Time Course Efficacy of Rimegepant to Relieve Accompanying Non-Headache Symptoms in the Acute Treatment of Migraine: Analysis of a Phase 3 Trial in Adults From China and South Korea

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Shengyuan Yu[1], Zhihong Lu[2], Yu Liu[3], Qian Zhao[4], Sun Yanhui[2], Yunjun Zou[2]

[1]Chinese PLA General Hospital, Beijing, China; [2]Pfizer (China) Research and Development Co Ltd, Shanghai, China; [3]Pfizer Inc, Beijing, China; [4]Pfizer Inc, Chengdu, China

BACKGROUND

- Migraine is a chronic, debilitating neurologic disorder that affects an estimated 151.6 million people in China.[1]
- Migraine is characterized by episodic headache pain of moderate to severe intensity and is typically accompanied by additional non-headache symptoms of photophobia, phonophobia, and/or nausea.[2]
- Rimegepant is an oral small-molecule calcitonin gene-related peptide receptor antagonist for the prophylactic and acute treatment of migraine.
  - A 75 mg dose of rimegepant orally disintegrating tablet (ODT) was demonstrated to be effective and safe for the acute treatment of migraine.[3-5]
- In a phase 3, double-blind, randomized, placebo-controlled trial of 1431 adults living in China or South Korea, a single dose of 75 mg rimegepant was demonstrated to be effective for the acute treatment of migraine.[6]
  - 2 h after dosing, rimegepant was superior to placebo for pain freedom (n=132/666 [20%] vs n=72/674 [11%], risk difference 9.2 [95% CI 5.4–13.0]; P<0.0001) and freedom from the most bothersome symptom (MBS; n=336/666 [50%] vs n=241/674 [36%], risk difference 14.8 [95% CI 9.6–20.0]; P<0.0001).[6]

OBJECTIVE

- Evaluate the time course for efficacy of rimegepant ODT compared with placebo in the acute treatment of migraine as measured by freedom from photophobia, phonophobia, and nausea and from MBS in adults from China and South Korea.

METHODS

STUDY DESIGN

- This was a planned secondary and exploratory analysis of the double-blind, randomized, placebo-controlled, multicenter phase 3 trial (NCT04574362) of the safety and efficacy of rimegepant compared with placebo in the treatment of moderate or severe migraine.[6]
- Participants were randomized 1:1 to rimegepant ODT 75 mg or placebo; randomization was stratified by the use of prophylactic migraine medications (yes or no) and country (Korea or China).
- The study comprised a 3–28 day screening period, an acute phase ≤45 days or until the participant had a migraine that reached moderate or severe intensity, followed by an end of treatment visit 7 days after the administration of the study medication.
- The total duration of the study was ~11 weeks.

PARTICIPANTS AND CONCOMITANT MEDICATIONS

- Eligible participants included adults aged ≥18 y with ≥1-y history of migraine, 2–8 migraine attacks of moderate to severe pain intensity per month, untreated migraine attacks lasting on average ~4–72 h, and <15 headache days per month during the 3 months prior to screening.
- Participants on prophylactic migraine medication were permitted to remain on therapy if they had been on a stable dose for ≥3 months prior to screening visit, and the dose was not expected to change during the course of the study.
- Participants with contraindications for triptans were included, provided all other study eligibility criteria were met.
- Prohibited medications, prior to randomization and throughout the study, included barbiturates, ergotamines, opioids, acetaminophen (<1000 mg/day allowed as a rescue medication), and strong CYP3A4 modulators.

PROCEDURES AND ASSESSMENTS

- Participants were instructed to treat a single migraine attack of moderate or severe pain intensity.
- Participants used an eDiary to record their migraine headache and non-headache symptoms upon experiencing a migraine attack.
- Assessment of migraine symptoms was performed immediately prior to dosing and at 15 min, 30 min, 45 min, 60 min, 90 min, 2 h, 3 h, 4 h, 6 h, 8 h, 24 h, and 48 h post dosing.
- Symptoms that were nominated as MBS were photophobia, phonophobia, and nausea.
- The migraine-associated symptoms of photophobia, phonophobia, and nausea and MBS were measured on a 2-point scale (present or absent).
- MBS had to be identified before the participant took study medication.
- All efficacy analyses were conducted based on the modified intent-to-treat population, defined as randomized participants who took study therapy, had a migraine of moderate or severe intensity at the time of treatment, and provided ≥1 post-treatment efficacy data point.

