Safety and Effectiveness of Rimegepant for Acute Treatment of Migraine in Adults Unsuitable for Triptan Use: Results From a 12-week Open-Label Extension Phase

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INTRODUCTION

- A recent randomized, double-blind (DB), placebo-controlled study of rimegepant (NCT05509400)[1] was the first to demonstrate efficacy of a gepant for acute treatment of migraine in adults unsuitable for triptans.[2]
- Since conclusions in the DB phase were limited to the use of 1 dose of rimegepant to treat a single migraine attack, the open-label (OL) extension of study NCT05509400 assessed use of rimegepant across multiple attacks in this patient population.

OBJECTIVE

- To evaluate the safety and attack-to-attack reliability of rimegepant 75 mg for acute treatment of migraine over 12 weeks in adults unsuitable for triptans, and to explore changes in monthly migraine days (MMDs).

METHODS

TRIAL DESIGN

- Study NCT05509400 was a phase 4 multinational study consisting of a 45-day randomized, DB, placebo-controlled phase followed by a 12-week OL extension phase (**Figure 1**).

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 treated a single qualifying migraine attack within 45 days with 1 dose of placebo or rimegepant 75 mg orally disintegrating tablet (ODT).
  - 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, NSAID).
- In the OL phase, eligible participants took OL rimegepant 75 mg ODT as needed (up to 1 dose per day, up to 18 doses per month) for acute treatment of qualifying migraine attacks.
- 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.

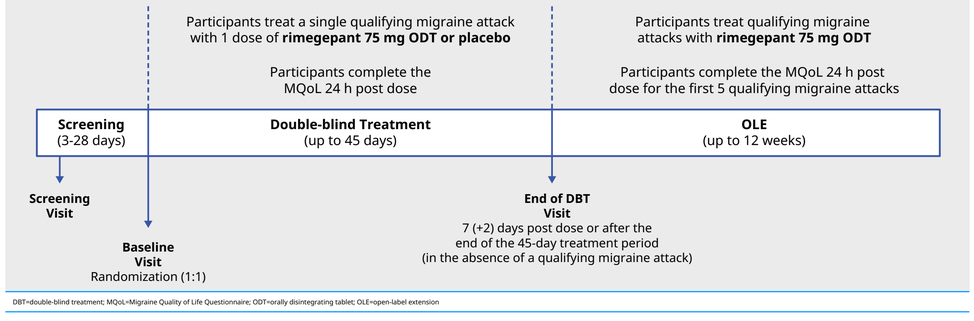
ASSESSMENTS

- In the DB and OL phases, participants recorded headache occurrence and migraine pain intensity (0 = none, 1 = mild, 2 = moderate, 3 = severe) in an electronic diary (eDiary) prior to taking study intervention.
- Participants completed the Migraine Quality of Life Questionnaire (MQoL) 24 h after treating the single qualifying migraine attack in the DB phase and after each of the first 5 qualifying migraine attacks in the OL phase.

ENDPOINTS

- Secondary and exploratory safety endpoints in the OL phase included adverse events (AEs) and liver function test elevations (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >3x upper limit of normal [ULN]; total bilirubin >1.5x ULN).
- Secondary effectiveness endpoints in the OL phase included (1) reliability of rimegepant effect, (2) mean change from historical baseline in the number of MMDs, and (3) the proportion of participants with ≥50% reduction from historical baseline in the number of MMDs.
  - Reliability of rimegepant effect was based on the response rate for the single evaluable qualifying migraine attack (EQMA) in the DB phase and response rates for the first 5 EQMAs ≥23 h apart during the OL phase.
    - Response was defined as migraine symptoms being "moderately better" or "very much better" at 24 h post dose in response to MQoL Question #16, "What is your overall change in migraine symptoms since taking study medication". Participants using rescue medication (in the DB or OL phase) or an intervening dose of rimegepant (in the OL phase) before answering MQoL Question #16 at 24 h post dose were considered nonresponders.
    - An EQMA was defined as a qualifying migraine attack with a non-missing response to MQoL Question #16.
    - The reliability endpoint was considered met if response rates for ≥4 of the 5 EQMAs in the OL phase were no more than 7% lower than the response rate for the single EQMA in the DB phase.
  - A migraine day was defined as either (1) a day on which a participant experienced a migraine headache attack (with migraine headache pain intensity of mild, moderate, or severe) as reported in the eDiary or (2) an acute migraine-specific medication day.
    - An acute migraine-specific medication day was defined as a day on which either (1) OL rimegepant was taken as reported in the eDiary, or (2) triptan, ergotamine, ubrogepant, or lasmiditan was taken, as reported on the Concomitant Medications or Rescue Medications Case Report Form.
- All endpoints were summarized descriptively.

