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SYNOPSIS

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rimegepant for Migraine Prevention in Japanese Subjects

Study Number: C4951021 (BHV3000-309)

Regulatory Agency or Public Disclosure Identifier Number:

ClinicalTrials.gov ID: NCT05399485

jRCT Number: jRCT2031220237

Study Phase: 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:

Interim CSR (amendment to 03 October 2024) Version 3.0, 07 November 2024

Interim CSR (amendment to 09 August 2024) Version 2.0, 03 October 2024

Interim CSR (primary completion date [PCD]) Version 1.0, 09 August 2024

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

A total of 613 participants were enrolled at 44 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 Date (first participant first visit): 09 August 2022

PCD: 18 January 2024

This study was neither discontinued nor interrupted.

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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 (BHV-3000, PF-07899801) 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 PCD interim clinical study report (CSR) presents results of Study C4951021 (BHV3000-309), a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of rimegepant 75 mg ODT taken every other day (EOD) for the prevention of migraine based on PCD database lock. The purpose of the study was to provide confirmatory evidence of the efficacy of rimegepant for migraine prophylaxis in Japanese participants with migraine, thus permitting bridging to the results from the global rimegepant efficacy and safety program. Results presented in this PCD interim CSR are based on the data obtained as of the PCD database release, which occurred on 07 May 2024, and include complete data for PCD database lock (i.e., all treated participants have completed the last visit in the double-blind treatment [DBT] Phase). Participants continued to be treated in the open-label extension (OLE) Phase of this study at the time of the preparation of this CSR.

Objectives, Endpoints, and Statistical Methods:

The study objectives and endpoints are summarized in Table S1.

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Table S1. Study Objectives and Endpoints

Type and Objective	Endpoints
Primary	
Efficacy	
To compare the efficacy of rimegepant relative to placebo as a preventive treatment for migraine as measured by the mean reduction from baseline in the number of migraine days per month in the last 4 weeks of the DBT Phase.	Mean change from baseline in the number of migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase.
Secondary	
Efficacy	
To compare the efficacy of rimegepant to placebo on the proportion of the participants that have ≥ 50% reduction from baseline in the number of moderate to severe migraine days per month in the last 4 weeks of the DBT Phase.	Proportion of participants with ≥ 50% reduction from baseline in the number of moderate to severe migraine days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase.
To compare the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per month over the entire course of the DBT Phase.	Mean change from baseline in the number of migraine days per month over the entire DBT Phase (Weeks 1 to 12).
To compare the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per month in the first 4 weeks of the DBT Phase.	Mean change from baseline in the number of migraine days per month in the first 4 weeks (Weeks 1 through 4) of the DBT Phase.
To compare the efficacy of rimegepant to placebo on the mean number of acute migraine-specific medication (i.e., triptans and ergotamine) days per month in the last 4 weeks of the DBT Phase.	Mean number of acute migraine-specific medication days per month in the last 4 weeks (Weeks 9 to 12) of the DBT Phase. Acute migraine-specific medications were triptans and ergotamine.
To compare the mean change from baseline in the MSQoL v2.1 role function - restrictive domain score at Week 12 of the DBT Phase between rimegepant and placebo.	Mean change from baseline in the MSQoL v2.1 role function - restrictive domain score at Week 12 of the DBT Phase.
To compare the mean change from baseline in the MIDAS total score at Week 12 of the DBT Phase between rimegepant and placebo.	Mean change from baseline in the MIDAS total score at Week 12 of the DBT Phase.
To compare the mean change from baseline in the EQ-5D-5L VAS score at Week 12 of the DBT Phase between rimegepant and placebo.	Mean change from baseline in the EQ-5D-5L VAS score at Week 12 of the DBT Phase.
Safety	
To evaluate the frequencies of AEs by intensity, SAEs, AEs leading to discontinuation from study intervention, and grade 3 to 4 laboratory test abnormalities in participants treated with rimegepant during the DBT and OLE Phases.	Number and percentage of participants with AEs by intensity, SAEs, AEs leading to discontinuation from study intervention and grade 3 to 4 laboratory test abnormalities on treatment during the DBT and OLE Phases.
To evaluate the frequency of ALT or AST >3 x ULN concurrent with T bili >2 x ULN in participants treated with rimegepant during the DBT and OLE Phases.	Number and percentage of participants with AST or ALT elevations > 3 x ULN concurrent (i.e., on the same laboratory collection date) with T bili > 2 x ULN on treatment during the DBT and OLE Phases.

