Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA

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Summary

Background Ubrogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist that is approved for acute treatment of migraine. The prodrome is the earliest phase of a migraine attack and is characterised by non-aura symptoms that precede headache onset. The aim of this trial was to evaluate the efficacy, safety, and tolerability of ubrogepant 100 mg compared with placebo for the acute treatment of migraine when administered during the prodrome.

Methods This PRODROME trial was a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial of ubrogepant 100 mg conducted at 75 research centres and headache clinics in the USA. Eligible participants were adults aged 18–75 years who had at least a 1-year history of migraine with or without aura and a history of two to eight migraine attacks per month with moderate to severe headache in each of the 3 months before screening. Eligible participants were randomly assigned (1:1) to either receive placebo to treat the first qualifying prodrome event and ubrogepant 100 mg to treat the second qualifying prodrome event or to receive ubrogepant 100 mg to treat the first qualifying prodrome event and placebo to treat the second qualifying prodrome event. An automated interactive web-response system used permuted blocks of four to manage randomisation. All people giving interventions and assessing outcomes were masked to group assignment during the study. People doing data analysis, which occurred after study completion, were not masked to group assignment. During the double-blind treatment period, each participant was instructed to orally take two tablets of the study drug at the onset of each qualifying prodrome event. The primary endpoint was absence of moderate or severe intensity headache within 24 h after study-drug dose; efficacy analyses were conducted with the modified intention-to-treat (mITT) population, defined as all randomly assigned participants with at least one headache assessment within 24 h after taking the study drug during the treatment period. The safety population included all treated participants who took at least one administration of study drug. The trial is registered with ClinicalTrials.gov (NCT04492020).

Findings Between Aug 21, 2020, and April 19, 2022, 518 participants were randomly assigned to double-blind crossover treatment. The safety population included 480 participants and the mITT population included 477 participants; 421 (88%) of 480 participants were female and 59 (12%) were male. Absence of moderate or severe headache within 24 h after a dose occurred after 190 (46%) of 418 qualifying prodrome events that had been treated with ubrogepant and after 121 (29%) of 423 qualifying prodrome events that had been treated with placebo (odds ratio 2·09, 95% CI 1·63–2·69; p<0·0001). Adverse events that occurred within 48 h after study-drug administration were reported after 77 (17%) of 456 qualifying prodrome events that had been treated with ubrogepant and after 55 (12%) of 462 events that had been treated with placebo.

Interpretation Ubrogepant was effective and well tolerated for the treatment of migraine attacks when taken during the prodrome.

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Introduction

Migraine is a highly prevalent and debilitating neurological disease that is characterised by recurrent attacks of moderate or severe headache and associated symptoms.[1,2] Regulatory clinical trials evaluating the efficacy of acute treatments for migraine have required the presence of moderate or severe headache before treatment is administered.[3] However, treatment response is more favourable when headache is treated early after its onset, when headache intensity is mild.[4,5]

Although migraine attacks and treatment outcomes are often defined by the duration and severity of headache pain, attacks are known to occur in multiple phases, each of which has a unique biology.[6] The prodrome (ie, premonitory phase) is often the earliest phase of a migraine attack and consists of various symptoms,

Research in context

Evidence before this study

We conducted an unrestricted PubMed search for original articles using the search terms "prodrome" or "premonitory" and "migraine" and "acute" from database inception to May 15, 2023. No placebo-controlled clinical trials that evaluated the efficacy of an acute treatment that was administered during the prodrome or premonitory phase of migraine were identified. A manual search identified two published reports that evaluated acute treatment during the prodrome. One small (n=19), double-blind, crossover study published in 1982 evaluated 30 mg domperidone versus placebo taken at the first appearance of so-called warning signals in people with migraine. A second report, published in 1987, evaluated dihydroergotamine nasal spray versus placebo administered during premonitory symptoms or aura in 91 patients with migraine. Both studies found a reduced occurrence of headache with active treatment versus placebo when participants administered treatment before the headache phase. Although suggestive, these studies had small sample sizes and numerous methodological differences from current clinical trials.

Added value of this study

This trial is the first phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial to evaluate the efficacy, safety, and tolerability of acute treatment compared with placebo when administered during the migraine prodrome. All participants underwent a rigorous screening period during which they were required to show that they could identify prodromal symptoms that were reliably (ie, at least 75% of the time) followed by migraine headache within 1–6 h. In clinical trials, ubrogepant has shown a favourable efficacy, safety, and tolerability profile when administered during the headache phase in people with migraine. The results of the PRODROME trial support these findings by showing the efficacy of ubrogepant when administered before the occurrence of headache pain in people with migraine with prodrome symptoms that are reliably followed by headache.

