ORIGINAL ARTICLE

Ubrogepant for the Treatment of Migraine

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ABSTRACT

BACKGROUND

Ubrogepant is an oral, small-molecule calcitonin gene–related peptide receptor antagonist for acute migraine treatment.

METHODS

We conducted a randomized trial to evaluate the efficacy, safety, and side-effect profile of ubrogepant. We assigned adults with migraine, with or without aura, in a 1:1:1 ratio to receive an initial dose of placebo, ubrogepant at a dose of 50 mg, or ubrogepant at a dose of 100 mg for treatment of a single migraine attack, with the option to take a second dose. The coprimary efficacy end points were freedom from pain at 2 hours after the initial dose and absence of the most bothersome migraine-associated symptom at 2 hours. Secondary end points included pain relief (at 2 hours), sustained pain relief (from 2 to 24 hours), sustained freedom from pain (from 2 to 24 hours), and absence of symptoms associated with migraine (photophobia, phonophobia, and nausea) at 2 hours.

RESULTS

A total of 1672 participants were enrolled; 559 were assigned to receive placebo, 556 to receive 50 mg of ubrogepant, and 557 to receive 100 mg of ubrogepant. The percentage of participants who had freedom from pain at 2 hours was 11.8% in the placebo group, 19.2% in the 50-mg ubrogepant group ($P=0.002$, adjusted for multiplicity, for the comparison with placebo), and 21.2% in the 100-mg ubrogepant group ($P<0.001$). The percentage of participants who had freedom from the most bothersome symptom at 2 hours was 27.8% in the placebo group, 38.6% in the 50-mg ubrogepant group ($P=0.002$), and 37.7% in the 100-mg ubrogepant group ($P=0.002$). Adverse events within 48 hours after the initial or optional second dose were reported in 12.8% of participants in the placebo group, in 9.4% in the 50-mg ubrogepant group, and in 16.3% in the 100-mg ubrogepant group. The most common adverse events were nausea, somnolence, and dry mouth (reported in 0.4 to 4.1%); these events were more frequent in the 100-mg ubrogepant group (reported in 2.1 to 4.1%). Serious adverse events reported within 30 days in the ubrogepant groups included appendicitis, spontaneous abortion, pericardial effusion, and seizure; none of the events occurred within 48 hours after the dose.

CONCLUSIONS

A higher percentage of participants who received ubrogepant than of those who received placebo had freedom from pain and absence of the most bothersome symptom at 2 hours after the dose. The most commonly reported adverse events were nausea, somnolence, and dry mouth. Further trials are needed to determine the durability and safety of ubrogepant for acute migraine treatment and to compare it with other drugs for migraine. (Funded by Allergan; ClinicalTrials.gov number, NCT02828020.)

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Migraine is a chronic disease characterized by episodic attacks of headache, sensitivity to light and sound, and nausea. The major classes of medications for acute migraine treatment are analgesics, including nonsteroidal antiinflammatory drugs, ergots, and triptans.[1-3] Triptans have been the most effective treatment.[4]

Calcitonin gene–related peptide (CGRP) is a neurotransmitter expressed in peripheral sensory trigeminal neurons that innervate the pain-sensitive dura and meningeal blood vessels. The transmitter is released during a migraine attack and facilitates pain transmission in the trigeminovascular system.[5] The efficacy of small-molecule CGRP receptor antagonists (gepants) for acute migraine treatment has been shown.[6-10] Ubrogepant is an oral gepant for acute migraine treatment.[11] We conducted a trial to compare a 50-mg dose and a 100-mg dose of ubrogepant with placebo for acute migraine treatment.

Methods

Trial Design and Oversight

This randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 89 centers in the United States from July 22, 2016, to December 14, 2017. Participants were randomly assigned in a 1:1:1 ratio, with the use of an automated Web-response system, to receive placebo, ubrogepant at a dose of 50 mg, or ubrogepant at a dose of 100 mg. Randomization was stratified according to the participant's previous response to triptans (history of a response, history of an insufficient response, or no history of receiving triptans) and use of preventive medication for migraine (yes or no). If participants did not take a dose of ubrogepant or placebo to treat a qualifying migraine attack (i.e., a migraine headache with moderate or severe pain) within 60 days after randomization, they were withdrawn from the trial.

There were four clinic visits. Screening was performed at visit 1, and participants underwent randomization at visit 2. Visit 3 occurred 2 to 7 days after participants had taken an initial dose to treat a qualifying migraine. Follow-up telephone calls occurred 14 days after the initial dose. Visit 4 was the safety follow-up visit, which occurred 4 weeks after the initial dose.