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Table S1. Study Objectives and Endpoints

Type and Objective	Endpoints
To evaluate the frequencies of hepatic-related AEs and hepatic-related AEs leading to discontinuation from study intervention in participants treated with rimegepant during the DBT and OLE Phases.	Number and percentage of participants with hepatic-related AEs and hepatic-related AEs leading to discontinuation from study intervention on treatment during the DBT and OLE Phases.
Exploratory	
Efficacy	
To evaluate the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the DBT Phase.	Mean change from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the DBT Phase.
To evaluate the efficacy of rimegepant to placebo on the proportion of the participants that have ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the DBT Phase.	Proportion of participants with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the DBT Phase.
To evaluate the efficacy of rimegepant to placebo on the mean reduction from baseline in the number of migraine days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.	Mean change from baseline in the number of migraine days per week by pain intensity (total; moderate or severe) in each week of the first 4 weeks of the DBT Phase.
To evaluate the mean reduction in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the OLE Phase.	Mean change from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the OLE Phase.
To evaluate the proportion of the participants that have ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the OLE Phase.	Proportion of participants with ≥ 50% reduction, ≥ 75% reduction, and 100% reduction from baseline in the number of migraine days per month by pain intensity (total; moderate or severe) in each month and the entire course of the OLE Phase.
To evaluate the efficacy of rimegepant to placebo on the mean number of acute migraine-specific medication (i.e., triptans and ergotamine) days per month and acute migraine medication days per month in each month and the entire course of the DBT Phase.	Mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and the entire course of the DBT Phase. Acute migraine medications were triptans, ergotamine, and other medications used to treat headache or aura.
To evaluate the mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and the entire course of the OLE Phase.	Mean number of acute migraine-specific medication days per month and acute migraine medication days per month in each month and the entire course of the OLE Phase.
To evaluate the mean changes from baseline in MSQoL domain scores, MIDAS scores, and EQ-5D-5L VAS score over time during the DBT and OLE Phases.	Mean change from baseline in MSQoL domain scores (restrictive role function, preventive role function, emotional function), MIDAS scores (total, absenteeism, presenteeism), EQ-5D-5L VAS score over time during the DBT Phase and OLE Phase.

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Table S1. Study Objectives and Endpoints

Type and Objective	Endpoints

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DBT=double-blind treatment; EQ-5D-5L=EuroQol 5 Dimensions 5-level; MIDAS=Migraine Disability Assessment; MSQoL=Migraine-Specific Quality-of-Life Questionnaire; OLE=open-label extension; SAE=serious adverse event; ULN=upper limit of normal; VAS=visual analog scale.
A month is defined as 4 weeks for the purpose of this study.

Methodology:

Study C4951021 (BHV3000-309) was a Phase 3, multicenter, randomized, double-blind, placebo-controlled bridging study to assess the efficacy and safety of rimegepant in migraine prevention in Japanese participants with an OLE Phase. Pfizer Inc. completed the process of taking over the role of sponsor from Biohaven Pharmaceuticals Holding Company Limited on 5 October 2023.

The study included a 28-day Screening Phase, a 12-week DBT phase, a 40-week OLE phase, and a Follow-up Week 2 Visit. The total duration of the study was up to approximately 52 weeks.

