.1% (95% CI, 2.0%-12.2%) at 2 hours, 11.8% (95% CI, 5.9%-17.7%) at 3 hours, 15.2% (95% CI, 8.8%-21.5%) at 4 hours, 16.9% (95% CI, 10.5%-23.3%) at 6 hours, and 18.1% (95% CI, 11.9%-24.2%) at 8 hours after dosing.

In the pooled ubrogepant group, 37.6% (338 of 899) received an optional second dose of the study medication within 24 hours after the initial dose compared with 42.8% (195 of 456) in the placebo group. Rates of rescue medication use after the first dose of the study medication were 16.4% for the 50-mg group, 20.5% for the 25-mg group, and 25.7% for the placebo group. Rates of rescue medication use after an optional second dose of study medication were 9.7% for the 50-mg group, 10.1% for the 25-mg group, and 19.5% for the placebo group.

Excluding data collected after using an optional second dose or rescue medication, maximal efficacy of a single initial dose of ubrogepant was also apparent over the 3- to 8-hour time points (Figure 2C and D). Treatment differences when excluding data collected after use of an optional second dose of the study medication or rescue medication when comparing 25 mg of ubrogepant with placebo (Figure 2C) were 6.6% (95% CI, 1.4%-11.8%) at 2 hours, 12.8% (95% CI, 4.2%-21.5%) at 3 hours, 18.6% (95% CI, 8.4%-28.8%) at 4 hours, 20.6% (95% CI, 9.6%-31.6%) at 6 hours, and 13.5% (95% CI, 2.4%-24.7%) at 8 hours after dosing. When comparing 50 mg of ubrogepant with placebo, the treatment differences were 7.2% (95% CI, 2.0%-12.3%) at 2 hours, 13.8% (95% CI, 5.5%-22.0%) at

Table 1. Baseline Demographics and Clinical Characteristics

	No. (%) of Patients		
	Ubrogepant		
	50 mg (n = 488)	25 mg (n = 478)	Placebo (n = 499)
Safety Population			
Age, mean (SD) [range], y	41.2 (12.5) [18-75]	41.6 (12.4) [18-71]	41.7 (12.1) [18-73]
Age group, y			
<20	9 (1.8)	5 (1.0)	9 (1.8)
20-29	91 (18.6)	90 (18.8)	91 (18.2)
30-39	121 (24.8)	128 (26.8)	124 (24.8)
40-49	134 (27.5)	120 (25.1)	129 (25.9)
50-59	97 (19.9)	89 (18.6)	105 (21.0)
60-69	30 (6.1)	42 (8.8)	40 (8.0)
≥70	6 (1.2)	4 (0.8)	1 (0.2)
Sex			
Men	44 (9.0)	47 (9.8)	57 (11.4)
Women	444 (91.0)	431 (90.2)	442 (88.6)
Race			
White	398 (81.6)	399 (83.5)	399 (80.0)
Black	82 (16.8)	67 (14.0)	82 (16.4)
Asian	2 (0.4)	6 (1.3)	7 (1.4)
American Indian or Alaska Native	2 (0.4)	1 (0.2)	3 (0.6)
Native Hawaiian or other Pacific Islander	1 (0.2)	1 (0.2)	1 (0.2)
Multiple[a]	3 (0.6)	4 (0.8)	7 (1.4)
Hispanic or Latino ethnicity	107 (21.9)	110 (23.0)	99 (19.8)
Weight, mean (SD), kg	83.5 (21.8)	80.8 (20.8)	81.5 (22.4)
Height, mean (SD), cm	165.3 (8.4)	165.1 (8.4)	165.4 (8.5)
BMI, mean (SD)	30.5 (7.5)	29.6 (7.0)	29.8 (7.7)
Cardiovascular risk category[b]			
High risk (>20% 10-y risk)	19 (3.9)	13 (2.7)	16 (3.2)
Moderate risk (10%-20% 10-y risk)	42 (8.6)	38 (7.9)	37 (7.4)
Low risk (<10% 10-y risk)	427 (87.5)	427 (89.3)	446 (89.4)
Migraine diagnosis			
Without aura	249 (51.0)	237 (49.6)	264 (52.9)
With aura	106 (21.7)	128 (26.8)	113 (22.6)
Both	133 (27.3)	113 (23.6)	122 (24.4)
Migraine disorder duration, y			
Mean (SD)	18.1 (12.3)	18.9 (12.2)	19.2 (12.6)
Median (IQR)	16.0 (8.0-26.0)	17.0 (10.0-27.0)	17.0 (10.0-28.0)
Average frequency of moderate to severe migraines per month in last 3 mo, mean (SD) [range]	4.4 (1.8) [2-8]	4.8 (1.8) [2-8]	4.6 (1.8) [2-8]
Acute treatment of migraine[c]			
Yes	470 (96.3)	467 (97.7)	481 (96.4)
NSAID	324 (66.4)	321 (67.2)	315 (63.1)
Triptan	191 (39.1)	205 (42.9)	193 (38.7)
Antiemetic agent	21 (4.3)	34 (7.1)	31 (6.2)
Opiate or opiate combination	19 (3.9)	17 (3.6)	19 (3.8)
Barbiturates	6 (1.2)	1 (0.2)	4 (0.8)
Ergot or ergot combinations	2 (0.4)	3 (0.6)	4 (0.8)
Other	118 (24.2)	139 (29.1)	153 (30.7)
Primary Analysis Set			
Total, No.	464	435	456
Historical triptan response			
Triptan responder[d]	160 (34.5)	151 (34.7)	159 (34.9)
Triptan insufficient responder[e]	110 (23.7)	100 (23.0)	106 (23.2)
Insufficient efficacy, No./total (%)	92/110 (83.6)	87/100 (87.0)	81/106 (76.4)
Insufficient tolerability, No./total (%)	15/110 (13.6)	12/100 (12.0)	20/106 (18.9)
Contraindications, warnings, or precautions, No./total (%)	2/110 (1.8)	1/100 (1.0)	3/106 (2.8)
Triptan naïve	194 (41.8)	184 (42.3)	191 (41.9)
Concomitant preventive medication for migraine[f]	116 (25.0)	100 (23.0)	111 (24.3)