Implications of all the available evidence

These results emphasise the clinical value of identifying the prodrome in people with migraine and highlight an important opportunity to intervene in the earliest phase of a migraine attack to prevent progression to the headache phase, reduce disability, and improve outcomes.

including sensitivity to light, fatigue, and neck pain.[2,7] In people with migraine with a prodromal phase, symptoms can occur between hours and days before the onset of headache.[2] The prodromal phase can be highly predictive of the headache phase in some people and could provide an opportunity for treatment to prevent the development of or attenuate the severity of the headache phase.[8,9]

Calcitonin gene-related peptide (CGRP) is an important mediator of migraine attacks; antagonism of the CGRP pathway is effective for acute and preventive treatment of migraine.[10] Small-molecule CGRP receptor antagonists (known as gepants) are well tolerated and have not been associated with medication-overuse headache; atogepant reduces migraine frequency when used every day and rimegepant reduces migraine frequency when used every other day for preventive treatment.[11–13] Ubrogepant, approved by the US Food and Drug Administration for acute treatment of migraine, might therefore be a feasible option for intervention during the prodrome to prevent or reduce the pain and disability that is associated with the headache phase.

Ubrogepant is effective, well tolerated, and safe for the acute treatment of migraine when administered after the onset of headache.[14,15] The aim of this trial was to evaluate the efficacy, safety, and tolerability of ubrogepant 100 mg compared with placebo for the acute treatment of migraine when administered during the prodrome in people with migraine who could identify prodromal symptoms that were reliably (ie, at least 75% of the time) followed by headache.

Methods

Study design

This trial was a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial conducted at 75 research centres and headache clinics in the USA. The trial included a 60-day screening period followed by a 60-day double-blind treatment period. During the double-blind treatment period, participants treated two separate qualifying prodrome events that were separated by a 7-day washout period, which started after taking the study intervention for the first qualifying prodrome event (figure 1). Eligible participants were randomly assigned (1:1) to sequence A or sequence B. Participants in sequence A received placebo to treat the first qualifying prodrome event and ubrogepant 100 mg to treat the second qualifying event; participants in sequence B received ubrogepant 100 mg to treat the first qualifying prodrome event and placebo to treat the second qualifying event.

In the study protocol, a qualifying prodrome event was defined by the presence of prodromal symptoms that were, based on participant judgement, likely to be followed by headache within 1–6 h. Headache could not be present during the prodrome, and the participant could not have had a headache or used acute treatment

within 48 h before the onset of the qualifying prodrome event.

This trial was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice. An independent ethics committee or institutional review board at each site approved the protocol and any written information that was provided to participants (appendix pp 9–128).

Participants

Eligible participants were adults aged 18–75 years who had at least a 1-year history of migraine with or without aura that was consistent with a diagnosis according to the International Classification of Headache Disorders, third edition,[2] and a history of two to eight migraine attacks per month with moderate to severe headache in each of the 3 months before screening. Additional inclusion criteria were onset of migraine before age 50 years, current or previous use of at least one prescription medication for the acute treatment of migraine or of prescription medication for the preventive treatment of migraine, and BMI of 40 kg/m² or less. At the screening visit, participants were asked "Do you have warning signs that tell you that a headache is about to start?" Participants were then taken through a symptom checklist of more than 25 specific symptoms and asked whether they regularly experienced each symptom before headache onset and, if so, how much time passed between symptom onset and headache onset. Participants were also able to report prodromal symptoms that were not on the checklist as the checklist included a free-text answer option. Finally, participants were asked "After experiencing your prodrome symptoms, how reliably does a headache occur within 1–6 hours?" Participants who responded "greater than 75% of the time" were asked to show this occurrence by recording all qualifying prodrome events during the 60-day screening period. After the screening period, to be eligible for randomisation, the participant needed to record 3–16 qualifying prodrome events with at least 75% of these events followed by a headache of any intensity within 1–6 h.

Participants were excluded if they had difficulty distinguishing migraine from tension-type or other headache types or if they had chronic migraine, trigeminal autonomic cephalalgia, or painful cranial neuropathy. Other exclusion criteria were any clinically significant disease; history of migraine aura with diplopia or impairment of level of consciousness, hemiplegic migraine, or retinal migraine (as defined by the International Classification of Headache Disorders, third edition); or presence of a chronic, non-headache pain condition requiring daily pain medication. Participants who overused medication for migraine or had previous exposure to an anti-CGRP monoclonal antibody within 3 months of visit 1 were excluded (appendix pp 9–12).

See Online for appendix

Sex was reported by the investigator on the basis of self-reported answers from participants; the options were Male or Female only.

Participants provided written informed consent before trial entry.

Randomisation and masking

An automated interactive web-response system used permuted blocks of four to manage randomisation. Blister cards were dispensed at randomisation (ie, visit 2) and at the visit after the first treated attack (ie, visit 3). Each card was identical in appearance and contained two tablets of placebo or ubrogepant 50 mg, which were identical in appearance. Participants in sequence A received placebo at visit 2 and ubrogepant at visit 3; participants in sequence B received ubrogepant at visit 2 and placebo at visit 3. No person had any involvement in generating the group-assignment sequence. All people giving interventions and assessing outcomes were masked to group assignment during the study. People doing data analysis, which occurred after study completion, were not masked to group assignment. There was no assessment of the success of masking.

