Safety and efficacy of atogepant for the preventive treatment of episodic migraine in adults for whom conventional oral preventive treatments have failed (ELEVATE): a randomised, placebo-controlled, phase 3b trial

Cristina Tassorelli, Krisztián Nagy, Patricia Pozo-Rosich, Michel Lanteri-Minet, Sara Sacco, Tomáš Nežádal, Hua Guo, Rosa De Abreu Ferreira, Giovanna Forero, Joel M Trugman

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Department of Brain and Behavioral Science, University of Pavia, Pavia, Italy (Prof C Tassorelli MD); **Headache Science and Neurorehabilitation Centre, IRCCS C Mondino Foundation, Pavia, Italy** (Prof C Tassorelli); **AbbVie, Budapest, Hungary** (K Nagy MD); **Headache Unit, Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain** (P Pozo-Rosich MD); **Headache and Neurological Pain Research Group, Vall d'Hebron Institute of Research, Universitat Autonoma de Barcelona, Barcelona, Spain** (P Pozo-Rosich); **Pain Department and FHU InovPain, CHU Nice and Côte Azur University, Nice, France** (M Lanteri-Minet MD); **INSERM U1107 Migraine and Trigeminal Pain, Auvergne University, Clermont-Ferrand, France** (M Lanteri-Minet); **Carolinas Headache Clinic, Matthews, NC, USA** (S Sacco MD); **Neurology Department, Military University Hospital, 1st Faculty of Medicine, Charles University, Prague, Czech Republic** (T Nežádal MD); **AbbVie, Madison, NJ, USA** (H Guo PhD, G Forero MA, J M Trugman MD); **AbbVie, Lisbon, Portugal** (R De Abreu Ferreira MD)

Correspondence to: Prof Cristina Tassorelli, IRCCS C Mondino Foundation, Pavia, PV 27100, Italia **cristina.tassorelli@unipv.it**

Summary

Background Atogepant, an oral calcitonin gene-related peptide receptor antagonist, has been approved for the preventive treatment of migraine, but its efficacy and safety in people who have been failed by conventional oral preventive migraine treatments has not yet been evaluated in a dedicated clinical trial. The ELEVATE trial evaluated the safety, tolerability, and efficacy of atogepant for the preventive treatment of episodic migraine in participants for whom two to four classes of conventional oral preventive treatments have failed.

Methods ELEVATE was a randomised, double-blind, placebo-controlled, parallel-group, phase 3b trial done at 73 sites in Canada, the Czech Republic, Denmark, France, Germany, Hungary, Italy, the Netherlands, Poland, Russia, Spain, the UK, and the USA. Adults (18–80 years) with episodic migraine who had previously been failed by two to four classes of conventional oral treatments for migraine prevention were randomly assigned (1:1) using interactive web response technology to oral atogepant 60 mg once a day or placebo, stratified by baseline monthly migraine days, number of treatment classes participants have been failed by, and region. The primary endpoint was change from baseline in mean monthly migraine days across the 12-week treatment period in the off-treatment hypothetical estimand (OTHE) population, which included participants in the safety population (all participants who received ≥1 dose of study intervention) who had evaluable data available for the baseline period and for one or more of the 4-week post-baseline periods (whether on treatment or off treatment). The primary endpoint was analysed using a mixed model for repeated measures and a fixed-sequence procedure was used to control for multiple comparisons. The trial is registered with ClinicalTrials.gov (NCT04740827) and EudraCT (2019-003448-58), and is completed.

Findings Between March 5, 2021, and Aug 4, 2022, 540 participants were screened, 315 were randomly assigned, and 313 participants (280 [89%] female, 33 [11%] male, and 300 [96%] White) received at least one dose of study intervention. In the OTHE population, which comprised 309 participants (155 assigned to placebo and 154 to atogepant), least squares mean changes from baseline in monthly migraine days across 12 weeks were –1·9 (SE 0·4) with placebo and –4·2 (0·4) with atogepant (least squares mean difference –2·4, 95% CI –3·2 to –1·5; adjusted p<0·0001). The most common treatment-emergent adverse event with atogepant was constipation in 16 (10%) of 156 participants (*vs* four [3%] of 157 for placebo). Serious adverse events occurred in four [3%] of 156 participants in the atogepant group *vs* none in the placebo group, and treatment-emergent adverse events resulting in treatment discontinuation occurred in three [2%] in the atogepant group *vs* two [1%] in the placebo group.

Interpretation Atogepant 60 mg once a day was safe, well tolerated, and showed significant and clinically relevant reductions in mean monthly migraine days compared with placebo across 12 weeks in patients with episodic migraine who had previously been failed by two to four classes of conventional oral preventive treatments. Atogepant might be an effective preventive treatment option for patients in this difficult-to-treat population.

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Introduction

Migraine, a chronic neurological disorder typified by recurring, long-lasting attacks with headache, nausea, vomiting, and sensitivity to light, sound, or both, is one of the most common and burdensome disorders in the world today.[1–3] Episodic migraine,[4] which is diagnosed in individuals who have migraine with or without aura as per International Classification of Headache Disorders, 3rd Edition (ICHD-3) and fewer than 15 headache days per month, occurs in 91–93% of people with migraine.[5] Among people with episodic migraine, 27% experience more than 3 headache days per month.[6] Scientific and expert consensus is generally that treating physicians should consider initiating preventive treatment when

Research in context

Evidence before this study

We searched PubMed for "migraine", "prevention", and "CGRP" with a filter for clinical trial, meta-analysis, randomised controlled trial, review, and systematic review and we found 419 articles on these topics published in English between Jan 1, 2008, and Dec 20, 2023. Conventional oral preventive medications include beta-blockers, antiepileptics, antidepressants, and other treatments that were not designed to specifically target migraine, have moderate efficacy against migraine, and have tolerability issues and contraindications that limit their use. Novel specific treatments, including monoclonal antibodies against CGRP or its receptor, showed efficacy and good tolerability in people with episodic and chronic migraine, including those who had previously been failed by conventional oral preventive treatments. Atogepant, an oral CGRP receptor antagonist, has shown efficacy and tolerability in preventive treatment of both episodic and chronic migraine, but these trials did not focus specifically on patients with multiple previous preventive treatment failures.