The Screening Phase included a Screening Visit and a 28-day observation period (OP). Upon completion of the Screening Visit, participants were provided an electronic diary (eDiary) to document migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication on each day of the 28-day OP. Participants recorded the standard of care migraine treatment received on a paper diary. For participants to be eligible for the study, they had to report having had 4 to 18 migraine attacks of moderate to severe intensity per 4-week period within the 12 weeks prior to the Screening Visit, and at least 4 migraine days and no more than 18 headache days during the 28-day OP. After completing the 28-day OP, the participants returned to the clinical with both diaries for the Baseline Visit.

At the Baseline Visit, eligibility for continued participation in the study was assessed before randomization occurred and before study intervention was dispensed. Participants who met all eligibility criteria were randomized in a 1:1 ratio to the rimegepant or placebo treatment groups. The randomization was stratified by the use of prophylactic migraine medications (yes or no). Participants were instructed that they had to take 1 ODT of blinded study intervention (rimegepant 75 mg or placebo) every other calendar day. If participants had a migraine attack during the DBT Phase, if needed, they could treat the migraine attack with their standard of care medication and continue to take study intervention on their regular schedule (scheduled dosing days only).

At the completion of the 12-week DBT Phase, participants could be entered into the 40-week OLE Phase following laboratory results within acceptable ranges. During the OLE Phase, participants were instructed that they had to take 1 rimegepant 75 mg every other calendar day. If participants had a migraine on a day that they were not scheduled to dose with

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rimegepant, they could take 1 rimegepant 75 mg on that calendar day to treat a migraine. Therefore, during the OLE Phase, participants could take a maximum of 1 rimegepant 75 mg ODT per calendar day up to 40 weeks.

At the end of Week 52 (+/-3 days), participants returned to the study site for the end of treatment (EOT) Visit. Any participant who discontinued early, at any time during the study, returned to the study site for the EOT Visit. There was a Follow-up Visit 14 days (+/-2 days) after the EOT Visit. Participants who did not complete the DBT Phase and/or did not enter or complete the OLE Phase were to complete the EOT and the Follow-up Week 2 Visits.

Participants were required to record their migraine occurrence, migraine pain features and associated symptoms, and use of acute migraine medication in the eDiary. Participants were also required to record any rescue medication taken on a paper diary and women of childbearing potential (WOCBP) recorded their menstrual period information on a paper log.

At select study visits, participants completed or were administered the Migraine-Specific Quality-of-Life Questionnaire (MSQoL) v2.1, the Migraine Disability Assessment (MIDAS), EuroQol 5 dimensions 5-level (EQ-5D-5L) and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Number of Participants (planned and analyzed):

A total of 490 participants were planned to be randomized in this study. Overall, 613 participants were enrolled in this study. Of these, 496 participants were randomized and treated with rimegepant 75 mg (247 participants) or placebo (249 participants) in the DBT phase. Of the 496 treated participants, 471 (95.0%) participants completed the DBT phase and 465 participants continued to the OLE phase after completing the DBT phase.

The number of participants included in each analysis population is provided in Table S2.

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Table S2. Analysis Sets

Analysis Set: n	RMG	PBO	Not Randomized	Overall
Enrolled			117	613
Full	247	249		496
DBT efficacy	247	249		496
DBT migraine	240	244		484
DBT first month migraine	235	237		472
OL rimegepant efficacy	223	224		447
OL rimegepant migraine	218	220		438
Safety*	247	249	0	496
DBT safety	247	249	0	496
OL rimegepant safety	223	224	0	447
Interim safety	30	36	0	66
DB or OL rimegepant safety	247	224	0	471
Follow-up safety	92	94	0	186