Procedures

During double-blind treatment, each participant was instructed to orally take two tablets of the study drug at the onset of each qualifying prodrome event. Study visits 3 and 4 occurred 4 days after taking the study drug to treat their first and second qualifying prodrome events. At each study visit, intervention compliance was

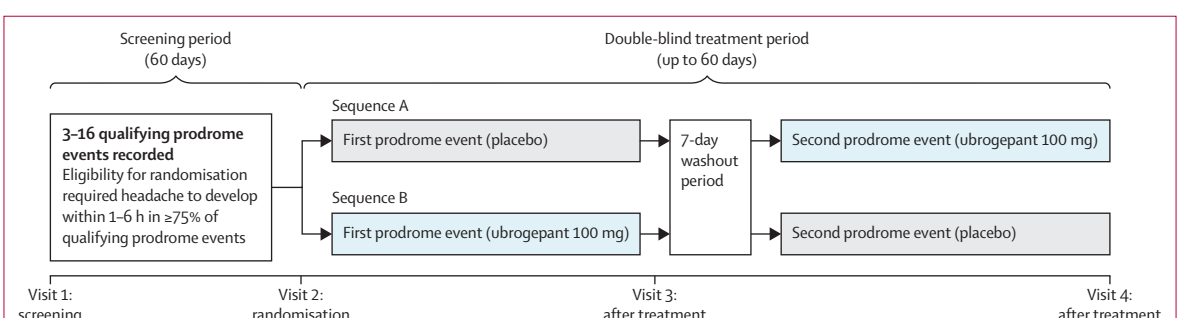

Figure 1: **Study design**

monitored by counting the number of tablets that were dispensed and were returned. Before dispensing new study drugs at study visits, study-centre staff collected unused study drugs and empty blister cards.

Efficacy assessments during the double-blind treatment period were recorded by the participant in an electronic diary, known as an eDiary. Upon identifying a qualifying prodrome event in which the participant was confident a headache would follow within 1–6 h, the participant entered this qualifying prodrome event into their eDiary and reported the presence or absence of prodromal symptoms (up to six prodromal symptoms). Entries in the eDiary could not be altered retrospectively. After treating the qualifying prodrome event with study medication and completing their initial eDiary entry, participants were required to report the absence or presence of a headache at 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 24 h, and 48 h after the dose. Participants could also report the onset of headache between timepoints. If a headache was reported, participants rated the intensity as mild, moderate, or severe and reported whether rescue medication (ie, acute treatment) was taken to treat it.

Outcomes

The primary endpoint was the absence of a headache of moderate or severe intensity within 24 h after taking the double-blind study drug for a qualifying prodrome event, which was centrally assessed. Participants who did not report a headache of moderate or severe intensity within 24 h and did not use rescue medication within 24 h were classified as treatment responders. If no headache or mild headache was reported at the scheduled timepoints, the participant had to confirm this absence of headache with a recall question at the 24-h timepoint (appendix pp 6–8).

Secondary endpoints were absence of moderate or severe headache within 48 h, "no disability, able to function normally" (as stated in the eDiary) within 24 h, and absence of headache of any intensity within 24 h of taking the study drug.

Functional disability was assessed with the Functional Disability Scale (FDS) before each dose of study drug (ie, baseline) and 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 24 h, and 48 h after each dose of the study drug. Ability to function was rated on a four-point scale. Participants who reported "no disability, able to function normally" were considered to be responders at each timepoint.

Safety assessments were adverse events, serious adverse events, adverse events leading to discontinuation, clinical safety laboratory variables, vital signs, electrocardiographic variables, and Columbia Suicide Severity Rating Scale score. Adverse events were measured from the time of providing informed consent until 30 days after the last dose of the study drug. The safety population included all treated participants who received at least one administration of the study drug.

Statistical analysis

A sample size of 480 participants in the modified intention-to-treat (mITT) population was estimated to provide 95% power to detect a treatment difference of 16 percentage points in response rate (80% for ubrogepant *vs* 64% for placebo) for the primary endpoint at a two-sided 5% significance level. Assuming that 20% of randomly assigned participants would drop out, 600 participants were originally planned for randomisation. A sample size re-estimation that was conducted with a masked datacut from July 5, 2021, found that only 7% of participants had no determinable data for the primary endpoint. On the basis of this observation, the sample size was revised to 516 randomly assigned participants to maintain the effective sample size of 480 participants.

Efficacy analyses were conducted with the mITT population, defined as all randomly assigned participants with at least one headache assessment within 24 h after taking the study drug during the double-blind treatment period. The safety population included all treated participants who took at least one administration of study drug.

A serial gatekeeping procedure was used to control the overall type I error rate at the 0·05 level for multiple comparisons across the primary endpoint and the three secondary efficacy endpoints. The order for endpoint hierarchy was primary, first secondary, second secondary, and third secondary. Sensitivity analyses were conducted to evaluate the robustness of the primary analysis (appendix p 2).

Absence of moderate or severe headache within 24 h, absence of moderate or severe headache within 48 h, and absence of headache of any intensity within 24 h after taking the double-blind study drug were analysed with a generalised linear mixed model (GLMM) based on determinable primary-endpoint data (appendix pp 6–8). This GLMM assumed a binary distribution for the response and used a logit link. The analysis included study intervention period and treatment as categorical fixed effects. An unstructured covariance matrix was used for the covariance matrix of the residual effect for the repeated measurements, corresponding to the two qualifying prodrome events, within a participant. The treatment difference was expressed as the odds ratio (OR) between ubrogepant and placebo. All statistical tests were two-sided hypothesis tests at the 5% level for main effects.