Added value of this study

This randomised placebo-controlled trial showed that oral atogepant is an efficacious and safe preventive treatment for episodic migraine in patients with documented failures of two to four oral migraine preventive treatment classes. To our knowledge, ELEVATE is the first study of an oral CGRP receptor antagonist in this difficult-to-treat population, which resembles patient populations typically seeking care at specialised headache centres. Atogepant 60 mg once a day showed statistically significant improvements compared with placebo for the primary and all secondary endpoints pertaining to headache-related clinical outcomes analysed in the off-treatment hypothetical estimand population. Treatment-related treatment-emergent adverse events in the atogepant group led to the withdrawal of only three patients, versus two patients in the placebo group.

Implications of all the available evidence

Many local guidelines that define access to medications currently restrict the use of novel preventive migraine treatments to patients who have been failed by two or more classes of conventional oral medications. Atogepant was efficacious and well tolerated in patients with episodic migraine who had previously been failed by multiple classes of conventional oral therapies, and it might be especially suitable for those who would like flexibility in their treatment regimen, owing to the shorter half-life of atogepant compared with CGRP monoclonal antibodies.

migraine attacks are severely disabling and occur on at least 2 days per month despite use of optimised acute treatments, especially if the patient is overusing acute medications.[7,8] According to expert opinion, preventive treatment might lower the likelihood of migraine progression (from episodic to chronic migraine) by reducing acute medication use and attack frequency.[9]

Conventional oral preventive medications include beta-blockers, antiepileptic drugs, calcium channel blockers, and antidepressants, which were not specifically developed to treat migraine.[7,10] These drugs have moderate efficacy against migraine, tolerability issues, and contraindications that limit their use.[11,12] Migraine burden, in terms of quality of life, disability, loss of work productivity, and economic cost, is higher in patients with previous preventive treatment failure, and this burden increases with successive treatment failures.[13–15] There is a substantial unmet need for effective, safe, and tolerable preventive treatments for this patient population.

Recent advancements in migraine therapy have centered on calcitonin gene-related peptide (CGRP), which has an important role in migraine pathophysiology.[10,16] Injectable monoclonal antibodies against CGRP (eptinezumab, fremanezumab, and galcanezumab) or its receptor (erenumab) have shown efficacy and good tolerability in the preventive treatment of migraine in large investigational programmes.[17] Many patients with migraine have reported a preference for oral treatments over injectable preventive treatments, and have noted the ease and familiarity of oral treatment regimens.[18–20] Gepants are oral, small molecule, CGRP receptor antagonists that were also developed specifically to treat migraine.[10,21]

Atogepant is an oral high-affinity gepant approved by the US Food and Drug Administration, European Medicines Agency, and the Medicines and Healthcare products Regulatory Agency for the preventive treatment of migraine. The efficacy and safety of atogepant for the preventive treatment of episodic migraine was established in the ADVANCE study, and its efficacy and safety for the preventive treatment of chronic migraine was established in the PROGRESS study, each of which enrolled both patients with and without previous preventive treatments.[22,23] In the ELEVATE study, we aim to evaluate the efficacy and safety of atogepant 60 mg once a day for the preventive treatment of episodic migraine in participants with documented previous treatment failures by two to four classes of oral preventive treatments.

Methods

Study design

ELEVATE was a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3b clinical trial done at 73 hospitals, universities, and clinical research sites across Canada, the Czech Republic, Denmark, France, Germany, Hungary, Italy, the Netherlands, Poland, Russia, Spain, the UK, and the USA. Two sites in Australia recruited patients, but none of these patients was enrolled

in the trial. The protocol was approved by institutional review boards or ethics committees at each participating institution. The study was designed and conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and guidelines originating from the Declaration of Helsinki. Full details of the study methods are available in the protocol (appendix pp 22–144). This trial is registered with ClinicalTrials.gov (NCT04740827) and EudraCT (2019-003448-58).

See Online for appendix

Participants

Eligible participants were aged 18–80 years at visit 1, with at least a 1-year history of migraine with or without aura consistent with a diagnosis according to the ICHD-3,[1] and migraine onset before the age of 50 years. Participants had 4 to 14 monthly migraine days and fewer than 15 monthly headache days in the 3 months before visit 1 per their medical history (collected at visit 1 by the investigator) and in the 4-week screening (baseline) period per the electronic diary (eDiary). To be eligible, participants needed to have completed at least 20 of 28 days in the eDiary during the baseline period.

Participants had to have documented (medical record or physician affidavit) failures by two to four classes of oral migraine preventive treatments, with classes defined as (1) beta-blockers (propranolol, metoprolol, atenolol, bisoprolol, timolol, or nadolol); (2) antiepileptic class 1 (topiramate); (3) calcium channel blockers (flunarizine); (4) antiepileptic class 2 (valproate or divalproex); (5) tricyclic antidepressants (amitriptyline or nortriptyline); (6) serotonin-norepinephrine reuptake inhibitors (venlafaxine or desvenlafaxine); (7) angiotensin-converting enzyme inhibitors (lisinopril); (8) angiotensin receptor blockers (candesartan); or (9) other locally approved products (including cinnarizine, iprazochrome, oxeterone, pizotifen, and cyproheptadine). Some medications, including cinnarizine, desvenlafaxine, and nortriptyline were included on the basis of therapeutic guidelines and medical consensus, despite the absence of controlled trial data showing efficacy. Additionally, participants had to have been failed by at least one of four specific treatments: (1) propranolol or metoprolol, (2) topiramate, (3) flunarizine, or (4) amitriptyline. Preventive treatment failure was based on lack of efficacy or of tolerability, per investigator judgement from medical records and participant interview conducted at visit 1 (appendix pp 136–37). Treatment failure due to lack of efficacy was defined as no meaningful reduction in frequency of migraine days after an adequate trial of at least 2 months at generally accepted therapeutic doses during the 7 years preceding screening. For tolerability, treatment failure was defined as discontinuation of a drug due to adverse effects at any previous time. Contraindications were not considered as treatment failures. Participants were required to use medically acceptable and effective birth control throughout the trial.

