Efficacy of Ubrogepant in the Acute Treatment of Migraine With Mild Pain Versus Moderate or Severe Pain

Author(s):
Richard B. Lipton, M.D.; David Dodick, MD; Peter J Goadsby, MD; Rami Burstein, PhD; Aubrey M Adams, PhD; Jeff Lai, PhD; Sung Yun Yu, BA; Michelle Finnegan, MPH; Amy W Kuang, PhD; Joel M Trugman, MD

Corresponding Author:
Richard B. Lipton, richard.lipton@einsteinmed.org

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.
Affiliation Information for All Authors: 1. Albert Einstein College of Medicine and Montefiore Headache Center, Bronx, NY, USA; 2. Mayo Clinic, Phoenix, AZ, USA; 3. Department of Neurology, University of California, Los Angeles CA USA and NIHR-Wellcome Trust King’s Clinical Research Facility, King’s College, London, UK; 4. Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA; 5. AbbVie Inc, Irvine, CA, USA; 6. AbbVie Inc, Madison, NJ, USA.

Equal Author Contribution:

Contributions:
Richard B. Lipton: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
David Dodick: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Peter J Goadsby: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Rami Burstein: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Aubrey M Adams: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Jeff Lai: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Sung Yun Yu: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Michelle Finnegan: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Amy W Kuang: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Joel M Trugman: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Figure Count:
4
Table Count:
2

Search Terms:

Acknowledgment:
The authors thank all the trial participants, investigators, and site staff for their participation in this trial and Rujun Teng, of AbbVie, for additional statistical analysis support on this manuscript. Medical writing support including revising and formatting the manuscript and preparation of tables and figures was provided by Amy Kuang, Ph.D., of AbbVie, a coauthor on the manuscript.

Study Funding:
Study sponsored by AbbVie.

Disclosures:
R.B. Lipton, MD, has received research support from the National Institutes of Health, the FDA and the National Headache Foundation; he serves as consultant, advisory board member, or has received honoraria or research support from AbbVie/Allergan, Amgen, Biohaven, Dr. Reddy's Laboratories (Promius), electroCore, Eli Lilly, GlaxoSmithKline, Lilly, Lundbeck, Merck, Novartis, Teva, Vector, and Vedanta Research; he receives royalties from Wolff's Headache, 8th edition (Oxford University Press, 2009), and Informa; he holds stock/options in Biohaven and Manistee. D.W. Dodick reports the following conflicts within the past 12 months: Consulting: Amgen, Atria, Cerecin, Cooltech, Ctrl M, Allergan, Biohaven, GSK, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Nocira, Praxis, AYVA Biosciences, Revance; Honoraria: Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press; Research Support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI). Stock Options/Shareholder/Patents/Board of Directors: Ctrl M (options), Aural analytics (options), ExSano (options), Palion (options), Healint (Options), Theranica (Options), Second
Opinion/Mobile Health (Options), Epien (Options/Board), Nocira (options), Matterhorn (Shares/Board), Ontologics (Shares/Board), King-Devick Technologies (Options/Board), Precon Health (Options/Board), AYYA Biosciences; Patent 17189376.1-1466; Title: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. P.J. Goadsby received grants and personal fees from Amgen and Eli Lilly and Company, grant from Celgene, and personal fees from Aeon Biopharma, Alder Biopharmaceuticals, Allergan, Biohaven Pharmaceuticals Inc., Clexio, ElectroCore LLC, eNeura, Epalex, GastroSmithKline, Impel Neuropharma, Lundbeck, MundiPharma, Novartis, Pfizer, Praxis, Sanofi, Santara Therapeutics, Satsuma, Teva Pharmaceuticals, Trigema Inc., WL Gore, MedicoLegal work, Up-to-Date, Oxford University Press, Massachusetts Medical Society, and Wolters Kluwer; and a patent magnetic stimulation for headache assigned to eNeura without fee. R. Burstein reports grant support, consulting, or advisory board with Alder, Allergan, Amgen, ATI, Avanir, Biohaven, Depomed, Dr. Reddy Laboratories, Electrocore, Eli Lilly, Johnson&Johnson, Neurorelief, Pernix, Percept, Revance, Teva, Theranica, Trigema and is an inventor and co-founder of Allay. A.M. Adams is a full-time employee and stockholder of AbbVie Inc. J. Lai is a full-time employee of AbbVie Inc. S.Y. Yu is a full-time employee of AbbVie Inc. M. Finnegan was a full-time employee of AbbVie Inc at the time of trial conduct and manuscript drafting. A.W. Kuang is a full-time employee of AbbVie and stockholder of AbbVie Inc. J.M. Trugman is a full-time employee and stockholder of AbbVie Inc.

