Safety and efficacy of rimegepant orally disintegrating tablet for the acute treatment of migraine in China and South Korea: a phase 3, double-blind, randomised, placebo-controlled trial

Shengyuan Yu, Byung-Kun Kim, Aihong Guo, Man-Ho Kim, Mingjie Zhang, Zhen Wang, Jianguang Liu, Heui-Soo Moon, Ge Tan, Qian Yang, Donnie McGrath, Michael Hanna, David A Stock, Yanfei Gao, Robert Croop, Zhihong Lu

Lancet Neurol 2023; 22: 476–84

See **Comment** page 456

For the Chinese translaton of the abstract see **Online** for appendix 1

For the Korean translaton of the abstract see **Online** for appendix 2

Chinese PLA General Hospital, Beijing, China (Prof S Yu MD, M Zhang MD); **Nowon Eulji Medical Center, Seoul, South Korea** (Prof B-K Kim MD); **Yan'an University Xianyang Hospital, Xianyang, China** (Prof A Guo MD); **Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea** (Prof M-H Kim MD); **Changsha Central Hospital, Changsha, China** (Prof Z Wang MD); **Wuhan Third Hospital, Wuhan, China** (Prof J Liu MD); **Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea** (Prof H-S Moon MD); **The First Affiliated Hospital of Chongqing Medical University, Chongqing, China** (Prof G Tan MD); **Shaanxi Provincial Hospital, Xi'an, China** (Prof Q Yang MD); **Biohaven Pharmaceuticals, New Haven, CT, USA** (D McGrath MD, M Hanna MD, D A Stock PhD, R Croop MD); **BioShin Limited, Shanghai, China** (Y Gao MSc, Z Lu MD)

Correspondence to:
Dr Zhihong Lu, Pfizer (China) Researh and Development, Shanghai, 201203, China
sarah.lu@pfizer.com

Summary

Background No acute treatments targeting calcitonin gene-related peptide (CGRP) have been approved for use in China or South Korea. We aimed to compare the efficacy and safety of rimegepant—an orally administered small molecule CGRP antagonist—with placebo in the acute treatment of migraine among adults in these countries.

Methods This double-blind, randomised, placebo-controlled, multicentre phase 3 trial was done at 86 outpatient clinics at hospitals and academic medical centres (73 in China and 13 in South Korea). Participants were adults (≥18 years) with at least a 1-year history of migraine who had two to eight moderate or severe attacks per month and fewer than 15 headache days per month within the 3 months before the screening visit. Participants were randomly assigned (1:1) to 75 mg rimegepant or placebo to treat a single migraine attack of moderate or severe pain intensity. Randomisation was stratified by the use of preventive medication and by country. The allocation sequence was generated and implemented by study personnel using an interactive web-response system accessed online from each study centre. All participants, investigators, and the sponsor were masked to treatment assignment. The coprimary endpoints of freedom from pain and freedom from the most bothersome symptom (nausea, phonophobia, or photophobia) 2 h after dosing were assessed in the modified intention-to-treat (mITT) population (randomly assigned participants who took study medication for a migraine attack of moderate or severe pain intensity, and provided at least one efficacy datapoint after treatment) using Cochran-Mantel Haenszel tests. Safety was assessed in all participants who received rimegepant or placebo. The study is registered with ClinicalTrials.gov, number NCT04574362, and is completed.

Findings 1431 participants were randomly assigned (716 [50%] to rimegepant and 715 [50%] to placebo). 668 (93%) participants in the rimegepant group and 674 (94%) participants in the placebo group received treatment. 1340 participants were included in the mITT analysis (666 [93%] in the rimegepant group and 674 [94%] in the placebo group). 2 h after dosing, rimegepant was superior to placebo for pain freedom (132 [20%] of 666 *vs* 72 [11%] of 674, risk difference 9·2, 95% CI 5·4–13·0; p<0·0001) and freedom from the most bothersome symptom (336 [50%] of 666 participants *vs* 241 [36%] of 674 participants, 14·8, 9·6–20·0; p<0·0001). The most common (≥1%) adverse events were protein in urine (8 [1%] of 668 participants in the rimepegant group *vs* 7 [1%] of 674 participants in the placebo group), nausea (7 [1%] of 668 *vs* 18 [3%] of 674), and urinary tract infection (5 [1%] of 668 *vs* 8 [1%] of 674). There were no rimegepant-related serious adverse events.

Interpretation Among adults living in China or South Korea, a single dose of 75 mg rimegepant was effective for the acute treatment of migraine. Safety and tolerability were similar to placebo. Our findings suggest that rimegepant might be a useful new addition to the range of medications for the acute treatment of migraine in China and South Korea, but further studies are needed to support long-term efficacy and safety and to compare rimegepant with other medications for the acute treatment of migraine in this population.

Funding BioShin Limited.

Introduction

Migraine is a chronic neurological condition characterised by periodic attacks of unilateral, often pulsatile, moderate to severe headache accompanied by nausea or vomiting, or photophobia and phonophobia.[1] Among the most prevalent neurological conditions worldwide, with 1·1 billion people thought to be affected,[2] migraine affects approximately 9·3% of adults living in China (approximately 151·6 million people)[3] and an estimated 5·2% of adults living in South Korea (approximately 2·7 million people).[4] As in other nations,[2,5] migraine-related disability has been associated with

Research in context

Evidence before this study

Small molecule calcitonin gene-related peptide (CGRP) antagonists (gepants) were first approved for the acute treatment of migraine in the USA in 2019. Two gepant medications are currently approved by the US Food and Drug Administration in the USA for the acute treatment of migraine: rimegepant and ubrogepant. Rimegepant was approved by the European Medicines Agency in the EU in 2022. A PubMed search with no language restrictions and a date range from Jan 1, 1982, to March 1, 2023 using the search string "gepant acute clinical trial" retrieved 127 articles, 24 of which were clinical trials evaluating gepant medications (rimegepant, ubrogepant, and zavegepant) for the acute treatment of migraine. The evidence from these trials indicates that medications in the gepant class are effective and well tolerated for the acute treatment of migraine. In the USA, rimegepant was approved for the preventive treatment of episodic migraine in 2021 and in the EU in 2022; it is the only antimigraine drug to receive approval for both indications.