(continued)

Table 1. Baseline Demographics and Clinical Characteristics (continued)

	No. (%) of Patients		
	Ubrogepant		
	50 mg (n = 488)	25 mg (n = 478)	Placebo (n = 499)
Headache severity of treated migraine attack			
Moderate pain	289 (62.3)	257 (59.1)	258 (56.6)
Severe pain	175 (37.7)	178 (40.9)	198 (43.4)
Migraine-associated symptoms of treated attack			
Photophobia	420 (90.5)	399 (91.7)	404 (88.6)
Phonophobia	374 (80.6)	353 (81.1)	370 (81.1)
Nausea	297 (64.0)	284 (65.3)	279 (61.2)
Vomiting	21 (4.5)	19 (4.4)	22 (4.8)
Most bothersome migraine-associated symptom of treated attack[g]			
Photophobia	265 (57.1)	257 (59.1)	245 (53.7)
Phonophobia	115 (24.8)	102 (23.4)	136 (29.8)
Nausea	83 (17.9)	75 (17.2)	75 (16.4)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

[a] Participants who report 2 or more races, including participants who report white and more than 1 other race.

[b] Assessed using an algorithm based on National Cholesterol Education Program, Framingham risk factors, presence of heart disease, and other forms of vascular disease, and diabetes.[7]

[c] Reflects use as recorded at screening.

[d] Defined as (1) currently using a triptan or had used in the past 6 months, and on the occasions that a triptan dose was taken, achieved pain freedom (no headache pain) at 2 hours after dosing on more than half of those occasions or as (2) had a response to a triptan as described above but no longer used a triptan for other reasons.

[e] Defined as (1) currently using a triptan or had used a triptan in the past 6 months, and on the occasions that a triptan dose was taken, had not achieved pain freedom at 2 hours after dosing on more than half of those occasions; (2) no longer used a triptan due to lack of efficacy; (3) no longer used a triptan due to adverse effects; or (4) never used a triptan due to warnings, precautions, or contraindications.

[f] Recorded at time of randomization.

[g] Includes 2 participants (0.1%) with missing data.

