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Time Course of Rimegepant Effect for Acute Treatment of Migraine in Adults Unsuitable for Triptans: Exploratory Endpoints From a Phase 4 Randomized Double-Blind Placebo-Controlled Study

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BACKGROUND

- In a recent randomized, double-blind, placebo-controlled trial (NCT05509400),[1] a single dose of rimegepant 75 mg orally disintegrating tablet (ODT) demonstrated efficacy and a favorable safety profile for the acute treatment of 1 migraine attack in adults unsuitable for triptans.[2]
- Rimegepant was superior to placebo on the primary endpoint (migraine pain relief at 2 h post dose) and all 10 alpha-protected key secondary endpoints assessing acute (2 h post dose) and sustained (2–48 h post dose) effects on pain, function, and other migraine symptoms.[2]
- However, the full time course of rimegepant effect, including time points prior to 2 h post dose, has not been reported previously for this study population.

OBJECTIVE

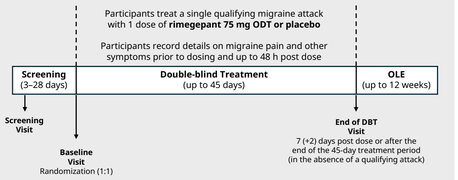
- To evaluate the time course of rimegepant effect at time points from 15 min to 48 h post dose in adults unsuitable for triptans, based on exploratory endpoints in Study NCT05509400.

METHODS

TRIAL DESIGN

- Study NCT05509400 was a phase 4, multinational, randomized, double-blind (DB), placebo-controlled study with a 12-week open-label extension phase (**Figure 1**).

Figure 1: Study design



DBT=double-blind treatment; ODT=orally disintegrating tablet; OLE=open-label extension

PARTICIPANTS

- Eligible participants were aged ≥18 years with ≥1-year history of migraine attacks (with or without aura), migraine onset prior to age 50 years, migraine attacks lasting an average of 4–72 h if untreated, and an average of 4–14 migraine days per month in the 3 months prior to screening.
- Participants were unsuitable for triptan therapy due to documented (A) history of prior intolerance or lack of efficacy to ≥2 triptans or (B) the presence of a contraindication.
  - Documentation was within the medical/pharmacy record – complemented by participant interview, if needed – or via principal investigator interview of the treating physician.
- Participants on stable (≥3 months) preventive migraine treatment (excluding calcitonin gene-related peptide antagonists) were eligible.

TREATMENT

- In the DB phase, participants were randomized in a 1:1 manner to a single dose of rimegepant 75 mg ODT or placebo to treat a single qualifying migraine attack within 45 days.
  - A qualifying migraine attack was defined as an attack of moderate or severe headache pain intensity first treated with study intervention, not with non-study medication (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]).
- No acute migraine medications were allowed for 2 h post dose, after which time rescue medication (NSAIDs, acetaminophen [≤2000 mg per day for ≤2 consecutive days], antiemetics, baclofen, other recognized standard of care medications) could be used as needed.

ASSESSMENTS

- Participants used an electronic diary (eDiary) to record migraine occurrence and migraine symptoms prior to dosing with study medication to treat a qualifying migraine attack and at 15, 30, and 45 min, and 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 h post dose.
  - Headache pain intensity was rated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).
  - Level of functional disability was rated on a 4-point scale (0 = normal, 1 = mild impairment, 2 = severe impairment, 3 = requires bedrest).
  - Migraine symptom (nausea, phonophobia, or photophobia) status (present or absent) and intensity (mild, moderate, or severe) was also recorded.
    - Participants identified their current most bothersome symptom (MBS) among nausea, phonophobia, or photophobia prior to taking study medication.

ENDPOINTS

- Exploratory endpoints included the percentage of participants with migraine pain relief, migraine pain freedom, return to normal function, and MBS freedom at each time point from 15 min to 48 h post dose.
  - Migraine pain relief was defined as a score of 0 (no pain) or 1 (mild pain) on the pain intensity scale.
  - Migraine pain freedom was defined as a score of 0 (no pain) on the pain intensity scale.
  - Return to normal function was defined as a score of 0 (normal) on the functional disability scale.
    - This endpoint was only assessed in participants with some level of functional disability prior to taking study medication to treat a qualifying migraine attack.
  - MBS freedom was defined as the MBS being absent.