Abbreviations: DB=double-blind; DBT=double-blind treatment; IWRS= Interactive Web Response System; OL=open-label; OLE=open-label extension; OP= observation period; PBO=placebo; RMG=rimegepant.
Enrolled: Subjects who signed an informed consent form and were assigned a subject identification number
Full: Subjects in the enrolled analysis set who were assigned a randomized treatment group by IWRS
DBT efficacy: Subjects in the full analysis set who (1) are randomized only once, and (2) take ≥ 1 dose of DB study drug
DBT migraine: Subjects in the DBT efficacy analysis set with >= 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and >= 1 month (4-week interval) during the DBT Phase
DBT first month migraine: Subjects in the DBT efficacy analysis set with >= 24 days of eDiary efficacy data (not necessarily consecutive) in both the OP and in first month (4-week interval) of the DBT Phase
OL rimegepant efficacy: Subjects in the DBT efficacy analysis set who take ≥ 1 dose of OL rimegepant
OL rimegepant migraine: Subjects in the OL rimegepant efficacy analysis set with ≥ 14 days of eDiary efficacy data (not necessarily consecutive) in both the OP and in ≥ 1 month (4-week interval) in the OLE Phase
Safety: Subjects in the enrolled analysis set who take >= 1 dose of study drug (DB or OL)
DBT safety: Subjects in the safety analysis set who take >= 1 dose of DB study drug (rimegepant or placebo)
OL rimegepant safety: Subjects in the safety analysis set who take >= 1 dose of OL rimegepant
Interim safety: Subjects in the OL rimegepant safety analysis set with OL rimegepant start date – DB study drug last date > 7 days
DB or OL rimegepant safety: Subjects in the safety analysis set who take >= 1 dose of DB or OL rimegepant
Follow-up safety: Subjects in the safety analysis set whose last contact date is in the follow-up safety analysis period
* Displayed by as-treated treatment group

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were male and female participants of age ≥ 18 years with migraines.

Key inclusion criteria were as follows:

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- Participants 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:
    - Age of onset of migraines prior to 50 years of age
    - Migraine attacks, on average, lasting 4 to 72 hours if untreated
    - Per participant report, 4 to 18 migraine attacks of moderate or severe intensity per month within the last 3 months prior to the Screening Visit

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

For this study, the study interventions were rimegepant ODT (75 mg) and its matching placebo. The manufacturing lot numbers for the study interventions dispensed in this study are provided in Table S3.

Table S3. Study Interventions Administered

Study Intervention	Strength	Formulation	Vendor Lot Number	Pfizer Lot Number
Rimegepant	75 mg	ODT	4775281	3000309.01
Rimegepant	75 mg	ODT	4775281	3000309.02
Placebo	0 mg	ODT	4775284	3000309.01

Abbreviations: ODT=orally disintegrating tablet.

Study intervention was packaged in blistered packaging, which was heat sealed into a wallet. There were no dose adjustments in this study and participants received rimegepant or placebo in wallets. Participants were dispensed study intervention at the Baseline Visit, and the participants were instructed that they had to take 1 ODT every other calendar day, regardless of whether they had a migraine on that day or not. This was the scheduled dosing regimen for the DBT Phase and the OLE Phase. The ODT was to be placed on top of or under the tongue until fully dissolved then swallowed. Participants were to be instructed to use dry hands when handling the study intervention.

Duration of Study Intervention:

During the 12-week DBT phase, participants received 1 ODT of blinded study intervention (rimegepant 75 mg or placebo) every other calendar day. If participants had a migraine attack during the DBT Phase, if needed, they could treat the migraine attack with their standard of care medication and continue to take study intervention on their regular schedule (scheduled dosing days only). During the 40-week OLE phase, participants received 1 rimegepant 75 mg every other calendar day. If participants had a migraine on a day that they were not scheduled to dose with rimegepant, they could take 1 rimegepant 75 mg on that calendar day to treat a migraine. Therefore, during the OLE Phase, participants could take a maximum of 1 rimegepant 75 mg ODT per calendar day up to 40 weeks.

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Summary of Results:

Demographic and Other Baseline Characteristics:

Distribution of demographics was well balanced between the rimegepant group and placebo group in the DBT Migraine Analysis Set. Overall, the median age was 45.0 years and the majority of participants were female (90.1%). A total of 161 (33.3%) participants used stable prophylactic migraine medication through randomization. Demographic results for the open-label (OL) Rimegepant Safety Analysis Set were consistent with those for the DBT Migraine Analysis Set.