3 hours, 18.0% (95% CI, 8.3%-27.7%) at 4 hours, 15.8% (95% CI, 5.2%-26.4%) at 6 hours, and 17.9% (95% CI, 7.3%-28.4%) at 8 hours after dosing.

Rates of pain freedom 2 hours after the optional second dose were greater among participants who took an initial 50-mg dose of ubrogepant followed by a second 50-mg dose of ubrogepant (36.1% [26 of 72]) than among those who took an initial 50-mg dose of ubrogepant followed by placebo (19.0% [15 of 79]; OR, 2.18 [95% CI, 1.02 to 4.69]; absolute difference, 17.1% [95% CI, 2.9% to 31.1%]). The response rates for participants who took an initial 25-mg dose of ubrogepant followed by a second 25-mg dose of ubrogepant (30.1% [25 of 83]) were not significantly different from those for participants who took an initial 25-mg dose of ubrogepant followed by placebo (22.7% [15 of 66]; OR, 1.56 [95% CI, 0.72 to 3.36]; absolute difference, 7.4% [95% CI, -7.2% to 21.1%]).

For the secondary outcomes of pain relief from 2 to 24 hours, the responder rates in the 50-mg group were significantly greater than in the placebo group (OR, 1.77 [95% CI, 1.35-2.32]; adjusted P = .01) as they were for sustained pain relief from 2 to 24 hours (OR, 2.16 [95% CI, 1.59-2.92]; adjusted P = .01) and for sustained pain freedom from 2 to 24 hours (OR, 1.85 [95% CI, 1.20-2.83]; adjusted P = .01). Although the trend held at the 2-hour mark for the absence of photophobia (OR, 1.52 [95% CI, 1.14-2.02]; adjusted P = .02) and the absence of phonophobia (OR, 1.39 [95% CI, 1.05-1.84]; adjusted P = .04), responder rates were not significantly greater for the secondary outcome of absence of nausea (OR, 1.12 [95% CI, 0.83-1.51]; Table 2).

More participants in the 50-mg group than in the placebo group reported the ability to function normally on the Functional Disability Scale (additional efficacy variable) at 2 hours (OR, 1.47 [95% CI, 1.09-1.99]), 4 hours (OR, 1.94 [95% CI, 1.46-2.58]), and 8 hours (OR, 2.02 [95% CI, 1.49-2.73]) after the initial dose (**Table 3**). Post hoc analyses of the primary and secondary outcomes that included trial site as a random effect in the model yielded almost identical results as the primary analyses (eTable 2 in Supplement 2).

Adverse Events and Tolerability

The safety population (n = 1465) included 488 participants who took at least 1 dose of 50 mg of ubrogepant; 478 who took at least 1 dose of 25 mg of ubrogepant; and 499 who took at least 1 dose of placebo. An optional blinded second dose was taken by 384 participants in the ubrogepant groups (99 received 25 mg, 89 received 50 mg, and 196 received placebo) and by 224 participants in the placebo group (all received placebo for the second dose). In addition, 464 participants in the 50-mg group and 453 in the 25-mg group took the additional pharmacokinetic dose at visit 3.

Treatment-emergent adverse events were reported within 48 hours of taking the initial or optional second dose by 12.9% (63 of 488) of participants in the 50-mg group, 9.2% (44 of 478) in the 25-mg group, and 10.2% (51 of 499) in the placebo group. Within 30 days after any dose, treatment-emergent adverse events were reported by 27.3% (133 of 488) of participants in the 50-mg group, 22.0% (105 of 478) in the 25-mg group, and 22.4% (112 of 499) in the placebo group (**Table 4**). The incidence of treatment-emergent adverse events was similar between the ubrogepant groups and the placebo group. Nausea was the most commonly reported event within the first 48 hours (2% [32 of 1465]) and within 30 days (2% [36 of 1465]).

