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Efficacy and Safety of Rimegepant 75 mg for Acute Treatment of Migraine: A Pooled Analysis of 4 Randomized, Placebo-Controlled Trials

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BACKGROUND

- Rimegepant is an oral small-molecule calcitonin gene-related peptide receptor antagonist approved for acute and preventive treatment of migraine in adults.[1,2]
- The efficacy and safety of rimegepant 75 mg for acute treatment of migraine has been established in 4 randomized, placebo-controlled, phase 3 clinical trials.[3-6] Though findings from individual studies have been presented, results have not been summarized across these pivotal studies.

OBJECTIVE

- To provide an overview of the efficacy and safety of rimegepant 75 mg for acute treatment of migraine through a pooled analysis of patient-level data from the 4 randomized, placebo-controlled, phase 3 clinical trials of rimegepant published to date.

METHODS

PARTICIPANTS

- Key inclusion criteria in each study included age ≥18 years, ≥1-year history of migraine (with or without aura), 2–8 attacks of moderate or severe pain intensity per month, attacks that last an average of 4–72 h if untreated, and <15 headache days per month during the 3 months before screening.

TREATMENT

- Participants were randomized in a double-blind 1:1 manner to rimegepant 75 mg or matching placebo and provided a single dose of study medication to treat a migraine attack of moderate or severe pain intensity within the next 45 days.
  - A conventional tablet was used in 2 studies and an orally disintegrating table (ODT) was used in 2 studies; the 2 formulations have been shown to be bioequivalent.[7]
- Rescue medication (aspirin, ibuprofen, acetaminophen ≤1000 mg/day, NSAIDs, antiemetics, or baclofen) was allowed 2 h after administration of study medication. Preventive migraine medications were permitted during the study provided dosing was stable for ≥3 months prior to screening.

ENDPOINTS

- Co-primary endpoints in each study were pain freedom at 2 h post dose and freedom from the most bothersome symptom (MBS) at 2 h post dose.
- Prespecified secondary or exploratory endpoints common to each trial included pain relief at 2 h post dose; normal function at 2 h post dose; freedom from nausea, photophobia, and phonophobia at 2 h post dose; sustained pain freedom and sustained pain relief from 2–24 h and from 2–48 h post dose; use of rescue medication within 24 h post dose; and pain relapse from 2–48 h post dose.
- Pain relief and pain freedom at 15, 30, 45, 60, and 90 min post dose were secondary, exploratory, or post hoc endpoints (depending on study) and are presented to characterize the onset of rimegepant's analgesic effects.
- On-treatment adverse events (AEs), defined as events with an onset date on or after (up to 7 days) dosing of study medication, were also assessed.

STATISTICAL ANALYSIS

- Pain was assessed on a 4-point scale from 0=none to 3=severe. Pain freedom was defined as a score of 0, pain relief was defined as a score of 0 or 1, and pain relapse was defined as a score of 1, 2, or 3 at any time point after 2 h post dose (among those with pain freedom at 2 h post dose).
- MBS freedom and freedom from nausea, photophobia, and phonophobia were defined as a score of 0 on a binary scale of 0=absent and 1=present. Normal function was defined as a score of 0 on a 4-point scale from 0=normal function to 3=requires bedrest.
- Treatment comparisons utilized Mantel-Haenszel risk estimation with stratification by study and prophylactic migraine medication use randomization stratum, except sustained pain freedom endpoints, which used stratification only by study.
  - Participants with missing data at the time point being assessed or who used rescue medication before the time point being assessed were classified as failures for all endpoints except for the endpoint of rescue medication use within 24 h post dose. All *P* values are nominal

