A Phase 4 Randomized Double-blind Placebo-Controlled Study of Rimegepant for Acute Treatment of Migraine in Adults Unsuitable for Triptan Use

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67th Annual Meeting of the American Headache Society (AHS)
June 19–22, 2025, Minneapolis, MN, USA

Disclosure

MA: Advisory board/consultant/speaker: AbbVie, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Pfizer, Teva; institutional research grant: Lundbeck, Lundbeck Foundation, Novartis, Novo Nordisk Foundation; associate editor: Journal of Headache and Pain; Brain.

PM: Advisory board/speaker/consultant: AbbVie, ANI, BrightMind.AI, Dompe, Lilly, Lundbeck, Pfizer.

LMR, **CN**, **LA**, **RF**, **TF**: Employees of and hold stock/options in Pfizer.

AT: Former employee of Biohaven Pharmaceuticals; owns stock in Biohaven Ltd; employee and owns stock/options in Pfizer.

This study was sponsored by Pfizer. Medical writing support was provided by Matt Soulsby, PhD, CMPP, of Engage Scientific Solutions and was funded by Pfizer. A proprietary generative AI tool was used to develop the first draft; authors take responsibility for content.

Background

- There is an unmet treatment need for individuals with migraine who are unsuitable for triptans due to insufficient response, intolerance, or contraindication[1-3]

- Prospectively designed trials in individuals unsuitable for triptans have not previously been conducted with gepants

- Post-hoc subgroup analyses from previous phase 3 trials suggest that rimegepant may be effective for acute treatment of migraine in individuals who previously discontinued triptans[4]

Study Objective

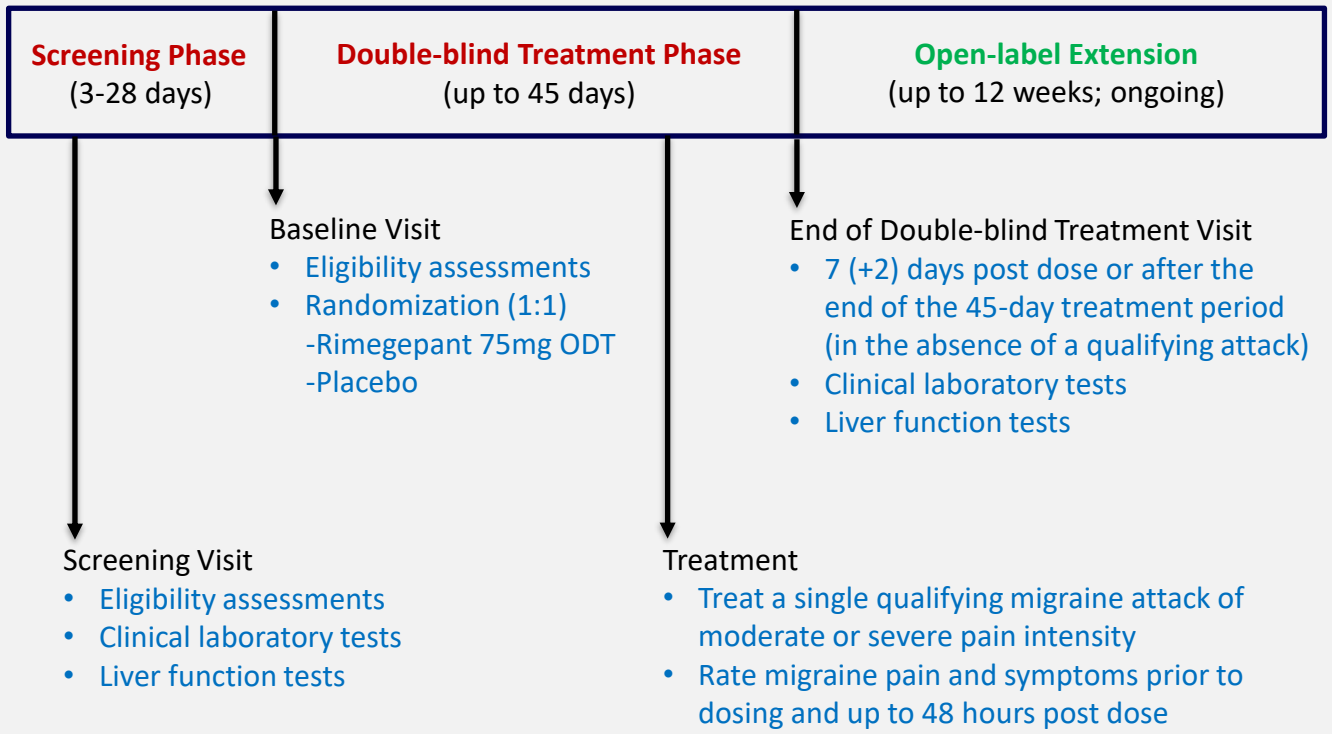
- To investigate the efficacy and tolerability of rimegepant for acute treatment of migraine in individuals unsuitable for triptans due to a documented history of prior inadequate response and/or intolerance to multiple agents, or due to the presence of a contraindication