Figure 1: Study design



DBT=double-blind treatment; MQoL=Migraine Quality of Life Questionnaire; ODT=orally disintegrating tablet; OLE=open-label extension

RESULTS

PARTICIPANTS AND EXPOSURE

- 585 participants took DB study medication (rimegepant n=295; placebo n=290); 552 participants took ≥1 dose of OL rimegepant, with 94.0% (n=519/552) completing the 12-week OL phase.
- In the OL phase, most participants were female (89.7%), White (87.7%), had a mean (SD) age of 42.8 (11.7) years, and 85.1% had a history of documented failure to ≥2 triptans with ≥1 reason due to lack of efficacy.
- Mean (SD) time on OL rimegepant was 9.4 (2.9) weeks and mean (SD) exposure was 4.9 (2.9) ODTs per month.

SAFETY

- Severe AEs (0.5%), serious AEs (0.4%), and AEs leading to rimegepant discontinuation (0.9%) were infrequent during the OL phase (**Table 1**).
- AEs occurring in ≥2% of participants included nasopharyngitis (10.3%), upper respiratory tract infection (3.6%), headache (3.4%), influenza (2.5%), back pain (2.4%), sinusitis (2.4%), upper abdominal pain (2.2%), arthralgia (2.2%), and dysmenorrhea (2.0%).
- No participants had ALT or AST >3x ULN on OL rimegepant; 2 participants had total bilirubin >1.5x ULN.

Table 1: Summary of AEs on OL rimegepant[a]

AE, n (%) of participants	Overall N=552
Any AE	260 (47.1)
Mild AE[b]	183 (33.2)
Moderate AE[b]	118 (21.4)
Severe AE[b]	3 (0.5)
Serious AE	2 (0.4)
AE leading to rimegepant discontinuation	5 (0.9)
AE related to rimegepant	59 (10.7)
Serious AE related to rimegepant	1 (0.2)
Hypertension AE	5 (0.9)
Raynaud's phenomenon AE	1 (0.2)

[a] Summarized in all participants who took OL rimegepant.
[b] Based on preferred term worst intensity.
AE=adverse event; OL=open-label

EFFECTIVENESS

- The reliability of rimegepant effect endpoint was met during the OL phase (**Table 2**).
  - Response (migraine symptoms being "moderately better" or "very much better" at 24 h post dose) rates were 64.2% for the DB EQMA and 65.1%–71.1% across the first 5 OL EQMAs.
  - All 5 OL EQMAs (exceeding the prespecified threshold of ≥4 of the 5 EQMAs) had a response rate that was greater than the DB EQMA response rate; differences (DB EQMA – OL EQMA) in response rates between the DB EQMA and the first 5 OL EQMAs ranged from –6.9% to –0.9%.

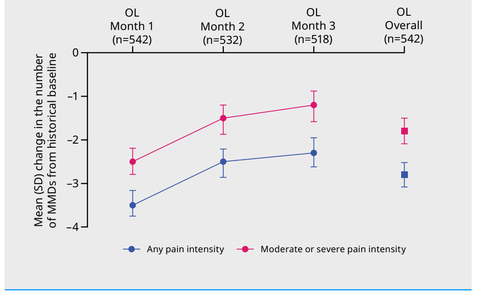
Table 2: Analysis of reliability of rimegepant effect

EQMA[a]	Response[b]	Percentage Difference (DB phase – OL phase)
DB phase EQMA		
n/N[c]	156/243	
% (95% CI)	64.2 (58.2, 70.2)	–
OL phase first EQMA		
n/N[d]	345/530	
% (95% CI)	65.1 (61.0, 69.2)	–0.9*
OL phase second EQMA		
n/N[d]	342/511	
% (95% CI)	66.9 (62.8, 71.0)	–2.7*
OL phase third EQMA		
n/N[d]	340/492	
% (95% CI)	69.1 (65.0, 73.2)	–4.9*
OL phase fourth EQMA		
n/N[d]	317/488	
% (95% CI)	70.8 (66.5, 75.0)	–6.6*
OL phase fifth EQMA		
n/N[d]	248/349	
% (95% CI)	71.1 (66.3, 75.8)	–6.9*

