Rimegepant, an Oral Calcitonin Gene–Related Peptide Receptor Antagonist, for Migraine

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BACKGROUND
Calcitonin gene–related peptide receptor has been implicated in the pathogenesis of migraine. Rimegepant is an orally administered, small-molecule, calcitonin gene–related peptide receptor antagonist that may be effective in acute migraine treatment.

METHODS
In a multicenter, double-blind, phase 3 trial, we randomly assigned adults with at least a 1-year history of migraine and two to eight migraine attacks of moderate or severe intensity per month to receive rimegepant orally at a dose of 75 mg or matching placebo for the treatment of a single migraine attack. The primary end points were freedom from pain and freedom from the most bothersome symptom (other than pain) identified by the patient, both of which were assessed 2 hours after the dose of rimegepant or placebo was administered.

RESULTS
A total of 1186 patients were randomly assigned to receive rimegepant (594 patients) or placebo (592 patients); of these, 537 patients in the rimegepant group and 535 patients in the placebo group could be evaluated for efficacy. The overall mean age of the patients evaluated for efficacy was 40.6 years, and 88.7% were women. In a modified intention-to-treat analysis, the percentage of patients who were pain-free 2 hours after receiving the dose was 19.6% in the rimegepant group and 12.0% in the placebo group (absolute difference, 7.6 percentage points; 95% confidence interval [CI], 3.3 to 11.9; P<0.001). The percentage of patients who were free from their most bothersome symptom 2 hours after the dose was 37.6% in the rimegepant group and 25.2% in the placebo group (absolute difference, 12.4 percentage points; 95% CI, 6.9 to 17.9; P<0.001). The most common adverse events were nausea and urinary tract infection.

CONCLUSIONS
Treatment of a migraine attack with the oral calcitonin gene–related peptide receptor antagonist rimegepant resulted in a higher percentage of patients who were free of pain and free from their most bothersome symptom than placebo. (Funded by Biohaven Pharmaceuticals; ClinicalTrials.gov number, NCT03237845.)
Migraine is a common chronic neurologic disease that may affect nearly 1 billion people worldwide. Serotonin 5-HT_{18} and 5-HT_{1D} receptor agonists (triptans) have been the most widely prescribed acute migraine treatments for decades. However, some patients who use triptans either do not have a response (34%) or have recurrences of attacks (30 to 40%); in addition, up to 52% have adverse effects from triptans, and concerns about these effects were reported in one study to result in delays in treatment or avoidance of treatment in two thirds of patients. Triptans also are either contraindicated or must be used with caution in patients with cardiovascular disease because of concerns about cardiovascular effects.

Calcitonin gene–related peptide (CGRP) plays a role in the pathophysiological features of migraine, and small-molecule CGRP receptor antagonists (gepants) have been shown to be effective in acute migraine treatment in several previous trials. Gepants may be effective in patients whose symptoms do not respond to triptans, owing to their different mechanisms of action. Unlike triptans, which are contraindicated in patients with cardiovascular disease because of the possibility of vasoconstriction, rimegepant does not have vasoconstrictive effects.

In a previous randomized, double-blind, placebo-controlled, dose-ranging, phase 2b trial that evaluated multiple oral dose levels of rimegepant, the 75-mg dose was superior to placebo with respect to the elimination of pain, nausea, photophobia, and phonophobia 2 hours after administration of the dose and had sustained effects through 24 and 48 hours. The current phase 3 trial was conducted to evaluate the efficacy and safety of rimegepant (at an oral dose of 75 mg), as compared with placebo, in acute migraine treatment.

**METHODS**

**TRIAL POPULATION**

Men and women 18 years of age or older were recruited by referral from physicians and other health care professionals and by standard methods of recruitment, including enrollment from clinical practices and through advertising. Treatment settings included clinics, institutions, and private office practices. Eligible participants had migraine, with or without aura, that met the criteria specified in the International Classification of Headache Disorders, 3rd edition (beta version); had a 1-year history of migraine, with an onset before the age of 50 years; had two to eight migraine attacks of moderate or severe intensity per month; and had any headache on fewer than 15 days per month during the previous 3 months. Persons who were receiving preventive migraine medication had to be receiving a stable dose for at least 3 months before trial entry.

A key exclusion criterion was a history of any clinically significant or unstable medical condition, including alcohol or drug abuse and substance-use disorder, that would expose patients to an undue risk of an adverse event or that could interfere with assessments of safety or efficacy. Patients were also excluded if they had received nonbiologic investigational agents within 30 days before the baseline visit or if they had received biologic investigational agents within 90 days before the baseline visit. Complete criteria for participation are listed in the protocol, available with the full text of this article at NEJM.org.

