

# Efficacy of Ubrogепant in the Acute Treatment of Migraine With Mild Pain vs Moderate or Severe Pain

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## Abstract

### Background and Objectives

To examine the efficacy of ubrogепant in the treatment of migraine with mild vs moderate or severe pain.

### Methods

This was a phase 3, open-label, dose-blinded, 52-week extension trial. Adults with migraine were randomized 1:1:1 (usual care, ubrogепant 50 mg, or ubrogепant 100 mg). Participants treated up to 8 migraine attacks of any pain intensity every 4 weeks. Efficacy outcomes (only collected for ubrogепant) included 2-hour pain freedom (2hPF), freedom from associated symptoms, and from disability. A generalized linear mixed model with binomial distribution and logit link function was used to assess the influence of baseline pain intensity on treatment outcomes in this post hoc analysis.

### Results

Data for 19,291 attacks from 808 participants were included. 2hPF rates were higher for attacks treated when pain was mild vs moderate or severe: ubrogепant 50 mg (47.1% vs 23.6%; odds ratio [95% CI] 2.89 [2.57–3.24]) and ubrogепant 100 mg (55.2% vs 26.1%; 3.50 [3.12–3.92];  $p < 0.0001$  both doses). Rates of freedom from photophobia, phonophobia, and nausea 2 hours after treatment were also significantly higher following the treatment of mild vs moderate or severe pain ( $p < 0.001$  all symptoms, both doses). At 2 hours, the proportion of attacks with normal function was more than double for both doses of ubrogепant ( $p < 0.001$ ). The most common adverse event was upper respiratory tract infection (~11% both doses). Serious adverse events were reported by 2% in ubrogепant 50 mg and 3% in ubrogепant 100 mg.

### Discussion

Relative to treatment of attacks with moderate or severe pain, treatment with ubrogепant during mild pain resulted in significantly higher rates of freedom from pain, freedom from associated symptoms, and achieving normal function 2 hours after administration.


### Trial Registration Information

ClinicalTrials.gov, NCT02873221.

### Classification of Evidence

This trial provides Class III evidence that treatment of migraine with ubrogепant when pain is mild vs moderate or severe increases the likelihood of achieving pain freedom, absence of symptoms, and normal function within 2 hours postdose.

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## Glossary

ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; MOH = medication overuse headache; OR = odds ratio; TEAE = treatment-emergent adverse event.

During migraine attacks, mild pain at onset often escalates to moderate or severe pain.<sup>1,2</sup> The escalation in pain intensity is often associated with emergence or exacerbation of migraine-associated symptoms including nausea, photophobia, phonophobia, and allodynia.<sup>3-5</sup> The temporal evolution of migraine pain and associated symptoms is variable person to person and within individuals from attack to attack.<sup>1,2,6</sup>

For acute treatments, regulatory guidance for acute treatment trials requires the treatment of migraine when pain is moderate or severe.<sup>7,8</sup> However, clinical guidance recommends treatment early in the migraine attack, when pain is mild.<sup>9</sup> Despite clinical advice to treat early, many patients delay treatment to preserve limited medication supplies, avoid side effects, reduce the risk of medication overuse, or hope for spontaneous remission.<sup>10</sup> Research has shown that acute treatment of migraine, especially with triptans, early in the attack or when pain is mild results in improved outcomes for the patient.<sup>11-14</sup>

Ubrogepant is an oral calcitonin gene-related peptide receptor antagonist approved for the acute treatment of migraine, with efficacy demonstrated in 2 phase 3 trials. Multiple studies demonstrated efficacy in the treatment of migraine with moderate or severe pain.<sup>15-17</sup> The efficacy of ubrogepant when patients treat during mild pain has not yet been studied. The primary hypothesis was that the treatment of migraine with ubrogepant when pain is mild would increase the likelihood of achieving positive outcomes, including pain freedom, relative to the treatment of moderate or severe pain, in adults with migraine. This post hoc analysis examines the efficacy of ubrogepant in treating migraine attacks with mild pain vs moderate or severe pain in a 1-year, long-term treatment trial (ClinicalTrials.gov, NCT02873221).

## Methods

### Standard Protocol Approvals, Registrations, and Patient Consents

The trial protocol and amendments were approved by properly constituted local and central institutional review boards. All participants provided written consent before participation in the trial. The trial is registered on ClinicalTrials.gov, including the primary and secondary safety outcomes; efficacy outcomes analyzed here were prespecified but not registered (NCT02873221).

### Trial Design

This was a phase 3, multicenter, randomized, open-label, 52-week, dose-blinded extension trial designed to evaluate the safety and tolerability of ubrogepant for the acute treatment of migraine. The response measures reported here were also

collected as exploratory endpoints to evaluate the efficacy of ubrogepant. The trial design and methods were previously published in detail.<sup>18</sup>

Adults with migraine with or without aura were randomized 1:1:1 to ubrogepant 50 mg, ubrogepant 100 mg, or usual care. Those randomized to usual care continued to treat their migraine attacks with medication they had historically been using. Enrollment began September 13, 2016, and the last participant exited August 2, 2018. Participants were required to have completed 1 of the 2 lead-in trials, ACHIEVE I (NCT02828020) or ACHIEVE II (NCT02867709). Participants could treat up to 8 migraine attacks of mild, moderate, or severe pain intensity every 4 weeks over 1 year. An optional second dose of ubrogepant was permitted 2 hours after the initial dose. The maximum daily dose of ubrogepant was 200 mg/d. The optional second dose was identical to the first based on randomization at the start of the trial.