A similar GLMM model was fitted to examine the carryover effect. This model included period and treatment as categorical fixed effects and period by treatment as an interaction effect. The carryover effect was assessed via the confounded period by treatment interaction at the 0·05 significance level. If the carryover effect was significant, the analysis would only use data from the first period for the primary analysis. For sensitivity-analysis purposes, analysis with only data from the first period was done regardless of the

significance level of the carryover effect via a logistic-regression model with treatment effect.

"No disability, able to function normally" within 24 h after taking the double-blind study drug was assessed with repeated measures of dichotomised FDS responses. The dichotomised response had a value of 1 if the participant recorded no disability and a value of 0 otherwise. The repeated binary responses were analysed with a generalised estimating equation model with a logit link. Treatment effect was expressed as the geometric mean of the ORs of ubrogepant 100 mg relative to placebo, estimated at the scheduled timepoints within 24 h after taking the study drug. The geometric mean of the OR, 95% CI, and p value for "no disability, able to function normally" within 24 h were based on a generalised estimating equation model that used

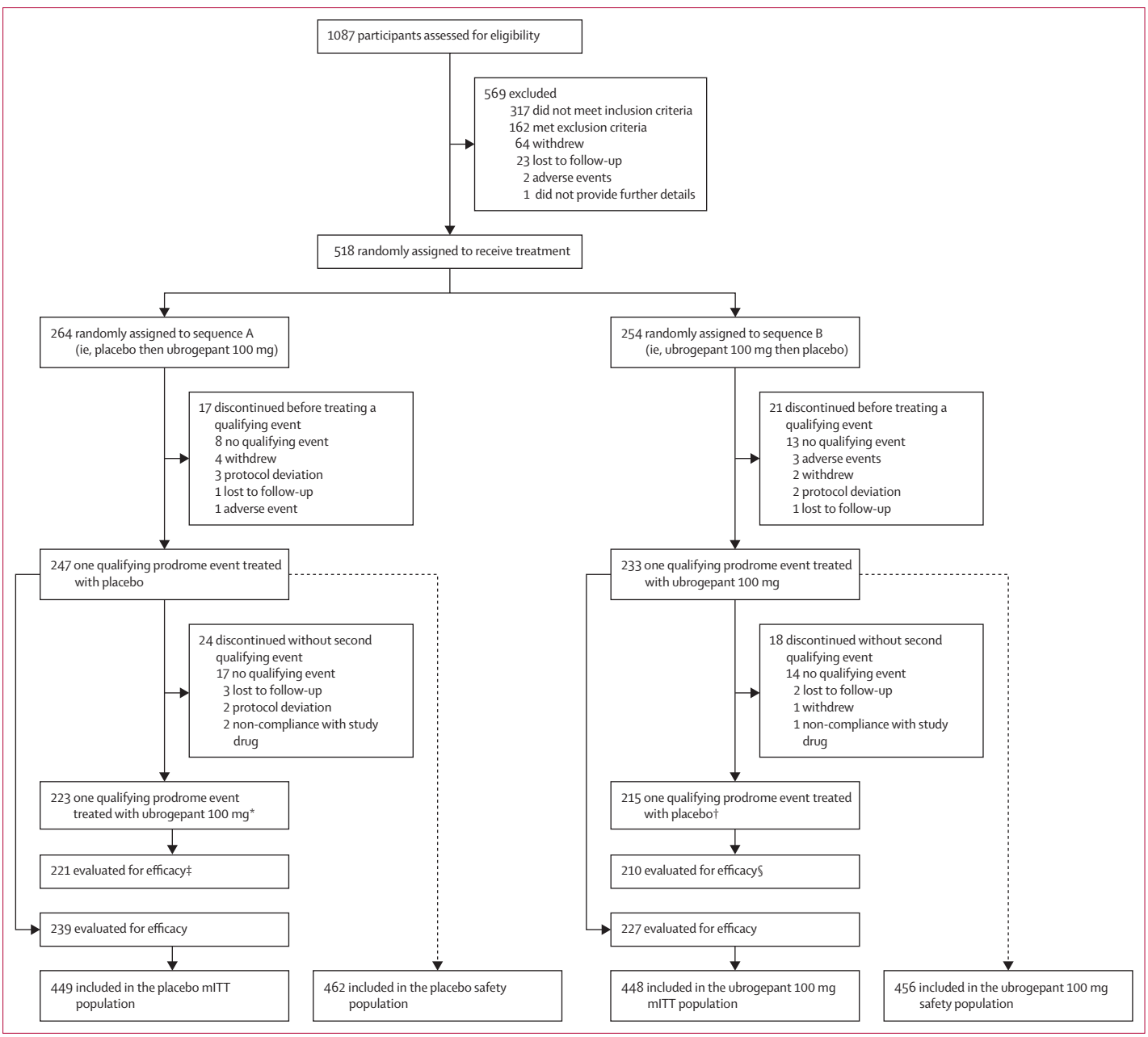

Figure 2: **Flow diagram**

The safety population included all treated participants who took at least one administration of the study drug. The mITT population included all randomly assigned participants with at least one assessment of headache occurrence within 24 h after taking the double-blind study drug for at least one qualifying prodrome event. mITT=modified intention-to-treat. *Crossed over and included in the ubrogepant 100 mg safety population. †Crossed over and included in the placebo safety population. ‡Crossed over and included in the ubrogepant 100 mg mITT population. §Crossed over and included in the placebo mITT population.