Participants were excluded if they had an ICHD-3-defined history of migraine accompanied by diplopia or decreased consciousness, or retinal migraine. They were also excluded if they had a current diagnosis of new persistent daily headache, chronic migraine, medication overuse headache, trigeminal autonomic cephalalgia (eg, cluster headache), or painful cranial neuropathy, as defined by ICHD-3. Participants who were pregnant, planning to become pregnant during the trial, or lactating were excluded. Participants with any clinically significant cardiovascular or cerebrovascular disease were excluded. Participants with clinically significant haematological, endocrine, pulmonary, hepatic, gastrointestinal, or neurological diseases were excluded, unless the condition had been stable for more than 1 year preceding baseline screening and was judged by the investigator as not likely to interfere with participation in the study.

Participants using analgesics containing barbiturates or opioids more than 2 days per month, triptans or ergots at least 10 days per month, or simple analgesics (eg, aspirin, NSAIDs, or acetaminophen) at least 15 days per month in the 3 months before visit 1 or during the baseline period were excluded. Opioid-containing medications were prohibited during the baseline period and throughout the study period, although episodic use for purposes not related to migraine or headache (eg, surgery) was allowed. Participants could use acute migraine treatments (eg, triptans, ergot derivatives, analgesics, NSAIDs, and antiemetic agents) without a limit on frequency or duration, except for those stated in the exclusion criteria (eg, opioids, barbiturates, and gepants).

Ubrogepant and rimegepant were prohibited during the baseline period and throughout the study; past use of atogepant was also exclusionary. Any medication with known efficacy for migraine prevention, including conventional oral migraine preventive treatments defined in the inclusion criteria, irrespective of the indication for use, was prohibited 30 days before screening and throughout the study. Injectable monoclonal antibodies targeting the CGRP pathway and therapeutic or cosmetic botulinum toxin injections into the head, face, or neck were prohibited 6 months before screening and throughout the study period. Participants gave written informed consent before screening. Full inclusion and exclusion criteria (appendix pp 59–64) and prohibited therapies (appendix pp 71–72) are detailed in the protocol.

Randomisation and masking

Eligible participants were randomly assigned (1:1) with interactive web response technology to receive either oral atogepant 60 mg or placebo once a day. Block randomisation was applied with a block size of 4 (two treatment groups × 2). Randomisation was stratified by number of migraine days during the baseline period (4 to <8 or ≥8), number of classes of preventive treatments participants had been failed by (two or more than two), and region (North America or Europe). A

randomisation cap was instituted to ensure that no more than 20% of overall participants experienced fewer than 8 monthly migraine days at baseline, and that approximately 50% of participants had been failed by more than two classes of preventive treatments. Atogepant tablets and matching placebo were dispensed in identical blister cards. Participants, investigators, and study site personnel were masked to treatment assignment.

Procedures

The trial included a 4-week screening (baseline) period, a 12-week double-blind treatment period, and a 4-week follow-up period (appendix p 3). At the screening visit, participants were provided with an eDiary, training, and instructions. Efficacy assessments, including baseline values, were recorded by participants at home using a daily eDiary; participants recorded headache occurrence, duration, characteristics (eg, unilateral, pulsating, intensity, aggravating factors, and impact), symptoms (eg, nausea, vomiting, photophobia or phonophobia, and aura), and acute medication use during the baseline and double-blind periods. Patient-reported outcomes were recorded at home using the daily eDiary or at the trial site using an electronic tablet. After the baseline period, eligible participants were randomly assigned and provided with the study intervention (atogepant or placebo) to be taken on an outpatient basis. To ensure compliance, participants received their first dose at the clinic and were instructed to take their study drug orally, once a day, at approximately the same time for 12 weeks.

Safety assessments included adverse events, laboratory parameters, vital signs, Columbia–Suicide Severity Rating Scale (C-SSRS; all visits), physical examination (visits 1, 7, and 8 or early termination), and electrocardiogram (ECG) assessments (visits 1, 5, and 7 or early termination). Participants of childbearing potential were required to have a urine pregnancy test at all visits. Adverse events were collected from the time of informed consent through to the last study visit (visit 8) or to 30 days after last dose of study drug for those who discontinued prematurely. The severity and causality of adverse events was assessed by investigators, who documented onset date, duration, seriousness, and any actions or treatments taken.

Individual adverse events were counted once for each participant for calculating percentages, unless stated otherwise. If the same adverse event occurred multiple times in the same participant, the highest severity and level of relationship to the investigational product was reported. Treatment-emergent adverse events were defined as any adverse events with onset after the first dose of study drug. Adverse events occurring on the same day as study drug start date were assumed to be treatment-emergent.

The protocol was amended to allow participants to complete remote visits if unable to attend in person due to the COVID-19 pandemic. Virtual or phone visits were permitted for up to 8 weeks, between visits 3 and 8. Results of at-home pregnancy tests were reported during virtual visits. Participants were required to attend office assessments at visit 3 or 4 to ensure laboratory samples were obtained within the first 4 weeks of treatment. Missed in-person safety assessments were done at the next in-person visit. Additional amendments to the protocol are listed in the appendix (pp 25–32).