An interactive web response system was used for randomization and treatment assignment. Randomization was stratified by participants' historical response to triptans and their use of preventive concomitant medication, which was determined in the lead-in trial. The trial sponsor generated the randomization code. All participants, site personnel, and trial sponsor personnel were aware of participants' randomization to ubrogepant or usual care, although all were blinded to the ubrogepant dose.

### Efficacy Measures

Response measures were only collected for participants randomized to ubrogepant treatment; therefore, only data for ubrogepant arms are included in these analyses. Efficacy measures included headache pain intensity, presence/absence of migraine-associated symptoms, use of rescue medication, and use of an optional second dose of ubrogepant. Allowed rescue medication included analgesics (e.g., acetaminophen, non-steroidal anti-inflammatory drugs, and opiates), antiemetics, or triptans. All efficacy data were collected through an eDiary. Participants entered the date and time of dosing. Based on medication dosing time entered, participants were prompted to enter data at 2, 24, and 48 hours after dose to evaluate efficacy. Alarms were programmed to ring at each time point as reminders.

Headache pain intensity was rated on a scale of no pain, mild pain, moderate pain, and severe pain at predefined time points: predose, 2, 24, and 48 hours after the initial dose. The presence or absence of migraine-associated symptoms (i.e., photophobia, phonophobia, nausea, and vomiting) was recorded at predose, 2, 24, and 48 hours after the initial dose. Participants were asked to rate their level of functional disability using the single-item

Functional Disability Scale predose and 2 hours after each initial dose. The performance of daily activities was rated using 4 response options ranging from 0 (no disability, able to function) to 3 (severely impaired, cannot do all or most things, or bed rest may be necessary). The approach to measuring pain, migraine-associated symptoms, and functional disability corresponds to the recommendations of the International Headache Society's guideline for controlled trials of acute treatments for migraine as well as Food and Drug Administration guidance.<sup>8,19</sup> The use of an optional second dose of ubrogepant within 24 and 48 hours after dose due to inadequate response to the initial dose or return of headache after an initial response was recorded in the eDiary. The use of rescue medication within 24 and 48 hours after treating a migraine attack was recorded through eDiary, including the date and time the rescue medication was taken.

## Efficacy Outcomes

These post hoc analyses were primarily focused on the 2-hour time point, in alignment with the underlying endpoints in the pivotal trials.<sup>15,16</sup> The outcome of primary interest was 2-hour pain freedom rates in attacks treated while pain was mild vs those treated while moderate or severe. In addition, 2-hour nausea, photophobia, phonophobia, and functional disability were evaluated. Exploratory analyses examined pain freedom, absence of symptoms, and functional disability at 24 and 48 hours after dose as well as the use of an optional second dose of ubrogepant and the use of rescue medication.

## Safety Measures

Adverse events were collected throughout the trial. Physical examinations (screening and week 52), clinical laboratory determinations (screening and each 4-week visit), vital signs (screening, day 1, and each 4-week visit), ECGs (screening and weeks 12, 24, 36, 48, and 52), and a suicidality assessment through the Columbia-Suicide Severity Rating Scale (screening, day 1, and each 4-week visit) were completed by the investigator or site personnel.

## Statistical Methods

No sample size calculations were conducted for this post hoc efficacy analysis. The sample size for the trial was driven by regulatory safety requirements for the duration and number of participants exposed rather than statistical considerations. All randomized participants were included in the intent-to-treat population. The safety population included all randomized participants who took at least 1 dose of ubrogepant. The analysis population was defined as all randomized participants who received at least 1 dose of ubrogepant and had at least 1 posttreatment efficacy assessment collected during the trial. If data were incomplete or missing at any time point(s) for a treated attack, data for the attack at the affected time point(s) were not included in this analysis; however, all other available data for that participants' treated attack(s) were included. All efficacy analyses were based on the analysis population and were defined as exploratory endpoints in this trial. Pain freedom was defined as a reduction in headache severity from mild, moderate, or severe at baseline to no pain. The absence

of photophobia, phonophobia, and nausea was assessed in all participants and includes participants who did not have the symptom present at the time of their treated migraine attack.

This post hoc analysis compared pain-free rates between attacks treated with mild pain vs moderate or severe pain. As participants could treat 1 or more migraine attacks throughout the 1-year trial, data for all treated attacks were included. Participants contributed varying numbers of attacks (e.g., 1 participant may have contributed data for a single attack vs a participant who contributed data for 6 attacks) in this analysis. Attacks from the same participant may be correlated with respect to attack characteristics or treatment response. To address correlations of attack characteristics and treatment response between and across participants, a generalized linear mixed model with binomial distribution and logit link function was used to perform subgroup comparisons based on all treated attacks. Each participant was treated as a random effect in the generalized linear regression model analysis with the migraine attacks nested within participants. Baseline migraine severity, dose of drug, interaction of baseline migraine severity and dose of drug, and ethnicity were included as factors in the model. A possible correlation of the outcomes within participant and within participants' variations was handled by using the mixed treatment with the repeated measurement method. There was no significant impact with the inclusion of other baseline characteristics in the model (e.g., age and gender). Responder rates, odds ratios (ORs), corresponding 95% CIs, and unadjusted *p* values are reported. Only observed data were included, and no imputation was applied. An additional subgroup analysis was performed using this model-based approach in participants who treated at least 1 mild and 1 moderate or severe attack during the trial.