Exposure:

The extent of DBT exposure for treated participants was similar between the rimegepant group and placebo group. The mean (standard deviation [SD]) time on DBT was 11.6 (1.97) weeks for the rimegepant group and 11.6 (2.02) weeks for the placebo group. The mean (SD) average exposure on DBT was 13.7 (1.85) tablets per month for the rimegepant group and 13.8 (1.81) tablets per month for the placebo group.

The mean (SD) time on OL rimegepant was 25.9 (12.72) weeks for participants in the OL Rimegepant Safety Analysis Set as of the PCD database release. The mean (SD) average OL rimegepant exposure was 15.3 (2.63) tablets per month. The mean (SD) cumulative OL rimegepant exposure was 101.0 (50.18) tablets. A total of 263 participants were on OL rimegepant therapy for more than 24 weeks.

Efficacy Results:

The efficacy of the rimegepant 75 mg tablet taken orally EOD for the prevention of migraine was demonstrated on the primary endpoint and numerically favored rimegepant across a variety of other efficacy endpoints in this study (Table S4). The efficacy of rimegepant was demonstrated with statistical significance in the primary endpoint. The results of the first secondary endpoint numerically favored rimegepant but the difference between treatment groups was not statistically significant. According to the hierarchical testing strategy, formal hypothesis testing was not conducted for the remaining secondary endpoints.

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Table S4. Overall Summary of Primary and Secondary Endpoints on DBT

Endpoint: n Statistic	RMG	PBO	Difference (RMG - PBO)
DBT migraine analysis set	N = 240	N = 244	
Primary endpoint			
(1) Mean change from the OP in the number of migraine days per month in the last 4 weeks of DBT Phase *	240	244	
LS mean change	-2.4	-1.4	-1.1
95% CI	(-2.93, -1.96)	(-1.87, -0.91)	(-1.73, -0.38)
P-value			0.0021 @
Secondary endpoints			
(2) >= 50% reduction from the OP in the number of moderate to severe migraine days per month in the last 4 weeks of DBT Phase #	240	244	
Response rate: n (%)	100 (41.7)	84 (34.4)	7.3
95% CI	(35.5, 47.9)	(28.5, 40.4)	(-1.4, 15.9)
P-value			0.0989
(3) Mean change from the OP in the number of migraine days per month over the entire DBT Phase *	240	244	
LS mean change	-2.5	-1.1	-1.5
95% CI	(-2.91, -2.15)	(-1.47, -0.64)	(-2.02, -0.92)
P-value			<0.0001
(4) Mean change from the OP in the number of migraine days per month in the first 4 weeks of the DBT Phase *	240	244	
LS mean change	-2.7	-0.8	-1.9
95% CI	(-3.11, -2.20)	(-1.26, -0.32)	(-2.51, -1.23)
P-value			<0.0001
(5) Mean number of acute migraine-specific medication days per month in the last 4 weeks of DBT Phase **	240	244	
LS mean	5.0	5.8	-0.8
95% CI	(4.40, 5.55)	(5.24, 6.40)	(-1.64, -0.05)
P-value			0.0371

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Table S4. Overall Summary of Primary and Secondary Endpoints on DBT

Endpoint: n Statistic	RMG	PBO	Difference (RMG - PBO)
DBT efficacy analysis set	N = 247	N = 249	
(6) Mean change from baseline in MSQoL restrictive role function domain score at Week 12 of DBT Phase ***	228	237	
LS mean change	7.8	3.7	4.1
95% CI	(6.20, 9.44)	(2.05, 5.36)	(1.89, 6.33)
P-value			0.0003
(7) Mean change from baseline in MIDAS total score at Week 12 of DBT Phase ***	228	237	
LS mean change	-4.0	-1.6	-2.4
95% CI	(-5.57, -2.42)	(-3.88, 0.70)	(-4.98, 0.17)
P-value			0.0672
(8) Mean change from baseline in EQ-5D-5L VAS score at Week 12 of DBT Phase ***	228	237	
LS mean change	3.5	0.8	2.7
95% CI	(1.60, 5.37)	(-1.40, 3.02)	(-0.19, 5.54)
P-value			0.0671