Added value of this study

The efficacy, safety, and tolerability of rimegepant have not been studied in people with migraine who live outside the USA. To our knowledge, this phase 3, double-blind, randomised, placebo-controlled trial was the first clinical trial of a gepant for the acute treatment of migraine in adults living in China or South Korea. To our knowledge, this is also the largest, fully powered, randomised, controlled study of acute treatment of migraine in China since 2008. Rimegepant was effective for the acute treatment of migraine, as shown by efficacy on the coprimary outcomes of freedom from pain and freedom from the most bothersome symptom 2 h after dosing and on all key secondary efficacy outcomes, including pain freedom from 2 h until 48 h after dosing. Rimegepant was safe and well tolerated, with no new safety signals identified.

Implications of all the available evidence

Rimegepant was effective, with an excellent safety and tolerability profile, for the acute treatment of migraine in adults living in China and South Korea. More than 150 million people living in China and Korea have migraine, many of whom have substantial disability and impaired quality of life. Furthermore, the rates of satisfaction with currently available options for acute treatment are low. The results of this clinical trial indicate that rimegepant could be a useful addition to the range of medications currently indicated for the acute treatment of migraine in China and South Korea. These findings are consistent with the results of previous trials with rimegepant in the USA and support their generalisability.

impaired academic and occupational performance, reduced participation in family and social activities, and lower quality of life compared with people who do not have migraine among adults living in China and South Korea.[3,4,6,7]

The currently available medications for the acute treatment of migraine in China and South Korea includes many antimigraine drugs that are commonly used worldwide, proprietary medicines, herbal medicines, traditional medicines, and alternative medicines. Although guidelines for the acute treatment of migraine in both countries[8,9] generally align with those published in Europe[10,11] and the USA,[12] the limited availability of prescription medications, widespread use of traditional therapies, and the low rates of triptan prescribing lead to important differences in prescribing patterns. In China, for example, individuals who are prescribed medication for the acute treatment of migraine most often receive nonsteroidal anti-inflammatory drugs (NSAID [69%], mostly ibuprofen [37%]), aspirin (8%), opioids (7%), ergot alkaloids (6%), and triptans (3%).[13] People consulting headache clinics are most likely to receive herbal medicine (47%); paracetamol (30%); a compound preparation containing aspirin, paracetamol, and caffeine (21%); and ibuprofen (20%).[14] In South Korea, most people with migraine use non-prescription medications (54%) or no treatment (26%[4]); the most frequently prescribed medications for acute migraine treatment among individuals who are candidates for preventive treatment (ie, >4 migraine days per month) are sumatriptan (29%), ergotamine (27%), naratriptan (19%), almotriptan (10%), zolmitriptan (9%), or frovatriptan (6%).[15] In the USA, NSAIDs are also widely used, but the most commonly prescribed medications are triptans, and the use of ergotamine-based and herbal medicines is low. At least 40% of people with migraine in China and South Korea are dissatisfied with the medication or medications that they currently use for acute treatment,[6,14,16] but no medications targeting CGRP for the acute treatment of migraine have been approved in either country.

Rimegepant is an orally administered small molecule CGRP receptor antagonist (gepant) indicated for the acute treatment of migraine and the preventive treatment of episodic migraine in the USA, EU, and UK. For the acute treatment of migraine, administration of a single 75 mg dose of rimegepant has shown efficacy, safety, and tolerability in three randomised controlled clinical trials and a 1-year safety study among people living in the USA.[17–20] However, because of differences in patient characteristics (eg, comorbid conditions and concomitant therapies) and prescribing patterns for migraine in China and South Korea, a trial was needed to assess whether the effects of rimegepant would be consistent with those previously shown among people living in the USA. We aimed to evaluate the efficacy and safety of rimegepant compared with placebo for the acute

treatment of migraine among adults living in China or South Korea.

Methods

Study design

This was a double-blind, randomised, placebo-controlled, multicentre, phase 3 trial of a single 75 mg dose of rimegepant (Catalent, Swindon, UK) orally disintegrating tablet versus placebo for the acute treatment of migraine. This trial was done at 86 study centres (outpatient clinics at hospitals and academic medical centres, 73 in China and 13 in South Korea) in accordance with the principles of the Guidelines for Good Clinical Practice, the Declaration of Helsinki, and all applicable local regulations. The protocol, which was approved by regulatory authorities in China and South Korea and the ethics committees of all participating study sites, is available in appendix 3 (p 5).

See Online for appendix 3

Participants

Men and women who were 18 years or older with at least a 1-year history of migraine with or without aura according to the criteria of the International Classification of Headache Disorders, 3rd edition (beta version)[21] were eligible. Participants were required to have self-reported migraine onset before age 50 years, and to have had between two and eight migraine attacks with moderate or severe pain intensity per month, and fewer than 15 days per month with migraine or non-migraine headache, within the 3 months before the screening. Participants provided previous medical or medication history records whenever possible. The principal investigator at each study centre asked participants to provide records from external hospitals or clinics. Participants also had to be able to distinguish migraine attacks from other primary headache attacks (ie, tension-type headache and cluster headache). Participants self-reported use of preventive migraine medication and confirmed at the screening visit if they had been on a stable dose for at least 3 months. Participants who used preventive migraine medication were eligible only if they were on a stable dose for at least 3 months. Individuals for whom triptans were contraindicated (eg, history of coronary artery disease or stroke) could participate if they met all other study entry criteria.