	Sequence A (n=247)	Sequence B (n=233)	Safety population (n=480)
Age, years	41·7 (12·6)	42·9 (13·1)	42·3 (12·9)
Sex			
Male	31 (13%)	28 (12%)	59 (12%)
Female	216 (87%)	205 (88%)	421 (88%)
Race			
White	214 (87%)	209 (90%)	423 (88%)
Black or African American	22 (9%)	15 (6%)	37 (8%)
Asian	7 (3%)	4 (2%)	11 (2%)
Native Hawaiian or other Pacific Islander	1 (>1%)	1 (>1%)	2 (>1%)
Multiple*	2 (1%)	4 (2%)	6 (1%)
Missing	1 (>1%)	0	1 (>1%)
Ethnicity			
Hispanic	17 (7%)	15 (6%)	32 (7%)
Non-Hispanic	229 (93%)	216 (93%)	445 (93%)
Missing	1 (>1%)	2 (1%)	3 (1%)
BMI, kg/m²	28·6 (5·6)	28·1 (5·6)	28·3 (5·6)
Aura-migraine diagnosis			
With aura	53 (22%)	42 (18%)	95 (20%)
Without aura	105 (43%)	110 (47%)	215 (45%)
With and without aura	89 (36%)	81 (35%)	170 (35%)
Duration with migraine, years			
Mean (SD)	21·6 (12·6)	23·8 (13·3)	22·7 (13·0)
Median (IQR)	20·0 (10·1–30·0)	22·8 (12·0–33·0)	21·0 (11·0–31·0)
Acute medication-use history†			
Triptan or triptan combinations	150 (61%)	135 (58%)	285 (59%)
Ergot or ergot combinations	1 (>1%)	0	1 (>1%)
NSAID	139 (56%)	115 (49%)	254 (53%)
Acetaminophen	53 (22%)	65 (28%)	118 (25%)
Opioid or opioid combinations	4 (2%)	8 (3%)	12 (3%)
Barbiturate or barbiturate combinations	4 (2%)	4 (2%)	8 (2%)
Gepant	0	0	0
Ditan	0	0	0
Devices	1 (>1%)	1 (>1%)	2 (>1%)
Other	104 (42%)	100 (43%)	204 (43%)
Preventive medication-use history	55 (22%)	39 (17%)	94 (20%)

Data are mean (SD), median (IQR), or n (%). Sequence A was placebo then ubrogepant 100 mg. Sequence B was ubrogepant 100 mg then placebo. NSAID=non-steroidal anti-inflammatory drug. *Participants who reported multiple races are only included in the Multiple category. †Participants could be counted more than once in this section.

Table 1: **Baseline demographics and migraine characteristics by treatment sequence in the safety population**

observed data at 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 24 h after the dose. The model included crossover period, treatment, scheduled timepoint after dose, and treatment-by-time interaction as categorical fixed effects and predose baseline FDS score for the crossover period and predose baseline-by-time interaction as covariates. Statistical analyses were conducted with SAS software version 9.4. This trial, the PRODROME trial, is registered with ClinicalTrials.gov (NCT04492020). There was no data monitoring committee.

Role of the funding source

The funder contributed to the study design and conduct; contributed to data collection, analysis, and interpretation; and reviewed and approved the manuscript for publication.

Results

Between Aug 21, 2020, and April 19, 2022, 1087 participants were recruited and assessed for eligibility. Of these 1087 participants, 23 (2%) individuals were excluded because they stated they could not, by history, identify migraine attacks in which they believed their prodromal symptoms were reliably (ie, at least 75% of the time) followed by headache. 920 participants recorded eDiary data during the 60-day screening period; 167 participants did not enter into the 60-day screening period (appendix p 3). 317 (29%) of 1087 participants did not meet inclusion criteria and 162 (15%) met exclusion criteria (appendix p 3). The most common reasons for not meeting inclusion criteria were not having 3–16 recorded qualifying prodrome events during screening (143 [45%] of 317) and no headache of any intensity reported within 1–6 h after at least 75% of qualifying prodrome events (123 [39%] of 317).

4802 qualifying prodrome events were reported by 920 participants during the screening period with a mean of 5·2 (SD 3·4) and a median of 5·0 (IQR 3·0–7·0) qualifying prodrome events reported per participant. The most common prodromal symptoms reported during screening were sensitivity to light (2748 [57%] of 4802), fatigue (2408 [50%]), neck pain (2013 [42%]), sensitivity to sound (1630 [34%]), and dizziness (1333 [28%]). Of the 911 participants with available headache-onset data for qualifying prodrome events, 701 (77%) were able to identify the events that were followed by headache within 1–6 h at least 75% of the time.

518 participants completed the screening period meeting all eligibility criteria and were randomly assigned to double-blind crossover treatment (figure 2; appendix p 4). The safety population included 480 participants. Of these participants, 477 (99%) completed at least one assessment of headache occurrence within 24 h after study-treatment dose for at least one qualifying prodrome event and were included in the mITT population. The mean age of participants was 42·3 years (SD 12·9); 421 (88%) of 480 participants were female and 59 (12%) were male (table 1). Of the 518 randomly assigned participants, 438 (85%) completed the trial. The most common reason for discontinuation during the treatment period was not treating two qualifying prodrome events (52 [10%] of 518) within 60 days. Of these 52 participants, 21 (40%) discontinued involvement in the trial without treating any qualifying prodrome event and 31 (60%)

discontinued involvement in the trial after treating only one qualifying prodrome event.