The protocol, with the statistical analysis plan, is available with the full text of this article at NEJM.org. The trial was approved by a local or central institutional review board at each participating institution. All participants provided written informed consent before enrollment in the trial. All the authors vouch for the accuracy and completeness of the data and analyses, the fidelity of the trial to the protocol, and the completeness of reporting of adverse events. Confidentiality agreements were in place between the sponsor (Allergan) and the authors. The sponsor developed the trial protocol in collaboration with external consultants, provided the trial drug and placebo, and gathered and analyzed the data. The manuscript was prepared by the sponsor, with contributions from all authors and with assistance from a professional medical writer employed by the sponsor.

Trial Participants

Participants were eligible if they were 18 to 75 years of age, had at least a 1-year history of migraine, with or without aura, that met the criteria specified in the *International Classification of Headache Disorders, 3rd edition* (*beta version*),[12] and had had migraine onset before the age of 50 years. Participants were required to have a history of migraines that lasted between 4 and 72 hours (if untreated or if treated unsuccessfully) and a history of migraine attacks that were separated by at least 48 hours of freedom from headache pain. In addition, participants had to have a history of two to eight migraines per month with moderate-to-severe headache pain in each of the 3 months before screening. All participants were required to be able to read, understand, and complete the trial questionnaires and to understand how to use the electronic diary.

Participants were excluded if they were pregnant, had a history of 15 or more headache days per month (on average) during the 6 months before screening, had a current diagnosis of chronic migraine, or if the investigator had difficulty distinguishing the participant's migraine from tension-type headaches or other headaches. However, if the opinion of the local investigator was that participants with chronic migraine had fewer than 15 headache days per month because of concomitant preventive treatment, the participants were eligible for the trial. Trial participants

who had taken an acute migraine treatment on 10 or more days in any of the 3 months before screening or who had participated in a trial with an injectable monoclonal antibody against CGRP or the CGRP receptor were excluded. Participants with moderate-to-severe cardiovascular risk factors, as defined by the National Cholesterol Education Program guidelines, were eligible.[13,14] However, participants with clinically significant cardiovascular or cerebrovascular disease were excluded. Participants were also excluded if they had levels of alanine aminotransferase or aspartate aminotransferase that were more than 1.5 times the upper limit of the normal range, a total bilirubin level of more than 1.5 mg per deciliter (26 μmol per liter), or a serum albumin level of less than 2.8 g per deciliter at screening.

TRIAL PROCEDURES

The trial tablets were identical in appearance and were provided to participants in identical blister cards to maintain masking of trial-group assignments. The participants, site personnel, and trial-sponsor personnel were unaware of the group assignments.

Participants were provided with two tablets to be taken at the time of a qualifying migraine attack (i.e., an attack of moderate or severe pain intensity). The placebo group received two tablets of placebo, the 50-mg ubrogepant group received one 50-mg tablet of ubrogepant and one tablet of placebo, and the 100-mg ubrogepant group received two 50-mg tablets of ubrogepant. In the case of persistent or recurring moderate or severe headache, participants were allowed to take an optional second dose or their own rescue medication 2 to 48 hours after the initial dose. For the optional second dose, the placebo group received two tablets of placebo. Participants in the ubrogepant groups underwent rerandomization for the optional second dose; those who had been assigned to the 50-mg ubrogepant group for the initial dose received either two tablets of placebo or one 50-mg tablet of ubrogepant and one tablet of placebo, and those who had been assigned to the 100-mg ubrogepant group for the initial dose received either two tablets of placebo or two 50-mg tablets of ubrogepant. All participants remained unaware of the content of the optional second dose. Participants who took the optional second dose were not allowed to take rescue medication until at least 2 hours after they had taken the second dose. Participants who took rescue medication rather than the optional second dose were not allowed to subsequently take the second dose. At visit 3, participants received an additional dose for pharmacokinetic analysis that consisted of the same tablets that the participant received for the initial dose.

Efficacy was assessed on the basis of data recorded by the participants in an electronic diary. Participants rated headache severity as no pain, mild pain, moderate pain, or severe pain. Participants also recorded whether nonheadache symptoms associated with migraine (photophobia, phonophobia, nausea, and vomiting) were present or absent at various time points: before the initial dose; at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 hours after the initial dose; at the time of the second dose; and 2 hours after the second dose.

EFFICACY END POINTS

The coprimary efficacy end points were freedom from pain at 2 hours after the initial dose of ubrogepant or placebo and absence of the most bothersome symptom associated with migraine at 2 hours. Freedom from pain was defined as a change in the severity of headache pain from moderate or severe pain before the initial dose was taken to the presence of no pain at 2 hours after the dose. The most bothersome migraine-associated symptom (photophobia, phonophobia, or nausea) was selected by the participant immediately before taking the initial dose for a qualifying migraine attack; participants then recorded the presence or absence of that symptom at 2 hours after the dose.