**TRIAL OVERSIGHT**

The trial was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and all applicable local regulations. The protocol was approved by an independent ethics committee or institutional review board at each trial center. All patients provided written informed consent. Biohaven Pharmaceuticals sponsored the trial, supplied the trial agents, reviewed the trial design, collected the data, and performed data management and analysis. The manuscript was written with the assistance of a medical writer funded by Biohaven Pharmaceuticals. All the authors have confidentiality agreements with Biohaven Pharmaceuticals, either as a condition of employment or in their role as consultants. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

**TRIAL DESIGN**

In this multicenter, randomized, double-blind, phase 3 trial, we evaluated the safety and efficacy of rimegepant at an oral dose of 75 mg, as compared with placebo, for acute migraine treat-
Patients were provided with one 75-mg dose of rimegepant or matching placebo and were instructed to take the tablet when a single migraine attack of moderate or severe intensity occurred. Before taking the tablet, they answered questions in the electronic diary about their current pain and symptoms, and they identified and recorded their current most bothersome migraine-associated symptom, other than pain (i.e., phonophobia, photophobia, or nausea). Patients completed the electronic diary for up to 48 hours after taking the trial agent. Pain intensity, the presence or absence of associated symptoms, and ratings of functional disability were assessed at the onset of the treated attack; at 15, 30, 45, 60, and 90 minutes after the dose; and at 2, 3, 4, 6, 8, 24, and 48 hours after the dose.

Patients were asked to return to the trial center within 7 days after taking the dose of rimegepant or placebo. At that visit, trial personnel reviewed adherence to the electronic diary assessments, confirmed that the patient had taken the dose, and monitored safety variables. Patients who had not had an attack of sufficient severity within 45 days after randomization were withdrawn and were instructed to return the unused trial agent and the electronic diary.

**End Points**

The primary efficacy end points were freedom from pain (which was defined by the presence of no pain in a person who had had pain of moderate or severe intensity immediately before administration of the dose) and freedom from the patient’s most bothersome symptom associated with migraine (i.e., phonophobia, photophobia, or nausea), 2 hours after the dose. Secondary end points were freedom from photophobia and from phonophobia, pain relief (which was defined by the presence of mild pain or no pain in a patient who had had pain of moderate or severe intensity immediately before administration of the dose), and freedom from nausea, each assessed 2 hours after the dose of rimegepant or placebo; the probability of using rescue medication within 24 hours after the dose; sustained freedom from pain and sustained pain relief from 2 hours to 24 hours after the dose; sustained freedom from pain and sustained pain relief from 2 hours to 48 hours after the dose; pain relapse (which was defined by the return of headache pain of any intensity after being pain-free 2 hours after the dose) from 2 hours to 48 hours after the dose;
The ability to function at a normal level 2 hours after the dose. The methods used to measure efficacy end points are described in the Supplementary Appendix, available at NEJM.org. Safety and other assessments included evaluation of adverse events, electrocardiography, vital signs, measurements of height and weight, routine laboratory testing and the Sheehan Suicidality Tracking Scale.19

### Statistical Analysis

We estimated that approximately 90% of the 600 patients randomly assigned to each treatment group would have a migraine attack that met the protocol-specified criteria in the allotted time period, which would result in approximately 550 patients in each group who would receive rimegepant or placebo. On the basis of the results of the previous phase 2b trial,16 we estimated that a sample of 550 patients in each group would provide the trial with more than 95% power to detect a significant difference between the rimegepant group and the placebo group in each of the two primary end points and hence at least 90% power to detect a significant difference between the groups in both end points jointly.

