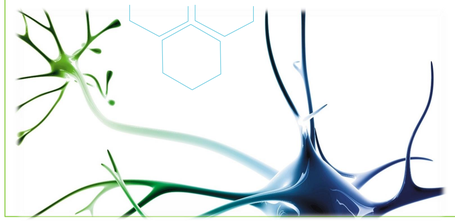

Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Rimegepant for the Preventive Treatment of Migraine

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Background

- Rimegepant is a Food and Drug Administration-approved, orally administered small-molecule calcitonin gene-related peptide receptor antagonist that has demonstrated efficacy and safety in the acute treatment of migraine across multiple randomized, placebo-controlled clinical trials[1-4]
- In a long-term, open-label safety study, a reduction in monthly migraine days (MMDs) was observed with rimegepant 75 mg dosed every other day for 12 weeks, with no signs of medication-overuse headache[5]
- The reduction in MMDs generated the hypothesis that an every-other-day dosing regimen of rimegepant might be safe and effective for preventive treatment of migraine
- This was the first randomized, placebo-controlled clinical trial designed to evaluate rimegepant for the preventive treatment of migraine[6]

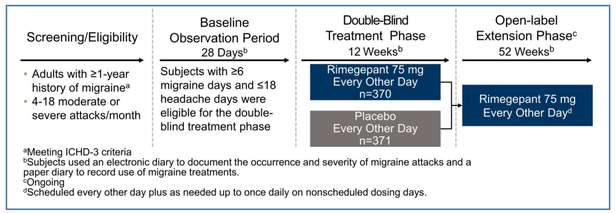
Purpose

- Compare the efficacy, safety, and tolerability of rimegepant with that of placebo for the preventive treatment of migraine

Methods

- This randomized, double-blind, placebo-controlled trial (NCT03732638) was conducted at 92 study centers in the United States

Figure 1. Study Design



[a]Meeting ICHD-3 criteria
[b]Subjects used an electronic diary to document the occurrence and severity of migraine attacks and a paper diary to record use of migraine treatments.
[c]Ongoing
[d]Scheduled every other day plus as needed up to once daily on nonscheduled dosing days.

Assessments

- Primary efficacy endpoint: mean change from the 4-week observation period in the mean number of migraine days per month in the last 4 weeks of the double-blind treatment phase (weeks 9-12)
- Safety assessments: adverse events (AEs), including hepatic-related, and laboratory tests, including liver function tests

Statistical Analysis

- Efficacy population: randomized subjects who received ≥1 dose of rimegepant or placebo and had ≥14 days of electronic diary efficacy data from the 4-week observation period and for ≥1 of the 4-week intervals during double-blind treatment
- The primary efficacy endpoint was tested for superiority versus placebo using a generalized linear mixed-effect model; secondary endpoints were tested hierarchically to control Type I error
- A post hoc analysis assessed mean percentage changes from the observation period in weekly migraine days at each week during the first 4 weeks of double-blind treatment; weekly migraine frequency in the observation period was computed using the number of migraine days over the 4-week period prorated to 7 days
- Safety population: subjects who received ≥1 dose of rimegepant or placebo

Results

Subjects

- In total, 747 subjects were randomized (rimegepant n=373, placebo n=374); 741 were treated (rimegepant n=370, placebo n=371); and 695 were evaluated for efficacy (rimegepant n=348, placebo n=347)
- Most subjects (82.7%) were female, with a mean (SD) age of 41.2 (13.1) years
- The treated population had a mean (SD) history of 7.8 (2.7) moderate or severe attacks per month; 23.3% had a history of chronic migraine (rimegepant n=78 [21.1%], placebo n=95 [25.6%])
- During the observation period, efficacy-evaluable subjects in the rimegepant (n=348) and placebo (n=347) groups had a mean (SD) of 10.3 (3.2) and 9.9 (3.0) MMDs, respectively

Efficacy

- Rimegepant 75 mg was superior to placebo for the primary endpoint of mean change in MMDs during Weeks 9 through 12 (−4.3 vs −3.5; *P*=.0099), as shown in Table 1

Table 1. Efficacy of Rimegepant in the Modified Intention-to-Treat Population[a]

	Rimegepant 75 mg n=348	Placebo n=347	Difference (95% CI)	*P* value
PRIMARY EFFICACY ENDPOINT				
Mean change in number of MMDs during Weeks 9-12[b]	−4.3	−3.5	−.8 (−1.5 to −.2)	.0099
SECONDARY EFFICACY ENDPOINTS				
≥50% reduction in mean number of moderate or severe MMDs during Weeks 9-12, %	49	41	8 (0 to 15)	.0438
Mean change in number of total MMDs during Weeks 1-12[b]	−3.6	−2.7	−.8 (−1.3 to −.3)	.0017
Rescue medication days per month during Weeks 9-12[b]	3.7	4.0	−.2 (−.8 to .3)	.3868[c]
Change in number of total MMDs during Weeks 1-4[b]	−2.9	−1.7	−1.2 (−1.7 to −.6)	<.0001[c]
Change in MSQ restrictive role function at Week 12[b,d]	18.0	14.6	3.5 (.2 to 6.7)	.0358[c]
Change in MIDAS total score at Week 12[b,d]	−11.8	−11.7	−.1 (−4.7 to 4.5)	.9616[c]

CI, confidence interval; MIDAS, Migraine Disability Assessment; MMDs, monthly migraine days; MSQ, migraine-specific quality of life questionnaire.
[a]Evaluable subjects had ≥14 days of electronic diary efficacy data (not necessarily consecutive) in the observation period and ≥1 month (4-week interval) in the double-blind treatment phase. To control the type I statistical error rate at .05, a preplanned hierarchical testing procedure was applied; endpoints are presented in the sequence in which they were evaluated; [b]Reported as least squares mean and analyzed using a generalized linear mixed-effects model with treatment group, preventive migraine medication use at randomization, study month, and month-by-treatment group interaction as fixed effects and subject as random effect; [c]Nominal *P* value in hierarchical testing; [d]Reported as least squares mean; analysis only included subjects who completed the MIDAS or MSQ within the prespecified on-treatment efficacy analysis window (Weeks 10-13; rimegepant n=269, placebo n=266).