Secondary efficacy end points were pain relief (defined as a change in the severity of headache pain from moderate or severe pain to mild pain or no pain) at 2 hours after the initial dose, sustained pain relief (defined as pain relief during the period from 2 to 24 hours after the initial dose without the use of the optional second dose or rescue medication), sustained freedom from pain (defined as freedom from pain during the period from 2 to 24 hours after the initial dose without the use of the optional second dose or rescue medication), and absence of photophobia, absence of phonophobia, and absence of nausea, all at 2 hours after the initial dose (Table S1 in the

Supplementary Appendix, available at NEJM.org). An exploratory analysis of efficacy over 48 hours was also conducted. Participants were asked to rate their ability to perform normal activities (a prespecified, exploratory efficacy end point) with the use of a single-question Functional Disability Scale before the initial dose and at 1, 2, 4, and 8 hours after the dose. Overall satisfaction with migraine treatment, also a prespecified, exploratory efficacy end point, was evaluated with the use of a 7-point rating scale (with higher values indicating greater satisfaction) at 2 hours and 24 hours after the initial dose.

SAFETY

Data on adverse events were collected and evaluated by the investigators, who were unaware of the trial-group assignments, 48 hours after the initial dose, 48 hours after the optional second dose, and within 30 days after the last dose. In addition, results of clinical laboratory testing, results of the Columbia Suicide Severity Rating Scale questionnaire (which evaluates suicidal ideation and suicidal behavior), vital signs, and electrocardiograms were assessed. Abnormal hepatic laboratory values were included as a prespecified adverse event of special interest. All cases of alanine aminotransferase or aspartate aminotransferase levels that were 3 or more times the upper limit of the normal range were adjudicated by an independent panel of liver experts who were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

We calculated that 550 participants per group would provide the trial with at least 85% power to detect differences in the coprimary end points between each of the two doses of ubrogepant and placebo. Efficacy analyses were conducted in the modified intention-to-treat population, which included all participants who underwent randomization, took an initial dose of ubrogepant or placebo, recorded a baseline rating for the severity of the migraine headache, and recorded at least one rating for the severity of the migraine headache after the initial dose or recorded the presence or absence of at least one migraine-associated symptom at or before the 2-hour time point after the initial dose. Safety analyses were performed in all participants who underwent randomization and who took a dose of ubrogepant or placebo.

The primary efficacy variables were evaluated with the use of a logistic-regression model that included the categorical terms of trial group, history of response to triptan, use of medication for migraine prevention, and the predose headache severity of the qualifying migraine. An additional categorical term for the underlying symptom that was identified as the most bothersome was used for the analysis of the most bothersome nonheadache migraine-associated symptom. Appropriate pairwise comparisons within the logistic-regression model were used to compare each ubrogepant dose with placebo. Treatment comparisons were based on the model-derived odds ratios and their associated 95% confidence intervals; two-sided P values are reported. The last-observation-carried-forward approach was used as the primary method of imputation for missing data after the initial dose or the optional second dose. In prespecified sensitivity analyses of the primary end points, participants with missing data at the 2-hour time point after the initial dose were considered to have had treatment failure. Sensitivity analyses were performed with the use of a prespecified generalized linear mixed model for the repeated measures of binary end points at 0.5, 1, 1.5, and 2 hours after the initial dose and with a post hoc multiple-imputation method.

The methods used for the analysis of the primary efficacy variables were also used to analyze the secondary end points of pain relief and absence of photophobia, phonophobia, and nausea; the last-observation-carried-forward method was used for imputation of missing data. For secondary end points of migraine-associated symptoms, the presence or absence of the symptom at baseline was included as an additional covariate. The analyses of the efficacy end points of sustained pain relief and sustained freedom from pain included only participants for whom the end point could be determined on the basis of all available data. In prespecified sensitivity analyses, data for participants for whom those end points could not be determined were included, and these participants were considered not to have had a response.

A graphical approach was used to control the overall type I error rate for multiple comparisons between the two ubrogepant groups and across

primary and secondary efficacy end points (Fig. S1).[15] For each ubrogepant dose, the coprimary efficacy end points served as gatekeepers for the secondary end points. Testing of secondary end points was undertaken only if significance was shown for the difference between the ubrogepant dose and placebo for both primary end points. Within each dose, secondary end points were tested in the order in which they appeared in the list of secondary end points, except for the three migraine-associated symptoms (absence of photophobia at 2 hours, absence of phonophobia at 2 hours, and absence of nausea at 2 hours), which were tested at the same level to allow the recycling of weights among these three symptom end points. Recycling of weights between the two different doses of ubrogepant was also allowed; there was no hierarchical testing of the two different doses.

The methods used for the primary efficacy analysis were also used to assess the percentage of participants who were able to function normally and the percentage of participants who reported satisfaction with the trial treatment. The baseline score on the Functional Disability Scale was also included as a covariate for the analysis. A response was defined as a score on the Functional Disability Scale of "no disability, able to function normally" and a score on the scale of satisfaction with trial treatment of "satisfied" or "extremely satisfied."