1. Lipton RB, et al. Cephalalgia 2020;40 (5):437-47.
2. Dodick DW, et al. J Prim Care Community Health 2020; 11:2150132720963680.
3. Lipton RB, et al. Headache 2025;65:164-79.
4. Lipton RB, et al. Cephalalgia 2023;43:1-11.

Design

- Phase 4, multinational, randomized, double-blind, placebo-controlled study (**Figure 1**; NCT05509400)
- Participants treated a single qualifying* migraine attack of moderate or severe pain intensity with rimegepant 75 mg ODT or placebo
- Participants rated migraine pain and other symptoms prior to dosing and up to 48 hours post dose

Figure 1. Study design



*A qualifying migraine attack was defined as an attack of moderate or severe pain intensity first treated with study intervention, not with non-study medication (eg, NSAID)

NSAID, nonsteroidal anti-inflammatory drug; ODT, orally disintegrating tablet.

Population

- Aged ≥18 years with ≥1-year history of migraine attacks (with or without aura)
- Migraine onset prior to age 50
- Migraine attacks lasting an average of 4–72 hours if untreated
- An average of 4–14 migraine days per month in the 3 months prior to screening
- Unsuitable for triptan therapy due to documented (within the medical/pharmacy record - complemented by participant interview if needed - or via principal investigator interview of the treating physician):
  - History of prior intolerance or lack of efficacy to ≥2 triptans

  OR

  - Presence of a contraindication
- Participants on stable (≥3 months) preventive migraine treatment (excluding CGRP antagonists) were eligible

CGRP, calcitonin gene-related peptide.

Endpoints and Analysis

- **Primary**
  - Pain relief (no or mild migraine pain) at 2 hours post dose
- **Key secondary** (in pre-specified order)
  - Pain freedom (no migraine pain) at 2 hours post dose
  - Rescue medication use within 24 hours post dose
  - Return to normal function at 2 hours post dose
  - Sustained return to normal function from 2–24 hours post dose
  - Sustained return to normal function from 2–48 hours post dose
  - Sustained pain relief from 2–24 hours post dose
  - Sustained pain relief from 2–48 hours post dose
  - Sustained pain freedom from 2–24 hours post dose
  - Sustained pain freedom from 2–48 hours post dose
  - MBS freedom (absence of symptom) at 2 hours post dose
- **On-treatment safety**
  - AEs
  - Grade 3 or 4 clinical laboratory abnormalities
  - Elevated liver function tests (AST or ALT >3x ULN, total bilirubin >1.5x ULN)

Efficacy was assessed in all participants who were randomized once, had a qualifying migraine attack at time of dosing, took study intervention, and had post dose efficacy data. Treatment groups were compared using Mantel-Haenszel risk estimation.

Type I error was controlled using hierarchical testing whereby the primary endpoint was evaluated at a 2-sided alpha level of 0.05. If the primary endpoint was significant, key secondary endpoints were each tested at a 2-sided alpha level of 0.05 in the pre-specified order.

Safety was summarized descriptively in all participants who took study intervention.

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; MBS, most bothersome symptom (nausea, photophobia, or phonophobia); ULN, upper limit of normal.

Participants

- 585 participants administered study intervention
  - Rimegepant: 295
  - Placebo: 290
- Demographic and clinical characteristics were similar between treatment groups (**Table 1**)
- 570 participants were analysed for efficacy
  - Rimegepant: 286
  - Placebo: 284
- 93.5% of participants analyzed for efficacy had a documented failure to ≥2 triptans due to lack of efficacy and/or prior intolerance and 9.1% had a contraindication (**Table 2**)

Table 1. Summary of demographics and baseline clinical characteristics

	Rimegepant 75 mg n = 295	Placebo n = 290
Age, mean (SD), y	43.0 (11.8)	42.7 (11.5)
Sex, n (%)		
Female	260 (88.1)	261 (90.0)
Male	35 (11.9)	29 (10.0)
Race, n (%)[a]		
White	52 (91.2)	45 (83.3)
Black or African American	5 (8.8)	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]	19.7 (9.0)	19.7 (9.5)
Number of moderate or severe migraine day per month in previous 3 months, mean (SD)[b]	6.7 (2.5)	6.6 (2.6)
Average duration of untreated attacks, mean (SD), h[b]	41.2 (21.6)	43.0 (20.2)
Primary migraine type, n (%)[b]		
Without aura	227 (76.9)	222 (76.6)
With aura	68 (23.1)	68 (23.4)

[a] Only assessed in participants in the United States (rimegepant n = 57, placebo n = 54).
[b] Based on self-reported migraine history.