Adverse events were coded using MedDRA version 20.1. MedDRA, the Medical Dictionary for Regulatory Activities terminology, is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA trademark is registered by the IFPMA on behalf of the ICH. Treatment-emergent adverse events (TEAEs), treatment-related TEAEs, serious adverse events, adverse events leading to discontinuation, and clinical laboratory assessments were summarized by treatment group.

## Data Availability

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor, including access to anonymized, individual, and trial-level data (analysis datasets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided after review and approval of a

research proposal, Statistical Analysis Plan, and execution of a Data Sharing Agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit [abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html](http://abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html).

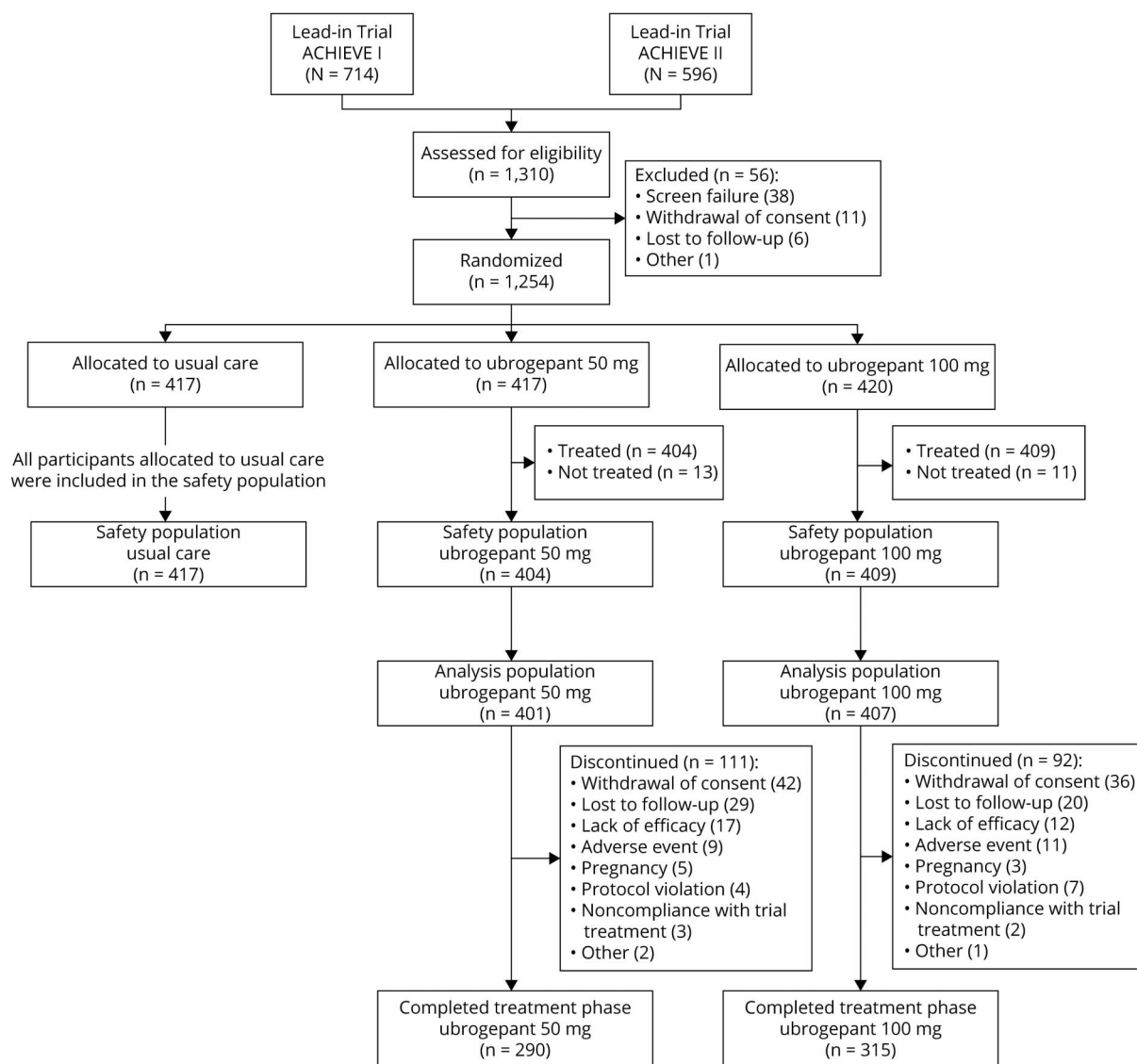
## Results

### Participants

A total of 1,310 participants from the lead-in ACHIEVE I and ACHIEVE II trials were assessed for eligibility, and 1,254 were randomized into this trial. There were 1,230 participants in the

safety population. The analysis population, which was only defined for those randomized to ubrogepant, included 808 participants (401 in the 50-mg dose and 407 in the 100-mg dose) (Figure 1). An additional 417 participants were allocated to usual care; efficacy data were not collected on this group. Over the 1-year course of the trial, 21,454 migraine attacks were treated with ubrogepant, of which 19,291 attacks were included in this analysis. The analysis excluded 3,408 attacks because of missing data on efficacy at 2 hours. Out of the attacks included in this analysis, 3,914 were treated when pain was mild, 11,227 when pain was moderate, and 4,150 when pain was severe. Over the course of the trial, most participants treated attacks of more than 1 pain intensity ( $n = 696/808$ , 86%). In the ubrogepant 50-mg group, 58% of participants (234/401) treated at least 1 attack when pain was mild, whereas 99% (395/401) treated at least 1 attack with moderate or severe