RESULTS

PARTICIPANTS

A total of 1672 participants underwent randomization; 559 were assigned to the placebo group, 556 to the 50-mg ubrogepant group, and 557 to the 100-mg ubrogepant group. The safety population included 1436 participants, and the modified intention-to-treat population included 1327 (Fig. 1). In the safety population, 98.5% of the participants (1414 of 1436) completed the treatment period; the most common reason for discontinuation of the trial was loss to follow up (15 of 1327 participants [1.1%] in the modified intention-to-treat population). Among the 1672 participants who underwent randomization, 345 (20.6%) were excluded from the efficacy analyses: 236 participants did not take the trial treatment, 19 did not record a baseline (predose) measurement of the severity of the migraine headache, and 90 did not record a postdose measurement of the severity of the migraine headache or migraine-associated symptoms at or before the 2-hour time point (Fig. 1). The number of participants who were excluded was similar in the three groups.

A total of 1436 participants took an initial dose: 485 in the placebo group, 466 in the 50-mg ubrogepant group, and 485 in the 100-mg ubrogepant group. The optional second dose was taken by 222 participants in the placebo group, 184 in the 50-mg ubrogepant group (of whom 107 were randomly assigned to receive 50 mg of ubrogepant and 77 to receive placebo for the second dose), and 198 in the 100-mg ubrogepant group (of whom 93 were randomly assigned to receive 100 mg of ubrogepant and 105 to receive placebo for the second dose). The additional dose of ubrogepant for pharmacokinetic analysis was taken at visit 3 by 424 participants in the 50-mg ubrogepant group and 453 in the 100-mg ubrogepant group; these data have not yet been fully analyzed.

The mean age of the participants was 40.5 years, 88.2% were women, and 82.5% were white. At screening, 98.2% of participants reported that they were using an acute migraine treatment. Immediately before taking the trial tablets for their qualifying migraine, 22.8% of participants reported that they were using a medication for prevention of migraine, 62.9% reported that the severity of their migraine headache pain was moderate, 37.1% reported severe migraine headache pain, and 56.4% reported photophobia as their most bothersome nonheadache migraine-associated symptom. No notable differences were observed among groups with regard to baseline demographics or clinical characteristics (Table 1 and Table S2).

EFFICACY END POINTS

The number of participants with freedom from migraine pain at 2 hours after the initial dose was 54 of 456 (11.8%) in the placebo group, 81 of 422 (19.2%) in the 50-mg ubrogepant group ($P=0.002$, adjusted for multiplicity, for the comparison with placebo), and 95 of 448 (21.2%) in the 100-mg ubrogepant group ($P<0.001$) (Table 2). Absence of the most bothersome migraine-associated symptom was reported in 126 of 454 participants (27.8%) in the placebo group, in 162