Preprint DOI:

Received Date: 2021-03-08

Accepted Date: 2022-06-13

Handling Editor Statement: Submitted and externally peer reviewed. The handling editor was Rebecca Burch, MD.
ABSTRACT

Objective
To examine the efficacy of ubrogepant in the treatment of migraine with mild versus moderate or severe pain.

Methods
Phase-3, open-label, dose-blinded, 52-week extension trial. Adults with migraine were randomized 1:1:1 (usual care, ubrogepant-50mg, or ubrogepant-100mg). Participants treated up to 8 migraine attacks of any pain intensity every 4 weeks. Efficacy outcomes (only collected for ubrogepant) 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 are included. 2hPF rates were higher for attacks treated when pain was mild versus moderate or severe: ubrogepant-50mg (47.1% versus 23.6%; OR[95%CI]=2.89[2.57,3.24] and ubrogepant-100mg (55.2% versus 26.1%; 3.50[3.12, 3.92]; P<.0001 both doses). Rates of freedom from photophobia, phonophobia, and nausea 2 hours post-treatment were also significantly higher following treatment of mild versus 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 ubrogepant (P<0.001). The most common adverse event was upper respiratory tract infection (~11% both doses). Serious adverse events were reported by 2% in ubrogepant-50mg and 3% in ubrogepant-100mg.
Conclusion

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

(Funded by Allergan plc [prior to acquisition by AbbVie]; ClinicalTrials.gov NCT02873221)

Classification of Evidence: This study provides Class III evidence that ubrogepant, 50 mg or 100 mg, used by adults when migraine headache is mild as compared to when migraine headache is moderate to severe increases the probability of freedom from migraine headache pain, migraine associated symptoms, and disability 2 hours later.

INTRODUCTION

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

For acute treatments, regulatory guidance for acute treatment trials requires the treatment of migraine when pain is moderate or severe.7, 8 However, clinical guidance recommends treatment early in the migraine attack, when pain is mild.9 Despite clinical advice to treat early, many patients delay treatment to preserve limited medication supplies, avoid side effects, reduce risk of medication overuse, or hoping for spontaneous remission.10 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.\textsuperscript{11-14}

Ubrogepant is an oral, calcitonin gene-related peptide receptor antagonist approved for the acute treatment of migraine, with efficacy demonstrated in two phase-3 trials. Multiple studies demonstrated efficacy in the treatment of migraine with moderate or severe pain.\textsuperscript{15-17} The efficacy of ubrogepant when patients treat during mild pain has not yet been studied. The primary hypothesis was that treatment of migraine with ubrogepant when pain is mild would increase the likelihood of achieving positive outcomes, including pain freedom, relative to 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 versus moderate or severe pain in a one-year, long-term treatment trial (ClinicalTrials.gov, NCT02873221).

METHODS

\textit{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 prior to 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).

\textit{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.\textsuperscript{18}

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 one of the two 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/day. 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 though all were blinded to
the ubrogepant dose.

\textit{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 (eg, acetaminophen, NSAIDs, opiates), anti-emetics, or triptans. All efficacy data were collected via 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 postdose to evaluate efficacy. Alarms were programmed to ring at each timepoint as reminders.