**Figure 1** Participant Enrollment and Disposition



All participants randomized to usual care were included in the safety population regardless of whether the participant used medication to treat migraine. For the ubrogepant treatment group, the safety population included all participants who received at least 1 dose of treatment. The analysis population was only defined for the ubrogepant treatment groups because efficacy measures were not collected for participants randomized to usual care. The analysis population is defined as all randomized patients who received at least 1 dose of ubrogepant and had at least 1 posttreatment efficacy assessment in this trial.



pain. In the ubrogepant 100-mg group, 57% of participants (234/407) treated at least 1 attack when pain was mild and 99% (404/407) treated at least 1 attack with moderate or severe pain. Overall, a higher number of moderate or severe attacks were treated by participants during the trial (eFigure 1, [links.lww.com/WNL/C252](https://links.lww.com/WNL/C252)). Participants in the analysis population were on average 42 years of age, with the majority being female and White (Table 1). No notable differences were seen in baseline characteristics between dose groups. Baseline data were also comparable when comparing those who treated only mild attacks, only moderate or severe attacks, or mild and moderate or severe attacks (eTable 1, [links.lww.com/WNL/C253](https://links.lww.com/WNL/C253)).

## Efficacy Outcomes

At 2 hours after dose, rates of pain freedom were higher for attacks treated when pain was mild vs those treated when moderate or severe for ubrogepant 50 mg (47.1% vs 23.6%; adjusted OR [95% CI] 2.89 [2.57–3.24]) and ubrogepant 100 mg (55.2% vs 26.1%; 3.50 [3.12–3.92];  $p < 0.0001$  both doses) (Figure 2A). Results were consistent in the subgroup of participants who treated both mild and moderate or severe attacks during the trial (Figure 2B). Significant differences in pain-free rates persisted at 24 and 48 hours after dose for both dose groups (eFigure 2 and eFigure 3, [links.lww.com/WNL/C252](https://links.lww.com/WNL/C252)).

Absence of each migraine-associated symptoms at 2 hours after dose occurred in a significantly higher proportion of attacks

treated when pain was mild vs moderate or severe ( $p < 0.001$  all symptoms, both doses; Figure 3). For attacks treated with mild vs moderate or severe pain, 63.5% vs 36.2% of attacks had absence of photophobia (adjusted OR [95% CI] 3.07 [2.74–3.43]) after treatment with ubrogepant 50 mg and 62.6% vs 38.1% (2.72 [2.43–3.04]) after treatment with ubrogepant 100 mg. After the treatment of attacks with mild vs moderate or severe pain, 68.9% vs 43.0% of attacks had absence of phonophobia with ubrogepant 50 mg (2.94 [2.62–3.30]) and 69.8% vs 47.1% with ubrogepant 100 mg (2.59 [2.30–2.91]). Absence of nausea at 2 hours after the treatment of attacks with mild vs moderate or severe pain was seen in 87.9% vs 68.3% of attacks treated with ubrogepant 50 mg (adjusted OR [95% CI] 3.38 [2.90–3.95]) and 85.0% vs 69.7% for ubrogepant 100 mg (2.46 [2.13–2.85]). Significant differences were maintained at 24 hours for both doses and at 48 hours for ubrogepant 50 mg; similar trends were observed in the subgroup that treated both mild and moderate or severe attacks (eFigures 4 and 5, [links.lww.com/WNL/C252](https://links.lww.com/WNL/C252)).

A significantly higher proportion of treated attacks had normal function at 2 hours after dose when treated while pain was mild vs moderate or severe for ubrogepant 50 mg (66.6% vs 34.3%; adjusted OR [95% CI] 3.83 [3.40–4.30]) and ubrogepant 100 mg (70.1% vs 37.2%; 3.95 [3.50–4.46];  $p < 0.001$  both doses) (Figure 4A). Significant differences were also seen in the subgroup that treated both mild and moderate or severe attacks (Figure 4B).

The need for an optional second dose of ubrogepant within 24 hours was significantly lower ( $p < 0.001$  both doses) for attacks treated when pain was mild vs moderate or severe for ubrogepant 50 mg (30.6% vs 39.9%; adjusted OR [95% CI] 0.66 [0.60–0.74]) and ubrogepant 100 mg (20.9% vs 36.9%; 0.45 [0.40–0.51]) (eFigure 6, [links.lww.com/WNL/C252](https://links.lww.com/WNL/C252)). Significant differences continued to be observed at 48 hours after dose for both dose groups. The use of rescue medication was significantly lower when attacks were treated when pain was mild vs moderate or severe only for ubrogepant 100 mg at 24 hours (7.4% vs 9.5%; 0.76 [0.63–0.91]); minimal differences were observed at 48 hours (eFigure 7).

## Adverse Events

A full detailed report of the safety findings has been published<sup>18</sup>; additional results are posted in the clinical trials registry (ClinicalTrials.gov; NCT02873221). Treatment-emergent adverse events were reported by 268 of 404 participants (66.3%) in ubrogepant 50 mg and 397 of 409 participants (72.6%) in ubrogepant 100 mg (Table 2). The most commonly reported TEAE was upper respiratory tract infection (~11% both doses). Treatment-related TEAEs were reported by ~10% of participants in both doses. Serious AEs were reported by 2.2% (ubrogepant 50 mg) and 2.9% (ubrogepant 100 mg) of participants. One serious AE in the ubrogepant 50-mg group was considered treatment-related by the investigator (exacerbation of sinus tachycardia). Discontinuation due to an AE was reported by 2.2% (ubrogepant 50 mg) and 2.7% (ubrogepant 100 mg) of participants. No deaths were reported during the trial.