STATISTICAL ANALYSIS

- All analyses were done in the DB efficacy population, which included all participants who were randomized once, had a qualifying migraine attack at time of dosing, took DB study medication, and had post-dose efficacy data in the DB treatment phase.
- Demographics and baseline characteristics for the DB efficacy population were summarized descriptively in the rimegepant and placebo groups.
- Efficacy was compared between the rimegepant and placebo groups using crude risk difference estimation based on the normal approximation to the binomial distribution.
  - Participants with missing data at the time point being assessed, or who took rescue medication at or before the time point being assessed, were imputed as failures. In addition, participants with missing MBS data prior to dosing with DB study medication were imputed as failures in the MBS freedom analyses.
  - All P values are nominal.

RESULTS

PARTICIPANTS

- Overall, 570 participants were included in the efficacy population (rimegepant n=286; placebo n=284).
- Most (89.3%) participants were female, with a mean (SD) age of 42.9 (11.7) years, had primarily migraine without aura (77.0%), and experienced a mean (SD) of 6.6 (2.5) migraine days with moderate or severe headache pain intensity per month in the 3 months before screening.
- Demographics and baseline clinical characteristics were similar between treatment groups (**Table 1**).
- Participants had documented failure to ≥2 triptans with ≥1 reason due to prior intolerance (30.5%) or lack of efficacy (84.9%); 9.1% had a contraindication.
- Previous triptan medications used by participants included sumatriptan (79.1%), zolmitriptan (45.4%), almotriptan (34.9%), rizatriptan (31.4%), eletriptan (18.8%), naratriptan (8.8%), and frovatriptan (5.6%).

Table 1: Summary of demographics and baseline clinical characteristics

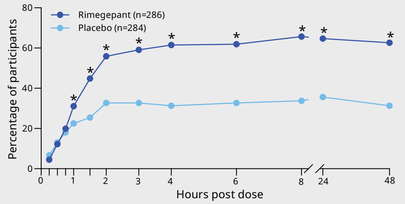
Demographic/Characteristic	Rimegepant 75 mg n=286	Placebo n=284
Age, mean (SD), y	43.1 (11.8)	42.6 (11.5)
Sex, n (%)		
Female	253 (88.5)	256 (90.1)
Male	33 (11.5)	28 (9.9)
Race, n (%)[a]		
White	51 (92.7)	45 (83.3)
Black or African American	4 (7.3)	8 (14.8)
Multiple	0	1 (1.9)
Body mass index, mean (SD), kg/m^2	25.3 (4.3)	25.5 (4.5)
Age at migraine onset, mean (SD), y[b]	19.8 (9.1)	19.9 (9.5)
Number of moderate to severe migraine days per month in the previous 3 months, mean (SD)[b]	6.7 (2.4)	6.6 (2.6)
Average duration of untreated attacks, mean (SD), h[b]	41.5 (21.7)	43.1 (20.2)
Primary migraine type, n (%)[b]		
Without aura	221 (77.3)	218 (76.8)
With aura	65 (22.7)	66 (23.2)
Historical most bothersome symptom, n (%)[b]		
Nausea	109 (38.1)	107 (37.7)
Photophobia	126 (44.1)	126 (44.4)
Phonophobia	51 (17.8)	51 (18.0)

[a] Race was only assessed among US participants (rimegepant, n=55; placebo, n=54).
[b] Based on self-reported migraine history.

EFFICACY

- The percentage of participants with pain relief (no or mild pain) at each time point is shown in **Figure 2**.
  - Improvements of ≥5% for rimegepant over placebo with P≤0.05 were first observed at 1 h; difference (95% CI): 8.6% (1.3–15.8); P=0.0201.
  - Improvements of ≥5% over placebo were observed at all subsequent time points; difference (95% CI): 31.2% (23.5–39.0) at 48 h; P<0.0001.

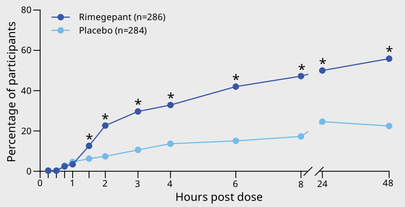
Figure 2: Time course of migraine pain relief



Treatment groups were compared using crude risk difference estimation.
* Treatment group difference ≥5% and P≤0.05.