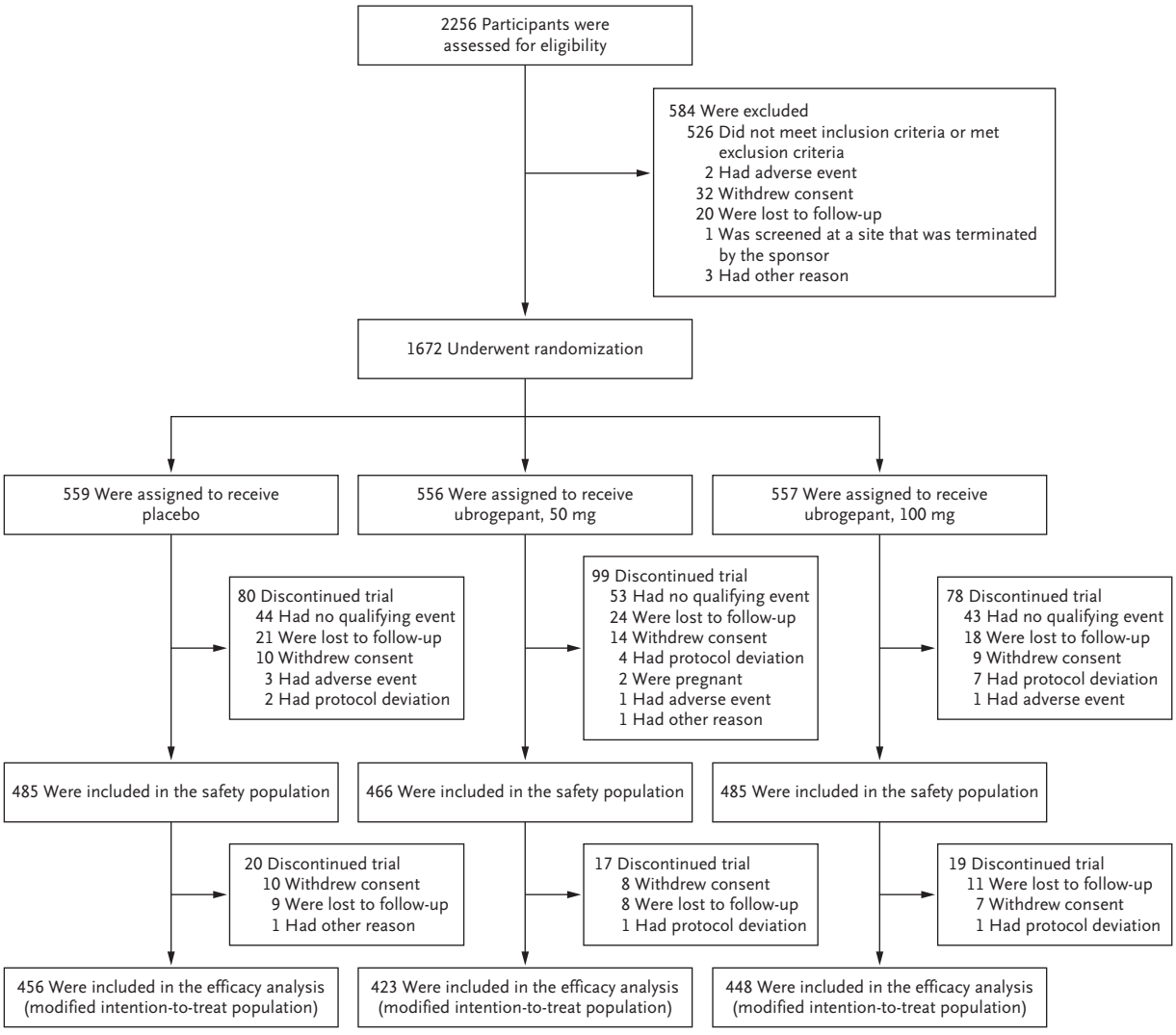


Figure 1. Screening, Randomization, and Analysis.

The safety population included all participants who underwent randomization and took an initial dose of ubrogepant or placebo. The modified intention-to-treat population included all participants who underwent randomization, took an initial dose of ubrogepant or placebo, recorded a baseline rating for the severity of the migraine headache, and recorded at least one rating for the severity of the migraine headache after the initial dose or recorded the presence or absence of at least one migraine-associated symptom up to 2 hours after the initial dose.

of 420 (38.6%) in the 50-mg ubrogepant group ($P=0.002$), and in 169 of 448 (37.7%) in the 100-mg ubrogepant group ($P=0.002$). The results of sensitivity analyses were generally in the same direction as those of the primary analysis. Unadjusted P values for sensitivity analyses with multiple imputation for missing data ranged from $P<0.001$ to $P=0.003$ for the comparison of 50 mg of ubrogepant with placebo and from $P<0.001$ to $P=0.003$ for the comparison of 100 mg of ubrogepant with placebo (Table S3).

Among the 871 participants in the two ubrogepant groups, 336 (38.6%) took the optional second dose; 174 (20.0%) received ubrogepant for the second dose. A total of 131 of 456 participants (28.7%) in the placebo group, 69 of 423

Table 1. Baseline Demographic and Clinical Characteristics.*

Characteristic	Placebo	Ubrogepant, 50 mg	Ubrogepant, 100 mg	Total
Safety population				
No. of participants	485	466	485	1436
Age — yr†	40.9±11.7	40.1±11.7	40.6±12.0	40.5±11.8
Female sex — no. (%)	430 (88.7)	418 (89.7)	418 (86.2)	1266 (88.2)
White race — no. (%)‡	410 (84.5)	383 (82.2)	392 (80.8)	1185 (82.5)
Body-mass index§	30.0±7.4	30.2±8.1	30.4±8.0	30.2±7.8
Use of acute migraine treatment at screening — no. (%)	480 (99.0)	460 (98.7)	470 (96.9)	1410 (98.2)
Modified intention-to-treat population				
No. of participants	456	423	448	1327
Use of concomitant preventive medication for migraine at the time of randomization — no. (%)	106 (23.2)	96 (22.7)	100 (22.3)	302 (22.8)
Headache severity of qualifying migraine attack — no. (%)				
Moderate pain	287 (62.9)	260 (61.5)	288 (64.3)	835 (62.9)
Severe pain	169 (37.1)	163 (38.5)	160 (35.7)	492 (37.1)
Most bothersome migraine-associated symptom of qualifying attack — no./total no. (%)				
Photophobia	254/456 (55.7)	248/423 (58.6)	246/448 (54.9)	748/1327 (56.4)
Phonophobia	98/456 (21.5)	82/423 (19.4)	116/448 (25.9)	296/1327 (22.3)
Nausea	102/456 (22.4)	90/423 (21.3)	86/448 (19.2)	278/1327 (20.9)
Missing data	2/456 (0.4)	3/423 (0.7)	0	5/1327 (0.4)

* Plus–minus values are means ±SD. The safety population included all participants who underwent randomization and took an initial dose of ubrogepant or placebo. The modified intention-to-treat population included all participants who underwent randomization, took an initial dose of ubrogepant or placebo, recorded a baseline rating for the severity of the migraine headache, and recorded at least one rating for the severity of the migraine headache after the initial dose or recorded the presence or absence of at least one migraine-associated symptom up to 2 hours after the initial dose.
† Age was reported on the date of informed consent.
‡ Race was reported by the participant.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