Exclusion criteria included any medical condition that, in the opinion of the investigator (ie, the prinicipal investigator at each study centre), might interfere with assessments of efficacy and safety or expose participants to undue risk of a clinically significant adverse event. Participants were excluded if they had a history with current evidence of uncontrolled or unstable cardiovascular disease (eg, ischaemic heart disease, coronary artery vasospasm, or cerebral ischaemia), or if they had myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, cardiac surgery, stroke, or transient ischaemic attack during the 6 months before the screening visit. Other reasons for exclusion included treatment for, or evidence of, alcohol or drug abuse within the 12 months before the screening visit; a history of drug allergy or other allergy that made the individual unsuitable for participation; or an electrocardiogram (ECG) or laboratory test findings that raised safety or tolerability concerns. The full list of exclusion criteria is provided in appendix 3 (p 46). Participants provided written informed consent before they were screened for eligibility.

Randomisation and masking

Investigators or study personnel used an interactive web-response system that was operated and managed by an independent contract research organisation to enter eligible participants into the study. The system randomly assigned participants in a 1:1 ratio to rimegepant or placebo, stratified by use or non-use of preventive migraine medication and by country. Randomisation schedules were generated and kept by the contract research organisation in a secure network folder with access restricted to only study personnel who were not masked to treatment allocation. The non-masked study personnel were statisticians who generated the randomisation code and the staff responsible for packaging the study medication. Randomisation assigned a number for a bottle containing the randomised treatment type. The study medications, orally disintegrating tablets of either rimegepant or placebo, were matched in appearance and flavour and were dispensed when participants were randomised. The contract research organisation that operated and managed the interactive web-response system was not involved in other operational study procedures. Participants, investigators, and study personnel were masked to treatment assignments.

Procedures

This study included a screening period lasting 3–28 days (to allow for the analysis and return of central laboratory test results to the study centres), an acute treatment phase lasting up to 45 days, and an end-of-treatment visit within 7 days after study medication was administered. After informed consent was signed, screening procedures were performed, inclusion and exclusion criteria were assessed, and laboratory tests (eg haematology, clinical chemistry panels including liver function testing panels, and urinalysis) were done. Participants returned to study centres within 3–28 days of the screening visit, and if they met all inclusion criteria, were randomised to rimegepant or matching placebo by investigators or qualified designees via the interactive web-response system and provided with an electronic diary. During this baseline visit, investigators or qualified designees taught participants how to use the electronic diary and confirmed that participants understood the instructions and could operate the electronic diary. Before concluding the baseline visit, investigators or qualified designees

confirmed that participants could distinguish migraine attacks from other primary headache types (ie, tension-type headache and cluster headache).

Participants were given one dose of study medication in an individual sealed blister card that was contained in a bottle—rimegepant 75 mg orally disintegrating tablet or placebo to be administered sublingually—and instructed to treat a migraine attack with moderate or severe pain intensity, after answering electronic diary questions about their current pain and symptoms and identifying their currently most bothersome symptom from among phonophobia, photophobia, and nausea. Participants completed the electronic diary for up to 48 h after taking study medication. Pain intensity, the presence or absence of associated symptoms, and ratings of functional disability were assessed: at the onset of the treated attack; 15 min, 30 min, 45 min, 60 min, and 90 min after dosing; and 2 h, 3 h, 4 h, 6 h, 8 h, 24 h, and 48 h after dosing. Participants were allowed to take rescue medication 2 h after taking the dose.

Within 7 days of the treated attack (plus 2 days if necessary), participants returned to the study site for review of the electronic diary, assessment of compliance with study procedures and monitoring of tolerability and safety. Participants who did not have a migraine attack with moderate or severe pain intensity within 45 days of randomisation or had an attack but did not take the study medication for other reasons returned unused study medication and the electronic diary to the study centre and completed the end-of-treatment visit.

This study was done during the COVID-19 pandemic. If a participant was unable to visit the study centre due to COVID-19 restrictions, remote visits were allowed on a case-by-case basis. If the remote visit required laboratory tests, a local laboratory could be used for tests instead of the central laboratory. With sponsor approval, shipping of study drug directly to the participant via overnight tracked and certified courier was also allowed.

Participants self-reported age, sex (choice of male or female), country, and previous migraine and medication history. Age and sex were also confirmed by checking the participant's identification cards. Migraine type was assessed by the clinical centre staff by comparing the self reported signs and symptoms against the migraine diagnosis criteria. Medication history was also confirmed with the participant's medical records from other hospitals or clinics whenever possible. If participants were patients of the study centre, the electronic system of this study centre was also searched.

Outcomes

The coprimary efficacy outcomes were pain freedom and freedom from the most bothersome symptom associated with migraine (ie, phonophobia, photophobia, or nausea) at 2 h after dosing. Pain intensity was measured on a four-point scale (0=none, 1=mild, 2=moderate, or 3=severe). Pain freedom was defined as a score of 0 on the four-point scale. The most bothersome symptom (nausea, phonophobia, or photophobia) was measured using a binary scale (0=absent or 1=present).