### Table 1. Characteristics of the Modified Intention-to-Treat Population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rimegepant (N = 537)</th>
<th>Placebo (N = 535)</th>
<th>Total (N = 1072)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>40.2±11.9</td>
<td>40.9±12.1</td>
<td>40.6±12.0</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>479 (89.2)</td>
<td>472 (88.2)</td>
<td>951 (88.7)</td>
</tr>
<tr>
<td>Race or ethnic group — no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>394 (73.4)</td>
<td>399 (74.6)</td>
<td>793 (74.0)</td>
</tr>
<tr>
<td>Black</td>
<td>111 (20.7)</td>
<td>118 (22.1)</td>
<td>229 (21.4)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (1.5)</td>
<td>8 (1.5)</td>
<td>16 (1.5)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>6 (1.1)</td>
<td>0</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>4 (0.7)</td>
<td>5 (0.9)</td>
<td>9 (0.8)</td>
</tr>
<tr>
<td>Multiple</td>
<td>14 (2.6)</td>
<td>5 (0.9)</td>
<td>19 (1.8)</td>
</tr>
<tr>
<td>Hispanic ethnic group — no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>77 (14.3)</td>
<td>83 (15.5)</td>
<td>160 (14.9)</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td>31.0±7.9</td>
<td>31.8±8.5</td>
<td>31.4±8.2</td>
</tr>
<tr>
<td>Migraine history</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Attacks per month — no.</td>
<td>4.5±1.9</td>
<td>4.6±1.8</td>
<td>4.6±1.8</td>
</tr>
<tr>
<td>Average duration of untreated attacks — hr</td>
<td>32.0±22.5</td>
<td>32.9±21.7</td>
<td>32.5±22.1</td>
</tr>
<tr>
<td>Most bothersome symptom — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photophobia</td>
<td>277 (51.6)</td>
<td>279 (52.1)</td>
<td>556 (51.9)</td>
</tr>
<tr>
<td>Phonophobia</td>
<td>72 (13.4)</td>
<td>92 (17.2)</td>
<td>164 (15.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>169 (31.5)</td>
<td>148 (27.7)</td>
<td>317 (29.6)</td>
</tr>
<tr>
<td>Missing data§</td>
<td>19 (3.5)</td>
<td>16 (3.0)</td>
<td>35 (3.3)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. The modified intention-to-treat population included patients who underwent randomization, had a migraine attack with pain of moderate or severe intensity, took a dose of rimegepant or placebo, and had at least one efficacy assessment after administration of the dose. There were no significant between-group differences at baseline for any characteristic. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the patient.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ In the analysis of the most bothersome symptom, patients with missing data were considered to have treatment failure.
2 hours after the dose and freedom from the most bothersome symptom 2 hours after the dose) if the P value for both comparisons was less than 0.05. These analyses were performed with the use of Cochran–Mantel–Haenszel tests, stratified according to the use of preventive migraine medication (yes vs. no); patients with missing data at the 2-hour time point after the dose was administered were considered to have treatment failure. Patients who used rescue medication were considered to have treatment failure as of the time the medications were used. We performed sensitivity analyses that took missing data into account; the results are shown in the Supplementary Appendix.

To maintain the type I error rate at 0.05, a prespecified hierarchical gatekeeping procedure was applied in which the secondary end points were tested in the order indicated above and in the protocol. A comparison was considered to be significant if that comparison and each of the preceding comparisons showed a significant difference between the treatment groups. If a significant difference was not observed for an end point, any subsequent comparisons were reported without P values.

The probability of freedom from pain and of freedom from the most bothersome symptom over the course of 8 hours after the dose was administered was estimated with the use of the Kaplan–Meier method in exploratory time-to-event analyses. For each time point, the number of patients eligible to become free from pain or free from their most bothersome symptom and the number of patients who reported the first occurrence of the event were used to calculate the probability estimate (with 95% confidence intervals). Data from patients whose pain or most bothersome symptom persisted for 495 minutes (8 hours plus a 15-minute margin for error) were censored at 495 minutes after the dose, and data from patients who used rescue medication were
censored at the time of the dose of rescue medication. The probability estimates shown in the Kaplan–Meier plots represent the probability of a first report of freedom from pain or freedom from the most bothersome symptom.

**RESULTS**

**PATIENTS**

From July 2017 through January 2018, a total of 1186 patients participated in the trial at 49 centers in the United States. Patients were randomly assigned to receive rimegepant (594 patients) or placebo (592 patients). A total of 1086 patients received the assigned dose of rimegepant or placebo, and 1080 of these patients (99.4%) completed the trial (538 in the rimegepant group and 542 in the placebo group) (Fig. 1). The demographic and clinical characteristics of the two treatment groups were similar (Table 1). Most of the patients (88.7%) were women, and the mean age of the overall population was 40.6 years. The patients reported a history of 4.6 migraine attacks per month, each of which lasted an average of 32.5 hours if left untreated. Among the 1072 patients in the modified intention-to-treat population, of whom 734 had migraine without aura and 338 had migraine with aura, the most bothersome symptom other than pain was photophobia in 51.9%, nausea in 29.6%, and phonophobia in 15.3%. The groups were balanced with respect to the distribution of the most bothersome symptom (Table 1).

**Efficacy**

Two hours after the dose of rimegepant or placebo, 19.6% of the patients in the rimegepant group, as compared with 12.0% in the placebo group, were free from pain (absolute difference, 7.6 percentage points; 95% confidence interval [CI], 3.3 to 11.9; P<0.001). The percentage of patients who had freedom from their most bothersome symptom 2 hours after the dose was reported in 37.6% in the rimegepant group and 25.2% in the placebo group (absolute difference, 12.4 percentage points; 95% CI, 6.9 to 17.9; P<0.001) (Table 2).

The analyses of the secondary end points, which were tested hierarchically in the order listed in Table 2, showed that freedom from photophobia at 2 hours after the dose was administered was reported in 37.4% in the rimegepant group and in 22.3% in the placebo group (P<0.001), and freedom from phonophobia was reported in 36.7% and 26.8%, respectively (P=0.004). The percentage of patients who had pain relief 2 hours after the dose was 58.1% in the rimegepant group as compared with 42.8% in the placebo group (P<0.001). The percentage of patients who had freedom from nausea 2 hours after the dose did not differ significantly between

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**Figure 2. Probability of Freedom from Pain and Freedom from the Most Bothersome Symptom.**

The probability of freedom from pain (Panel A) and freedom from the most bothersome symptom other than pain (Panel B) was estimated in an exploratory analysis in the modified intention-to-treat population, which included all patients who underwent randomization, had a migraine attack with pain of moderate or severe intensity, took a dose of rimegepant or placebo, and had at least one efficacy assessment after administration of the dose. Data were censored at the time a patient took rescue medication or 495 minutes after the dose. The reported probabilities are those at the actual time of data collection.
The treatment groups (48.1% in the rimegepant group and 43.3% in the placebo group, P = 0.21). (All percentages are Cochran–Mantel–Haenszel estimates.) As a result of this nonsignificant difference, and in accordance with the hierarchical analysis, no statistical inferences can be drawn from the remainder of the secondary end points. Exploratory analyses of freedom from pain and freedom from the most bothersome symptom during the first 8 hours after the dose of rimegepant or placebo are shown in Figure 2.

**SAFETY**

The most common adverse events were nausea (1.8% in the rimegepant group and 1.1% in the placebo group) and urinary tract infection (1.5% and 1.1%, respectively). Serious adverse events were reported in one patient in the rimegepant group (back pain) and in two patients in the placebo group (Table 3). Liver-function tests showed serum levels of alanine aminotransferase or aspartate aminotransferase that were above the upper limit of the normal range in 2.4% of the patients who received rimegepant and in 2.2% of the patients who received placebo (Table 3). No patient in either treatment group had an alanine aminotransferase level or an aspartate aminotransferase level of more than three times the upper limit of the normal range, and no total bilirubin level of more than two times the upper limit of the normal range was observed.

**DISCUSSION**

A single, oral, 75-mg dose of rimegepant was superior to placebo with respect to the primary end points of freedom from pain and freedom from the patient’s most bothersome symptom 2 hours after the dose; pain was eliminated in 19.6% of the patients who received rimegepant, as compared with 12.0% of the patients who received placebo. The results of the analyses of the secondary end points of freedom from photophobia, freedom from phonophobia, and pain relief, each assessed 2 hours after the dose of rimegepant or placebo, showed the superiority of rimegepant over placebo; however, rimegepant was not found to be superior to placebo with respect to freedom from nausea. Nausea and urinary tract infection were the only adverse events reported in more than 1% of the patients in each group.

Our trial had several limitations. First, the trial did not include an active comparator to rimegepant. Second, although the rimegepant and placebo groups were balanced with respect to baseline characteristics and features of the treated migraine attack immediately before ad-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rimegepant (N = 543)</th>
<th>Placebo (N = 543)</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of patients (percent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>93 (17.1)</td>
<td>77 (14.2)</td>
</tr>
<tr>
<td>Adverse events reported in ≥1% of patients in either treatment group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (1.8)</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>8 (1.5)</td>
<td>6 (1.1)</td>
</tr>
<tr>
<td>Serious adverse event†</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Liver-function tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum AST or ALT above ULN</td>
<td>13 (2.4)</td>
<td>12 (2.2)</td>
</tr>
<tr>
<td>Serum AST or ALT &gt;3× ULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total bilirubin &gt;2× ULN</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* The safety population included all patients who underwent randomization and took a dose of rimegepant or placebo. Patients could have had more than one adverse event. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† The serious adverse event reported in the rimegepant group was back pain, and the serious adverse events reported in the placebo group were chest pain (1 patient) and urinary tract infection (1 patient).
ministration of the dose, the single-attack design (i.e., assessment of treatment effect on a single episode of a condition) does not permit assessment of the consistency of the effects of the drug from attack to attack over time in the same patient. Third, although no evidence of adverse cardiac effects was observed, the trial population was not enriched for patients with cardiovascular disease.

This trial showed that among patients with migraine, treatment of an attack with rimegepant, which acts through inhibition of the CGRP receptor, resulted in a moderately higher percentage of patients who were free from pain and free from their most bothersome symptom 2 hours after the dose than placebo. Larger and longer trials are needed to determine the consistency of response and the safety and effectiveness of the drug as compared with other migraine treatments.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES


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