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

Messoud Ashina[1], Peter McAllister[2], Luz M Ramirez[3], Catherine Nalpas[4], Alexandra Thiry[5], Lucy Abraham[6], Robert Fountaine[5], Terence Fullerton[5]

[1]Danish Headache Center, Rigshospitalet, Copenhagen, Denmark;
[2]New England Institute for Neurology and Headache, Stamford, CT, USA;
[3]Pfizer Inc, Princeton, NJ, USA; [4]Pfizer Inc, Paris, France; [5]Pfizer Inc, Groton, CT, USA;
[6]Pfizer R&D UK Ltd, Tadworth, UK

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]
- Post-hoc subgroup analyses from previous phase 3 trials suggest that rimegepant, an oral calcitonin gene-related peptide (CGRP) receptor antagonist, may be effective for acute treatment of migraine in individuals who previously discontinued triptans.[4]
- Prospectively designed trials in individuals unsuitable for triptans have not previously been conducted with gepants.

OBJECTIVE

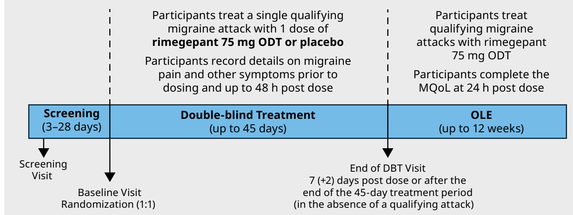
- To investigate the efficacy and tolerability of rimegepant for acute treatment of migraine in individuals unsuitable for triptans due to a documented history of prior inadequate response and/or intolerance to multiple agents, or due to the presence of a contraindication.

METHODS

STUDY DESIGN

- This was a phase 4, multinational, randomized, double-blind, placebo-controlled study (NCT05509400; **Figure 1**).

Figure 1: Study design



DBT=double-blind treatment; MQoL=Migraine Quality of Life Questionnaire; 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 CGRP antagonists) were eligible.

TREATMENT

- Participants treated a single qualifying migraine attack with rimegepant 75 mg orally disintegrating tablet (ODT) or placebo.
  - 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).
- Participants rated migraine pain and other symptoms prior to dosing and up to 48 h post dose.

ENDPOINTS

- The primary endpoint was the percentage of participants with migraine pain relief (no or mild migraine pain) at 2 h post dose.
- Key secondary endpoints included the percentage of participants with migraine pain freedom (no migraine pain) at 2 h post dose, rescue medication use within 24 h post dose, return to normal function at 2 h post dose, sustained return to normal function from 2–24 h and from 2–48 h post dose, sustained migraine pain relief from 2–24 h and from 2–48 h post dose, sustained pain freedom from 2–24 h and from 2–48 h post dose, and most bothersome symptom (MBS) freedom (absence of nausea, photophobia, or phonophobia) at 2 h post dose.
- On-treatment safety included the number and percentage of participants with adverse events (AEs), serious AEs, grade 3 or 4 clinical laboratory abnormalities, and liver function test elevations.

ANALYSIS

- Efficacy was assessed in all participants who were randomized once, had a qualifying migraine attack at time of dosing, took double-blind study intervention, and had post-dose efficacy data.
  - Treatment groups were compared using crude 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 prespecified order.
- Safety was summarized descriptively in all participants who took double-blind study intervention.

RESULTS

PARTICIPANTS

- 585 participants took double-blind study intervention (rimegepant, n=295; placebo, n=290) and 570 were analyzed for efficacy (rimegepant, n=286; placebo, n=284).
- Demographic and clinical characteristics were similar between treatment groups (**Table 1**).
- 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 1**).

Table 1: Summary of demographics and baseline clinical characteristics[a]

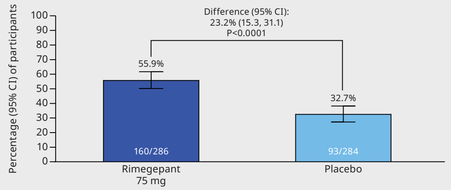
Characteristic	Rimegepant 75 mg n=295	Placebo n=290
Age, mean (SD), years	43.0 (11.8)	42.7 (11.5)
Sex, n (%)		
Female	260 (88.1)	261 (90.0)
Male	35 (11.9)	29 (10.0)
Race, n (%)[b]		
White	52 (91.2)	45 (83.3)
Black or African American	5 (8.8)	8 (14.8)
Multiple	0	1 (1.9)
Body mass index, mean (SD), kg/m^2	25.3 (4.3)	25.5 (4.5)
Age at migraine onset, mean (SD), years[c]	19.7 (9.0)	19.7 (9.5)
Number of moderate to severe migraine days per month in the previous 3 months, mean (SD)[c]	6.7 (2.5)	6.6 (2.6)
Average duration of untreated attacks, mean (SD), h[c]	41.3 (21.6)	43.0 (20.2)
Primary migraine type, n (%)[c]		
Without aura	227 (76.9)	222 (76.6)
With aura	68 (23.1)	68 (23.4)
Reason for triptan unsuitability, n (%)	Overall (N=570)[d]	
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)	
Contraindication to triptans	52 (9.1)	

[a] Summarized in all participants who took double-blind study intervention unless noted.
[b] Race was only assessed among US participants (rimegepant, n=57; placebo, n=54).
[c] Based on self-reported migraine history.
[d] Summarized in all participants who were randomized once, had a qualifying migraine attack at time of dosing, took double-blind study intervention, and had post-dose efficacy data (rimegepant, n=286; placebo, n=284).