There were five key secondary outcomes. Pain relief 2 h after dosing was assessed using the number of participants who reported moderate or severe pain at baseline who then reported no or mild pain at 2 h after dosing. The proportion of participants able to function normally 2 h after dosing was assessed using the number of participants who self-reported normal functioning on the functional disability scale (ie, normal function, mild impairment, severe impairment, or required bedrest) among the subset of participants who reported any level of disability just before taking study medication. The use of rescue medication was assessed using the number of participants who took rescue medication within 24 h after administration of rimegepant or placebo. Sustained pain freedom from 2 h to 24 h after dosing was assessed as the number of participants who did not have any headache pain during this time. Sustained pain freedom from 2 h to 48 h after dosing was assessed using the number of participants who did not have any headache pain during this time. Sustained pain freedom (from 2 h to 24 h after dosing or from 2 h to 48 h after dosing) was reported as a score of 0 on the four-point scale in the electronic diary.

There were three other secondary outcomes. Pain freedom 15 min, 30 min, 45 min, 60 min, and 90 min after dosing was assessed using the number of participants who reported moderate or severe pain just before taking study medication who then reported no pain at the timepoint of interest. Freedom from the most bothersome symptom at 15 min, 30 min, 45 min, 60 min, and 90 min after dosing was assessed using the number of participants who reported the absence of their most bothersome symptom at the timepoint of interest. Pain relapse was assessed using the number of participants who were free from pain at 2 h after dosing (score of 0 on the four-point scale) who had migraine pain of any intensity (ie, 1, 2, or 3 on the four-point scale) within 48 h after administration of study medication. The key secondary outcomes were those considered to be most clinically relevant and were thus prespecified for formal, α-controlled, statistical testing.

Safety and tolerability assessments included adverse events and serious adverse events; laboratory tests (haematology, blood chemistry and electrolytes, lipid panel, estimated glomerular filtration rate [eGFR], urinalysis, and drugs of abuse testing in urine); 12-lead ECG; physical examination; and vital signs. The Medical Dictionary for Regulatory Activities (MedDRA, version 23.0) was used to code adverse events and serious adverse events.

Statistical analysis

Sample size was calculated assuming that if approximately 85% of the 715 participants randomly assigned to each treatment group had a qualifying migraine attack within the 45-day period, there would have been approximately 600 treated participants per group. Over a

wide range of possible effect sizes, 600 treated participants provided 95% power to detect a difference between rimegepant and placebo on freedom from pain and the most bothersome symptom 2 h after dosing. For pain freedom, at least 95% power is provided when the placebo rate is 14% or less and the therapeutic gain is at least 8%. For the most bothersome symptom, at least 95% power is provided when the placebo rate is 28% or less and the therapeutic gain is at least 10%. Having 95% power on each coprimary outcome provided roughly 90% power to detect a difference on both outcomes jointly. The sample size calculations were based on target effects from previously published clinical trials comparing rimegepant with placebo,[18,19,22] as detailed in section 15.4 of the study protocol (appendix 3, p 78).

Efficacy was analysed in the modified intention-to-treat (mITT) population, which included randomly assigned participants who took study medication, had a migraine attack of moderate or severe pain intensity at the time of treatment, and provided at least one efficacy datapoint after treatment. These restrictions on the mITT analysis set are commonly used in acute migraine clinical trials. Rimegepant was tested for superiority to placebo at an α level of 0·05 on pain freedom 2 h after dosing and freedom from the most bothersome symptoms 2 h after dosing. Both outcomes were evaluated using Cochran-Mantel Haenszel tests to estimate the common risk difference in percentage of pain freedom and freedom from the most bothersome symptom at 2 h after dosing. The tests were stratified by use of preventive migraine medication (yes or no) and country (China or South Korea). These tests were done using the mITT population, with missing data at 2 h after dosing imputed as treatment failures (ie, participants who did not complete the assessment). Participants who took rescue medication before or at the time of assessment were also imputed as treatment failures.

The key secondary outcomes were protected by a gatekeeping procedure: they were tested for significance only if both coprimary endpoints were significant. For all key secondary outcomes, multiplicity was controlled using the Hochberg procedure. The safety population included all participants who took study medication (rimegepant or placebo). All statistical analyses were performed using SAS version 9.4 (Cary, NC, USA). Based on results from previous clinical trials and because the risks associated with single-dose administration were considered very low, a data monitoring committee was not used in this trial. The study is registered at ClinicalTrials.gov, NCT04574362.