Outcomes

The primary efficacy endpoint was change from baseline in mean monthly migraine days across the 12-week treatment period. Baseline values were defined as the number of migraine days during the 28 days before randomisation. Mean monthly migraine days during the double-blind period were calculated using the average number of monthly migraine days during weeks 1–4, 5–8, and 9–12. Secondary efficacy endpoints pertaining to headache-related clinical outcomes were the achievement of at least 50% reduction from baseline in the 3-month average of monthly migraine days, change from baseline in mean monthly headache days, and change from baseline in mean monthly acute medication use days across the 12-week treatment period. Secondary endpoints for patient-reported outcomes on disability and quality of life were 12-week changes from baseline in the Migraine-Specific Quality of Life Questionnaire (MSQ version 2.1), the Headache Impact Test (HIT-6) total score (Europe only), and scores from both domains of the Activity Impairment in Migraine-Diary (AIM-D; USA only); rather than grouping them with the headache-related clinical outcomes presented here, these patient-reported outcomes will be reported in future publications (appendix p 6).

Prespecified exploratory endpoints are described in the study protocol (appendix pp 53–56) and the statistical analysis plan (appendix pp 163–65). Change from baseline in mean monthly migraine days by 4-week interval is reported to support the primary endpoint. Achievement of at least 25%, at least 30%, at least 75%, and 100% reduction from baseline in the 3-month average of monthly migraine days is reported here to complement the at least 50% responder rate secondary endpoint, and responder rates by 4-week interval are also reported. Prespecified subgroup analyses were conducted on the primary efficacy endpoint, based on the number of preventive treatment class failures (two *vs* more than two), migraine frequency at baseline (4 to <8 *vs* ≥8 migraine days), and region (North America *vs* Europe).

Safety analysis included the incidence of adverse events, serious adverse events, adverse events leading to discontinuation, and laboratory parameters, vital signs, ECG parameters, and C-SSRS. Furthermore, post-baseline concentrations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at least three times the upper limit of normal, as well as potential occurrences

of Hy's law, were to be evaluated as prespecified adverse events of special interest and adjudicated by an independent panel of blinded hepatology experts. An independent data and safety monitoring board reviewed unblinded safety data and summary reports and assessed potential safety signals.

Statistical analysis

A sample size of 300 participants (150 per treatment group) was estimated to provide at least 95% power to detect a treatment difference of 1·6 mean monthly migraine days between atogepant and placebo (assuming a common SD of 3·5 days), controlling for an overall type I error rate of 0·05. The sample size provides more than 90% power for all secondary endpoints (appendix pp 158–62). Estimates for treatment difference and SD were based on previous trials of atogepant for episodic migraine and erenumab for patients with episodic migraine who had previously been failed by preventive treatments.[22,24,25]

Two efficacy analysis populations were specified for this study to meet requirements for potential regulatory submissions (appendix p 172). The off-treatment hypothetical estimand (OTHE) population was chosen to support potential regulatory submissions in Europe, and included all randomly assigned participants who received at least one dose of study intervention, had an evaluable baseline period of eDiary data, and had at least one evaluable post-baseline 4-week period (weeks 1–4, 5–8, and 9–12) of eDiary data during the double-blind treatment period and follow-up period, regardless of whether on or off study treatment.

The modified intent-to-treat (mITT) population included all randomly assigned participants who received at least one dose of study intervention, had an evaluable baseline period of eDiary data, and had at least one evaluable post-baseline 4-week period (weeks 1–4, 5–8, and 9–12) of eDiary data during the double-blind treatment period, while on study treatment. For patients with premature treatment discontinuation, efficacy data were collected up to 4 weeks, and off-treatment data were not included. The mITT analyses were conducted to meet regulatory requirements for submissions in the USA. The efficacy analyses reported in this Article are based on the OTHE population, as it more closely approached the ideal of a true intent-to-treat population, and because the majority of patients in this study were from Europe. The mITT population was used for supplementary analyses, which are reported on in the appendix.

If a participant provided 20–27 days of eDiary data during the baseline period, then monthly migraine days and other similar counting variables for baseline were prorated to standardise the count to a 28-day equivalent. If any post-baseline eDiary 4-week interval had at least 14 but fewer than 28 days of completed eDiary data, a similar prorated approach was used to obtain 28-day equivalent figures for monthly migraine days and other counting variables. The safety population included all participants who received at least one dose of study intervention.

The primary endpoint, change from baseline in mean monthly migraine days, was analysed using a mixed model for repeated measures on the OTHE population. The response variable was the change from baseline to each post-baseline month in monthly migraine days. The model included treatment group (placebo and atogepant), visit (weeks 1–4, 5–8, and 9–12), region (North America and Europe), number of classes of previous preventive treatment failures (two and more than two), and treatment group by visit interaction as categorical fixed effects. Baseline monthly migraine days and baseline-by-visit interactions were included as covariates. Within-participant correlation was modelled using the unstructured covariance matrix. Treatment effect and treatment comparison were estimated by least squares mean changes from baseline and their least squares mean differences, along with their SE and 95% CI, and the p value corresponding to the between-treatment group difference (with significance defined as $p<0·05$). Prespecified sensitivity analyses for missing data handling and possible violation of the normality assumption were performed for the primary endpoint, as described in the appendix (p 7).

The secondary endpoints for change from baseline in mean monthly headache days and acute medication use days were analysed in the same manner as the primary endpoint. The at least 50% responders were defined as participants who achieved an at least 50% reduction from baseline in the 3-month average of monthly migraine days. A logistic regression model was used to analyse the at least 50% responders across the 12-week treatment period. The model assumed a binary distribution for the response and used a logit link with model terms including treatment group, region, number of previous preventive treatment class failures, and baseline monthly migraine days. The treatment difference in terms of odds ratio between atogepant 60 mg once a day and placebo was estimated and tested from this model. The at least 25%, at least 30%, and at least 75% responder rate endpoints were analysed in the same manner as the at least 50% responder rate endpoint. The analysis of the 100% responder rate endpoint was completed using a logistic regression model with the Firth correction due to a quasi-complete separation of the data. Firth's bias-reducing penalised likelihood was used to fit the model.