RESULTS

PARTICIPANTS

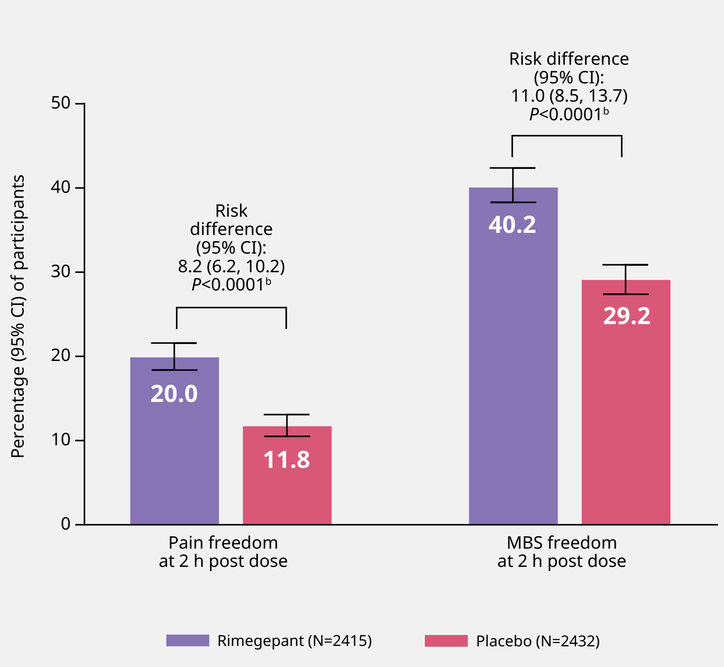
- 4895 participants received rimegepant 75 mg (N=2439) or placebo (N=2456). Participant demographics and clinical characteristics were similar between treatment groups (**Table 1**).

Table 1: Demographics and clinical characteristics of all participants receiving study treatment

Demographic	Rimegepant (n=2439)	Placebo (n=2456)
Age, mean (SD), y	40.0 (11.7)	39.9 (11.8)
Sex, n (%)		
Female	2055 (84.3)	2097 (85.4)
Male	384 (15.7)	359 (14.6)
Race, n (%)[a]		
White	1322 (74.6)	1378 (77.3)
Black or African American	365 (20.6)	331 (18.6)
Other[b]	82 (4.6)	73 (4.1)
Body mass index[c], mean (SD), kg/m^2	28.6 (7.8)	28.6 (7.9)
Primary migraine type, n (%)		
Without aura	1806 (74.0)	1805 (73.5)
With aura	633 (26.0)	651 (26.5)
Age at disease onset[d], mean (SD), y	22.8 (10.3)	22.5 (10.2)
Average duration of untreated attacks[e], mean (SD), h	27.4 (21.0)	28.0 (20.7)
Number of attacks with moderate or severe pain intensity per month, mean (SD)	4.4 (1.8)	4.3 (1.7)

[a] Not collected in study NCT04574362, percentages are based on studies NCT03235479, NCT03237845, and NCT03461757.
[b] Includes Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or multiple responses.
[c] n=2437 for rimegepant and n=2454 for placebo.
[d] n=2433 for rimegepant and n=2451 for placebo.
[e] n=2439 for rimegepant and n=2455 for placebo.

Figure 1: Analysis of co-primary efficacy endpoints[a]



[a] Includes all randomized participants who received study medication, had a migraine attack of moderate or severe pain intensity at the time of dosing, and provided at least one efficacy datapoint after receiving study treatment. Comparisons between treatments utilized Mantel-Haenszel risk estimation with stratification by study and prophylactic migraine medication use randomization stratum. Participants with missing data at 2 h or using rescue medication prior to 2 h were classified as failures.
[b] *P* values are nominal.
MBS=most bothersome symptom

COPRIMARY EFFICACY ENDPOINTS

- The proportion of participants with pain freedom 2 h post dose (20.0% vs 11.8%; risk difference [95% CI] = 8.2 [6.2, 10.2]; nominal *P*<0.0001) and MBS freedom 2 h post dose (40.2% vs 29.2%; risk difference [95% CI] = 11.0 [8.5, 13.7]; nominal *P*<0.0001) was higher in the rimegepant group than in the placebo group (**Figure 1**).