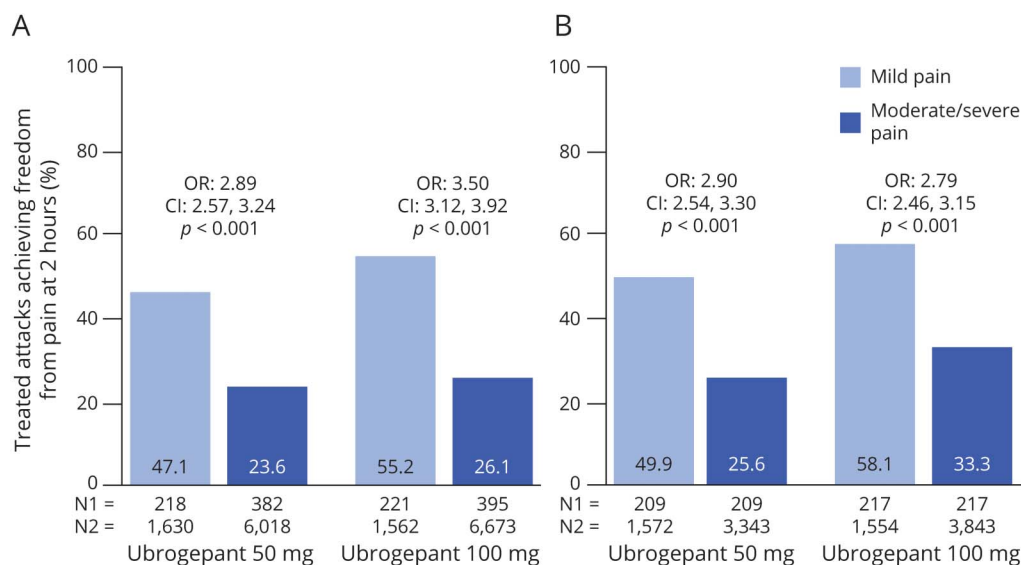
**Table 1** Participant Baseline Demographics and Clinical Characteristics (Analysis Population)

	Ubrogepant 50 mg (N = 401)	Ubrogepant 100 mg (N = 407)
<b>Age (y)</b>		
Mean (SD)	42.4 (12.2)	41.5 (11.2)
Min, max	18, 72	18, 73
<b>Sex, n (%)</b>		
Female	370 (92.3)	364 (89.4)
Male	31 (7.7)	43 (10.6)
<b>Race, n (%)</b>		
White	347 (86.5)	336 (82.6)
Black/African American	48 (12.0)	57 (14.0)
Others <sup>a</sup>	6 (1.5)	14 (3.4)
<b>BMI (kg/m<sup>2</sup>)<sup>b</sup></b>		
Mean (SD)	29.4 (7.3)	30.1 (7.9)
Min, max	17, 54	17, 56
Concomitant preventive migraine medication, n (%)	101 (25.2)	102 (25.1)

<sup>a</sup> Others include Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and those who reported multiple races.

<sup>b</sup> Data for n = 400 reported for ubrogepant 50 mg.

**Figure 2** Pain Freedom at 2 Hours After Dose by Headache Severity Across All Treated Attacks in the (A) Overall Population and (B) Subgroup Who Treated Both Mild and Moderate or Severe Attacks (Analysis Population)



The analysis population is defined as all randomized patients who received at least 1 dose of ubrogepant and had at least 1 posttreatment efficacy assessment in this trial. Pain freedom is a reduction in headache severity from mild/moderate or severe at baseline to no headache pain. N1 is the total number of participants, and N2 is the total number of treated attacks. Responder rates, odds ratios (ORs), 95% CIs, and *p* values are based on a generalized linear mixed model that addresses the within-participant correlation. All available data are used in the analysis.

### Classification of Evidence

The primary hypothesis was that the treatment of migraine with ubrogepant when pain is mild would increase the likelihood of achieving positive outcomes, relative to the treatment of moderate or severe pain, in adults with migraine. This trial provides Class III evidence that treatment of migraine with ubrogepant when pain is mild vs moderate or severe increases the likelihood of achieving pain freedom, absence of symptoms, and normal function within 2 hours postdose.