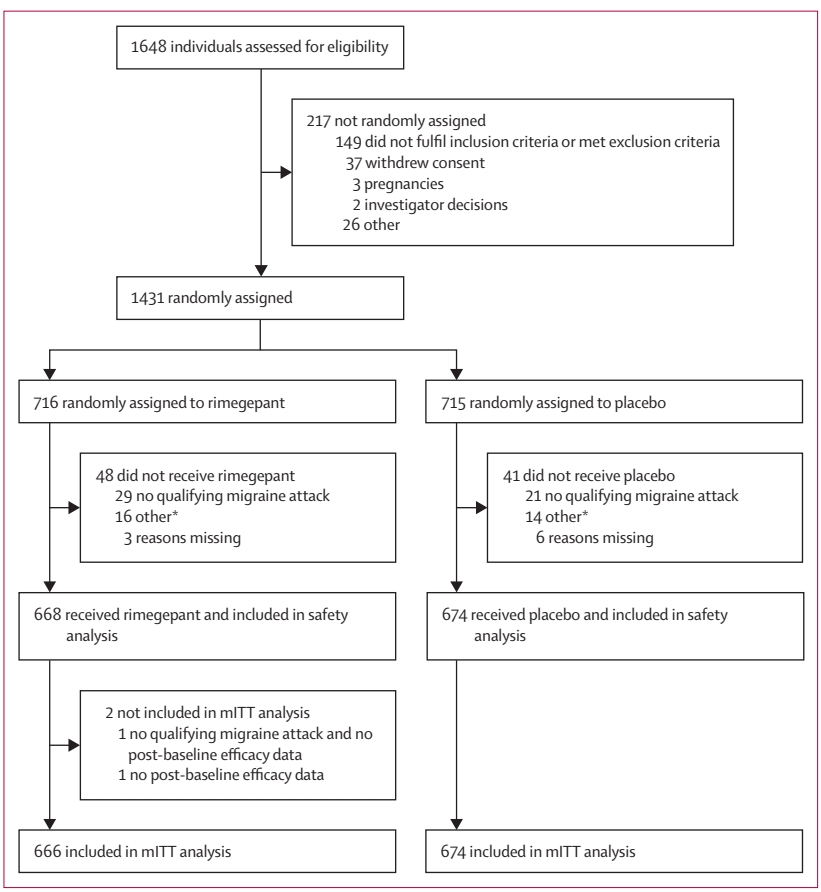

Figure: **Trial profile**
mITT=modified intention-to-treat. *Examples included restrictions at the participant's place of work (ie, could not bring electronic diary to work and had qualified migraine attacks during working hours) or the electronic diary not functioning when a qualified attack happened.

Role of the funding source
This study was sponsored by BioShin Limited (Shanghai, China), a fully owned subsidiary of Biohaven Pharmaceuticals, which was involved with study design, data collection, data analysis, data interpretation, and writing the manuscript.

Results
In total, 1648 individuals were screened between Oct 22, 2020, and Oct 8, 2021 (figure). 217 (13%) individuals were not randomly assigned due to ineligibility or other reasons (eg, withdrawal of consent). 1431 (87%) participants were enrolled in the study and assigned treatment. 716 (50%) participants were randomly assigned to rimegepant and 715 (50%) participants were randomly assigned to placebo. 668 (93%) participants in the rimegepant group and 674 (94%) participants in the placebo group received treatment. 1340 participants were included in the mITT analysis and (666 [93%] participants in the rimegepant group and 674 [94%] participants in the placebo group).

Participants had a median age of 37·8 years (IQR 30·0–44·0). Most participants were women (1088 [81%] of 1340 participants) and lived in China (1074 [80%] of 1340 participants). Participants had a median of 3·3 (IQR 2·6–4·3) moderate or severe migraine attacks per month, and the most common historical most bothersome symptom was nausea (729 [54%] of 1340 participants). 27 (4%) participants in the rimegepant group and 16 (2%) participants in the placebo group

reported a history of cardiovascular diseases, and 36 (5%) participants in the rimegepant group and 35 (5%) participants in the placebo group reported history of vascular disorders. Overall, 98 (7%) of 1340 participants were using preventive migraine medication (50 [8%] of 666 participants in the rimegepant group and 48 [7%] of 674 participants in the placebo group), most commonly topiramate or flunarizine. Demographics and baseline characteristics are presented in table 1.

2 h after dosing, rimegepant was superior to placebo for pain freedom (132 [20%] of 666 participants in the rimegepant group *vs* 72 [11%] of 674 participants in the placebo group, risk difference 9·2%; 95% CI 5·4–13·0; p<0·0001) and freedom from the most bothersome symptom (336 [50%] of 666 participants in the rimegepant group *vs* 241 [36%] of 674 participants in the placebo group, 14·8, 9·6–20·0; p<0·0001). Rimegepant was also more effective than placebo on all five key secondary efficacy outcomes (table 2), including sustained pain freedom from 2 h through to 24 h after dosing and from 2 h through to 48 h after dosing (table 2).

The overall incidence of adverse events was similar in the rimegepant group (108 [16%] of 668 participants) and placebo group (115 [17%] of 674 participants). The proportion of participants who had treatment-emergent adverse events was also similar in the rimegepant group (92 [14%] of 668 participants) and placebo group (96 [14%] of 674 participants). The most common adverse events (≥1%) were protein in urine, nausea, and urinary tract infection (table 3). Participants treated with rimegepant had no drug-related serious adverse events (table 3). No signal of drug-induced liver injury was associated with rimegepant. No participants had concentrations of alanine transaminase greater than three times the upper limit of normal and total concentrations of bilirubin greater than two times the upper limit of normal (ie, Hy's law).

Of the 18 participants who were randomly assigned but discontinued before they had a qualified migraine attack or before the completion of the entire 45 days acute treatment period (7 participants in the rimegepant group and 11 participants in the placebo group), one (1%) participant in the placebo group cited COVID-19 as the reason. Of the six participants (2 participants in the rimegepant group and 4 participants in the placebo group) who had visits affected by COVID-19, one (17%) was diagnosed with COVID-19 at the screening visit, one (17%) had a local laboratory test result collected by remote visit due to COVID-19 related quarantine, and four (67%) had clinical site visits affected by COVID-19-related site closure or travel restriction or were unwilling or unable to visit the study site.

Discussion

In this double-blind, randomised, placebo-controlled, multicentre, phase 3 trial in adults living in China or South Korea—the first trial, to our knowledge, to evaluate rimegepant in people living outside the USA—a single 75 mg dose of rimegepant was superior to placebo on the coprimary efficacy outcomes of pain freedom and freedom from the most bothersome symptom 2 h after dosing, showing efficacy for the acute treatment of migraine. Rimegepant was also superior to placebo on all key secondary endpoints, including pain relief and normal functioning 2 h after dosing, use of rescue medication within 24 h after dosing, and sustained pain freedom from 2 h through to 24 h and from 2 h through to 48 h. Rimegepant was well tolerated, with safety similar to placebo.