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Table S4. Overall Summary of Primary and Secondary Endpoints on DBT

Endpoint: n Statistic	RMG	PBO	Difference (RMG - PBO)

Abbreviations: CI=confidence interval; DBT=double-blind treatment; EQ-5D-5L=EuroQol 5 dimensions 5-level; LS=least-squares; MIDAS=Migraine Disability Assessment; MSQoL= Migraine-Specific Quality-of-Life Questionnaire; OP=observation period; PBO=placebo; RMG=rimegepant; VAS=visual analog scale.

If the primary endpoint is significant at the 2-sided alpha level of 0.05, then secondary efficacy or outcomes research endpoints are tested hierarchically, each at a 2-sided alpha level of 0.05, in the order in which they appear in the table.

If a test in the hierarchy is not significant, then any further tests on endpoints in the sequence have p-values presented only for descriptive purposes.

@ denotes statistically significant in a hierarchical gate-keeping testing.

* Linear mixed effects model with repeated measures with number of total migraine days per month in the OP as a covariate, treatment group, randomization stratum (stable prophylactic migraine medication use throughout randomization), month, and month-by-treatment group interaction as fixed effects. DBT migraine analysis set was used.

** Linear mixed effects model with repeated measures with treatment group, randomization stratum, month, and month-by-treatment group interaction as fixed effects. DBT migraine analysis set was used.

*** Linear regression model with treatment group and randomization stratum as fixed effects and baseline score as covariate. DBT efficacy analysis set was used. Analysis was based on DBT efficacy analysis set with paired data (i.e., nonmissing scores at both baseline and Week 12).

Stratified by randomization stratum using Mantel-Haenszel risk estimation. DBT migraine analysis set was used.

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Primary Efficacy Endpoint

The efficacy of rimegepant 75 mg versus placebo in the migraine prevention was demonstrated with statistical significance in the primary endpoint of mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT phase (the difference between treatment groups, -1.1 days; 95% CI, -1.73 to -0.38 days; p = 0.0021).

Secondary Endpoints

The response rate of the first secondary endpoint of ≥ 50% reduction from the OP in the number of moderate to severe migraine days per month in the last 4 weeks of DBT Phase was numerically greater in rimegepant 75 mg compared with placebo, but the difference was not statistically significant (p = 0.0989). According to the hierarchical testing strategy, formal hypothesis testing was not conducted for the remaining secondary endpoints (i.e., p-values were shown only for descriptive purposes). Numerically preferable efficacy was generally observed in rimegepant compared with placebo across the secondary endpoints. The secondary endpoints showed consistent numerical trend of rimegepant efficacy over placebo, supporting the result of primary endpoint.

Safety Results:

Brief Summary of Adverse Events

During the DBT phase, adverse events (AEs) were reported in 135 (54.7%) participants in the rimegepant group and 102 (41.0%) participants in the placebo group. The majority of AEs were mild or moderate in intensity (Table S5).

Table S5. Adverse Events on DBT Summary – DBT Safety Analysis Set

Any Adverse Event (AE): n (%)	RMG N = 247	PBO N = 249
AE	135 (54.7)	102 (41.0)
Mild AE	110 (44.5)	96 (38.6)
Moderate AE	24 (9.7)	6 (2.4)
Severe AE	1 (0.4)	0
AE related to study drug	24 (9.7)	11 (4.4)
AE leading to study drug discontinuation	4 (1.6)	2 (0.8)
Serious AE	2 (0.8)	1 (0.4)
SAE related to study drug	0	0
Medication-overuse headache AE	0	0
Hepatic-related AE	3 (1.2)	4 (1.6)
Hepatic-related AE leading to study drug discontinuation	0	1 (0.4)
Potential drug abuse AE	4 (1.6)	5 (2.0)
Cardiovascular AE	1 (0.4)	1 (0.4)
Suicidality AE	0	0

Abbreviations: AE=adverse event; DBT=double-blind treatment; PBO=placebo; SAE=serious adverse event; RMG=rimegepant.