Absence of moderate or severe headache within 24 h after a dose occurred after 190 (46%) of 418 qualifying prodrome events that were treated with ubrogepant and after 121 (29%) of 423 qualifying prodrome events that were treated with placebo. The OR for ubrogepant 100 mg versus placebo was 2·09 (95% CI 1·63–2·69; p<0·0001; figure 3; appendix p 5). Sensitivity analyses, including an analysis of the first qualifying prodrome event only, supported this finding and there was no evidence of a carryover effect (appendix p 2).

Absence of moderate or severe headache within 48 h after treatment dose occurred after 159 (41%) of 391 qualifying prodrome events that were treated with ubrogepant 100 mg and after 100 (25%) of 407 qualifying prodrome events that were treated with placebo (OR 2·13, 95% CI 1·63–2·78; p<0·0001). More participants had "no disability, able to function normally" during 24 h after treatment with ubrogepant 100 mg following a qualifying prodrome event than after treatment with placebo (geometric mean of the OR 1·66, 95% CI 1·40–1·96; p<0·0001). The absence of a headache of any intensity within 24 h after treating a qualifying prodrome event was reported after 103 (24%) of 434 events that were treated with ubrogepant 100 mg and after 61 (14%) of 439 events that were treated with placebo (OR 1·93, 95% CI 1·39–2·66; p<0·0001).

Adverse events that occurred within 48 h after study-drug administration were reported after 77 (17%) of 456 qualifying prodrome events that were treated with ubrogepant and after 55 (12%) of 462 events that were treated with placebo (table 2). The most commonly reported adverse events after ubrogepant and placebo administration were nausea (23 [5%] of 456 *vs* 15 [3%] of 462), fatigue (12 [3%] of 456 *vs* seven [2%] of 462), dizziness (11 [2%] of 456 *vs* 12 [3%] of 462), and somnolence (11 [2%] of 456 *vs* five [1%] of 462).

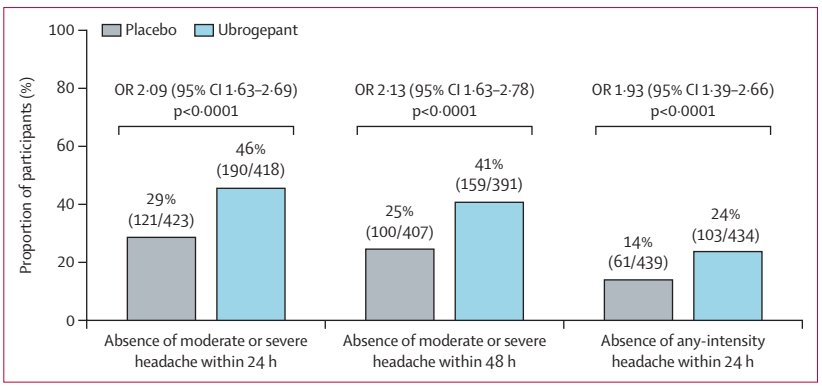

Figure 3: **Proportion of participants with absence of moderate or severe headache within 24 h, absence of moderate or severe headache within 48 h, and absence of any-intensity headache within 24 h after treatment during the prodrome**

ORs, 95% CIs, and p values are based on a generalised linear mixed model with treatment group and treatment period as categorical fixed effects. Analyses of primary and secondary endpoints only included determinable data for each endpoint (appendix pp 6–8). OR=odds ratio.

	Placebo (n=462)	Ubrogepant 100 mg (n=456)
Any adverse event	55 (12%)	77 (17%)
Adverse event leading to discontinuation	0	0
Treatment-related adverse event	42 (9%)	60 (13%)
Serious adverse event	0	0
Serious treatment-related adverse event	0	0
Death	0	0
Most common adverse events (ie, occurred in ≥2% of participants)		
Nausea	15 (3%)	23 (5%)
Dizziness	12 (3%)	11 (2%)
Fatigue	7 (2%)	12 (3%)
Somnolence	5 (1%)	11 (2%)

Data are n (%).

Table 2: **Adverse events within 48 h after the study intervention in the safety population**

Discussion

This trial showed the efficacy of ubrogepant 100 mg for the acute treatment of migraine when taken during the prodrome in people who experience prodromal symptoms reliably (ie, at least 75% of the time) followed by headache. Ubrogepant was superior to placebo in reducing the development of moderate or severe headache within 24 h and 48 h after administration. Ubrogepant was also superior to placebo in reducing disability and the development of headache of any intensity within 24 h after study-drug dose. The treatment was well tolerated; nausea, fatigue, dizziness, and somnolence were reported by 5% of participants or less. Our results challenge the generally accepted recommendation to treat migraine attacks at the first sign of headache pain,[5] suggesting that acute treatment administered before headache onset, during the prodrome, can prevent headache occurrence.