(16.3%) in the 50-mg ubrogepant group, and 68 of 448 (15.2%) in the 100-mg ubrogepant group used rescue medication after the first dose; 96 participants (21.1%) in the placebo group, 38 (9.0%) in the 50-mg ubrogepant group, and 45 (10.0%) in the 100-mg ubrogepant group used rescue medication after the optional second dose. In prespecified exploratory analyses, separation of the ubrogepant treatment groups from the placebo group with respect to the percentage of participants with freedom from pain increased after the 2-hour time point, with maximum efficacy observed from 3 to 8 hours. These data are presented in a Kaplan–Meier plot of estimates of the time to freedom from pain and reflect in part the use of the optional second dose or rescue medication (Fig. 2).

The number of participants who had pain relief at 2 hours was 224 of 456 (49.1%) in the placebo group, 256 of 422 (60.7%) in the 50-mg ubrogepant group (P=0.002, adjusted for multiplicity, for the comparison with placebo), and 275 of 448 (61.4%) in the 100-mg ubrogepant group (P=0.002) (Table 2). At 2 hours, 136 of 456 participants (29.8%) in the placebo group had no disability and were able to function normally, as compared with 171 of 421 (40.6%) in the 50-mg ubrogepant group (odds ratio vs. placebo, 1.67; 95% confidence interval [CI], 1.22 to 2.27) and 192 of 448 (42.9%) in the 100-mg

Table 2. Efficacy End Points (Modified Intention-to-Treat Population).*

End Point	Placebo (N=456)	Ubrogepant, 50 mg (N=423)	Ubrogepant, 100 mg (N=448)
Primary efficacy end points			
Freedom from pain at 2 hr — no./total no. (%)†	54/456 (11.8)	81/422 (19.2)	95/448 (21.2)
Odds ratio (95% CI)		1.83 (1.25–2.66)	2.04 (1.41–2.95)
Adjusted P value		0.002	<0.001
Absence of the most bothersome symptom at 2 hr — no./total no. (%)‡	126/454 (27.8)	162/420 (38.6)	169/448 (37.7)
Odds ratio (95% CI)		1.70 (1.27–2.28)	1.63 (1.22–2.17)
Adjusted P value		0.002	0.002
Secondary efficacy end points			
Pain relief at 2 hr — no./total no. (%)†	224/456 (49.1)	256/422 (60.7)	275/448 (61.4)
Odds ratio (95% CI)		1.69 (1.28–2.23)	1.69 (1.28–2.21)
Adjusted P value		0.002	0.002
Sustained pain relief, 2 to 24 hr — no./total no. (%)§	93/447 (20.8)	150/413 (36.3)	165/434 (38.0)
Odds ratio (95% CI)		2.25 (1.65–3.07)	2.39 (1.77–3.24)
Adjusted P value		0.002	0.002
Sustained freedom from pain, 2 to 24 hr — no./total no. (%)§	39/452 (8.6)	53/418 (12.7)	68/441 (15.4)
Odds ratio (95% CI)		1.57 (1.01–2.44)	1.95 (1.28–2.97)
Adjusted P value		NE	0.004
Absence of photophobia at 2 hr — no./total no. (%)‡	143/456 (31.4)	172/423 (40.7)	205/448 (45.8)
Odds ratio (95% CI)		1.63 (1.22–2.19)	1.81 (1.36–2.42)
Adjusted P value		NE	0.004
Absence of phonophobia at 2 hr — no./total no. (%)‡	215/456 (47.1)	245/423 (57.9)	244/448 (54.5)
Odds ratio (95% CI)		1.56 (1.16–2.09)	1.47 (1.10–1.95)
Absence of nausea at 2 hr — no./total no. (%)‡	284/456 (62.3)	297/423 (70.2)	310/448 (69.2)
Odds ratio (95% CI)		1.31 (0.96–1.79)	1.35 (1.00–1.83)