A fixed-sequence procedure was used to control multiple comparisons, at two-sided α of 0·05 for primary and secondary endpoint comparisons between atogepant 60 mg once a day and placebo. Testing started from the primary endpoint, then secondary endpoints were tested in a prespecified order (appendix p 6). Efficacy analyses other than the primary and secondary endpoints were not controlled for type I error. Statistical analyses were performed using SAS software (version 9.4 or newer).

Role of the funding source
AbbVie funded this study and participated in the study design, data collection, data analysis, data interpretation, and review and approval of the manuscript.

Results

Between March 5, 2021, and Aug 4, 2022, 540 participants were screened for eligibility and 315 participants were randomly assigned to oral placebo (n=158) or atogepant 60 mg once a day (n=157; figure). Of these participants, 313 (99%) received study medication and were included in the safety population (157 assigned to placebo and 156 to atogepant); 309 were included in the OTHE population (155 assigned to placebo and 154 to atogepant) and 305 were included in the mITT population (154 assigned to placebo and 151 to atogepant). Most randomly assigned participants completed the trial and study discontinuation (seven [4%] of 158 assigned to placebo and 13 [8%] of 157 assigned to atogepant) was uncommon. Protocol deviations (three [2%] in the placebo group and five [3%] in the atogepant group) and adverse events (two [1%] in the placebo group and four [3%] in the atogepant group) were the most frequent reasons for study discontinuation (appendix p 8). Mean treatment compliance across the treatment period, defined as the number of treatment units taken divided by the number of units prescribed during each visit interval, was 99·4% in each treatment group.

Baseline demographics and clinical characteristics were similar between treatment groups in the safety population (table 1). At baseline, 72 (23%) of 313 participants who received treatment had 4 to fewer than 8 monthly migraine days, whereas 240 (77%) had between 8 and fewer than 15. The most common previous preventive treatment class failures were antiepileptic class 1 (233 [74%]), tricyclic antidepressants (173 [55%]), and beta-blockers (165 [53%]). The most common previous preventive treatment failures were topiramate (233 [74%]) and amitriptyline (166 [53%]). Most patients reported failure by two classes of previous preventive treatments (176 [56%]), whereas 110 (35%) had been failed by three, and 27 (9%) had been failed by four. More participants were failed by at least one previous preventive medication due to lack of efficacy (274 [88%]) than due to tolerability (175 [56%], table 1).

At baseline, the number of mean monthly migraine days was similar between treatment groups across the OTHE population (table 2). Atogepant significantly reduced mean monthly migraine days across the 12-week treatment period compared with placebo (primary endpoint). The least squares mean changes from baseline in mean monthly migraine days across 12 weeks were –1·9 (SE 0·4) with placebo and –4·2 (SE 0·4) with atogepant. The least squares mean difference from placebo was –2·4 days with atogepant (95% CI –3·2 to –1·5; adjusted p<0·0001). The results of sensitivity analyses were consistent with the primary analysis (appendix p 9). Compared with placebo, greater mean decreases from baseline in mean monthly migraine days were observed with atogepant during the first 4 weeks of treatment and continued for the second and third 4-week intervals (prespecified exploratory endpoints; appendix p 4).

Atogepant showed significant improvements compared with placebo for all secondary efficacy endpoints