Table 2. Co-Primary and Secondary Efficacy Outcomes (Primary Analysis Set)

	No./Total (%)			50 mg of Ubrogepant vs Placebo			25 mg of Ubrogepant vs Placebo		
	Ubrogepant								
	50 mg (n = 464)	25 mg (n = 435)	Placebo (n = 456)	OR (95% CI)	Absolute Difference (95% CI), %[a]	Adjusted *P* Value	OR (95% CI)	Absolute Difference (95% CI), %[a]	Adjusted *P* Value
Co-primary Efficacy Outcomes 2 h After Initial Dose									
Pain Freedom[b]									
Analyses									
Primary[c,d]	101/464 (21.8)	90/435 (20.7)	65/456 (14.3)	1.62 (1.14 to 2.29)	7.5 (2.6 to 12.5)	.01	1.56 (1.09 to 2.22)	6.4 (1.5 to 11.5)	.03
Sensitivity[d,e]	97/464 (20.9)	85/435 (19.5)	59/456 (12.9)	1.72 (1.21 to 2.46)	8.0 (3.1 to 12.8)		1.62 (1.13 to 2.34)	6.6 (1.8 to 11.5)	
Absence of most bothersome migraine-associated symptom									
Analyses									
Primary[c,f]	180/463 (38.9)	148/434 (34.1)	125/456 (27.4)	1.65 (1.25 to 2.20)	11.5 (5.4 to 17.5)	.01	1.37 (1.02 to 1.83)	6.7 (0.6 to 12.7)	.07
Sensitivity[e,f]	172/463 (37.1)	143/434 (32.9)	115/456 (25.2)	1.72 (1.29 to 2.29)	11.9 (6.0 to 17.8)		1.45 (1.08 to 1.95)	7.7 (1.8 to 13.7)	
Secondary Efficacy Outcomes									
Pain relief achieved									
2 h[c,d,g]	291/464 (62.7)	263/435 (60.5)	220/456 (48.2)	1.77 (1.35 to 2.32)	14.5 (8.1 to 20.8)	.01	1.65 (1.25 to 2.17)	12.2 (5.7 to 18.6)	
2-24 h[d,h,i]	165/449 (36.7)	138/424 (32.5)	93/443 (21.0)	2.16 (1.59 to 2.92)	15.8 (9.9 to 21.6)	.01	1.82 (1.33 to 2.48)	11.6 (5.7 to 17.4)	
Sustained pain freedom, 2-24 h[d,j,k]	66/457 (14.4)	55/432 (12.7)	37/451 (8.2)	1.85 (1.20 to 2.83)	6.2 (2.1 to 10.4)	.01	1.62 (1.04 to 2.53)	4.5 (0.5 to 8.7)	
Absence of symptoms at 2 h[l,m]									
Photophobia	203/464 (43.8)	171/435 (39.3)	162/456 (35.5)	1.52 (1.14 to 2.02)	8.2 (1.9 to 14.5)	.02	1.28 (0.96 to 1.72)	3.8 (−2.6 to 10.1)	
Phonophobia	251/464 (54.1)	233/435 (53.6)	211/456 (46.3)	1.39 (1.05 to 1.84)	7.8 (1.4 to 14.2)	.04	1.38 (1.04 to 1.83)	7.3 (0.7 to 13.8)	
Nausea	331/464 (71.3)	307/435 (70.6)	319/456 (70.0)	1.12 (0.83 to 1.51)	1.4 (−4.5 to 7.3)	.95	1.10 (0.81 to 1.49)	0.6 (−5.4 to 6.6)	

[a] Absolute risk difference vs placebo is based on the Miettinen-Nurminen method.

[b] Reduction in headache pain severity from moderate or severe at baseline to no pain.

[c] Missing data considered using last observation carried forward approach.

[d] Odds ratio (OR), 95% CI, and *P* value are based on logistic regression, with treatment group, historical triptan response, use of medication for migraine prevention, and baseline headache severity as explanatory variables.

[e] The sensitivity analysis for the primary efficacy outcomes imputed participants with missing data at 2 hours as nonresponders, provided that the participant had at least 1 postdose value before 2 hours after the initial dose.

[f] Odds ratio (95% CI) and *P* value are based on logistic regression, with treatment group, historical triptan response, use of medication for migraine prevention, baseline headache severity, and the underlying symptom as explanatory variables.

[g] Reduction of a moderate or severe migraine headache to a mild headache or to no headache.

[h] Relief at 2 hours with no administration of either rescue medication or the second dose of study medication, and with no occurrence thereafter of a moderate or severe headache during the relevant number of hours after dosing with study medication.