- The percentage of participants with pain freedom at each time point is shown in **Figure 3**.
  - Improvements of ≥5% for rimegepant over placebo with nominal P≤0.05 were first observed at 1.5 h; difference (95% CI): 6.2% (1.5–11.0); P=0.0103.
  - Improvements of ≥5% over placebo were observed at all subsequent time points; difference (95% CI): 33.4% (25.9–40.9) at 48 h; P<0.0001.

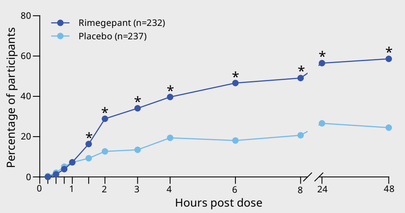
Figure 3: Time course of migraine pain freedom



Treatment groups were compared using crude risk difference estimation.
* Treatment group difference ≥5% and P≤0.05.

- The percentage of participants with return to normal function at each time point is shown in **Figure 4**.
  - Improvements of ≥5% for rimegepant over placebo with P≤0.05 were first observed at 1.5 h; difference (95% CI): 7.1% (1.1–13.1); P=0.0210.
  - Improvements of ≥5% over placebo were observed at all subsequent time points; difference (95% CI): 34.1% (25.8–42.5) at 48 h; P<0.0001.

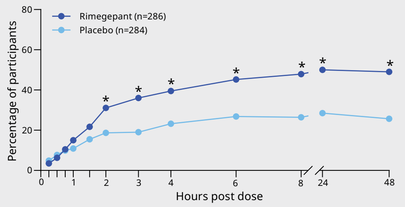
Figure 4: Time course of return to normal function



Treatment groups were compared using crude risk difference estimation.
* Treatment group difference ≥5% and P≤0.05.

- The percentage of participants with MBS freedom at each time point is shown in **Figure 5**.
  - Improvements of ≥5% for rimegepant over placebo with P≤0.05 were first observed at 2 h; difference (95% CI): 12.5% (5.4–19.5); P=0.0005.
  - Improvements of ≥5% over placebo were observed at all subsequent time points; difference (95% CI): 23.2% (15.5–31.0) at 48 h; P<0.0001.

Figure 5: Time course of MBS freedom



Treatment groups were compared using crude risk difference estimation.
* Treatment group difference ≥5% and P≤0.05.
MBS=most bothersome symptom

CONCLUSIONS

- Improvements over placebo in migraine symptoms occurred within 1–2 h of treatment with rimegepant and were observed at all subsequent time points (up to 48 h post dose) in adults unsuitable for triptans.
- Calcitonin gene-related peptide antagonism may be a valuable option for the acute treatment of migraine when triptans are unsuitable.

REFERENCES

1. https://clinicaltrials.gov/study/NCT05509400.
2. Ashina M, et al. Headache 2025;65:1217-58 [Abstr #IOR-09].

DISCLOSURES

MLM: Personal fees for consultancy activities from AbbVie/Allergan, Amgen, Eli Lilly, IPSEN, Lundbeck, Novartis, Orion Pharma, Perfood, Pfizer, Reckitt-Benckiser, Teva, and UPSA. **TS:** Personal fees for speaker's bureau: Amgen, Allergan/AbbVie, Biohaven, Novartis, Lilly; advisory boards: Allergan/AbbVie, Biohaven, Amgen, Lilly, Alder/Lundbeck, Impel Neuropharma, Neurolief, Nocira, Nuvie, Theranica, Teva, Vorso/Nesos; research support: Amgen, Alder/Lundbeck, Alnylam, Lilly, Teva, Allergan/AbbVie, Biohaven, Boehringer Ingelheim, Graviton, Structure Therapeutics, Electrocore, Merz Therapeutics, Novartis, Novo Nordisk, Impel Neuropharma, Pfizer, Aeon, Charleston Labs, Nocira, Teva, Terns Pharmaceuticals, Theranica, Vorso/Nesos. **CN, LMR, SM, SR, RF:** Employees of and hold stock/options in Pfizer. **AT:** Former employee of Biohaven Pharmaceuticals, owns stock in Biohaven Ltd, is an employee of Pfizer, and owns stock/options in Pfizer.

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