This is the first large placebo-controlled trial evaluating the efficacy of an acute treatment administered during the prodrome. Two previously published, placebo-controlled studies evaluated the feasibility of treatment during the prodrome. However, these studies were both conducted more than 30 years ago and had small sample sizes. In a double-blind, placebo-controlled, crossover trial in 19 patients with migraine with aura, domperidone 30 mg administered during the prodrome prevented the development of headache in 66% of active-treated attacks versus 5% of placebo-treated attacks.[16] In another double-blind, placebo-controlled, crossover trial involving 91 participants who were treated during the premonitory phase or with aura, intranasal dihydroergotamine 2 mg was superior to placebo in preventing headache occurrence (36% *vs* 26%).[17]

In a prospective, electronic-diary study, prodromal symptoms were found in 82% of participants.[8] In 72% of

these participants, prodromal symptoms could accurately predict the headache phase.[8] In a clinic sample of 461 patients with migraine who were questioned about the presence of 12 predefined prodromal symptoms, 87% reported at least one prodromal symptom.[18] The prodrome phase, therefore, provides an opportunity for the use of acute treatment that could prevent or attenuate the headache phase, reduce attack-related disability, and improve outcomes. In this trial, ubrogepant 100 mg prevented the development of moderate or severe headache after 46% of treated qualifying prodrome events compared with 29% of placebo-treated events in the 24-h period after treatment and after 41% of ubrogepant-treated events compared with 25% of placebo-treated events in the 48-h period after treatment. Ubrogepant treatment significantly reduced disability in the 24-h period after treatment.

Outcomes are improved when acute migraine treatment is administered when pain intensity is still mild, compared with when pain is moderate or severe.[4] Effective acute treatment is also important as suboptimal acute-treatment outcomes increase the risk of disease progression.[19] However, treatment when pain is mild is not possible in a substantial proportion of patients or attacks, as the most common demanding characteristic of a migraine attack is rapid onset.[20] In a cross-sectional study, pain intensity was reported to peak within 30 min of headache onset in 50·4% of patients; in a prospective questionnaire, pain intensity became moderate or severe within 60 min of headache onset in 64·4% of patients.[20,21] In addition to attacks that peak quickly, more than half of all migraine attacks occur during sleep, and pain intensity might be moderate or severe upon awakening.[22] Up to 71% of people with migraine report nocturnal migraine attacks, and 42% of people with migraine report that more than 75% of migraine attacks occur between 0300 h and 0700 h.[23,24] This nocturnal occurrence, in part, explains why many people with migraine, even when access to medication is not an issue, are not able to treat when pain intensity is mild. Treatment during the prodrome in people with daytime migraine attacks that peak quickly could therefore prevent pain from occurring or progressing to moderate or severe pain.

Although the biology of the prodrome phase of migraine is still being elucidated, hypothalamic activation and functional coupling between the hypothalamus and trigeminal nucleus caudalis has been shown.[25,26] CGRP receptors are highly expressed in these and other CNS regions that are involved in migraine pathogenesis, as well as in peripheral trigeminovascular nociceptors.[27] Both CGRP ligand-targeted and receptor-targeted monoclonal antibodies have been shown to reduce hypothalamic activation.[28,29] Such deactivation is associated with treatment response, especially in people who are treated with a CGRP receptor-targeted monoclonal antibody.[28,29] Furthermore, salivary CGRP-like immunoreactivity levels are increased between migraine attacks and progressively increase in the prodrome and headache phase.[30] These findings suggest a pathophysiological role for CGRP in the prodrome. The presence of a CGRP receptor antagonist during the prodrome might reduce CGRP-mediated activation of hypothalamic and other CNS sites that are involved in the generation or progression of the migraine attack, or reduce the activation of peripheral trigeminal sensory afferents that are involved in the headache phase of the attack.

This trial has limitations that are associated with the novel study design (ie, the population studied, small sample size, and only being conducted in one high-income country) and efficacy endpoints. Furthermore, the ability of some people with migraine to identify prodrome symptoms that can predict headache onset is controversial, and assessing the lack of occurrence of something during a short time (ie, 24 h) is difficult. However, randomly assigned participants underwent a 60-day screening period in which they showed that they could identify prodromal symptoms followed by headache within 1–6 h at least 75% of the time. This screening process was therefore necessary because the primary endpoint was the absence of headache after treatment during the prodrome. The generalisability of our results to the broader migraine population in the USA is supported by literature showing that prodrome symptoms are common and showing the association between the prodrome and headache phases of the acute migraine attack.[7,8,26] However, our trial, which was designed to assess the headache phase specifically, did not assess the influence of ubrogepant that was administered during the prodrome on other non-headache phases, such as aura and postdrome. Furthermore, as we evaluated treatment with only ubrogepant 100 mg versus placebo, the efficacy of other acute treatments administered during the prodrome is unknown and should be investigated in future research.