RESULTS

PARTICIPANTS

- 1340 participants (rimegepant n=666, placebo n=674) were evaluated for efficacy.
- Participant demographics, baseline characteristics, and medical history are summarized in **Table 1**.
- Treatment groups were well balanced according to demographic variables and migraine disease history.
- Mean (SD) age at baseline was 37.8 (10.2) vs 37.7 (10.7) y, and mean age at migraine onset was 27.1 (9.2) vs 26.4 (9.1) y, in the rimegepant vs placebo groups.
- At baseline, mean (SD) number of moderate or severe migraine attacks was 3.7 (1.4) vs 3.6 (1.4) in the rimegepant vs placebo groups.
- Historically, nausea was the most common MBS in each treatment group (rimegepant n=362 [54.4%], placebo n=367 [54.5%]).

TIME COURSE EFFICACY – PHOTOPHOBIA, PHONOPHOBIA, AND NAUSEA

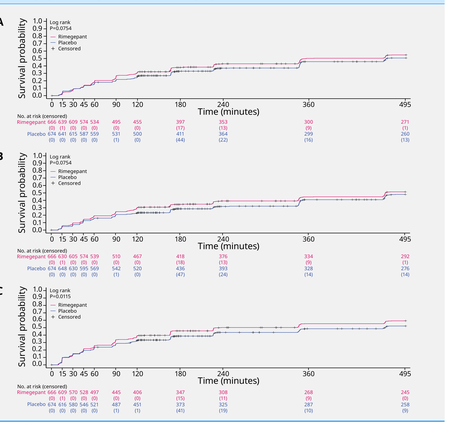
- At the onset of a moderate to severe migraine attack, 848 (rimegepant n=422, placebo n=426), 831 (rimegepant n=406, placebo n=425), and 856 (rimegepant n=439, placebo n=417) participants recorded symptoms of photophobia, phonophobia, and nausea, respectively.
- Rimegepant significantly (nominal P<0.05) increased the proportion of participants free of accompanying phonophobia as early as 60 min, and photophobia and nausea as early as 90 min, post dose compared with placebo (**Table 2**).
- Rimegepant was superior to placebo (nominal P<0.05) at all subsequent time points for the proportion of participants free of each evaluated migraine-accompanying symptom (**Table 2**).
- At 24 h post dose, >80% of participants were free of photophobia, phonophobia, or nausea, and this response was maintained at 48 h post dose (**Table 2**).
- Kaplan–Meier analyses of time to first report of absence of photophobia, phonophobia and nausea ≤8 h post dose are shown in **Figure 1**.

Table 1: Participant demographics, baseline characteristics, and medical history – mITT population

	Placebo n=674	Rimegepant n=666	Overall N=1340
Age, mean (SD), y	37.7 (10.7)	37.8 (10.2)	37.8 (10.4)
Gender, n (%)			
Female	563 (83.5)	525 (78.8)	1088 (81.2)
Male	111 (16.5)	141 (21.2)	252 (18.8)
Country, n (%)			
China	537 (79.7)	537 (80.6)	1074 (80.1)
Korea	137 (20.3)	129 (19.4)	266 (19.9)
Weight, mean (SD), kg	61.3 (11.4)	61.9 (12.1)	61.6 (11.8)
BMI, mean (SD), kg/m²	23.0 (3.4)	23.00 (3.6)	23.0 (3.5)
Height, mean (SD), cm	163.0 (7.0)	163.7 (7.8)	163.4 (7.4)
Age at migraine onset, mean (SD), y	26.4 (9.1)	27.1 (9.2)	26.7 (9.1)
No. moderate to severe migraines per month, mean (SD)	3.6 (1.4)	3.7 (1.4)	3.6 (1.4)
Average duration of untreated migraine attack, mean (SD), h	20.3 (15.5)	19.8 (15.6)	20.0 (15.5)
Prophylactic migraine medications, n (%)			
Yes	48 (7.1)	50 (7.5)	98 (7.3)
No	626 (92.9)	616 (92.5)	1242 (92.7)
Primary migraine type, n (%)			
Without aura	606 (89.9)	596 (89.5)	1202 (89.7)
With aura	68 (10.1)	70 (10.5)	138 (10.3)
Historical MBS, n (%)			
Photophobia	131 (19.4)	125 (18.8)	256 (19.1)
Phonophobia	175 (26.0)	179 (26.9)	354 (26.4)
Nausea	367 (54.5)	362 (54.4)	729 (54.4)
Missing	1 (0.1)	0	1 (<0.1)