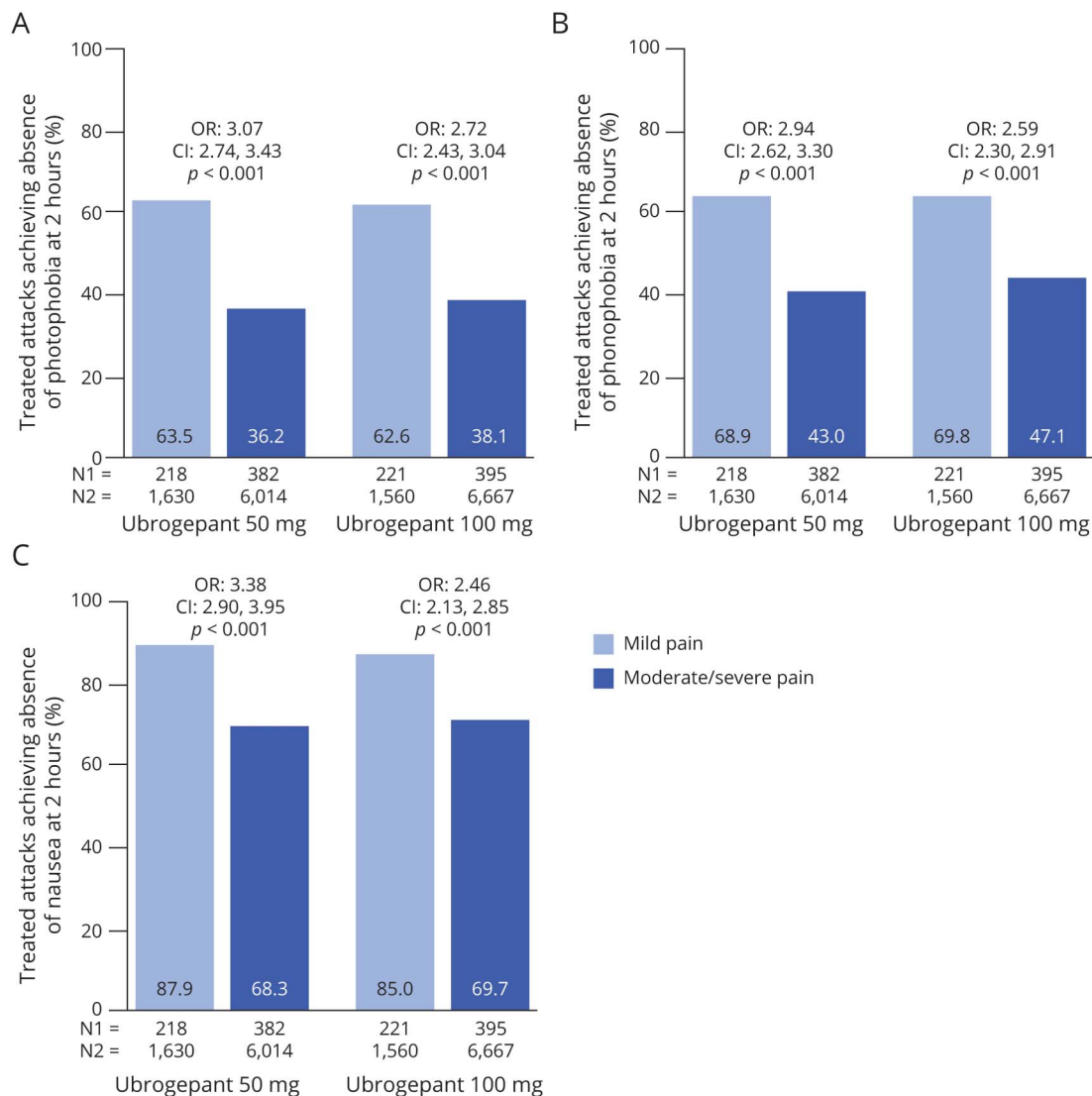
### Discussion

In this long-term treatment trial, participants had the option of treating attacks while pain was mild, moderate, or severe. Results for treating moderate or severe pain in this open-label study were in line with observations from the placebo-controlled pivotal efficacy trials, whereas attacks treated when pain was mild resulted in significantly higher rates of pain freedom at 2 hours.<sup>15,16</sup> A significantly higher proportion of attacks also had absence of associated symptoms and normal function at 2 hours after dose for migraine attacks treated when pain was mild vs those treated when pain was moderate or severe. In addition, use of an optional second dose of ubrogepant or rescue medication was reduced for attacks treated when pain was mild. The findings were also consistent in the subgroup of participants who treated attacks of both mild and moderate or severe pain. These data suggest that treating while pain is mild is associated with more favorable treatment outcomes compared with treating attacks when pain is moderate

or severe. There are several possible nonmutually exclusive explanations for greater efficacy with the treatment of mild pain. When pain is mild, one view is that it may depend primarily on pain signals that originate in the meninges, a site that is readily available to ubrogepant; when pain progresses to moderate or severe pain, pain may depend more on neurons in the trigeminal cervical complex, in areas where ubrogepant's access may be limited because of the blood-brain barrier.<sup>17,20-22</sup> Another view is that terminating an attack once sensitization of the second- and third-order trigeminovascular neurons occurs may be more difficult regardless of the drug's properties or mechanism of action.<sup>12,14,23-27</sup>

There are several factors to consider when evaluating the efficacy of an acute treatment for migraine. For phase III regulatory trials in the United States, attacks of moderate or severe pain are treated, and the primary endpoints include rates of freedom from pain and from participant-designated most bothersome symptom 2 hours after dose.<sup>8,19,28</sup> Based on these endpoints, the efficacy of ubrogepant has been demonstrated in 2 phase 3 pivotal trials.<sup>15,16</sup> Prior research has also shown that factors such as early efficacy, sustained benefit, and return to normal function are important considerations for patients.<sup>29</sup> These factors have also been examined for ubrogepant, and findings demonstrate the utility of ubrogepant throughout the course of a migraine attack and the superior efficacy of ubrogepant vs placebo in achieving normal function.<sup>15,16,30</sup> Although regulatory guidance requires treatment when pain is moderate or severe, clinical guidance recommends treating early in the attack while pain is mild.<sup>9</sup>

**Figure 3** Absence of (A) Photophobia, (B) Phonophobia, and (C) Nausea at 2 Hours After Dose by Headache Severity Across All Treated Attacks (Analysis Population)