[i] Denominator for responder calculation is the number of participants with determinable sustained pain relief from 2 to 24 hours after initial dose based on the observed headache severity at scheduled time points, use of rescue medication or optional second dose between 2 and 24 hours, and the answer to the headache recurrence question at 24 or 48 hours.

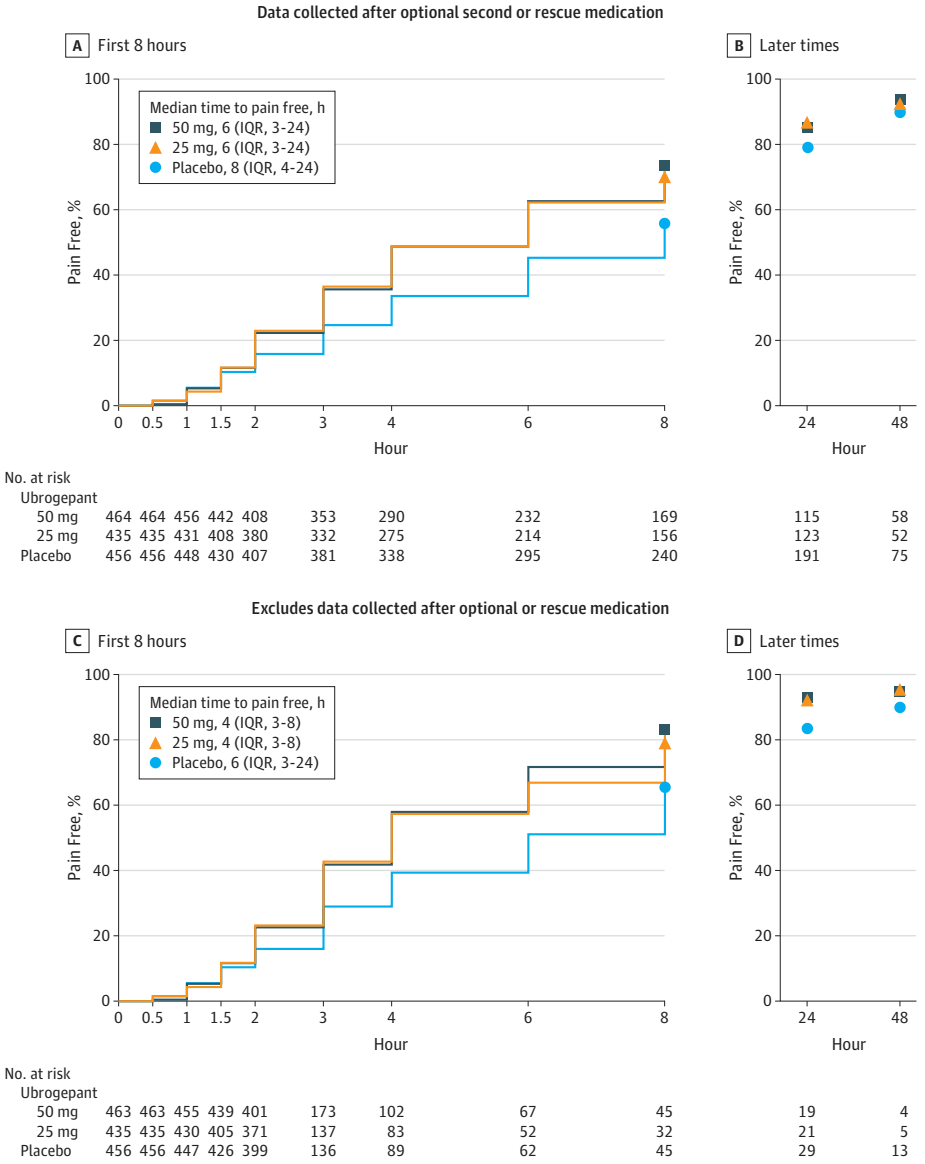
[j] Pain freedom at 2 hours with no administration of either rescue medication or the second dose of study medication, and with no occurrence thereafter of a mild, moderate, or severe headache during the relevant number of hours after dosing with study medication.