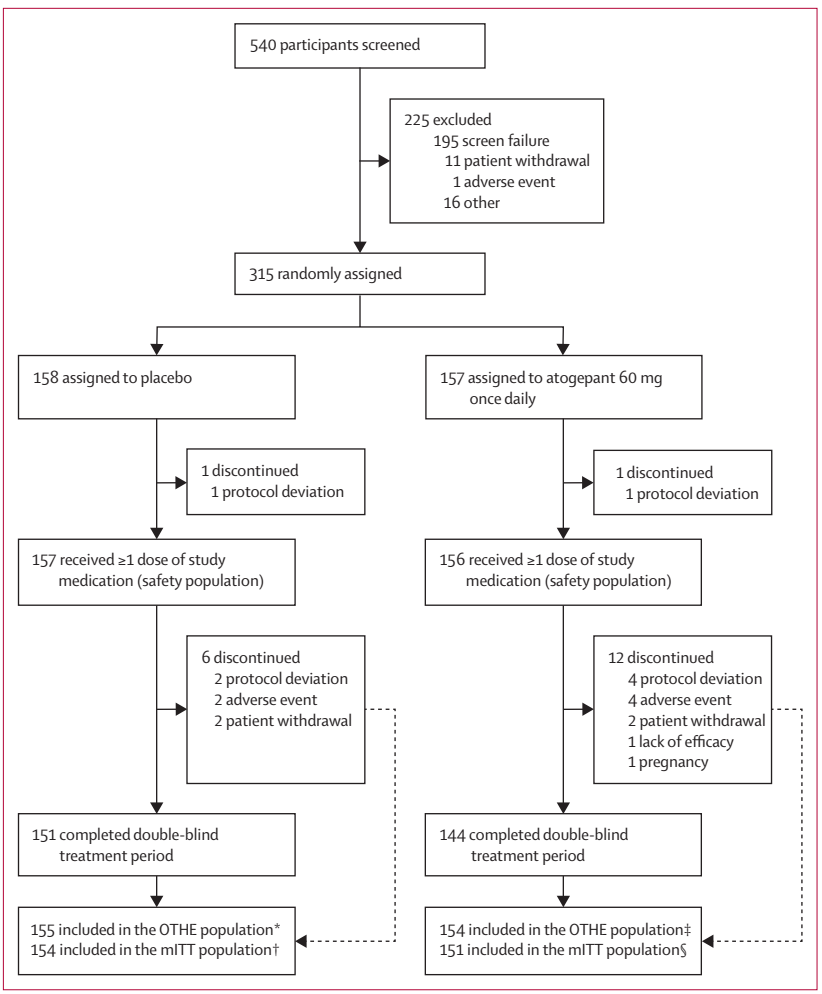

Figure: **Trial profile**
eDiary=electronic diary. mITT=modified intent-to-treat. OTHE=off-treatment hypothetical estimand. The OTHE population included all randomly assigned participants who received at least one dose of atogepant or placebo, had an evaluable baseline period of eDiary data, and had at least one evaluable post-baseline 4-week period (weeks 1–4, 5–8, and 9–12) of eDiary data during the double-blind treatment period and follow-up period, regardless of whether on or off study treatment. The mITT population included all randomly assigned participants who received at least one dose of atogepant or placebo, had an evaluable baseline period of eDiary data, and had at least one evaluable post-baseline 4-week period (weeks 1–4, 5–8, and 9–12) of eDiary data during the double-blind treatment period, while on study treatment. *In the placebo group, one participant was excluded from the OTHE population because they did not have an evaluable baseline period of eDiary data and one participant was excluded because they did not have an evaluable post-baseline 4-week period of eDiary data. †In the placebo group, one participant was excluded from the mITT population (but included in the OTHE population) because they did not have an evaluable post-baseline 4-week period of eDiary data while on study treatment. ‡In the atogepant group, two participants were excluded from the OTHE population because they did not have an evaluable post-baseline 4-week period of eDiary data. §In the atogepant group, three participants were excluded from the mITT population (but included in the OTHE population) because they did not have an evaluable post-baseline 4-week period of eDiary data while on study treatment.

	Placebo (n=157)	Atogepant 60 mg once daily (n=156)
Age, years	43·4 (10·3)	40·9 (10·7)
Sex		
Female	141 (90%)	139 (89%)
Male	16 (10%)	17 (11%)
Race		
White	151 (96%)	149 (96%)
Black or African American	4 (3%)	3 (2%)
Asian	2 (1%)	2 (1%)
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Multiple*	0	2 (1%)
Ethnicity		
Hispanic	4 (3%)	7 (4%)
Non-Hispanic	153 (97%)	149 (96%)
Region		
North America	20 (13%)	20 (13%)
Europe	137 (87%)	136 (87%)
Weight, kg	74·0 (16·1)	71·7 (14·8)
Height, cm	167·9 (7·1)	167·3 (7·9)
BMI (kg/m²)	26·2 (5·2)	25·6 (4·9)
Years since initial migraine diagnosis	20·7 (11·2)	20·3 (11·6)
Migraine frequency		
4 to <8 monthly migraine days	35 (22%)	37 (24%)
8 to <15 monthly migraine days	121 (77%)	119 (76%)
Acute medication use	154 (98%)	156 (100%)
Prior preventive treatment failure classes		
Two classes	86 (55%)	90 (58%)
Three classes	56 (36%)	54 (35%)
Four classes	15 (10%)	12 (8%)
Reasons for prior preventive treatment failures		
Failure by at least one medication owing to lack of efficacy	131 (83%)	143 (92%)
Failure by at least one medication owing to tolerability	85 (54%)	90 (58%)
Failure by at least one medication owing to lack of efficacy and at least one owing to tolerability	59 (38%)	77 (49%)
(Continued from previous column)		
Previous preventive treatments		
Beta-blockers	93 (59%)	72 (46%)
Propranolol	51 (32%)	41 (26%)
Metoprolol	38 (24%)	30 (19%)
Bisoprolol	4 (3%)	2 (1%)
Atenolol	2 (1%)	3 (2%)
Antiepileptic class 1 (topiramate)	116 (74%)	117 (75%)
Calcium channel blocker (flunarizine)	25 (16%)	27 (17%)
Antiepileptic class 2	28 (18%)	27 (17%)
Valproate	28 (18%)	25 (16%)
Divalproex	0	2 (1%)
Tricyclic antidepressant	81 (52%)	92 (59%)
Amitriptyline	78 (50%)	88 (56%)
Nortriptyline	3 (2%)	6 (4%)
SNRI (venlafaxine)	10 (6%)	19 (12%)
ACE inhibitor (lisinopril)	1 (1%)	1 (1%)
ARB (candesartan)	11 (7%)	6 (4%)
Other locally approved products	35 (22%)	29 (19%)
Cinnarizine	22 (14%)	18 (12%)
Iprazochrome	8 (5%)	9 (6%)
Oxeterone	3 (2%)	2 (1%)
Pizotifen	2 (1%)	0
Cyproheptadine	1 (1%)	0

Data are mean (SD) or n (%). Race and ethnicity were self-reported. Data are presented for the safety population. ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blocker. SNRI=serotonin-norepinephrine reuptake inhibitor. *Participants who reported multiple races are listed only in the multiple category.

Table 1: **Demographic and baseline characteristics (safety population)**

pertaining to headache-related clinical outcomes analysed in the OTHE population (table 2). In the placebo group, 28 participants (18%) had a reduction of at least 50% in the 3-month average of mean monthly migraine days, compared with 78 (51%) in the atogepant group (OR 4·8 [95% CI 2·9 to 8·1]; adjusted p<0·0001). The least squares mean change from baseline in mean monthly headache days was –1·9 (SE 0·4) in the placebo group and –4·1 (SE 0·4) in the atogepant group (least squares mean difference –2·2 [95% CI –3·1 to –1·3]; adjusted p<0·0001). The least squares mean change from baseline in mean monthly acute medication use days was –1·1 (SE 0·4) in the placebo group and –3·7 (SE 0·4) in the atogepant group (least squares mean difference –2·6 [–3·4 to –1·9]; adjusted p<0·0001).