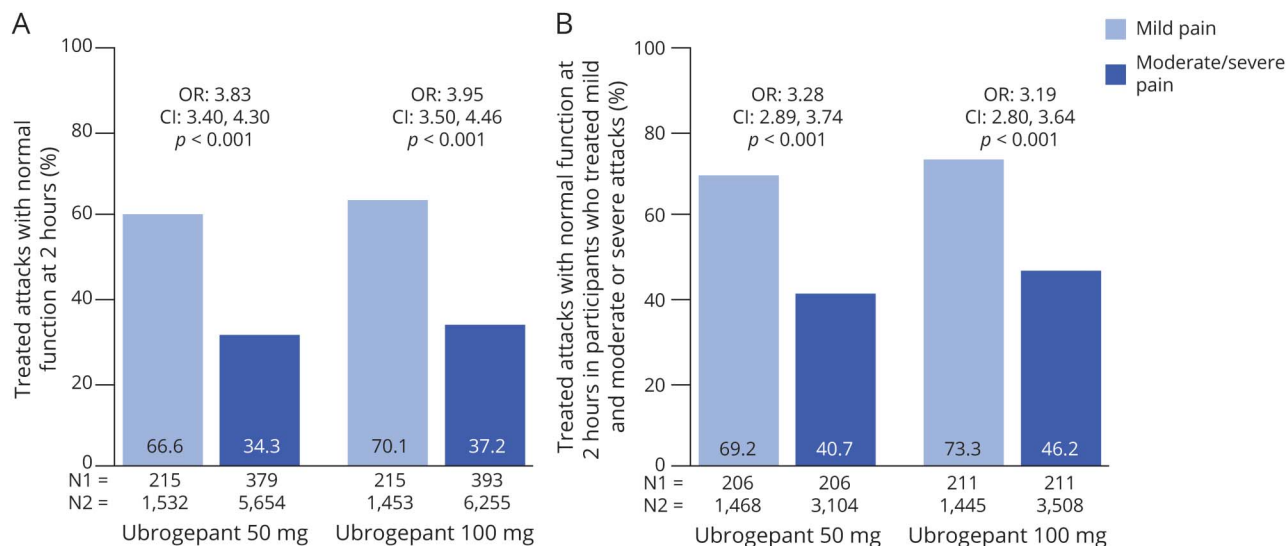


The analysis population is defined as all randomized patients who received at least 1 dose of ubrogepant and had at least 1 posttreatment efficacy assessment in this trial. Absence of symptom includes data for all treated attacks regardless of the presence/absence of the symptom before treatment for a particular attack. N1 is the total number of participants, and N2 is the total number of treated attacks. Responder rates, odds ratios (ORs), 95% CIs, and  $p$  values are based on a generalized linear mixed model that addresses the within-participant correlation. All available data are used in the analysis.

Benefits of early treatment while pain is mild have been demonstrated for an array of acute treatments for migraine.<sup>12,14,24-27</sup> Specifically, data published on triptans show that increased efficacy and cost-effectiveness were achieved with early treatment (i.e., within 1 hour of onset) and when pain was mild.<sup>31</sup> These data demonstrate that the treatment of a migraine attack when pain is mild results in a higher likelihood of achieving positive outcomes compared with the treatment of a migraine attack when pain is moderate or severe. Although participants had the option of treating mild pain, in this trial 80% of attacks were treated with moderate or severe pain. Slightly less than 60% of the participants treated at least 1 attack when pain was mild, indicating that a sizeable minority treated no attacks with mild pain over the course of up to 1 year.

Other studies show that treatment while pain is mild is not feasible for every patient or every attack. A study that examined the progression of headache pain found that in 19% of participants with aura and 11% without aura, the onset of moderate or severe pain was nearly instantaneous.<sup>32</sup> The study also showed that most of the participants, 60% with aura and 48% without aura, experienced an increase in headache pain from no pain to moderate or severe pain within 11–60 minutes. In these instances, treating when pain is mild may prove challenging. Furthermore, the time of the day of headache onset may influence the ability to treat early. A report on the circadian rhythm of migraine attacks showed a significant proportion of attacks occur during sleeping hours or on waking; for these attacks, pain may be of moderate or severe intensity by the time

**Figure 4** Normal Function at 2 Hours After Dose by Headache Severity Across All Treated Attacks in the (A) Overall Population and (B) Subgroup Who Treated Both Mild and Moderate or Severe Attacks (Analysis Population)



The analysis population is defined as all randomized patients who received at least 1 dose of ubrogepant and had at least 1 posttreatment efficacy assessment in this trial. Normal function per the Functional Disability Scale refers to a response option of 0 (no disability, able to function). N1 is the total number of participants, and N2 is the total number of treated attacks. Responder rates, odds ratios (ORs), 95% CIs, and *p* values are based on a generalized linear mixed model that addresses the within-participant correlation. All available data are used in the analysis.

treatment is possible.<sup>33</sup> Although this analysis shows the increased benefit of treating a migraine attack when pain is mild, the overall data support the utility of ubrogepant for treating a migraine attack of mild or moderate or severe pain intensity.