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A severe AE of pancreatitis acute was reported in 1 (0.4%) participant in the rimegepant group and considered unrelated. No severe AE was reported in the placebo group. Adverse events related to study intervention were reported in 24 (9.7%) participants in the rimegepant group and 11 (4.4%) participants in the placebo group.

No deaths were reported as of the PCD database release.

Serious Adverse Events

During the DBT phase, serious adverse events (SAEs) were reported in 2 (0.8%) participants in the rimegepant group and 1 (0.4%) participant in the placebo group. Serious adverse events in the rimegepant group included pancreatitis acute and Coronavirus Disease of 2019 (COVID-19) (each in 1 participant). The SAE in the placebo group was appendicitis. All the SAEs were considered unrelated to study intervention and noted as recovered/resolved.

Adverse Events Leading to Discontinuations From Study Intervention

During the DBT phase, AEs leading to discontinuation from study intervention were reported in 4 (1.6%) participants in the rimegepant group and 2 (0.8%) participants in the placebo group. No event occurred in more than 1 participant. Hepatic-related AE leading to discontinuation from study intervention was reported in 1 (0.4%) participant in the placebo group and the reported AE was hepatic function abnormal.

Other Significant Adverse Events

Hepatic-Related Adverse Events

During the DBT phase, hepatic-related AEs were reported in 3 (1.2%) participants in the rimegepant group and 4 (1.6%) participants in the placebo group.

Potential Drug Abuse Adverse Events

During the DBT phase, potential drug abuse AEs were reported in 4 (1.6%) participants in the rimegepant group and 5 (2.0%) participants in the placebo group. All the potential drug abuse AEs were mild in severity.

Cardiovascular Adverse Events

During the DBT phase, cardiovascular AEs were reported in 1 (0.4%) participant in the rimegepant group and 1 (0.4%) participant in the placebo group.

Suicidality Adverse Events

During the DBT phase, no suicidality AEs were reported.

CLINICAL STUDY REPORT SYNOPSIS

Clinical Laboratory Evaluation

There were no elevations of ALT or AST > 3 x ULN concurrent with TBIL > 2 x ULN. No apparent trends were identified for any of the laboratory parameters.

Other Safety Evaluations

There were no signals of clinically meaningful changes from baseline for any of the vital signs, physical measurements, and electrocardiograms (ECGs) in either treatment group, nor was there any clinically meaningful proportion of abnormalities.

No participants presented with suicidal ideation or behavior as of the PCD database release.

Conclusions:

Rimegepant 75 mg EOD demonstrated efficacy superior to placebo for the prevention of migraine with a favorable safety profile as of the PCD database release.

- The primary objective was met in this study. The efficacy of rimegepant 75 mg versus placebo in the migraine prevention was demonstrated with statistical significance in the primary endpoint of mean change from the OP in the number of migraine days per month in the last 4 weeks of the DBT phase (the difference between treatment groups, -1.1 days; 95% CI, -1.73 to -0.38 days; p = 0.0021).

- The response rate of the first secondary endpoint of ≥ 50% reduction from the OP in the number of moderate to severe migraine days per month in the last 4 weeks of DBT Phase was numerically greater in rimegepant 75 mg compared with placebo, but the difference was not statistically significant (p = 0.0989). According to the hierarchical testing strategy, formal hypothesis testing was not conducted for the remaining secondary endpoints (i.e., p-values were shown only for descriptive purposes).

    - Numerically preferable efficacy was generally observed in rimegepant 75 mg compared with placebo across the secondary endpoints. The secondary endpoints showed consistent numerical trend of rimegepant 75 mg efficacy over placebo, supporting the result of primary endpoint.

- Rimegepant 75 mg was safe and well tolerated, with no new safety signals identified.