Table 2. Reasons for triptan unsuitability

Reason, n (%)	Participants Analyzed for Efficacy n = 570
Documented failure to ≥2 triptans	533 (93.5)
With ≥1 reason due to lack of efficacy	484 (84.9)
With ≥1 reason due to prior intolerance	174 (30.5)
With ≥1 reason due to lack of efficacy and ≥1 reason due to prior intolerance	125 (21.9)
Documented contraindication to triptans	52 (9.1)

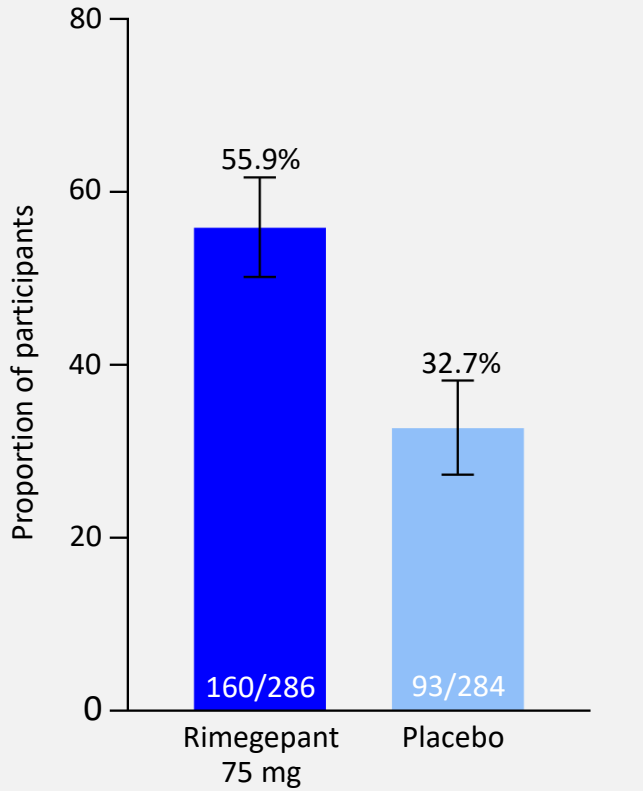
Percentages do not add up to 100 since participants could be in more than one category

SD, standard deviation

Primary Endpoint

- Rimegepant was superior to placebo for the primary endpoint of migraine pain relief at 2 hours post dose (**Figure 2**)
  - 55.9% (rimegepant) vs 32.7% (placebo)
  - Difference (95% CI): 23.2% (15.3%, 31.1%)
  - P<0.0001