Headache pain intensity was rated on a scale of no pain, mild pain, moderate pain, and severe pain at predefined timepoints: pre-dose, 2, 24, and 48 hours after the initial dose. The presence or absence of migraine-associated symptoms (ie, photophobia, phonophobia, nausea, vomiting) were recorded at pre-dose, 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 pre-dose and 2 hours after each initial dose. 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, 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 FDA guidance.\textsuperscript{8,19} The use of an optional second dose of ubrogepant within 24 hours and 48 hours post 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 hours and 48 hours after treating a migraine attack was recorded via 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.\textsuperscript{15,16} The outcome of primary interest was 2-hour pain freedom rates in attacks treated while pain was mild versus 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 post dose as well as looking at 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), electrocardiograms (screening, weeks 12, 24, 36, 48, and 52), and a suicidality assessment via 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 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 one dose of ubrogepant. The analysis population was defined as all randomized participants who received at least one dose of ubrogepant and had at least one post-treatment efficacy assessment collected during the trial. If data were incomplete or missing at any timepoint(s) for a treated attack, data for the attack at the affected timepoint(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. Absence of photophobia, phonophobia, and nausea were 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 versus moderate or severe pain. As participants could treat one or more migraine attacks throughout the 1-year trial, data for all treated attacks were included. Participants contributed varying numbers of attacks (eg, one participant may have contributed data for a single attack versus a participant who contributed data for six 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 carry out 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. Possible correlation of the outcomes within participant and within participants’ variations were handled by using the mixed treatment with repeated measurement method. There was no significant impact with the inclusion of other baseline characteristics in the model (eg, age, gender). Responder rates, odds ratios (OR), corresponding 95% confidence intervals (95% CI), and unadjusted p-values are reported. Only observed data were included and no imputation was applied. An additional subgroup analysis was carried out using this model-based approach in participants who treated at least one mild and one 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 IFPMA on behalf of ICH. Treatment-emergent adverse events (TEAE), treatment-related TEAE, serious adverse events, adverse events leading to discontinuation, and clinical laboratory assessments were summarized by treatment group.

**Data Availability Statement**

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor, including access to anonymized, individual and trial-level data (analysis data sets), as well as other information (eg, 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.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following 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 https://www.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 1310 participants from the lead-in ACHIEVE I and ACHIEVE II trials were assessed for eligibility and 1254 were randomized into this trial. There were 1230 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 was 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 3408 attacks due to missing data on efficacy at 2 hours. Out of the attacks included in this analysis, 3914 were treated when pain was mild, 11,227 when pain was moderate, and 4150 when pain was severe. Over the course of the trial, most participants treated attacks of more than one pain intensity (n=696/808, 86%). In the ubrogepant 50 mg group, 58% of participants (234/401) treated at least one attack when pain was mild while 99% (395/401) treated at least one attack with moderate or severe pain. In the ubrogepant 100 mg group, 57% of participants (234/407) treated at least one attack when pain was mild and 99% (404/407) treated at least one attack with moderate or severe pain. Overall, a higher number of moderate or severe attacks were treated by participants during the trial (eFigure 1). 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).
**Efficacy Outcomes**

At 2 hours post dose, rates of pain freedom were higher for attacks treated when pain was mild versus those treated when moderate or severe for ubrogepant 50 mg (47.1% versus 23.6%; adjusted OR [95% CI]: 2.89 [2.57, 3.24]) and ubrogepant 100 mg (55.2% versus 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 post dose for both dose groups (eFigure 2 and eFigure 3).

Absence of each migraine-associated symptoms at 2 hours post dose occurred in a significantly higher proportion of attacks treated when pain was mild versus moderate or severe (P<0.001 all symptoms, both doses; Figure 3). For attacks treated with mild versus moderate or severe pain, 63.5% versus 36.2% of attacks had absence of photophobia (adjusted OR [95% CI]: 3.07 [2.74, 3.43]) following treatment with ubrogepant 50 mg and 62.6% versus 38.1% (2.72 [2.43, 3.04]) following treatment with ubrogepant 100 mg. Following treatment of attacks with mild versus moderate or severe pain, 68.9% versus 43.0% of attacks had absence of phonophobia with ubrogepant 50 mg (2.94 [2.62, 3.30]) and 69.8% versus 47.1% with ubrogepant 100 mg (2.59 [2.30, 2.91]). Absence of nausea at 2 hours following treatment of attacks with mild versus moderate or severe pain was seen in 87.9% versus 68.3% of attacks treated with ubrogepant 50 mg (adjusted OR [95% CI]: 3.38 [2.90, 3.95]) and 85.0% versus 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 who treated both mild and moderate or severe attacks (eFigure 4 and eFigure 5).
A significantly higher proportion of treated attacks had normal function at 2 hours post dose when treated while pain was mild versus moderate or severe for ubrogepant 50 mg (66.6% versus 34.3%; adjusted OR [95%CI]: 3.83 [3.40, 4.30] and ubrogepant 100 mg (70.1% versus 37.2%; 3.95 [3.50, 4.46]; P<0.001 both doses) (Figure 4A). Significant differences were also seen in the subgroup who 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 versus moderate or severe for ubrogepant 50 mg (30.6% versus 39.9%; adjusted OR [95%CI]: 0.66 [0.60, 0.74]) and ubrogepant 100 mg (20.9% versus 36.9%; 0.45 [0.40, 0.51]) (eFigure 6). Significant differences continued to be observed at 48 hours post dose for both dose groups. The use of rescue medication was significantly lower when attacks were treated when pain was mild versus moderate or severe only for ubrogepant 100 mg at 24 hours (7.4% versus 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; additional results are posted in the clinical trials registry (clinicaltrials.gov; NCT02873221). Treatment-emergent adverse events were reported by 268/404 participants (66.3%) in ubrogepant 50 mg and 397/409 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% of participants (ubrogepant 50 mg) and 2.9% (ubrogepant 100 mg). 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). No deaths were reported during the trial.