Atogepant showed significant improvements in the number of patients who had a reduction of at least 25%, at least 30%, at least 75%, and 100% in the 3-month average of mean monthly migraine days compared with placebo in the OTHE population and in each 4-week interval during the treatment period (prespecified exploratory endpoints; appendix pp 10–11). In pre-specified subgroup analyses of the primary efficacy endpoint (change from baseline in mean monthly migraine days) based on the number of classes (two *vs* more than two) of previous preventive treatment failures (appendix p 12), migraine frequency at baseline (4 to <8 *vs* ≥8 monthly migraine days; appendix p 13), and region (North America *vs* Europe; appendix p 14), least squares mean differences from placebo in monthly migraine days were consistent with the overall patient population. Results for the mITT population were consistent with all analyses conducted for efficacy in the OTHE population (appendix pp 5, 15–20).

Treatment-emergent adverse events were reported by 84 (54%) participants in the placebo group versus 81 (52%) in the atogepant group (table 3). The most common (≥5%) treatment-emergent adverse events were constipation (in four [3%] of 157 participants in the placebo group *vs* 16 [10%] of 156 participants in the atogepant group), COVID-19 (in 15 [10%] participants in the placebo group *vs* 13 [8%] participants in the atogepant group), nausea (in five [3%] participants in the placebo group *vs* 11 [7%] participants in the atogepant group), and nasopharyngitis (in 12 [8%] participants in the placebo group *vs* eight [5%] participants in the atogepant group). Most treatment-emergent adverse events were considered by the investigator to be mild or moderate in severity. Severe treatment-emergent adverse events were reported by one participant (1%; severe migraine) in the placebo group versus four participants (3%) in the atogepant group (constipation, stage 2 breast cancer, invasive breast carcinoma, and induced abortion). Treatment-related treatment-emergent adverse events occurring in at least 2% of either group were constipation, nausea, and decreased appetite.

No deaths were reported during the study. Serious adverse events (ventricular tachycardia, stage 2 breast cancer, invasive breast carcinoma, and induced abortion) were reported in none of the participants in the placebo group and in four (3%) participants in the atogepant group. None of the serious adverse events were considered related to study medication by the investigator. Discontinuation rates due to treatment-emergent adverse events were low across both groups (two [1%] participants in the placebo group *vs* three [2%] in the atogepant group). No clinically meaningful differences were observed across treatment groups in the percentage of participants with post-baseline potentially clinically significant blood pressure or pulse rate. One participant in the atogepant group had a clinically significant alteration at the ECG during the double-blind treatment period and discontinued study drug (serious treatment-emergent adverse event of ventricular tachycardia, assessed as not related to treatment by the investigator). For hepatic laboratory values, mean baseline to post-baseline changes were small and similar between groups. No cases of post-baseline ALT or AST concentrations at least three times the upper limit of normal were reported, and no participants met criteria for potential Hy's law (appendix p 21). Per C-SSRS assessments, no participants reported active suicidal ideation (with or without intent) or suicidal behaviour in the 6 months before screening or in the double-blind treatment period; one participant in the placebo group experienced a type 1 suicidal ideation during the double-blind treatment period.

Discussion

Results from this phase 3b trial showed that atogepant 60 mg once a day is efficacious in patients with previous treatment failures (regardless of whether they had been

	Placebo (n=155)	Atogepant 60 mg once daily (n=154)	Atogepant *vs* placebo, LSMD or OR (95% CI, adjusted p value)
Primary efficacy endpoint			
Change from baseline in monthly migraine days across the 12-week treatment period			
Baseline (SD)	9·3 (2·4)	9·1 (2·3)	..
Change from baseline, LSM (SE)	−1·9 (0·4)	−4·2 (0·4)	−2·4 (−3·2 to −1·5, p<0·0001)
Secondary efficacy endpoints			
≥50% reduction in 3-month average of monthly migraine days, n (%)	28 (18%)	78 (51%)	4·8 (2·9 to 8·1, p<0·0001)
Change from baseline in monthly headache days across the 12-week treatment period			
Baseline (SD)	10·1 (2·4)	9·9 (2·4)	..
Change from baseline, LSM (SE)	−1·9 (0·4)	−4·1 (0·4)	−2·2 (−3·1 to −1·3, p<0·0001)
Change from baseline in monthly acute medication use days across the 12-week treatment period			
Baseline (SD)	7·7 (3·3)	7·5 (2·9)	..
Change from baseline, LSM (SE)	−1·1 (0·4)	−3·7 (0·4)	−2·6 (−3·4 to −1·9, p<0·0001)

Results are presented for the OTHE population; results for the modified intent-to-treat population can be found in the appendix (pp 5, 15–20). Baseline values were evaluated during the 28 days before randomisation; post-baseline values (change from baseline) were evaluated across the 12-week trial period. The overall type I error rate for multiple comparisons across primary and secondary endpoints (but not prespecified additional endpoints) was controlled at the 0·05 level using a fixed-sequence approach as described in the appendix (p 6) and is reflected in the adjusted p values. OR=odds ratio. OTHE=off-treatment hypothetical estimand. LSM=least-squares mean. LSMD=least-squares mean difference.

Table 2: **Primary and secondary endpoints pertaining to headache-related clinical outcomes**

	Placebo (n=157)	Atogepant 60 mg once daily (n=156)
Treatment-emergent adverse events	84 (54%)	81 (52%)
Treatment-emergent adverse events in ≥2% of participants in either group		
Constipation	4 (3%)	16 (10%)
COVID-19	15 (10%)	13 (8%)
Nausea	5 (3%)	11 (7%)
Nasopharyngitis	12 (8%)	8 (5%)
Decreased appetite	2 (1%)	5 (3%)
Insomnia	2 (1%)	5 (3%)
Urinary tract infection	4 (3%)	4 (3%)
Migraine	4 (3%)	3 (2%)
Diarrhoea	4 (3%)	2 (1%)
Dyspepsia	4 (3%)	1 (1%)
Treatment-related treatment-emergent adverse events*	14 (9%)	31 (20%)
Treatment-related treatment-emergent adverse events in ≥2% of participants in either group*		
Constipation	3 (2%)	13 (8%)
Nausea	3 (2%)	8 (5%)
Decreased appetite	0	5 (3%)
Treatment-emergent serious adverse events	0	4 (3%)
Treatment-emergent adverse events leading to treatment discontinuation	2 (1%)	3 (2%)
Deaths	0	0

*Treatment-related treatment-emergent adverse events as assessed by the investigator.