[k] Denominator for responder calculation is the number of participants with determinable sustained pain freedom from 2 to 24 hours after initial dose based on the observed headache severity at scheduled time points, use of rescue medication or optional second dose between 2 and 24 hours, and the answer to the headache recurrence question at 24 or 48 hours.

[l] Denominator is the number of participants with non-missing postdose photophobia, phonophobia, or nausea assessment at or before 2 hours after (respectively for each measure listed).

[m] Odds ratio, 95% CI, and *P* value are based on logistic regression with treatment group, historical triptan response, use of medication for migraine prevention, baseline headache severity, and baseline presence or absence of the migraine-associated symptom at interest (photophobia, phonophobia, or nausea) as explanatory variables.

Figure 2. Kaplan-Meier Plots of Time to Headache Pain Freedom After Initial Dose



A, The percentage of participants who were censored between 0 and 8 hours was 32% for the 25-mg dose, 28% for the 50-mg dose, and 45% for placebo. C, The percentage of participants who were censored between 0 and 8 hours was 59% for the 25-mg dose, 54% for the 50-mg dose, and 71% for placebo. B and D, Plots including and excluding data collected 24 and 48 hours after use of an optional second dose of the study medication.

No serious adverse events occurred within 48 hours after the initial or optional second dose. Within 30 days of any dose, 1 participant in the 25-mg group reported 7 serious adverse events related to a bicycle accident; none were considered treatment related. No deaths or discontinuations due to an adverse event were reported.

After the baseline measure, 4 participants had ALT or AST values that were 3 or more times the ULN (eTable 3 in Supplement 2). These cases were adjudicated by an independent review committee that was blinded to treatment (eTable 4 in Supplement 2). Three of the 4 cases (all in the 50-mg group) were deemed unlikely to be related to ubrogepant based on plausible alternative etiologies or confounding factors (eg, intense exercise leading to muscle injury, underlying fatty liver, and concomitant use of diclofenac and trimethoprim and sulfamethoxazole). One case was judged to be possibly related to treatment. That participant was initially randomized to the placebo group. No one in the 25-mg group had ALT or AST values after the baseline measure that were 3 or more times the ULN. There were no cases of concurrent elevations of ALT or AST that were 3 or more times the ULN and total bilirubin 1.5 or more times the ULN. No cases met potential Hy's law criteria.[18,19]

Discussion

In this phase 3 trial involving adults with migraine, the coprimary outcomes of pain freedom and absence of the most bothersome migraine-associated symptom at 2 hours after oral dosing were met for the 50-mg dose but not for the 25-mg dose of ubrogepant. Both doses of ubrogepant were significantly more effective than placebo for achieving pain freedom at 2

Table 3. Exploratory Efficacy Outcome of Normal Function

	No./Total (%)			50 mg of Ubrogepant vs Placebo		25 mg of Ubrogepant vs Placebo	
	Ubrogepant						
	50 mg (n = 464)	25 mg (n = 435)	Placebo (n = 456)	OR (95% CI)	Absolute Difference (95% CI), %[c]	OR (95% CI)	Absolute Difference (95% CI), %[a]
Ability to function normally[a,b]							
Baseline	135/464 (29.1)	134/435 (30.9)	146/456 (32.0)				
1 h	142/464 (30.6)	139/435 (32.0)	146/456 (32.0)	1.00 (0.71 to 1.41)	−1.4 (−7.4 to 4.6)	1.07 (0.75 to 1.51)	0.0 (−6.1 to 6.1)
2 h	188/464 (40.5)	185/435 (42.6)	156/456 (34.2)	1.47 (1.09 to 1.99)	6.3 (0.1 to 12.5)	1.65 (1.21 to 2.24)	8.4 (2.0 to 14.8)
4 h	282/464 (60.8)	261/435 (60.1)	217/456 (47.6)	1.94 (1.46 to 2.58)	13.2 (6.8 to 19.5)	1.93 (1.44 to 2.58)	12.6 (6.0 to 19.0)
8 h	347/464 (74.8)	319/435 (73.5)	283/456 (62.1)	2.02 (1.49 to 2.73)	12.7 (6.7 to 18.6)	1.93 (1.42 to 2.61)	11.4 (5.3 to 17.5)

[a] Normal function defined as participant response to the Functional Disability Scale of "no disability, able to function normally."