Figure 2. Pain relief at 2 hours post dose

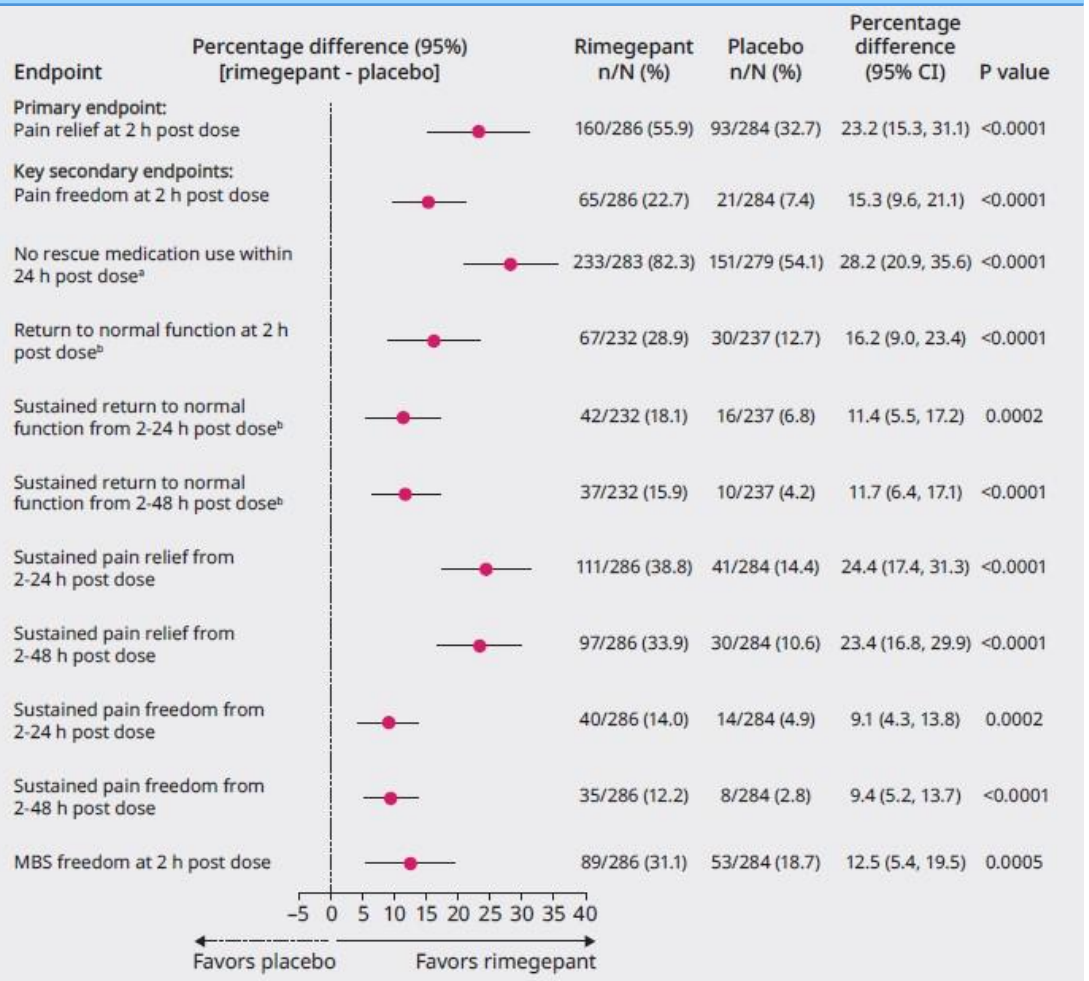


CI, confidence interval.

Key Secondary Endpoints

- Rimegepant was also superior to placebo for all 10 alpha-protected key secondary endpoints (**Figure 3**)
  - Acute endpoints (2-hours post dose)
    - Migraine pain freedom
    - Return to normal function
    - MBS freedom
  - Sustained endpoints (2-24 and 2-48 hours post dose)
    - Sustained migraine pain relief
    - Sustained migraine pain freedom
    - Sustained return to normal function
  - Rescue medication use within 24 hours post dose

Figure 3. Summary of primary and key secondary endpoints



[a] Direction reversed so that positive percentage favors rimegepant. Participants with a first rescue medication use date ≤ study intervention dosing date + 1 day, and missing the time of first rescue medication use, were excluded.

[b] Among participants with any level of functional disability (mild impairment, severe impairment, or requires bedrest) at time of dosing.

CI, confidence interval; MBS, most bothersome symptom.

Safety Results

- AE frequency was similar across treatments (**Table 3**)
  - 12.5% (rimegepant) vs 12.1% (placebo)
- Only nasopharyngitis occurred in ≥1% of participants in the rimegepant group
  - 1.7% (rimegepant) vs 1.0% (placebo)
- No reports of the following with rimegepant:
  - Severe AEs
  - Serious AEs
  - Grade 3 or 4 laboratory test abnormalities
  - ALT or AST levels >3× ULN
  - Total bilirubin levels >1.5× ULN

Table 3. Summary of on-treatment adverse events

AE, n (%)	Rimegepant 75 mg n = 295	Placebo n = 290
Any AE	37 (12.5)	35 (12.1)
AE related to study drug	10 (3.4)	10 (3.4)
Mild AE	31 (10.5)	19 (6.6)
Moderate AE	6 (2.0)	15 (5.2)
Severe AE	0	1 (0.3)
Serious AE	0	0
AEs of interest		
Hypertension AE	1 (0.3)	0
Raynaud's phenomenon AE	1 (0.3)	0

Intensity (mild, moderate, severe) is based on the MedDRA preferred term worst AE intensity

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; MedDRA, Medical Dictionary for Regulatory Activities; ULN, upper limit of normal.

Conclusions

- A single dose of rimegepant 75 mg ODT demonstrated superiority over placebo for the primary endpoint and all 10 key secondary endpoints
- Rimegepant demonstrated a favorable tolerability profile that was similar to placebo
- This is the first prospective controlled study to demonstrate efficacy of a gepant for the acute treatment of migraine in participants with a documented history of being unsuitable for triptans
- Rimegepant may be a suitable option that addresses an unmet treatment need in this patient population
- Findings from the 12-week open-label extension phase of this trial (currently ongoing) will allow for evaluation of the effectiveness of rimegepant and provide additional safety data in this population

ODT, orally disintegrating tablet.