Classification of Evidence

The primary hypothesis was that treatment of migraine with ubrogepant when pain is mild would increase the likelihood of achieving positive outcomes, relative to 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 versus moderate or severe increases the likelihood of achieving pain freedom, absence of symptoms, and normal function.

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, while attacks treated when pain was mild resulted in significantly higher rates of pain freedom at 2 hours.\textsuperscript{15, 16} A significantly higher proportion of attacks also had absence of associated symptoms and normal function at 2 hours post dose for migraine attacks treated when pain was mild versus 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 to treating attacks when pain is moderate or severe. There are several possible, non-mutually exclusive explanations for greater efficacy with 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 due to the blood-brain barrier. 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.

There are several factors to consider when evaluating the efficacy of an acute treatment for migraine. For Phase III regulatory trials in the US, 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 post-dose. Based on these endpoints, the efficacy of ubrogepant has been demonstrated in two phase 3, pivotal trials. Prior research has also shown that factors such as early efficacy, sustained benefit, and return to normal function are important considerations for patients. 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 versus placebo in achieving normal function. Though regulatory guidance requires treatment when pain is moderate or severe, clinical guidance recommends treating early in the attack while pain is mild.

Benefits of early treatment while pain is mild have been demonstrated for an array of acute treatments for migraine. Specifically, data published on the triptans show increased efficacy and cost-effectiveness were achieved with early treatment (ie, within 1 hour of onset) and when pain was mild. These data demonstrate that treatment of a migraine attack when pain is mild results in a higher likelihood of achieving positive outcomes compared to treatment of a migraine attack when pain is moderate or severe. Though 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 one attack when pain was mild indicating that a sizeable minority treated no attacks with mild pain over the course of up to one 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, onset of moderate or severe pain was nearly instantaneous. 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 to 60 minutes. In these instances, treating when pain is mild may prove challenging. Furthermore, the time of 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 upon wakening; for these attacks, pain may be of moderate or severe intensity by the time treatment is possible. While 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; these are particular concerns for triptans and opioids among other medication classes. 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). However, the pathophysiology of MOH is complex. Ubrogepant has poor central nervous system penetration and many medications that cause MOH act centrally; yet, some poorly penetrant medications have been shown to lead to MOH. Studies have shown that increased levels of CGRP may play a role in MOH,
suggesting CGRP receptor antagonists may help in preventing the development of MOH.\textsuperscript{38, 39}

This class of compounds has proven efficacy in reducing the frequency and severity of migraine headache (ie, migraine prevention).\textsuperscript{49, 50} Further, 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 were evaluated with no safety concerns identified, to date.\textsuperscript{18} 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 provides further evidence to support guidance to patients to treat migraine when pain is mild.

**Strengths and Limitations**

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 one 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.\textsuperscript{13, 14} 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.\textsuperscript{15, 16} 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 as 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 versus 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. While 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 prior to treatment or the presence or absence of allodynia. We cannot therefore assess the contribution of these possible prognostic factors on treatment outcomes.

Additionally, 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 five main endpoints (at each of two ubrogepant doses) occurred due to 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 mg and 100 mg. Among the twelve 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 due to 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 versus moderate or severe range from 2.4 to 3.4 and the lower bound of all CI 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. This is true even when restricting the analysis to individuals who treated both mild and moderate or severe attacks.

CONCLUSIONS

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 versus 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 which 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.