SECONDARY AND OTHER EFFICACY ENDPOINTS

- Rimegepant also demonstrated improvements (nominal *P*<0.05) vs placebo on all secondary efficacy endpoints (**Table 2**), including pain relief (60.3% vs 45.1%), return to normal function (33.5% vs 21.1%), nausea freedom (51.2% vs 44.5%), photophobia freedom (37.7% vs 27.1%), phonophobia freedom (41.4% vs 30.2%), rescue medication use within 24 h post dose (15.5% vs 28.9%), sustained pain relief from 2–24 h post dose (48.0% vs 31.3%), sustained pain relief from 2–48 h post dose (43.1% vs 28.5%), sustained pain freedom from 2–24 h post dose (14.5% vs 7.1%), sustained pain freedom from 2–48 h post dose (12.6% vs 6.4%), and pain relapse from 2–48 h post dose (36.9% vs 45.6%).

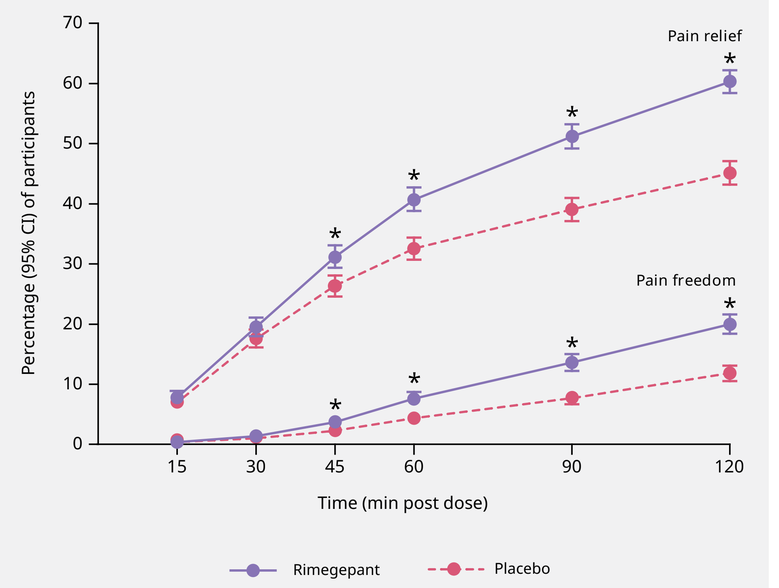
Table 2: Summary of secondary and other efficacy endpoints[a]

Endpoint	Percentage of participants (95% CI)		Risk difference[b] (rimegepant – placebo)	*P* value
	Rimegepant (n=2415)	Placebo (n=2432)		
Pain relief at 2 h post dose	60.3 (58.4, 62.2)	45.1 (43.2, 47.1)	15.2 (12.4, 17.9)	< 0.0001
Return to normal function at 2 h post dose[c]	33.5 (31.5, 35.4)	21.1 (19.4, 22.8)	12.4 (9.8, 15.0)	< 0.0001
Nausea freedom at 2 h post dose[d]	51.2 (48.6, 53.6)	44.5 (42.0, 47.0)	6.7 (3.1, 10.2)	0.0002
Photophobia freedom at 2 h post dose[e]	37.7 (35.6, 39.8)	27.1 (25.1, 29.0)	10.6 (7.8, 13.5)	< 0.0001
Phonophobia freedom at 2 h post dose[f]	41.4 (39.0, 43.9)	30.2 (28.0, 32.5)	11.2 (7.9, 14.5)	< 0.0001
Rescue medication use within 24 h post dose	15.5 (14.1, 16.9)	28.9 (27.2, 30.7)	–13.4 (–15.7, –11.2)	< 0.0001
Pain relief from 2–24 h post dose	48.0 (46.0, 49.9)	31.3 (29.5, 33.1)	16.7 (14.0, 19.3)	< 0.0001
Pain relief from 2–48 h post dose	43.1 (41.2, 45.0)	28.5 (26.7, 30.2)	14.6 (12.0, 17.3)	< 0.0001
Pain freedom from 2–24 h post dose	14.5 (13.1, 15.9)	7.1 (6.1, 8.1)	7.4 (5.7, 9.2)	< 0.0001
Pain freedom from 2–48 h post dose	12.6 (11.3, 14.0)	6.4 (5.4, 7.4)	6.2 (4.6, 7.9)	< 0.0001
Pain relapse from 2–48 h post dose[g]	36.9 (32.9, 41.4)	45.6 (40.2, 51.4)	–8.7 (–15.7, –1.6)	0.0166