The efficacy results in this trial, which are similar to the positive results seen in previous randomised, placebo-controlled trials of rimegepant done in the USA,[18,19] suggest that rimegepant could help to address an unmet need for acute migraine therapies in China and South Korea. More than 150 million people living in China and South Korea have migraine, many of whom have substantial disability and impaired quality of life.[3,4] Migraine is increasingly

	Rimegepant 75 mg (n=666)	Placebo (n=674)
Age, years	37·0 (30·0–45·0)	36·0 (30·0–44·0)
Sex		
Female	525 (79%)	563 (84%)
Male	141 (21%)	111 (16%)
Country		
China	537 (81%)	537 (80%)
South Korea	129 (19%)	137 (20%)
Weight, kg	61·9 (12·1)	61·3 (11·4)
Height, cm	163·7 (7·8)	163·0 (7·0)
BMI, kg/m^2	22·5 (20·5–25·1)	22·7 (20·5–25·0)
Primary migraine type		
Migraine without aura	596 (89%)	606 (90%)
Migraine with aura	70 (11%)	68 (10%)
Age at disease onset, years	27·0 (20·0–34·0)	26·0 (20·0–32·0)
Duration of untreated attacks, h	12·5 (7·5–24·0)	16·0 (8·0–24·0)
Number of moderate to severe migraine attacks per month	3·3 (2·6–4·3)	3·3 (2·6–4·3)
Most bothersome symptom (historical)		
Nausea	362 (54%)	367 (54%)
Phonophobia	179 (27%)	175 (26%)
Photophobia	125 (19%)	131 (19%)
Missing	0	1 (<1%)
Took preventive migraine medication (ever used in entire history)		
Yes	50 (8%)	48 (7%)
No	616 (92%)	626 (93%)

Data are n (%), mean (SD), or median (IQR). The mITT population included randomly assigned participants who took study medication, had a migraine attack of moderate or severe pain intensity at baseline, and provided at least one evaluable efficacy datapoint after taking study drug. Data pertaining to race and ethnicity were not collected because these factors were considered unlikely to influence outcomes.

Table 1: **Demographics and baseline characteristics in the mITT population**

	Rimegepant 75 mg (n=666)	Placebo (n=674)	Rimegepant *vs* placebo, risk difference (95% CI)	p value*
Primary outcomes				
Pain freedom 2 h after dosing	132 (20%)	72 (11%)	9·2 (5·4 to 13·0)	<0·0001
Freedom from the most bothersome symptoms 2 h after dosing	336 (50%)	241 (36%)	14·8 (9·6 to 20·0)	<0·0001
Key secondary outcomes				
Pain relief 2 h after dosing	443 (67%)	327 (49%)	18·1 (13·0 to 23·3)	<0·0001
Normal functioning 2 h after dosing†	222/545 (41%)	131/551 (24%)	16·9 (11·4 to 22·3)	<0·0001
Rescue medication within 24 h after dosing	56 (8%)	135 (20%)	−11·5 (−15·0 to −8·0)	<0·0001
Sustained pain freedom from 2 h to 24 h after dosing	104 (16%)	53 (8%)	7·7 (4·3 to 11·2)	<0·0001
Sustained pain freedom from 2 h to 48 h after dosing	99 (15%)	48 (7%)	7·7 (4·4 to 11·0)	<0·0001
Other secondary outcomes‡				
Pain freedom 15 min after dosing	5 (1%;)	10 (1%)	−0·7 (−1·9 to 0·4)	0·21
Pain freedom 30 min after dosing	7 (1%)	7 (1%)	0 (−1·1 to 1·1)	0·97
Pain freedom 45 min after dosing	22 (3%)	15 (2%)	1·0 (0·7 to 2·8)	0·24
Pain freedom 60 min after dosing	45 (7%)	30 (4%)	2·4 (−0·1 to 4·8)	0·060
Pain freedom 90 min after dosing	82 (12%)	48 (7%)	5·2 (2·1 to 8·4)	0·0012
Freedom from the most bothersome symptom 15 min after dosing	68 (10%)	75 (11%)	−0·7 (−3·9 to 2·5)	0·68
Freedom from the most bothersome symptom 30 min after dosing	112 (17%)	100 (15%)	2·2 (−1·6 to 6·0)	0·26
Freedom from the most bothersome symptom 45 min after dosing	161 (24%)	134 (20%)	4·5 (0·2 to 8·8)	0·042
Freedom from the most bothersome symptom 60 min after dosing	207 (31%)	167 (25%)	6·6 (1·8 to 11·3)	0·0066
Freedom from the most bothersome symptom 90 min after dosing	276 (41%)	214 (32%)	9·9 (4·8 to 14·9)	0·0002
Pain relapse§	33/132 (25%)	24/72 (33%)	−10·4 (−23·5 to 2·8)	0·11

Data are n (%), unless otherwise specified. The mITT population included randomly assigned participants who took study medication, had a migraine attack of moderate or severe pain intensity at baseline, and provided at least one evaluable efficacy datapoint after treatment. Participants taking rescue medication at or before the timepoint were imputed as treatment failures for all endpoints, except rescue medication within 24 h after dosing. mITT=modified intention-to-treat. *Cochran-Mantel-Haenszel test stratified by preventive migraine medication use and country. †Among participants with functional disability at time of dosing (545 participants in the rimegepant group and 551 participants in the placebo group). ‡Outcomes not controlled for multiplicity. §Participants who were pain free 2 h after dosing (132 participants in the rimegepant group and 72 participants in the placebo group) who then had migraine pain of any intensity (response of 1, 2, or 3 on the four-point scale) within 48 h after dosing.