Compared with placebo, treatment with ubrogepant 100 mg during the prodrome significantly reduced the development of moderate or severe headache for 24 h after study-drug dose, the development of moderate or severe headache for 48 h after study-drug dose, and the development of headache of any intensity and functional disability for 24 h after study-drug dose. These results emphasise the clinical value of identifying the prodrome in people with migraine and highlight an important opportunity to intervene in the earliest phase of a migraine attack to prevent progression to the headache phase, reduce disability, and improve outcomes. Despite the regulatory guidance[3] and the International Headache Society clinical trial guidelines[2] that recommend acute treatment of migraine once pain becomes moderate or severe in intensity, treating migraine headache when pain is mild in intensity has led to the currently accepted clinical-practice standard of treating a migraine attack at the onset of pain. The results of this trial suggest that

evaluating the efficacy of acute medications that are taken during the prodrome versus the mild pain phase is an area that is worthy of future exploration. The prospect of treatment during the prodrome to prevent the onset of pain is substantially disruptive to currently accepted clinical-management strategies and warrants further examination.

Contributors

All authors contributed to the design of this study and acquired and analysed data. CL and KL did the statistical analysis. DWD and PJG directly accessed and verified the data. All authors had full access to all the data in the study; interpreted the data; prepared, reviewed, revised, and approved the final manuscript; and had final responsibility for the decision to submit for publication.

Declaration of interests

DWD is a consultant for Amgen, Atria, CapiThera, Cerecin, Ceruvia Lifesciences, CoolTech, Ctrl M, Allergan, AbbVie, Biohaven, GlaxoSmithKline, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Genentech, Nocira, Perfood, Praxis, AYYA Biosciences, Revance, and Pfizer; receives honoraria from the American Academy of Neurology, Headache Cooperative of the Pacific, Canadian Headache Society, MF Med Ed Research, Biopharm Communications, CEA Group, Clinical Education Alliance, Teva, Amgen, Eli Lilly, Lundbeck, Pfizer, Vector Psychometric, Clinical Care Solutions, CME Outfitters, Curry Rockefeller, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin, Medlogix Communications, Medica Communications, MJH Life Sciences, Miller Medical Communications, WebMD Health, Medscape, Wolters Kluwer, Oxford University Press, and Cambridge University Press; receives speaker fees from Teva, Amgen, Eli Lilly, Lundbeck, and Pfizer; is a board member for the American Brain Foundation, American Migraine Foundation, OneNeurology, Precon Health Foundation, International Headache Society Global Patient Advocacy Coalition, Atria Health Collaborative, Arizona Brain Injury Alliance, Domestic Violence HOPE Foundation, Panfila, Epien, Matterhorn, Ontologics, King-Devick Technologies, Precon Health, Axon Therapeutics, and Cephalgia; receives research support from the US Department of Defense, US National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, and US Patient-Centered Outcomes Research Institute; holds stock options in Ctrl M, Aural Analytics, ExSano, Palion, Man and Science, Healint, Theranica, Second Opinion, Mobile Health, Epien, Nocira, King-Devick Technologies, Precon Health, AYYA Biosciences, Axon Therapeutics, Cephalgia, and Atria Health; is a shareholder in Matterhorn and Ontologics; is an employee of Atria Health; holds patent 17189376.1-1466 (Onabotulinum toxin dosage regimen for chronic migraine prophylaxis); and has submitted a patent application for SynaQuell via Precon Health. PJG receives financial support for this study and personal fees from AbbVie; receives a grant from Celgene; receives personal fees from Aeon Biopharma, Amgen, BioDelivery Sciences International, CoolTech, Dr Reddy's, Eli Lilly, Epalex, Impel NeuroPharma, Lundbeck, Novartis, Praxis, Sanofi, Satsuma, ShiraTronics, Teva Pharmaceuticals, Tremeau, Gerson Lehrman, Guidepoint, SAI Med Partners, and Vector Metric; receives fees for educational materials from CME Outfitters, Omnia Education, and WebMD; receives fees for publishing and for medicolegal advice for headache from Massachusetts Medical Society and Oxford University Press; and holds a patent for Magnetic stimulation for headache, licensed to eNeura. TJS is on the board of directors for the American Headache Society and the American Migraine Foundation; receives research support from Amgen, Henry Jackson Foundation, Mayo Clinic, US National Institutes of Health, US Patient-Centered Outcomes Research Institute, SPARK Neuro, and US Department of Defense; is a consultant or advisory board member for AbbVie, Allergan, Axsome, Collegium, Eli Lilly, Linpharma, Lundbeck, Satsuma, and Theranica; holds stock options in Aural Analytics and Nocira; and receives royalties from UpToDate. RBL receives financial support for this study from AbbVie; receives research support, paid to his institution, from the US National Institutes of Health, the S&L Marx Foundation, the Czap Foundation, the National Headache Foundation, and the US Food and Drug Administration; is a consultant or advisory board member for and receives honoraria or research support from AbbVie, Allergan, American Academy of Neurology, American Headache Society, Amgen, Biohaven, Biovision, Boston, Dr Reddy's, Promius, electroCore, Eli Lilly, GlaxoSmithKline, Grifols, Lundbeck, Alder, Merck Sharp & Dohme, Pernix, Pfizer, Teva, Vector, and Vedanta Research; and holds stock options in Biohaven and Manistee. CL and JMT are employees of AbbVie and hold AbbVie stock. KL, SYY, LS, and MF are former employees of AbbVie and hold AbbVie stock.

Data sharing

The study protocol and statistical analysis plan are available in the appendix (pp 18–189). AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), 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 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 after approval in the USA and Europe and after acceptance of this manuscript for publication. 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://vivli.org/ourmember/abbvie/ then select "Home".

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