For some treatments, early administration while pain is mild raises concerns about adverse events and medication overuse<sup>10,34</sup>;

**Table 2** Summary of Adverse Events (Safety Population)

n (%)	Ubrogepant 50 mg (N = 404)	Ubrogepant 100 mg (N = 409)
<b>Treatment-emergent adverse event (TEAE)</b>	268 (66.3)	297 (72.6)
<b>Treatment-related TEAE</b>	42 (10.4)	43 (10.5)
<b>Commonly reported TEAE (≥5% of participants in any dose group)</b>		
Upper respiratory tract infection	47 (11.6)	45 (11.0)
Nasopharyngitis	33 (8.2)	47 (11.5)
Sinusitis	28 (6.9)	26 (6.4)
Urinary tract infection	22 (5.5)	26 (6.4)
Influenza	17 (4.2)	25 (6.1)
Nausea	19 (4.7)	19 (4.6)
<b>Serious adverse event (SAE)</b>	9 (2.2)	12 (2.9)
<b>Treatment-related SAE</b>	1 (0.2)	0
<b>Death</b>	0	0
<b>AE leading to discontinuation</b>	9 (2.2)	11 (2.7)

these are particular concerns for triptans and opioids among other medication classes.<sup>35</sup> For calcitonin gene-related peptide receptor antagonists such as ubrogepant, adverse event profiles are favorable, and there is no evidence that frequent use leads to medication overuse headache (MOH).<sup>15,16,18,36,37</sup> However, the pathophysiology of MOH is complex. Ubrogepant has poor CNS penetration, and many medications that cause MOH act centrally; yet, some poorly penetrant medications have been shown to lead to MOH.<sup>40-48</sup> Studies have shown that increased levels of CGRP may play a role in MOH, suggesting that CGRP receptor antagonists may help in preventing the development of MOH.<sup>38,39</sup> This class of compounds has proven efficacy in reducing the frequency and severity of migraine headache (i.e., migraine prevention).<sup>49,50</sup> Furthermore, during this long-term safety trial, an average annual dose of 38.5 doses of ubrogepant 50 mg and 40.2 doses of ubrogepant 100 mg was evaluated with no safety concerns identified, to date.<sup>18</sup> Data from the pivotal trials and results from this long-term evaluation continue to support the favorable safety and tolerability profile of ubrogepant with no reported risk of MOH. As such, ubrogepant may be well suited to this treatment approach and these data provide further evidence to support guidance to patients to treat migraine when pain is mild.

There are several strengths to this trial and analysis. The trial included a large number of participants treating many attacks, resulting in high power for studying the effects of interest. Instructing participants to treat attacks of mild, moderate, or severe pain at their discretion, up to 8 times per month for 1 year, provides information about real-world patterns of use, efficacy, tolerability, and safety of ubrogepant.



An important limitation is the absence of a placebo comparison in this trial; we do not know how attacks treated during mild pain with placebo might have responded. We know that in placebo-controlled trials of other treatments, the magnitude of the treatment effect for attacks treated during mild pain is substantial.<sup>13,14</sup> The open-label design of the trial could introduce bias; however, data for attacks treated during moderate or severe pain are very consistent with the randomized controlled phase 3 trials.<sup>15,16</sup> The analysis of associated symptoms included those who did not have the symptom at the time of treatment; data may be biased in favor of those who treated when pain was mild because fewer symptoms may be associated with mild pain. We also note that associated symptoms may emerge as attacks evolve after treatment with either active drug or placebo. Another limitation is that attacks were not randomly assigned to treatment when pain was mild vs moderate or severe. There may be an unmeasured confounding factor associated with early treatment that also predicts favorable treatment outcomes, such as a very gradual onset of pain. There may also be confounding factors associated with treatment when pain is moderate or severe that adversely influences outcomes, such as awakening from sleep with a moderate or severe headache. Although we cannot control for these unmeasured factors, the results suggest that treatment while pain is mild is associated with improved outcomes. Furthermore, we did not measure the duration of the attack before treatment or the presence or absence of allodynia. We cannot therefore assess the contribution of these possible prognostic factors on treatment outcomes.

In addition, these analyses were post hoc; there was no per-protocol plan for alpha control and no correction for multiple comparisons. The 2-hour data were specified as the time point of primary interest before conducting the analysis, and a total of 10 statistical tests were conducted at 2 hours, all of which were statistically significant. It is very unlikely that these positive results for the 5 main endpoints (at each of 2 ubrogepant doses) occurred because of chance alone. We conducted 24 additional tests at 24 and 48 hours examining freedom from pain and symptoms, as well as the use of rescue medication or an optional second dose for ubrogepant 50 and 100 mg. Among the 12 endpoints, all were statistically significant at 24 hours for both doses. At 48 hours, 11 of 12 endpoints were statistically significant for ubrogepant 50 mg, and 10 of 12 endpoints were statistically significant for ubrogepant 100 mg. Data for all the analyses that were performed are provided. Given that 30 of 34 total tests had *p* values of <0.001, it is extremely unlikely that these results could have arisen because of chance. Given the sample size, we may be at risk for detecting differences that are not clinically significant. To address that, we provide OR and CI to show the magnitude of the differences in treatment effects by pain intensity. The large OR for differences in outcomes for attacks treated when mild vs moderate or severe pain ranges from 2.4 to 3.4 and the lower bound of all CIs are always above 2, meaning attacks treated with mild pain are more than twice as likely to meet a definition of treatment success than

those with moderate or severe pain. This is true even when restricting the analysis to individuals who treated both mild and moderate or severe attacks.

These data demonstrate that a higher proportion of people achieve pain freedom, absence of associated symptoms, and normal function for attacks treated with ubrogepant during mild vs moderate or severe pain. Treatment during mild pain is also associated with a reduced use of rescue medication and optional second dose of ubrogepant. These findings suggest that treatment during mild pain may have benefits beyond greater efficacy. By reducing the number of tablets per treated attack and the need for rescue medication, early treatment during mild pain could have pharmacoeconomic benefits that should be explored. These data suggest that clinical guidance to treat early when pain is mild extends to ubrogepant. This paradigm may be particularly appropriate for gepants based on their favorable safety and tolerability profiles and lack of evidence for a risk of medication overuse that is a concern with other acute treatment options.

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## Appendix (continued)

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