Table 2: **Primary outcomes, key secondary outcomes, and other secondary outcomes in the mITT population**

	Rimegepant 75 mg (n=668)	Placebo (n=674)
Any adverse event	108 (16%)	115 (17%)
Treatment-emergent adverse events		
Protein in urine	8 (1%)	7 (1%)
Nausea	7 (1%)	18 (3%)
Urinary tract infection	5 (1%)	8 (1%)
Blood creatine phosphokinase increased	5 (1%)	3 (<1%)
Proteinuria	4 (1%)	1 (<1%)
Photophobia	4 (1%)	3 (<1%)
Upper respiratory tract infection	3 (<%)	4 (1%)
Anaemia	2 (<1%)	5 (1%)
Vomiting	1 (<1%)	4 (1%)
Serious treatment-emergent adverse events*	1 (<1%)	2 (<1%)
Total treatment-emergent adverse events	92 (14%)	96 (14%)
Drug-related serious treatment-emergent adverse events	0	1 (<1%)

Data are n (%). The safety population included all participants who took study medication (rimegepant or placebo). *In the rimegepant group, one participant had an infection that was considered unrelated to treatment. In the placebo group, one participant had haemoperitoneum and a second participant had decreased embryo viability. The only event in either group that was considered related to treatment by the investigator was decreased embryo viability in the placebo group.

Table 3: **Adverse events in the safety population for 75 mg orally disintegrating tablet and placebo**

recognised as an important public health problem, yet rates of satisfaction with medications available for acute treatment remain low. The use of migraine-specific medications (ie, triptans) is rare in China and South Korea, and widely used agents (eg, ibuprofen and caffeinated analgesics), traditional medicines, and alternative medicines can be inadequate for migraine attacks with severe pain and associated symptoms.[8,9,12] However, no new medication targeting CGRP for acute treatment has been approved in either country. In a previously published randomised, double-blind, placebo-controlled, dose-ranging study in adults with migraine, observed treatment effects with rimegepant and sumatriptan were similar.[23] A post-hoc analysis of data from three randomised trials suggests that rimegepant might be useful for patients with inadequate response or a contraindication to triptans and other currently used agents.[24] Furthermore, ibuprofen and other NSAIDs are not advised for some people with gastrointestinal conditions[25] or cardiovascular risk factors.[26] Triptans are also contraindicated for some people with specific cardiovascular conditions (eg, history of coronary artery disease or stroke), and caution is advised for those with multiple cardiovascular risk factors.[27] Because stroke and ischaemic heart disease are the two most common

causes of mortality in China and South Korea,[2] and because no clinical research or real-world use has so far suggested an association between rimegepant and increased cardiovascular risk, adults with migraine and cardiovascular disease or risk factors might benefit from the absence of cardiovascular safety issues with rimegepant. Furthermore, the use of opioids for migraine, which is common in China and South Korea but is not recommended by guidelines, could also be curtailed with the availability of a therapeutic option without current evidence of an association with misuse.

The safety profile of rimegepant in this trial was similar to placebo and consistent with previous research.[17–20] Most adverse events were mild or moderate, unrelated to study therapy, and resolved without treatment. There was no signal of drug-induced liver injury and no clinically meaningful changes in vital signs, ECG, or physical examination results.

Despite its strengths, this study has some limitations. A strength is that observed treatment effects exceeded prospectively defined target effects, which supports the consistency of response to rimegepant across different trial populations. However, the design of study, in which a single migraine attack was treated, which is required for regulatory approval, provides no data about the consistency of treatment effects over time, nor does it permit evaluation of safety issues that might only become apparent after medium-term or long-term use. Inclusion of an active control group would have facilitated judgments about the efficacy, safety, and tolerability of rimegepant relative to existing antimigraine agents. Although the placebo group response for freedom from the most bothersome symptoms 2 h after dosing was elevated in this trial compared with previous research with rimegepant,[18,19] the risk difference from placebo was similar to that in the previous trials; it is possible that foreknowledge of participation in a clinical trial of a new drug class that had previously shown efficacy in populations outside of China and South Korea could have raised expectations of receiving active drug versus placebo among some participants.

Rimegepant 75 mg was shown to be effective—with rapid relief of pain and return to normal function and excellent safety and tolerability—for the acute treatment of migraine in adults living in China and South Korea. Because no CGRP antagonists have been approved in China or South Korea for acute treatment, the results of this clinical trial suggest that the rimegepant 75 mg orally disintegrating tablet might be a useful addition to the range of medications for the acute treatment of migraine in these countries.

Contributors

DM, MH, DAS, YG, RC, ZL, MZ, and SY participated in study design. SY, B-KK, AG, M-HK, MZ, ZW, JL, H-SM, GT, and QY enrolled most of the participants in this study. MH and ZL supervised the trial. DAS and YG did the statistical analysis. SY and ZL verified the data. All authors were involved in data interpretation and edited the manuscript for content and accuracy. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

B-KK has received personal compensation for serving on a scientific advisory board for Lundbeck Korea, Pfizer Korea, and Novartis; he has received personal compensation for serving as a speaker or moderator for Allergan Korea, Lilly Korea, Teva Korea, GSK Korea, Lundbeck Korea, and SK-Pharma. M-HK has received personal compensation for serving on a scientific advisory board for Lundbeck Korea, Novartis, Allergan Korea, Lilly Korea, and Teva Korea. H-SM was a principal investigator for a multicentre trial sponsored by Lundbeck, Novartis, and Eli Lilly; she received lecture honoraria from GSK Korea, SK Pharma, Teva Korea, Lundbeck Korea, Allergan Korea, and Yuyu Pharma in the past 24 months. DM, MH, DAS, and RC were employed by Biohaven Pharmaceuticals, the developer of rimegepant, during the trial. RC and ZL are currently employed by Pfizer, the development and commercial rights owner of rimegepant. YG and ZL were employed by BioShin Limited, the trial sponsor, during the conduct of the trial. SY, AG, MZ, ZW, JL, GT, and QY declare no competing interests