WNL-2022-200981_etab1 -- http://links.lww.com/WNL/C253
REFERENCES

20. Vermeersch SGG, de Hoon J, De Saint-Hubert B, et al. PET imaging in healthy subjects and migraineurs suggests CGRP receptor antagonists do not have to act centrally to achieve clinical efficacy. The journal of headache and pain 2013;14:P224-P224.
33. de Tommaso M, Delussi M. Circadian rhythms of migraine attacks in episodic and chronic patients: a cross sectional study in a headache center population. BMC neurology 2018;18:94.
### Table 1. Participant Baseline Demographics and Clinical Characteristics (Analysis Population)

<table>
<thead>
<tr>
<th></th>
<th>Ubrogepant 50 mg</th>
<th>Ubrogepant 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=401</td>
<td>N=407</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>42.4 (12.2)</td>
<td>41.5 (11.2)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>18, 72</td>
<td>18, 73</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>370 (92.3)</td>
<td>364 (89.4)</td>
</tr>
<tr>
<td>Male</td>
<td>31 (7.7)</td>
<td>43 (10.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>347 (86.5)</td>
<td>336 (82.6)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>48 (12.0)</td>
<td>57 (14.0)</td>
</tr>
<tr>
<td>Other&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6 (1.5)</td>
<td>14 (3.4)</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>29.4 (7.3)</td>
<td>30.1 (7.9)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>17, 54</td>
<td>17, 56</td>
</tr>
<tr>
<td>Concomitant Preventive Migraine Medication, n (%)</td>
<td>101 (25.2)</td>
<td>102 (25.1)</td>
</tr>
</tbody>
</table>
a Other includes Asian, American Indian or Alaska native, native Hawaiian or other Pacific Islander, and those who reported multiple races.

b Data for n=400 reported for ubrogepant 50 mg
Table 2. Summary of Adverse Events (Safety population)

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Ubrogepant 50 mg N=404</th>
<th>Ubrogepant 100 mg N=409</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent adverse event (TEAE)</td>
<td>268 (66.3)</td>
<td>297 (72.6)</td>
</tr>
<tr>
<td>Treatment-related TEAE</td>
<td>42 (10.4)</td>
<td>43 (10.5)</td>
</tr>
<tr>
<td>Commonly reported TEAE (≥5% of participants in any dose group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>47 (11.6)</td>
<td>45 (11.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>33 (8.2)</td>
<td>47 (11.5)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>28 (6.9)</td>
<td>26 (6.4)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>22 (5.5)</td>
<td>26 (6.4)</td>
</tr>
<tr>
<td>Influenza</td>
<td>17 (4.2)</td>
<td>25 (6.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (4.7)</td>
<td>19 (4.6)</td>
</tr>
<tr>
<td>Serious adverse event (SAE)</td>
<td>9 (2.2)</td>
<td>12 (2.9)</td>
</tr>
<tr>
<td>Treatment-related SAE</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>9 (2.2)</td>
<td>11 (2.7)</td>
</tr>
</tbody>
</table>
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 one dose of treatment. The analysis population was only defined for the ubrogepant treatment groups as 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 post-treatment efficacy assessment in this trial.
Figure 2. Pain Freedom at 2 Hours Post 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)

Analysis population is defined as all randomized patients who received at least 1 dose of ubrogepant and had at least 1 post-treatment 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, 95% confidence intervals, and p-values are based on a generalized linear mixed model that addresses within participant correlation. All available data are used in the analysis.
Analysis population is defined as all randomized patients who received at least 1 dose of ubrogepant and had at least 1 post-treatment efficacy assessment in this trial. Absence of symptom includes data for all treated attacks regardless of presence/absence of the symptom pre-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, 95% confidence intervals, and p-values are based on a generalized linear mixed model that addresses within participant correlation. All available data are used in the analysis.
Figure 4. Normal Function at 2 Hours Post 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)

Analysis population is defined as all randomized patients who received at least 1 dose of ubrogepant and had at least 1 post-treatment 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, 95% confidence intervals, and p-values are based on a generalized linear mixed model that addresses within participant correlation. All available data are used in the analysis.
Efficacy of Ubrogepant in the Acute Treatment of Migraine With Mild Pain Versus Moderate or Severe Pain
Richard B. Lipton, David Dodick, Peter J Goadsby, et al.
Neurology published online August 17, 2022
DOI 10.1212/WNL.0000000000201031

This information is current as of August 17, 2022

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/early/2022/08/17/WNL.0000000000201031.full

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Headache
http://n.neurology.org/cgi/collection/all_headache
All Pain
http://n.neurology.org/cgi/collection/all_pain
Class III
http://n.neurology.org/cgi/collection/class_iii
Clinical trials Randomized controlled (CONSORT agreement)
http://n.neurology.org/cgi/collection/clinical_trials_randomized_controlled_consort_agreement
Migraine
http://n.neurology.org/cgi/collection/migraine

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise