CLINICAL STUDY REPORT SYNOPSIS

SYNOPSIS

Study Title: Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of Rimegepant for the Acute Treatment of Migraine in Japanese Subjects

Study Number: C4951022 (BHV3000-313)

Regulatory Agency or Public Disclosure Identifier Number:

ClinicalTrials.gov ID: NCT05399459

jRCT Number: jRCT2031220236

Study Phase: 2/3

Name of Study Intervention: Rimegepant/PF-07899801/BHV-3000

Trade Name: Nurtec® orally disintegrating tablet (ODT)

Name of Sponsor/Company: Pfizer, Inc, which completed the process of taking over the role of sponsor from Biohaven Pharmaceuticals Holding Company Limited on 5 October 2023

CSR Version and Report Date:

Final CSR (amendment to 29 August 2024) Version 3.0, 1 November 2024

Final CSR (amendment to 2 July 2024) Version 2.0, 29 August 2024

Final CSR (last participant last visit [LPLV] date) Version 1.0, 2 July 2024

Number of Study Center(s) and Investigator(s):

A total of 897 participants were enrolled at 50 centers in Japan. A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Not Applicable.

Study Period:

Study Initiation (first participant first visit) Date: 9 August 2022

Study Completion (LPLV) Date: 19 January 2024

CLINICAL STUDY REPORT SYNOPSIS

This study was neither discontinued nor interrupted.

Rationale:

Migraine is a common and debilitating neurological disorder that affects approximately 8.4% of the adult population in Japan. It is characterized by moderate-to-severe episodic unilateral pulsating headaches that last for 4 to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.

Rimegepant (PF-07899801, BHV-3000) is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the acute and preventive treatment of migraine. The CGRP receptor is located within pain-signaling pathways, intracranial arteries and mast cells and its activation is thought to play a causal role in migraine pathophysiology.

This clinical study report presents results of the completed study, C4951022 (BHV3000-313), a Phase 2/3, double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant as compared with placebo in the treatment of moderate or severe migraine.

Objectives, Endpoints, and Statistical Methods:

The study objectives and endpoints are summarized in Table S1.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints

Type and Objective	Endpoints[a]
Primary	
Efficacy	
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on pain freedom at 2 hours postdose.	Percentage of participants with a headache pain intensity of none at 2 hours postdose. Pain intensity was measured on a 4-point numeric rating scale (0=none, 1=mild, 2=moderate, 3=severe).
Secondary	
Efficacy	
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on pain relief at 2 hours postdose.	Percentage of participants with pain intensity of none or mild at 2 hours postdose.
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on freedom from the MBS associated with migraine at 2 hours postdose.	Percentage of participants with MBS reported before dosing that was absent at 2 hours postdose. The MBS before dosing was reported as nausea, phonophobia, or photophobia. Symptom status was reported postdose as present or absent for each symptom (nausea, phonophobia, and photophobia).
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on the ability to function normally at 2 hours postdose.	Percentage of participants with a functional disability level of normal at 2 hours postdose; evaluated for the subset with functional disability at the time of dosing. Functional disability level was measured on a 4-point numeric rating scale (0=normal, 1=mildly impaired, 2=severely impaired, 3=requires bedrest), and functional disability was defined as mildly impaired, severely impaired, or requires bedrest.
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on sustained pain relief from 2 to 24 hours postdose.	Percentage of participants with pain intensities of none or mild at all time points from 2 to 24 hours postdose.
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on rescue medication use within 24 hours of initial treatment.	Percentage of participants taking rescue medication within 24 hours postdose.
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on sustained pain relief from 2 to 48 hours postdose.	Percentage of participants with pain intensities of none or mild at all time points from 2 to 48 hours postdose.
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on freedom from photophobia at 2 hours postdose.	Percentage of participants with photophobia absent at 2 hours postdose; evaluated for the subset with photophobia present at the time of dosing.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints

Type and Objective	Endpoints[a]
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on sustained pain freedom from 2 to 24 hours postdose.	Percentage of participants with pain intensities of none at all time points from 2 to 24 hours postdose.
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on freedom from phonophobia at 2 hours postdose.	Percentage of participants with phonophobia absent at 2 hours postdose; evaluated for the subset with phonophobia present at the time of dosing.
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on sustained pain freedom from 2 to 48 hours postdose.	Percentage of participants with pain intensities of none at all time points from 2 to 48 hours postdose.
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on freedom from nausea at 2 hours postdose.	Percentage of participants with nausea absent at 2 hours postdose; evaluated for the subset with nausea present at the time of dosing.
To compare the efficacy of rimegepant 75 mg with placebo in the acute treatment of migraine in Japanese participants on pain relapse from 2 to 48 hours postdose.	Percentage of participants with a pain intensity of mild, moderate, or severe at any time point after 2 hours through 48 hours postdose; evaluated for the subset with pain freedom at 2 hours postdose.
Efficacy	
To compare the efficacy of rimegepant 25 mg with placebo in the acute treatment of migraine in Japanese participants on the same efficacy endpoints.	Primary and secondary efficacy endpoints evaluated for rimegepant 75 mg.
Safety	
To evaluate the tolerability and safety of rimegepant 75 mg and 25 mg in the acute treatment of migraine.	Tolerability and safety were evaluated by the percentage of participants with AEs by intensity, SAEs, and grade 3 to 4 laboratory test abnormalities.

Abbreviations: AE=adverse event; MBS=most bothersome symptom; SAE=serious adverse event.
a: Participants who took rescue medication were classified as failures for all efficacy assessments that were reported at or after taking rescue medication. This method applied to all endpoints listed above, except the secondary endpoint of rescue medication use within 24 hours postdose.

Methodology:

Study C4951022 (BHV3000-313) was a Phase 2/3, double-blind, randomized, multicenter, outpatient evaluation of the safety and efficacy of rimegepant 75 mg as compared with placebo in the treatment of moderate or severe migraine in Japanese participants. The investigational product was formulated as rimegepant 25-mg ODT, rimegepant 75-mg ODT or a matching placebo. The 25 mg rimegepant dose was included in the study to permit an assessment of the dose response for rimegepant in Japanese participants. Pfizer Inc. completed the process of taking over the role of sponsor from Biohaven Pharmaceuticals Holding Company Limited on 5 October 2023.

CLINICAL STUDY REPORT SYNOPSIS

This included a 3- to 28-day Screening Period, a Treatment Phase that could last up to 45 days or until the participant had a migraine that reached moderate or severe intensity, followed by an End of Treatment Visit within 7 days after the administration of the study intervention. A month was defined as 4 weeks for the purpose of this study. Participants who met all eligibility criteria were randomized in a 1:1:1 ratio to the rimegepant 25 mg, rimegepant 75 mg, or placebo treatment groups at the Baseline Visit. The randomization was stratified by the use of prophylactic migraine medications (yes or no). The total duration of the study was approximately 11 weeks.

A participant whose usual migraine attack resulted in headache pain of moderate or severe intensity and who was otherwise found acceptable for entry into this study based on inclusion and exclusion criteria first participated in the screening phase (3- to 28-day period). Participants on prophylactic migraine medication were permitted to remain on therapy provided they had been on a stable dose for at least 3 months prior to study entry.

After randomization, the participants were dispensed a single dose of the double-blind study intervention that was to be taken at the time a migraine attack reached moderate or severe pain intensity (described below) on the numeric rating scale as indicated in the electronic diary (eDiary). The participants were instructed to take their study intervention, as outpatients, when (if) they had a migraine headache which reached moderate or severe pain intensity and only after they had identified their most bothersome migraine-associated symptom (phonophobia, photophobia, or nausea). The participants were to complete an eDiary for up to 48 hours after taking study intervention. The participants were to contact the study center immediately if they experienced any adverse events (AEs). The participants were to record efficacy data in their eDiary. This included the following: onset time of headache, intensity of the headache prior to and at the time of taking study intervention. The participants were to record all headache intensity leading up to dosing, but were not to dose with study intervention until the headache reached moderate or severe pain intensity. Headache severity was recorded using a 4-point numeric rating scale (no pain, mild pain, moderate pain, severe pain) at the onset of the migraine and after dosing at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24, and 48 hours. The presence or absence of associated symptoms (nausea, photophobia, phonophobia) and ratings of functional disability (4-point scale: normal, mildly impaired, severely impaired, requires bedrest) were recorded at the same time points as the headache severity ratings. Participants who experienced reduction of headache pain to a mild intensity or pain free intensity level were considered to have achieved pain relief. The participants who did not experience relief of their migraine headache at the end of 2 hours after dosing with study intervention (and after the 2-hour assessments were completed on the eDiary) were permitted to use the following rescue medications: aspirin, ibuprofen, acetaminophen (up to 2000 mg/day), naproxen (or any other type of nonsteroidal anti-inflammatory drug), antiemetics (e.g., metoclopramide), or baclofen. These were the only medications allowed for rescue treatment after 2 hours postdose of study intervention. If at the end of 48 hours after dosing with study intervention (but before the End of Treatment Visit) participants were in need of migraine relief, they could take their prescribed standard of care medications, including triptans if not

CLINICAL STUDY REPORT SYNOPSIS

contraindicated, provided all of the assessments had been completed on the eDiary. Exclusionary rescue medication such as opioids, ergotamines, butalbital compounds, and muscle relaxants (except baclofen as a rescue medication, see above) were not allowed during this study. Similarly, if the migraine was relieved by study intervention at 2 hours after dosing but then recurred to a moderate or severe intensity level between 2 and 48 hours, the participants were permitted to take the same rescue therapy as outlined above. In all circumstances, the participants always continued to complete their eDiary for up to 48 hours after taking the study intervention.

Number of Participants (planned and analyzed):

A total of 795 participants were planned to be randomized in this study. A total of 897 participants were included in the enrolled analysis set. Out of 897 participants, 803 were randomized, and 706 took the study intervention. A total of 803 participants were included in the full analysis set, 706 participants were included in the efficacy analysis set and the safety analysis set.

The number of participants included in each analysis population is provided in Table S2. One participant who was randomized to the placebo group received rimegepant 25 mg, which led to the difference in the number of participants in the rimegepant 25 mg and placebo groups between the efficacy analysis set and the safety analysis set.

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Analysis Sets

Analysis Set: n	RMG25	RMG75	PBO	Not Randomized	Overall
Enrolled				94	897
Full	267	268	268		803
Efficacy	238	238	230		706
Safety[a]	239	238	229	0	706

Abbreviations: IWRS=interactive web response system; PBO=placebo; RMG=rimegepant.
Enrolled: Subjects who sign an informed consent form and are assigned a subject identification number
Full: Subjects in the enrolled analysis set who receive a randomized treatment assignment from the IWRS
Efficacy: Subjects in the full analysis set who meet all the following criteria:
(1) Randomized only once
(2) Take study drug, i.e., nonmissing study drug date/time
(3) Have moderate or severe pain intensity at the time of dosing
(4) Have postdose efficacy data. Defined as nonmissing efficacy data at ≥1 planned time point postdose.
Safety: Subjects in the enrolled analysis set who take (rimegepant 25 mg, rimegepant 75 mg, or placebo)
a: Displayed by as-treated treatment group.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were participants of age ≥18 years with migraine.

Key inclusion criteria were as follows:

- Participant had at least 1 year history of migraine (with or without aura) consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition including the following:
  - Migraine attacks present for more than 1 year with the age of onset of migraines prior to 50 years of age
  - Migraine attacks, on average, lasting 4 to 72 hours if untreated
  - Not more than 8 attacks of moderate to severe intensity per month within the last 3 months and not less than 2 attacks per month

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

For this study, the study interventions were rimegepant ODT (25 mg, 75 mg) and its matching placebo.

The manufacturing lot numbers for the study interventions dispensed in this study are provided in Table S3.

CLINICAL STUDY REPORT SYNOPSIS

Table S3. Study Interventions Administered

Study Intervention	Strength	Formulation	Vendor Lot Number	Pfizer Lot Number
Rimegepant	75 mg	ODT	4775281	3000313.01
Rimegepant	25 mg	ODT	4847948	3000313.01
Placebo for rimegepant 25 mg	0 mg	ODT	4908252	3000313.01
Placebo for rimegepant 75 mg	0 mg	ODT	4775284	3000313.01

Abbreviations: ODT=orally disintegrating tablet.

Study intervention was packaged in blister packaging, which was heat sealed into a wallet. Study intervention was a double-blind double dummy design to maintain the blind, as the different rimegepant strength ODTs had different flavors.

There were no dose adjustments in this study and participants received 2 ODTs to treat one migraine headache of moderate or severe intensity within 45 days of randomization (Baseline Visit). Participants were dispensed the study intervention at randomization (Baseline Visit) and took 2 ODTs at the time of moderate or severe migraine headache onset only after answering questions regarding their migraine symptoms in the eDiary device. The 2 ODTs were taken together (at the same time) placed on top of or under the tongue until fully dissolved then swallowed. Participants were instructed to use dry hands when handling the study intervention.

Duration of Study Intervention:

Participants received only 1 dose to treat one migraine headache of moderate or severe intensity within 45 days of randomization (Baseline Visit).

CLINICAL STUDY REPORT SYNOPSIS

Summary of Results:

Demographic and Other Baseline Characteristics:

Demographic and baseline characteristics were well balanced across the treatment groups.

The median (range) age for all 706 participants in the efficacy analysis set was 42.0 (range: 18, 72) years. Out of 706 participants, 550 (77.9%) were female and 156 (22.1%) were male.

Out of 706 participants, 47 participants (19.7%) in the rimegepant 25 mg group, 50 participants (21.0%) in the rimegepant 75 mg group, and 41 participants (17.8%) in the placebo group used stable prophylactic migraine medications through randomization in the efficacy analysis set.

Exposure:

A total of 706 participants received the study intervention (239 participants received rimegepant 25 mg, 238 participants received rimegepant 75 mg, and 229 participants received placebo).

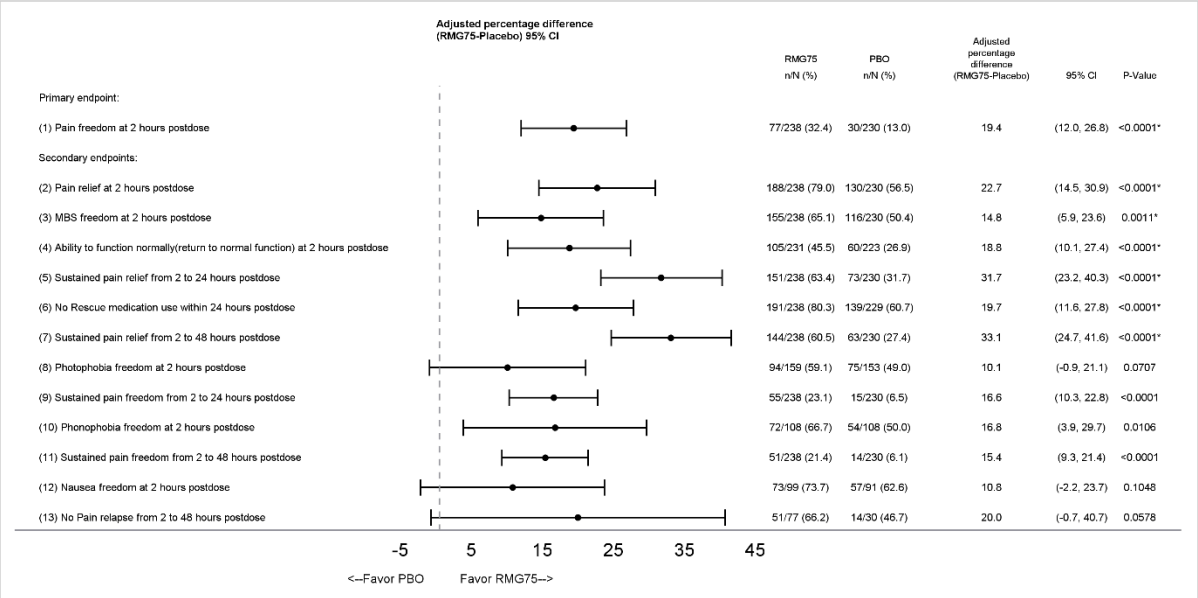
Efficacy Results:

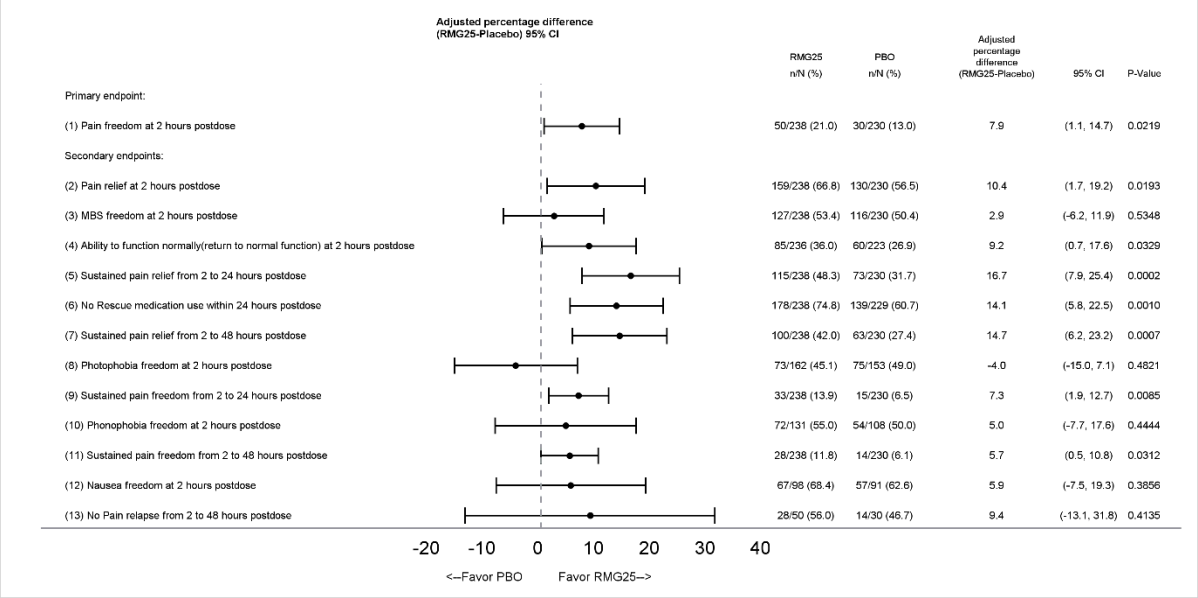
The efficacy of rimegepant 75 mg in the acute treatment of migraine was demonstrated across a variety of endpoints in this study (Figure S1).

A statistically significant efficacy of rimegepant 75 mg compared with placebo was demonstrated for the primary endpoint as well as for the first 6 secondary efficacy endpoints in the hierarchical order.

CLINICAL STUDY REPORT SYNOPSIS

Figure S1 Forest Plot of Primary and Secondary Endpoints, Efficacy Analysis Set





Abbreviations: CI=confidence interval; PBO=placebo; RMG=rimegepant; MBS=most bothersome symptom.
Asterisk denotes statistically significant in a hierarchical gate-keeping testing.

The formal hypothesis testing was conducted in rimegepant 75 mg group using hierarchical gate-keeping procedure. For rimegepant 25 mg, formal hypothesis testing was not conducted, and the nominal p-values were presented only for descriptive purposes.

CLINICAL STUDY REPORT SYNOPSIS

Primary Efficacy Endpoint

Pain Freedom at 2 Hours Postdose

The efficacy of rimegepant 75 mg versus placebo in the acute treatment of migraine was demonstrated with statistical significance in the primary endpoint of pain freedom at 2 hours postdose (adjusted percentage difference, 19.4%; 95% confidence interval [CI], 12.0% to 26.8%; p<0.0001). Pain freedom at 2 hours postdose also favored rimegepant 25 mg as compared with placebo.

Dose dependence was observed in the percentage of participants who had pain freedom at 2 hours postdose in the rimegepant 25 mg group and the rimegepant 75 mg group.

Secondary Efficacy Endpoints

A statistically significant efficacy of rimegepant 75 mg compared with placebo was demonstrated for the first 6 secondary efficacy endpoints in the hierarchical order (pain relief at 2 hours postdose, most bothersome symptom (MBS) freedom at 2 hours postdose, ability to function normally [return to normal function] at 2 hours postdose, sustained pain relief from 2 to 24 hours postdose, rescue medication use within 24 hours postdose, and sustained pain relief from 2 to 48 hours postdose), as well as the primary efficacy endpoint. For the percentage of participants who had photophobia freedom at 2 hours postdose, the 7th secondary efficacy endpoint, the difference was not statistically significant between the rimegepant 75 mg group and the placebo group (59.1% in the rimegepant 75 mg group and 49.0% in the placebo group, p=0.0707). In accordance with the hierarchical gate-keeping procedure, no formal hypothesis testing was conducted for the remainder of the secondary efficacy endpoints. For the remaining secondary efficacy endpoints, numerically preferable efficacy was consistently observed in rimegepant 75 mg compared with placebo.

Numerically preferable efficacy was generally observed in rimegepant 25 mg compared with placebo across the secondary efficacy endpoints, as well as the primary efficacy endpoint.

Dose dependence in the efficacy between rimegepant 25 mg and 75 mg was consistently observed in the treatment differences versus placebo for all the secondary efficacy endpoints, as well as the primary efficacy endpoint.

Safety Results:

Brief Summary of Adverse Events

On-treatment AEs were reported in 17 participants (7.1%) in the rimegepant 25 mg group, 22 participants (9.2%) in the rimegepant 75 mg group, and 15 participants (6.6%) in the placebo group (Table S4). All on-treatment AEs were mild or moderate in severity and no severe on-treatment AEs were reported. The only on-treatment serious adverse event (SAE) was suicidal ideation (mild) reported in the rimegepant 75 mg group, which was also reported as a suicidality AE.

CLINICAL STUDY REPORT SYNOPSIS

No deaths were reported in any of the treatment groups.

Table S4. Adverse Events on Treatment Summary – Safety Analysis Set

Any AE: n (%)	RMG25 N=239	RMG75 N=238	PBO N=229
AE	17 (7.1)	22 (9.2)	15 (6.6)
Mild AE	16 (6.7)	19 (8.0)	12 (5.2)
Moderate AE	1 (0.4)	3 (1.3)	3 (1.3)
Severe AE	0	0	0
AE related to study drug	3 (1.3)	6 (2.5)	7 (3.1)
Serious AE	0	1 (0.4)	0
Hepatic-related AE	1 (0.4)	0	1 (0.4)
Potential drug abuse AE	0	1 (0.4)	1 (0.4)
Cardiovascular AE	0	0	0
Suicidality AE	0	1 (0.4)	0

Abbreviations: AE=adverse event; PBO=placebo; RMG=rimegepant.

On Treatment AEs

The most frequently reported on-treatment AE by preferred term (PT) (≥1.0% in any of the treatment groups) was nasopharyngitis (1.3% in the rimegepant 25 mg group, 1.3% in the rimegepant 75 mg group, 0.9% in the placebo group).

On Treatment AEs Related to the Study Intervention

On-treatment AEs related to the study intervention were reported in 3 participants (1.3%) in the rimegepant 25 mg group, 6 participants (2.5%) in the rimegepant 75 mg group, and 7 participants (3.1%) in the placebo group. There were no on-treatment AEs related to the study intervention by PT reported in ≥1.0% of participants in any of the treatment groups.

Serious Adverse Events

One participant (0.4%) in the rimegepant 75 mg group reported on-treatment SAE of suicidal ideation. The suicidal ideation was mild in intensity, was considered unrelated to the study intervention, and was noted as recovered/resolved. The on-treatment SAE of suicidal ideation was also reported as a suicidality AE.

Adverse Events of Special Interest

Hepatic-Related AEs

In the rimegepant 75 mg group, no participant reported on-treatment hepatic-related AEs.

In the rimegepant 25 mg group, 1 participant (0.4%) reported 1 on-treatment hepatic-related AE of hepatic function abnormal.

CLINICAL STUDY REPORT SYNOPSIS

In the placebo group, 1 participant (0.4%) reported 1 on-treatment hepatic-related AE of hyperbilirubinaemia.

Potential Drug Abuse AEs

In the rimegepant 75 mg group, 1 participant (0.4%) reported 1 on-treatment potential drug abuse AE of somnolence.

In the rimegepant 25 mg group, no participant reported on-treatment potential drug abuse AEs.

In the placebo group, 1 participant (0.4%) reported 1 on-treatment potential drug abuse AE of feeling abnormal.

Cardiovascular AEs

No on-treatment cardiovascular AEs were reported in any of the treatment groups.

Suicidality AEs

In the rimegepant 75 mg group, 1 participant (0.4%) reported 1 on-treatment suicidality AE of suicidal ideation, which was considered serious.

In the rimegepant 25 mg group, no participant reported on-treatment suicidality AEs.

In the placebo group, no participant reported on-treatment suicidality AEs.

Clinical Laboratory Evaluation

No signals of clinically meaningful changes from baseline to the end of treatment or toxicity grade shifts from baseline were identified in hematologic parameters, chemistry parameters, and urinalysis parameters. No participant in any of the treatment groups had alanine aminotransferase or aspartate aminotransferase >3 x upper limit of normal (ULN) at any postbaseline time points and 1 participant in the rimegepant 75 mg group had total bilirubin >2 x ULN.

Other Safety Evaluations

No signals of clinically meaningful changes from baseline to the end of treatment for vital signs and physical measurements, and electrocardiograms were identified, nor were there any clinically meaningful proportion of abnormalities.

One participant (0.4%) in the rimegepant 75 mg group presented with suicidal ideation at the postbaseline time point. This event was reported as a mild SAE. This event was also reported as a suicidality AE. No participant presented with suicidal behavior in any of the treatment groups at any postbaseline time points.

CLINICAL STUDY REPORT SYNOPSIS

Conclusions:

Rimegepant 75 mg demonstrated efficacy superior to placebo in the treatment of acute migraine with a favorable safety profile.

- The primary objective was met in this study. The efficacy of rimegepant 75 mg versus placebo in the acute treatment of migraine was demonstrated with statistical significance in the primary endpoint of pain freedom at 2 hours postdose (adjusted percentage difference, 19.4%; 95% CI, 12.0% to 26.8%; $p<0.0001$).

- A statistically significant efficacy of rimegepant 75 mg compared with placebo was demonstrated for the first 6 secondary efficacy endpoints in the hierarchical order (pain relief at 2 hours postdose, MBS freedom at 2 hours postdose, ability to function normally [return to normal function] at 2 hours postdose, sustained pain relief from 2 to 24 hours postdose, rescue medication use within 24 hours postdose, and sustained pain relief from 2 to 48 hours postdose).

    - For the remaining secondary efficacy endpoints, numerically preferable efficacy was consistently observed in rimegepant 75 mg compared with placebo.

- Numerically preferable efficacy was observed in rimegepant 25 mg compared with placebo in the primary endpoint and most of the secondary efficacy endpoints.

    - Dose dependence in the efficacy between rimegepant 25 mg and 75 mg was consistently observed in the primary endpoint and all the secondary efficacy endpoints.

- Both rimegepant 25 mg and 75 mg were safe and well tolerated, with no new safety signals identified in this Japanese study.