[a] Includes all randomized participants who received study medication, had a migraine attack of moderate or severe pain intensity at the time of dosing, and provided ≥1 efficacy datapoint after receiving study treatment. Participants with missing data at the specified time point or used rescue medication before the specified time point were classified as failures for all endpoints except for the endpoint of rescue medication use within 24 h post dose.
[b] Mantel-Haenszel risk estimation with stratification by study and prophylactic migraine medication use randomization stratum (except for sustained pain freedom endpoints which used stratification only by study). All *P* values are nominal.
[c] Among those with functional disability at the time of dosing: rimegepant, n=2182; placebo, n=2195.
[d] Among those with nausea at the time of dosing: rimegepant, n=1509; placebo, n=1505.
[e] Among those with photophobia at the time of dosing: rimegepant, n=1974; placebo, n=1997.
[f] Among those with phonophobia at the time of dosing: rimegepant, n=1564; placebo, n=1612.
[g] Among those with pain freedom at 2 hours post dose: rimegepant, n=483; placebo, n=287.

- Rimegepant demonstrated improvements over placebo (nominal *P*<0.05) as early as 45 min post dose for both pain relief and pain freedom (**Figure 2**).

Figure 2: Proportion of participants with pain relief and pain freedom over the first 2 h post dose[a]



* Nominal *P*<0.05.
[a] Includes all randomized participants who received study medication, had a migraine attack of moderate or severe pain intensity at the time of dosing, and provided ≥1 efficacy datapoint after receiving study treatment. Comparisons between treatments utilized Mantel-Haenszel risk estimation with stratification by study and prophylactic migraine medication use randomization stratum. Participants with missing data at the specified time point or used rescue medication before the specified time point were classified as failures.

SAFETY

- 11.1% and 9.6% of participants in the rimegepant and placebo groups, respectively, reported an AE (**Table 3**). Few participants reported a serious (0.1% in both treatment groups) or severe (rimegepant = 0.3%; placebo = 0.1%) AE.
  - The only AE to occur in >1% of participants in either treatment group was nausea, which occurred at a similar rate in the rimegepant (1.4%) and placebo (1.3%) groups.
- The proportion of participants with an AE deemed related to study drug was 6.4% in the rimegepant group and 5.3% in the placebo group (**Table 3**). Few participants reported a severe AE (rimegepant = 0.2%; placebo = <0.1%) and no participants reported a serious AE deemed related to study drug.
  - Nausea was the most common AE deemed related to study drug in the rimegepant (1.2%) and placebo (1.3%) groups.

Table 3: Summary of on-treatment AEs in all participants receiving study treatment

Event, n (%)	Rimegepant (n=2439)	Placebo (n=2456)
All AEs		
AE of any severity	271 (11.1)	236 (9.6)
Mild AE	136 (5.6)	108 (4.4)
Moderate AE	61 (2.5)	58 (2.4)
Severe AE	7 (0.3)	3 (0.1)
Serious AE	2 (0.1)	2 (0.1)
Most common AEs of any severity[a]		
Nausea	33 (1.4)	32 (1.3)
Urinary tract infection	19 (0.8)	13 (0.5)
Dizziness	13 (0.5)	15 (0.6)
Diarrhea	11 (0.5)	11 (0.4)
Blood creatine phosphokinase increased	13 (0.5)	9 (0.4)
AEs related to study drug		
AE of any severity	157 (6.4)	130 (5.3)
Mild AE	82 (3.4)	62 (2.5)
Moderate AE	30 (1.2)	27 (1.1)
Severe AE	4 (0.2)	1 (< 0.1)
Serious AE	0	0
Most common AEs of any severity[a]		
Nausea	29 (1.2)	31 (1.3)
Dizziness	11 (0.5)	13 (0.5)

[a] Occurring in ≥0.5% of participants in either treatment group.
AE=adverse event

CONCLUSIONS

- In this pooled analysis of 4 randomized placebo-controlled trials, a single dose of rimegepant 75 mg demonstrated efficacy and a favorable safety profile for the acute treatment of migraine.

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DISCLOSURES

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