Results *cont.*

Efficacy

- Rimegepant was also superior to placebo on the secondary endpoints of ≥50% reduction in the number of moderate or severe MMDs during Weeks 9-12 (Figure 2) and mean change in the number of total MMDs during Weeks 1-12 (Table 1)
- A post hoc analysis assessed mean percentage changes from the observation period in weekly migraine days over the first 4 weeks of double-blind treatment (Figure 3); preventive effects of rimegepant were observed within the first week

Figure 2. Subjects With ≥50% Reduction in the Number of Moderate to Severe Migraine Days Per Month During Weeks 9–12

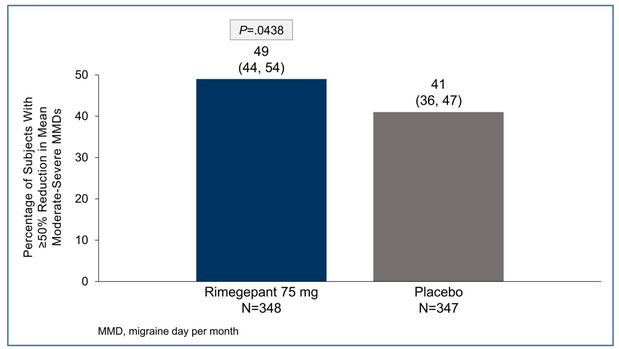
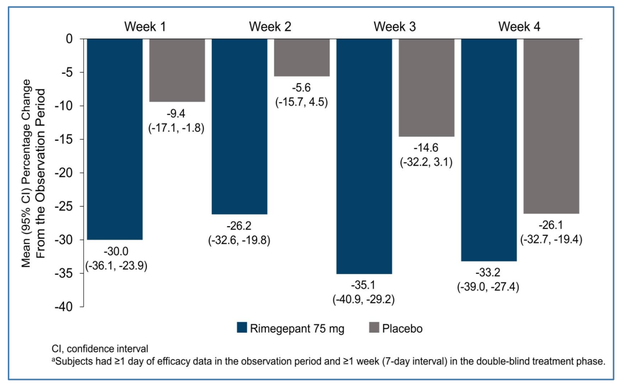


Figure 3. Percentage Change From the Observation Period in Migraine Days per Week During the First 4 Weeks of Double-Blind Treatment[a]



CI, confidence interval
[a]Subjects had ≥1 day of efficacy data in the observation period and ≥1 week (7-day interval) in the double-blind treatment phase.

Safety

- Subjects in the rimegepant and placebo treatment groups were equally likely to experience an AE, as shown in Table 2
- Nearly all AEs were mild or moderate in intensity
- No treatment-related serious AEs were reported in the rimegepant group
- The rate of discontinuations due to an AE was low in both treatment groups

Results *cont.*

- Four (1.1%) subjects who were treated with rimegepant and 2 (.5%) subjects who were treated with placebo had aspartate aminotransferase or alanine aminotransferase elevations >3x ULN
- One (.3%) subject in the rimegepant group had asymptomatic elevation of transaminases with ALT greater than 10x ULN, and alkaline phosphatase and bilirubin levels were always within normal limits; the site principal investigator deemed the increases not related to study drug, and an independent panel of liver experts concluded that the relation to study medication was not probable
- One (.3%) subject in the rimegepant group had bilirubin levels greater than 2x ULN and was diagnosed with Gilbert's syndrome after genotyping

Table 2. Adverse Events With Rimegepant 75 mg and Placebo

	Rimegepant 75 mg n=370 n (%)	Placebo n=371 n (%)
Subjects with any adverse event	133 (35.9)	133 (35.8)
Adverse events (≥2% of subjects)		
Nasopharyngitis	13 (3.5)	9 (2.4)
Nausea	10 (2.7)	3 (.8)
Urinary tract infection	9 (2.4)	8 (2.2)
Upper respiratory tract infection	8 (2.2)	10 (2.7)
Subjects with mild adverse event	92 (24.9)	91 (24.5)
Subjects with moderate adverse event	64 (17.3)	62 (16.7)
Subjects with adverse events related to treatment	40 (10.8)	32 (8.6)
Serious adverse events	3 (.8)	4 (1.1)
Serious adverse events related to treatment	0	1 (.3)
Adverse events leading to discontinuation	7 (1.9)	4 (1.1)

Conclusions

- Oral rimegepant 75 mg taken every other day was effective for the preventive treatment of migraine
- Preventive efficacy was observed within the first week of rimegepant treatment
- Tolerability was similar to placebo, and there were no unexpected or serious safety issues
- These preventive effects, along with previously established acute treatment efficacy, suggest that rimegepant may provide a new approach to treat migraine in an adaptive way–from acute to prevention–depending on an individual's treatment needs

References: 1. *Cephalalgia.* 2014;34(2):114-125. 2. *Headache.* 2018;58:1336–1337. [Poster #PS123LB]. 3. *N Engl J Med.* 2019;381(2):142-149. 4. *Lancet.* 2019;394(10200):737-745. 5. *Cephalalgia.* 2019;39(suppl):1-337 (IHC-PO-127). 6. *Lancet.* 2021;397(10268):51-60.

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