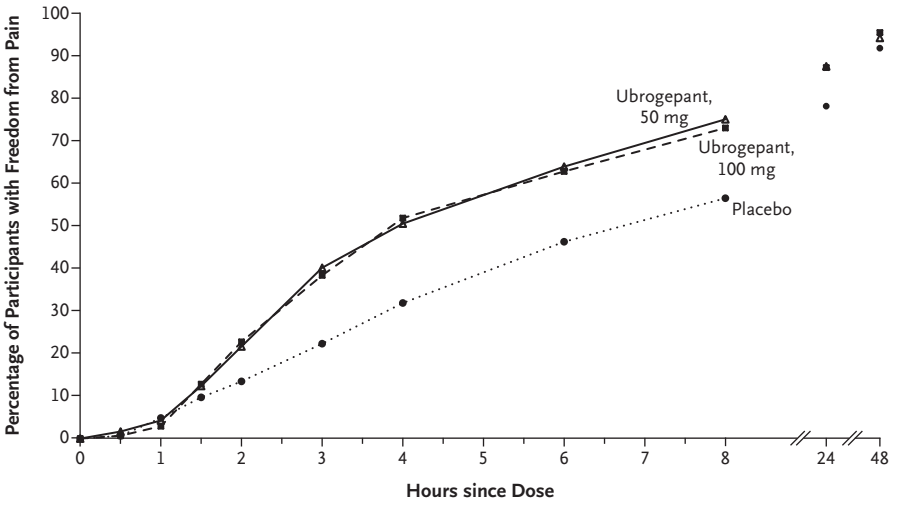
* Odds ratios were determined with the use of a logistic-regression model adjusted for the randomization stratification factors and baseline covariates. The confidence intervals were not adjusted for multiple comparisons. The P values were adjusted for multiple comparisons. The odds ratios and the P values are for each ubrogepant group as compared with placebo. Freedom from pain was defined as a change in the severity of headache pain from moderate or severe pain to the presence of no pain at 2 hours after the initial dose; pain relief was defined as a change in the severity of headache pain from moderate or severe pain to mild pain or no pain at 2 hours after the initial dose; sustained pain relief was defined as pain relief during the period from 2 to 24 hours after the initial dose without the use of the optional second dose or rescue medication; sustained freedom from pain was defined as freedom from pain during the period from 2 to 24 hours after the initial dose without the use of the optional second dose or rescue medication. Results are reported with the use of the last-observation-carried-forward method for missing data. NE denotes not evaluated in accordance with the hierarchical plan.

† The total number is the number of participants who did not have missing data for the assessment of pain severity up to 2 hours after the initial dose.

‡ The total number is the number of participants who did not have missing data for the presence or absence of the most bothersome symptom (photophobia, phonophobia, or nausea) up to 2 hours after the initial dose.

§ The total number is the number of participants for whom status with respect to sustained pain relief or sustained freedom from pain could be determined on the basis of the reported headache severity at scheduled time points, the use of rescue medication or optional second dose between 2 and 24 hours after the initial dose, and participants' report of whether they had recurrence of headache pain at 24 hours.

ubrogepant group (odds ratio vs. placebo, 1.93; 95% CI, 1.42 to 2.61) (Table S4). No statistical difference between groups was shown for the comparison between the 50-mg dose and placebo at the level of sustained freedom from pain during the period from 2 to 24 hours or for the comparison between the 100-mg dose and placebo at the level of absence of phonophobia at



No. at Risk											
Ubrogepant, 50 mg	422	422	414	402	368	326	248	203	146	98	44
Ubrogepant, 100 mg	448	448	442	432	386	341	270	211	160	114	46
Placebo	456	456	451	431	409	391	349	303	236	185	78

Figure 2. Kaplan–Meier Analysis of Freedom from Headache Pain (Exploratory Analysis).

The Kaplan–Meier plot was produced with the use of observed data. Data after the 2-hour time point include data from participants who took the optional second dose or rescue medication. Figure S2 shows a Kaplan–Meier plot that excludes data from participants after they took the optional second dose or rescue medication (i.e., at the time the participant took the second dose or rescue medication, that participant was removed from the risk pool for the subsequent time points).

2 hours; therefore, according to the hierarchical design, no inferences can be made about differences between the ubrogepant groups and placebo for subsequent outcomes. Results for additional secondary end points are provided in Table 2.

SAFETY

Adverse events that began or worsened within 48 hours after the initial dose or the optional second dose were reported in 12.9% of participants (185 of 1436 participants), and events that occurred within 30 days after any dose were reported in 26.3% of participants (378 of 1436 participants); the types and frequencies of events were similar across the groups (Table 3). The most commonly reported adverse events that were reported within 48 hours were nausea, somnolence, and dry mouth. Serious adverse events were reported in 5 participants in the ubrogepant groups after 48 hours but within 30 days: in the 50-mg ubrogepant group, 1 participant had appendicitis, 1 had a spontaneous abortion, and 1 had pericardial effusion; in the 100-mg ubrogepant group, 1 participant had appendicitis and 1 had a seizure. The seizure (in a participant who may have had alprazolam withdrawal syndrome) was considered by the investigator to be related to the trial treatment. Details of all reported serious adverse events are provided in Table S5. No participants discontinued the trial because of an adverse event.