[a] An EQMA was a migraine attack of moderate or severe pain intensity that was first treated with rimegepant (not non-study medication such as ibuprofen) and had non-missing quality of life data (MQoL) at 24 h post dose.
[b] Defined as migraine symptoms being "moderately better" or "very much better" at 24 h post dose in response to MQoL Question #16, "What is your overall change in migraine symptoms since taking study medication?"
[c] Number of evaluable participants who took rimegepant in the DB phase.
[d] Number of evaluable participants who took OL rimegepant in the OL phase.
* Difference between phases is ≤ the pre-specified threshold of +7%.
DB=double-blind; EQMA=evaluable qualifying migraine attack; MQoL=Migraine Quality of Life Questionnaire; n=number of participants with response (see methods for definition); N=number of participants evaluated; OL=open-label

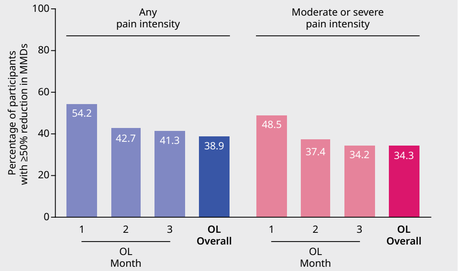
- Use of OL rimegepant reduced the number of MMDs compared to historical baseline (**Figure 2**).
  - The historical baseline mean (SD) number of MMDs was 7.8 (2.6) for MMDs of any pain intensity and 6.6 (2.5) for MMDs of moderate or severe pain intensity.
  - For the overall OL phase, mean (95% CI) change in MMDs from historical baseline was –2.8 (–3.1, –2.5) days for MMDs of any pain intensity and –1.8 (–2.1, –1.5) days for MMDs of moderate or severe pain intensity.
- Over one-third of participants experienced a ≥50% reduction from historical baseline in the number of MMDs for the overall OL phase (**Figure 3**).
  - For the overall OL phase, the percentage of participants with ≥50% reduction from historical baseline was 38.9% for MMDs of any pain intensity and 34.3% for MMDs of moderate to severe pain intensity.

Figure 2: Mean (SD) change from historical baseline in the number of MMDs during the OL phase[a]



[a] Evaluated in participants who were randomized only once, took DB study intervention, had a qualifying migraine attack at the time of dosing with DB study intervention, had post-dose DB efficacy data, took ≥1 dose of OL rimegepant, and had ≥14 days in the OL phase. To be evaluated in a particular OL month, participants must also have had ≥14 days in that month. The mean (SD) number of MMDs at historical baseline was 7.8 (2.6) for MMDs of any pain intensity and 6.6 (2.5) for MMDs of moderate or severe pain intensity.
DB=double-blind; MMDs=monthly migraine days; OL=open-label

Figure 3: Percentage of participants with ≥50% reduction from historical baseline in the number of MMDs during the OL phase[a]



[a] Evaluated in participants who were randomized only once, took DB study intervention, had a qualifying migraine attack at the time of dosing with DB study intervention, had postdose DB efficacy data, took ≥1 dose of OL rimegepant, and had ≥14 days in the OL phase. To be evaluated in a particular OL month, participants must also have had ≥14 days in that month. The number of participants evaluated was 542 for the historical baseline and OL Month 1, 532 for OL Month 2, 518 for OL Month 3, and 542 for the overall OL phase.
DB=double-blind; MMDs=monthly migraine days; OL=open-label

CONCLUSIONS

- In adults unsuitable for triptans, as-needed rimegepant 75 mg ODT for up to 12 weeks demonstrated a favorable safety profile, reliable response across repeated migraine attacks, and a reduction in MMDs.

REFERENCES

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

DISCLOSURES

MA: Advisory board/consultant/speaker: AbbVie, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Pfizer, and Teva; institutional research grants: Danish National Research Foundation, Lundbeck Foundation, Novo Nordisk Foundation, Novartis, and Lundbeck; associate editor: Journal of Headache and Pain and for Brain; editorial board: Neurotorium and has received honoraria. **PM:** Advisory board member/speaker/consultant: AbbVie, ANI, BrightMind.AI, Dompe, Lilly, Lundbeck, and Pfizer. **CG:** Consulting and lectures within the past 3 years: AbbVie, Chordate, Dr. Reddys, Hormosan Pharma, Lilly, Lundbeck, Merz, Novartis Pharma, Perfood, Orion, Organon, Pfizer, Reckitt-Benckiser, Sanofi-Aventis, TEVA, and Vectura Fertin Pharma; his research is supported by a grant from the German Research Foundation (DFG). **ALR:** Advisory board/speaker: Farmasa-Schwabe, Grünenthal, Lundbeck, Merz, Pfizer, Sunpharma, and Torrent. **LMR, CN, LA, RF, TF:** Current or former 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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