Data sharing

Biohaven Pharmaceuticals will provide access to deidentified participant data that underlie the results in this Article in response to scientifically valid research proposals. Data from this study, including the study protocol, will be made available beginning 9 months and ending 24 months after the publication of this Article. Biohaven will consider requests from qualified researchers for access to the data. Proposals should be directed to the corresponding author (ZL). Biohaven will review the request using an internal committee composed of Biohaven colleagues who are responsible for the programme, including a clinician, a statistician, and a data-sharing professional. Biohaven will make reasonable efforts to fulfil all data requests for legitimate research purposes, but there might be instances in which retrieval or delivery of data is not feasible, such as those involving, for example, patient privacy, requirements for permissions, contractual obligations, and conflicts of interest. All those receiving access to data will be required to enter into a data use agreement provided by Biohaven that will contain the terms under which the data will be provided.

Acknowledgments

This clinical trial was supported by BioShin, a wholly owned subsidiary of Biohaven Pharmaceuticals, the developer of rimegepant. Medical writing services were provided by Christopher Caiazza and supported by Biohaven Pharmaceuticals. The authors thank the study participants, investigators, and study site staff.

References

1 Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders. 3rd edition. *Cephalalgia* 2018; **38:** 1–211.

2 Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396:** 1204–22.

3 Yao C, Wang Y, Wang L, et al. Burden of headache disorders in China, 1990-2017: findings from the Global Burden of Disease Study 2017. *J Headache Pain* 2019; **20:** 102.

4 Kim KM, Cho SJ, Shin HJ, et al. Prevalence, disability, and management patterns of migraine in Korea: nationwide survey data from 2009 and 2018. *J Clin Neurol* 2021; **17:** 77–85.

5 Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. *J Headache Pain* 2022; **23:** 34.

6 Kim BK, Chu MK, Yu SJ, Dell'Agnello G, Han JH, Cho SJ. Burden of migraine and unmet needs from the patients' perspective: a survey across 11 specialized headache clinics in Korea. *J Headache Pain* 2021; **22:** 45.

7 Takeshima T, Wan Q, Zhang Y, et al. Prevalence, burden, and clinical management of migraine in China, Japan, and South Korea: a comprehensive review of the literature. *J Headache Pain* 2019; **20:** 111.

8 Chinese Medical Association Group. Guide to the prevention and treatment of migraine in China [zhong guo pian tou tong fang zhi zhi nan]. *Chin J Pain Med* 2016; **22:** 721–27 (in Chinese).

9 Kim SM, Ko YH, Yoon S, et al. The development of evidence-based guideline for diagnosis and management of headache in Korea. *Psychiatry Investig* 2019; **16:** 199–205.

10 Evers S, Áfra J, Frese A, et al. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. *Eur J Neurol* 2009; **16:** 968–81.

11 National Institute for Health and Care Excellence (NICE). Headaches in over 12s: diagnosis and management. 2021. https://www.nice.org.uk/guidance/cg150/resources/headaches-in-over-12s-diagnosis-and-management-pdf-35109624582853 (accessed March 19, 2023).

12 Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache* 2015; **55:** 3–20.

13 Yu S, Zhang Y, Yao Y, Cao H. Migraine treatment and healthcare costs: retrospective analysis of the China Health Insurance Research Association (CHIRA) database. *J Headache Pain* 2020; **21:** 53.

14 Luo N, Qi W, Zhuang C, et al. A satisfaction survey of current medicines used for migraine therapy in China: is Chinese patent medicine effective compared with western medicine for the acute treatment of migraine? *Pain Medicine* 2014; **15:** 320–28.

15 Kim Y, Park S, Kim E, Je N. Utilization of preventive therapy in Korean migraine patients. *Korean J Clin Pharm* 2021; **31:** 35–43.

16 Wang SJ, Chung CS, Chankrachang S, et al. Migraine disability awareness campaign in Asia: migraine assessment for prophylaxis. *Headache* 2008; **48:** 1356–65.

17 Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? *J Headache Pain* 2018; **19:** 17.

18 Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med* 2019; **381:** 142–49.

19 Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *Lancet* 2019; **394:** 737–45.

20 Croop R, Berman G, Kudrow D, et al. Long-term safety of rimegepant 75 mg for the acute treatment of migraine (Study 201). *Headache* 2020; **60:** 111–12.

21 Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; **33**: 629–808.

22 Lipton R, Conway C, Stock E, et al. Efficacy, safety, and tolerability of rimegepant 75 mg, an oral CGRP receptor antagonist, for the acute treatment of migraine: results from a double-blind, randomized, placebo-controlled trial, study 301. *Headache* 2018; **58**: 1336–37.

23 Marcus R, Goadsby PJ, Dodick D, Stock D, Manos G, Fischer TZ. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia* 2014; **34:** 114–25.

24 Lipton RB, Blumenfeld A, Jensen CM, et al. Efficacy of rimegepant for the acute treatment of migraine based on triptan treatment experience: pooled results from three phase 3 randomized clinical trials. *Cephalalgia* 2023; published online Feb 5. https://doi.org/10.1177/03331024221141686.

25 Felson DT. Safety of nonsteroidal antiinflammatory drugs. *N Engl J Med* 2016; **375:** 2595–96.

26 Dodick DW, Goadsby PJ, Silberstein SD, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. *Lancet Neurol* 2014; **13:** 1100–07.

27 Dodick DW, Shewale AS, Lipton RB, et al. Migraine patients with cardiovascular disease and contraindications: an analysis of real-world claims data. *J Prim Care Community Health* 2020; **11:** 2150132720963680.