Six participants had postbaseline levels of alanine aminotransferase or aspartate aminotransferase that were at least 3 times the upper limit of the normal range (1 participant in the placebo group, 2 in the 50-mg ubrogepant group, and 3 in the 100-mg ubrogepant group) (Table S6). These cases were adjudicated by an independent review committee whose members were unaware of the trial-group assignments; four of the six cases were considered most likely not related to the trial regimen on the basis of identification of alternative causes or confounding factors. Two cases (one in the placebo group and one in the 100-mg ubrogepant group) were

Table 3. Adverse Events According to Group (Safety Population).*

Event	Placebo (N=485)	Ubrogepant, 50 mg (N=466)	Ubrogepant, 100 mg (N=485)
		no. of participants (%)	
Adverse events that occurred within 48 hr after the initial dose or optional second dose			
Any adverse event	62 (12.8)	44 (9.4)	79 (16.3)
Adverse events reported in ≥2% of participants in any group			
Nausea	8 (1.6)	8 (1.7)	20 (4.1)
Somnolence	4 (0.8)	3 (0.6)	12 (2.5)
Dry mouth	2 (0.4)	3 (0.6)	10 (2.1)
Any adverse event related to the trial regimen	41 (8.5)	27 (5.8)	58 (12.0)
Adverse events related to the trial regimen reported in ≥2% of participants in any group			
Nausea	8 (1.6)	7 (1.5)	16 (3.3)
Somnolence	4 (0.8)	3 (0.6)	11 (2.3)
Dry mouth	2 (0.4)	3 (0.6)	7 (1.4)
Serious adverse events	0	0	0
Death	0	0	0
Adverse event that led to discontinuation of the trial regimen	0	0	0
Adverse events that occurred within 30 days after any dose			
Any adverse event	113 (23.3)	126 (27.0)	139 (28.7)
Adverse events reported in ≥2% of participants in any group			
Nausea	12 (2.5)	9 (1.9)	23 (4.7)
Somnolence	4 (0.8)	4 (0.9)	12 (2.5)
Dry mouth	3 (0.6)	3 (0.6)	10 (2.1)
Upper respiratory tract infection	8 (1.6)	5 (1.1)	10 (2.1)
Any adverse event related to the trial regimen	49 (10.1)	36 (7.7)	68 (14.0)
Serious adverse events	0	3 (0.6)	2 (0.4)
Appendicitis	0	1 (0.2)	1 (0.2)
Pericardial effusion	0	1 (0.2)	0
Seizure	0	0	1 (0.2)
Spontaneous abortion	0	1 (0.2)	0
Death	0	0	0
Adverse event that led to discontinuation of the trial regimen	0	0	0

* Adverse events were events that began or worsened after the initial dose of ubrogepant or placebo to the time of the 4-week safety follow-up visit; if participants had missing data for the safety follow-up visit, adverse events were assessed up to day 30 after any dose.

judged to be possibly related to the trial regimen; confounding factors were noted in both cases. No case met the criteria for a potential case of Hy's law (Table S7).[16]

DISCUSSION

In this trial of 50-mg and 100-mg doses of ubrogepant for acute migraine treatment, the percent-

age of participants who had freedom from pain and absence of the most bothersome migraine-associated symptom (the coprimary end points) was higher among participants who received either dose of ubrogepant than among those who received placebo. Freedom from pain occurred within 2 hours after a dose in approximately 20% of participants in each of the ubrogepant groups, as compared with 12% in the placebo group. Absence of the most bothersome symptom associated with migraine at 2 hours occurred in 38% of participants who received ubrogepant, as compared with 28% who received placebo.

Although the sites of action of ubrogepant are not known, CGRP receptors are expressed peripherally on cranial blood vessels and on neurons and glial cells in the trigeminal ganglion, as well as centrally on terminals of trigeminal afferents and at multiple sites in the brain stem, cerebellum, and cerebral hemispheres.[17] All these are potential signaling sites for CGRP and, correspondingly, potential sites of action of the gepant group of drugs.

This trial had limitations that may preclude generalizability. First, there was no active comparator and no evaluation of consistency of effect across multiple migraine attacks; therefore, it is not possible to determine whether the drug is more or less effective than standard therapies or consistently effective with repeated use. Second, odds ratios were used as a statistical test and may have magnified the risk ratio. Third, the use of the last-observation-carried-forward method for imputation of missing data in the planned primary analysis may have biased the results; however, sensitivity analyses under various assumptions confirmed the results of the primary analysis. Fourth, approximately 21% of the participants who underwent randomization were not included in the efficacy analysis, and the majority of them were excluded because they did not have a qualifying migraine during the 60-day period after randomization. Finally, safety and side-effect data from this trial were based on evaluation of a single attack, and therefore safety after repeated use cannot be inferred; an extension trial (ClinicalTrials.gov number, NCT02873221) has assessed the long-term safety of ubrogepant.

At 2 hours after the dose, approximately 20% of participants who received ubrogepant, as compared with 12% who received placebo, had freedom from headache pain, and approximately 38% and 28%, respectively, had absence of the most bothersome symptom. The most commonly reported adverse events were nausea, somnolence, and dry mouth. Trials evaluating consistency of effect, longer-term safety data, and comparative effectiveness are needed to assess the safety and clinical utility of ubrogepant for acute migraine treatment.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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