Table 3: **Adverse events in the safety population**

failed by two, three, or four preventive treatment classes), as shown by a statistically significant improvement over placebo in the primary endpoint of reduction in mean monthly migraine days across the 12-week treatment period. Furthermore, atogepant showed significant reductions in mean monthly headache days and mean monthly acute medication use days compared with placebo across the 12-week treatment period. Atogepant also resulted in a significantly higher proportion of participants achieving at least a 50% reduction in the 3-month average of monthly migraine days compared with placebo, as well as a considerably higher proportion of participants achieving at least a 25%, 30%, 75%, and 100% reduction in the 3-month average of mean monthly migraine days compared with placebo.

Atogepant was well tolerated across the double-blind treatment period. Most adverse events were mild or moderate in severity and no serious adverse events were considered by the investigator to be treatment-related. No clinically meaningful differences were observed across treatment groups in the percentage of participants with post-baseline potentially clinically significant blood pressure or pulse rate. No participant experienced ALT or AST concentrations at least three times the upper limit of normal or met the criteria for Hy's law. The most common adverse events were nausea and constipation, most of which were low to moderate in severity, and only one patient discontinued study participation due to each of these adverse events. The overall safety results in this study were consistent with previous atogepant studies and no new safety concerns were identified.[22,23,26]

Patients on conventional oral preventive medications often have lower adherence and persistence (ie, continued use) over time as they cycle through treatment classes,[13–15] increasing their burden over time and risking a transition to chronic migraine.[9] Other studies[25,27–29] have shown that monoclonal antibodies targeting CGRP and its receptor are safe and effective for preventing migraine in people with multiple previous preventive treatment class failures. Although monoclonal antibodies targeting CGRP or its receptor are effective and tolerable, many individuals might prefer oral treatments over injectables.[18–20] Two oral gepants (atogepant and rimegepant) show efficacy for the preventive treatment of episodic migraine but, until now, no data have been available on the efficacy of gepants as preventive treatments of episodic migraine in patients with previous treatment failures. This is, to our knowledge, the first study for an oral, small molecule CGRP receptor antagonist to show high efficacy, safety, and tolerability for this difficult-to-treat patient population.

ELEVATE was designed to have similar methods to other randomised, controlled trials for similar patient populations, to facilitate indirect treatment comparisons and meta-analyses in the future.[25,27–29] ELEVATE was a large, multicentre study with a broad range of patients in terms of age and location, primarily in Europe. Male and non-White patients are under-represented, which is typical of similar trials.[25,27–29] The average number of monthly migraine days at baseline is consistent with other randomised controlled trials for patients with episodic migraine and is representative of the episodic migraine patient population. In this study, 44% of patients had been failed by more than two classes of oral preventive migraine treatments, indicating that especially difficult-to-treat patients were well represented.

Limitations of this study include the relatively short (12 weeks) treatment duration, although the safety of atogepant 60 mg once a day over 52 weeks in patients with episodic migraine has been previously shown in an open-label, long-term trial.[26] An open-label extension of ELEVATE (NCT04686136) is currently evaluating the long-term safety and tolerability of atogepant 60 mg once a day in patients who have been failed by multiple classes of preventive treatments. ELEVATE did not include patients with more than four treatment class failures, or patients with chronic migraine (headache occurring on at least 15 days per month and migraine occuring on at least 8 days per month), potentially limiting the extrapolation of these data to the full migraine population. Although 91–93% of people with migraine have episodic migraine, those with chronic migraine have higher drug discontinuation rates and cycle through preventive medications more rapidly than those with episodic migraine, which creates a pressing need for effective treatments for chronic migraine in participants with multiple previous preventive treatments.[11] Similar trials with monoclonal antibodies in difficult-to-treat patients have shown that these treatments are effective in patients with chronic or episodic migraine.[27–29] Future studies should consider examining the efficacy, tolerability, and safety of atogepant in patients with chronic migraine and for whom two to four previous preventive treatment classes have failed.

In this pivotal phase 3 trial, we show that atogepant is efficacious compared with placebo for the preventive treatment of episodic migraine in adults who had been previously failed by two to four classes of preventive migraine treatments. The safety and tolerability profile of atogepant was consistent with previous trials.

Contributors

KN, HG, and JMT designed the study. CT, PP-R, ML-M, and TN collected the data. HG did the statistical analysis. KN, HG, RDAF, GF, and JMT contributed to study conduct, provided study oversight, and reviewed the data. All authors had access to all the data in the study. CT, KN, HG, and JMT accessed and verified the underlying data. All authors contributed to data interpretation and to the preparation, critical review and revision, and approval of the final manuscript. CT had the final responsibility to submit for publication.

Declaration of interests

JMT, KN, HG, RDAF, and GF are employees of AbbVie and may hold AbbVie stock. CT reports support from Abbvie and Novartis for investigator-initiated trials; consulting fees from Abbvie, Eli Lilly, Dompé, Teva, Lundbeck, Pfizer, and Medscape for participating in advisory boards; support from Abbvie, Eli Lilly, Dompé, Teva, Lundbeck, and Pfizer for attending meetings; and personal fees from Abbvie, Eli Lilly, Teva, Lundbeck, and Pfizer for lecturing at symposia. She is principal investigator of clinical trials sponsored by Abbvie, Eli Lilly, Lundbeck,

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Data sharing

The study protocol and statistical analysis plan are provided in the appendix. 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 also 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 and 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 from publication of this study, 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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