[b] Odds ratio (OR), 95% CI, and *P* value are based on logistic regression with treatment group, baseline severity, historical triptan response, and use of medication for migraine prevention as factors and baseline value as a covariate. Last observation carried forward approach was applied to impute missing values after baseline.

[c] Absolute risk difference vs placebo is based on the Miettinen-Nurminen method.

hours after taking a dose. Only the 50-mg dose was significantly more effective than placebo for achieving the absence of the most bothersome migraine–associated symptom at 2 hours after taking the dose. These results suggest that the 50-mg dose was more effective than the 25-mg dose in the present study. Additionally, the fact that 50 mg of ubrogepant was significantly more effective than placebo for achieving absence of the most bothersome migraine-associated symptom while 25 mg of ubrogepant was not significantly more effective suggests a dose response effect between the 25-mg and 50-mg doses for freedom from the most bothersome associated symptom.

Results of several randomized placebo-controlled trials support the conclusion that gepants are effective in the acute treatment of migraine.[13,14,21,22,24] Two recent trials of rimegepant generated results consistent with those observed in this trial.[21,22] However, these recent trials differ in timing of evaluated outcome measures, inclusion of a second dose of the study medication, and allowable rescue medications. Therefore, comparisons of findings should be avoided or made with an understanding of the design differences.

The current results indicate that 50 mg of ubrogepant has the potential to address key treatment goals in the acute treatment of migraine. Widely used acute prescription treatment options for migraine include triptans, NSAIDs, and opioids.[25] Triptans and ergotamine derivatives have a number of cardiovascular contraindications or precautions.[7] NSAIDs may cause serious gastrointestinal and cardiovascular effects.[7] It has been estimated that 18.6% of women and 19.1% of men aged 22 years or older with episodic migraine have at least 3 cardiovascular disease disease risk factors that could contraindicate the use of triptans.[26] These results were obtained in a population sample older than the US population and may therefore be overestimates. Ubrogepant's mechanism of action may make it an option for people who do not respond to currently available medications. However, people with cardiovascular and gastrointestinal contraindications to triptans or NSAIDs were not included in this study, so future studies involving these populations are needed.

Kaplan-Meier plots summarizing the benefit of ubrogepant relative to placebo and after the 2-hour time point selected for the primary study outcomes based on the exploratory analyses require further evaluation in future studies. Kaplan-Meier plots summarizing treatment effects from 3 to 8 hours confirm the benefits of ubrogepant relative to placebo.

The changes in neural function initiated by CGRP receptor antagonism in the setting of a migraine attack remain to be determined. According to the results of this study, the full benefits of ubrogepant are not captured by the rates of pain freedom at the 2-hour time point, and similar effects have been reported for other acute treatments of migraine. Other measures of efficacy outcome measures, such as the rates of pain relief (63%) and normal function (41%) at 2 hours, and the rate of rescue medication use (26%), should be considered when assessing the clinical benefit of 50 mg of ubrogepant.

Limitations

This study has several limitations. First, participants treated their migraine when headache pain was moderate or severe. This trial design is recommended for regulatory approval, but is at odds

Table 4. Overall Summary of Adverse Events by Treatment Group

	No. (%) of Patients[a]		
	Ubrogepant		
	50 mg (n = 488)	25 mg (n = 478)	Placebo (n = 499)
Occurring Within 48 Hours After Initial or Optional Second Dose			
Treatment-emergent adverse events[b]	63 (12.9)	44 (9.2)	51 (10.2)
≥2% of participants in any group			
Nausea	10 (2.0)	12 (2.5)	10 (2.0)
Dizziness	7 (1.4)	10 (2.1)	8 (1.6)
Treatment-related[b]	42 (8.6)	30 (6.3)	30 (6.0)
≥1% of participants in any group			
Nausea	9 (1.8)	9 (1.9)	9 (1.8)
Dizziness	7 (1.4)	8 (1.7)	6 (1.2)
Serious adverse event[c]	0	0	0
Death[c]	0	0	0
Adverse event leading to discontinuation[d]	0	0	0
Occurring Within 30 Days After Any Dose			
Treatment-emergent adverse events[b]	133 (27.3)	105 (22.0)	112 (22.4)
≥2% of participants in any group			
Upper respiratory tract infection	13 (2.7)	6 (1.3)	9 (1.8)
Nausea	12 (2.5)	14 (2.9)	10 (2.0)
Nasopharyngitis	11 (2.3)	5 (1.0)	1 (0.2)
Dizziness	10 (2.0)	11 (2.3)	9 (1.8)
Treatment-related[b]	54 (11.1)	34 (7.1)	39 (7.8)
Serious adverse event[c]	0	1 (0.2)[e]	0
Death[c]	0	0	0
Adverse event leading to discontinuation[d]	0	0	0