EFFICACY

- Rimegepant was superior to placebo for the primary endpoint of migraine pain relief at 2 h post dose (**Figure 2**).
  - The percentage of participants with pain relief at 2 h was 55.9% for rimegepant and 32.7% for placebo; difference: 23.2% (95% CI, 15.3, 31.1); P<0.0001.
- Rimegepant was also superior to placebo for all 10 alpha-protected key secondary endpoints (**Figure 3**).
  - This included assessments of acute effects at 2 h post dose (migraine pain freedom, return to normal function, MBS freedom), assessments of sustained effects from 2–24 and 2–48 h post dose (migraine pain relief, migraine pain freedom, return to normal function), and assessment of rescue medication use within 24 h post dose.

Figure 2: Migraine pain relief at 2 h post dose (primary endpoint)



Analyzed in all participants who were randomized only once, had a qualifying migraine attack at the time of dosing, took double-blind study intervention, and had post dose efficacy data. Groups were compared using crude risk estimation.

SAFETY

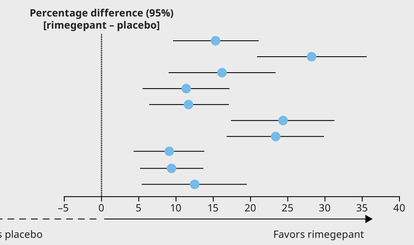
- AE frequency was similar in the rimegepant (12.5%) and placebo (12.1%) groups (**Table 2**).
  - Only nasopharyngitis occurred in ≥1% of participants in the rimegepant group (rimegepant, 1.7%; placebo, 1.0%).
- No severe AEs, serious AEs, grade 3 or 4 laboratory test abnormalities, alanine aminotransferase or aspartate aminotransferase levels >3x upper limit of normal (ULN), or total bilirubin levels >1.5x ULN were reported among rimegepant-treated participants.

Table 2: Summary of on-treatment adverse events[a]

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[b]	31 (10.5)	19 (6.6)
Moderate AE[b]	6 (2.0)	15 (5.2)
Severe AE[b]	0	1 (0.3)
Serious AE	0	0
Hypertension AE	1 (0.3)	0
Raynaud's phenomenon AE	1 (0.3)	0

[a] Summarized in all participants who took double-blind study intervention.
[b] Based on preferred term worst intensity.
AE=adverse event

Figure 3: Summary of key secondary endpoints



Endpoint	Rimegepant n/N (%)	Placebo n/N (%)	Percentage difference (95% CI)	P value
Migraine pain freedom at 2 h post dose	65/286 (22.7)	21/284 (7.4)	15.3 (9.6, 21.1)	<0.0001
No rescue medication use within 24 h post dose[a]	232/283 (82.0)	150/279 (53.8)	28.2 (20.8, 35.6)	<0.0001
Return to normal function at 2 h post dose[b]	67/232 (28.9)	30/237 (12.7)	16.2 (9.0, 23.4)	<0.0001
Sustained return to normal function from 2–24 h post dose[b]	42/232 (18.1)	16/237 (6.8)	11.4 (5.5, 17.2)	0.0002
Sustained return to normal function from 2–48 h post dose[b]	37/232 (15.9)	10/237 (4.2)	11.7 (6.4, 17.1)	<0.0001
Sustained migraine pain relief from 2–24 h post dose	111/286 (38.8)	41/284 (14.4)	24.4 (17.4, 31.3)	<0.0001
Sustained migraine pain relief from 2–48 h post dose	97/286 (33.9)	30/284 (10.6)	23.4 (16.8, 29.9)	<0.0001
Sustained migraine pain freedom from 2–24 h post dose	40/286 (14.0)	14/284 (4.9)	9.1 (4.3, 13.8)	0.0002
Sustained migraine pain freedom from 2–48 h post dose	35/286 (12.2)	8/284 (2.8)	9.4 (5.2, 13.7)	<0.0001
MBS freedom at 2 h post dose	89/286 (31.1)	53/284 (18.7)	12.5 (5.4, 19.5)	0.0005

Analyzed in all participants who were randomized only once, had a qualifying migraine attack at the time of dosing, took double-blind study intervention, and had post dose efficacy data. Testing utilized a hierarchical gate-keeping approach to control type I error. First, the significance of the primary endpoint was evaluated at a 2-sided alpha level of 0.05 level. Because the primary endpoint was significant, key secondary endpoints were each tested hierarchically at a 2-sided alpha-level of 0.05 in the prespecified order. Groups were compared using crude risk estimation.
[a] Direction reversed so that positive percentage favors rimegepant. Participants with a first rescue medication use date being less than or equal to the 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.
MBS=most bothersome symptom; n=number of participants meeting the endpoint; N=number of evaluable participants

CONCLUSIONS

- A single dose of rimegepant 75 mg ODT demonstrated superiority over placebo for the primary endpoint and all 10 key alpha-protected secondary endpoints, with 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.

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DISCLOSURES

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.

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