[a] Participants are counted only once within each category.

[b] Events that began or worsened on or after the treatment start date and within 30 days of the treatment end date for participants without the safety follow-up visit. For participants with the safety follow-up visit, events that occurred at or before the safety follow-up visit are considered.

[c] Events that occurred on or after the treatment start date and within 30 days of the treatment end date for participants without the safety follow-up visit. For participants with the safety follow-up visit, events that occurred at or before the safety follow-up visit are considered.

[d] Discontinuation events that occurred between the treatment start date and the safety follow-up visit or within 30 days after the treatment end date for participants without the safety follow-up visit.

[e] One participant in the 25-mg group reported 7 serious adverse events (ligament sprain, loss of consciousness, renal hematoma, road traffic accident, splenic rupture, syncope, and traumatic renal injury) related to a bicycling accident; none was judged as related to study treatment.

with the American Headache Society's guideline recommendationto treat at the first sign of headache, usually before moderateor severe pain is reached.[7] The current results may, therefore, not reflect treatment outcomes for individuals who are treated while headache pain intensity is mild. Second, adverse event and tolerability data from this trial are based on outcomes after a single migraine attack and do not reflect tolerability after repeated use. Tolerability data from a long-term extension trial will be reported separately. Third, the consistency with which ubrogepant relieves recurrent attacks of migraine, an important treatment consideration for patients, cannot be determined in a single-attack trial.

Conclusions

Among adults with migraine, acute treatment with ubrogepant compared with placebo led to significantly greater rates of pain freedom at 2 hours with the 50-mg and 25-mg doses, and absence of the most bothersome migraine-associated symptom at 2 hours only with the 50-mg dose. Further research is needed to assess the effectiveness of ubrogepant against other acute treatments for migraine and to evaluate the long-term safety of ubrogepant among unselected patient populations.

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Concept and design: Lipton, Lu, Finnegan, Szegedi, Trugman.
Acquisition, analysis, or interpretation of data: Lipton, Dodick, Ailani, Lu, Finnegan, Szegedi, Trugman.
Drafting of the manuscript: Lipton, Ailani, Szegedi, Trugman.
Critical revision of the manuscript for important intellectual content: Lipton, Dodick, Ailani, Lu, Finnegan, Szegedi, Trugman.
Statistical analysis: Lu.
Administrative, technical, or material support: Finnegan, Trugman.
Supervision: Ailani, Szegedi, Trugman.

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without fee for Aural Analytics, Healint, Second Opinion/Mobile Health, and Epien; sits on the board of directors for Epien, Matterhorn/Ontologics, and King-Devick Technologies; has a patent (17189376.1-1466) for a botulinum toxin dosage regimen for chronic migraine prophylaxis, for which he receives no fee; receives research support from the American Migraine Foundation, Henry Jackson Foundation, Department of Defense, and Sperling Foundation; receives professional society fees or reimbursement for travel from the American Academy of Neurology, American Brain Foundation, American Headache Society, American Migraine Foundation, International Headache Society, and Canadian Headache Society; and has a use agreement through employer, Myndshft, Neuroassessment Systems. Dr Ailani reports that she serves as a consultant for, speaks on behalf of, or both for Allergan, Amgen, Alder, Avanir, Biohaven, Electrocore, Eli Lilly, Promius, Impel, Satsuma, Aptus, Miller Medical Communications, and Alpha sites and has served on clinical trials for Allergan, the American Migraine Foundation, and Theranica; and is an editor for *Current Pain and Headache Reports*. Drs Lu, Finnegan, Szegedi, and Trugman are full-time employees and stockholders of Allergan plc.

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