BMI=body mass index; MBS=most bothersome symptom; mITT=modified intent-to-treat

Figure 1: Kaplan–Meier survival plot of time to first report of absence of (A) photophobia, (B) phonophobia, and (C) nausea up to 8 h post dose of rimegepant or placebo – mITT population



mITT=modified intent-to-treat

Table 2. Proportion of participants who were free of the accompanying symptoms of photophobia, phonophobia and nausea at each time point after taking rimegepant or placebo – mITT population

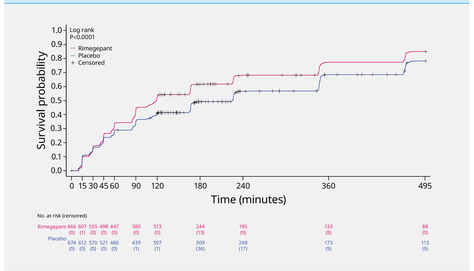
	Participants free of photophobia			Participants free of phonophobia			Participants free of nausea		
Time post dose	Placebo n=426	Rimegepant n=422	CRD (95% CI)[a]	Placebo n=425	Rimegepant n=406	CRD (95% CI)[a]	Placebo n=417	Rimegepant n=439	CRD (95% CI)[a]
15 min	42 (9.9%)	33 (7.8%)	–2.1 (–5.9, 1.7)	32 (7.5%)	40 (9.9%)	2.2 (–1.6, 6.1)	69 (16.5%)	65 (14.8%)	–0.9 (–5.6, 3.8)
30 min	60 (14.1%)	58 (13.7%)	–0.5 (–5.1, 4.1)	47 (11.1%)	61 (15.0%)	3.8 (–0.7, 8.4)	86 (20.6%)	93 (21.2%)	1.3 (–3.9, 6.6)
45 min	80 (18.8%)	87 (20.6%)	1.7 (–3.6, 7.0)	78 (18.4%)	91 (22.4%)	3.9 (–1.5, 9.3)	107 (25.7%)	131 (29.8%)	4.8 (–1.1, 10.7)
60 min	108 (25.4%)	123 (29.1%)	3.9 (–2.0, 9.8)	93 (21.9%)	116 (28.6%)*	6.8 (0.9, 12.6)	138 (33.1%)	160 (36.4%)	3.8 (–2.5, 10.1)
90 min	127 (29.8%)	168 (39.8%)*	9.9 (3.5, 16.3)	126 (29.6%)	155 (38.2%)*	8.5 (2.1, 14.9)	169 (40.5%)	211 (48.1%)*	8.0 (1.4, 14.6)
2 h	165 (38.7%)	200 (47.4%)*	8.7 (2.0, 15.3)	139 (32.7%)	194 (47.8%)*	15.0 (8.4, 21.6)	196 (47.0%)	249 (56.7%)*	10.1 (3.5, 16.8)
3 h	191 (44.8%)	240 (56.9%)*	12.0 (5.3, 18.7)	164 (38.6%)	215 (53.0%)*	14.3 (7.6, 21.0)	224 (53.7%)	288 (65.6%)*	12.1 (5.5, 18.6)
4 h	205 (48.1%)	261 (61.8%)*	13.6 (7.0, 20.3)	183 (43.1%)	239 (58.9%)*	15.9 (9.2, 22.6)	244 (58.5%)	305 (69.5%)*	10.8 (4.4, 17.2)
6 h	251 (58.9%)	292 (69.2%)*	10.7 (4.3, 17.1)	230 (54.1%)	264 (65.0%)*	11.1 (4.5, 17.7)	272 (65.2%)	332 (75.6%)*	10.1 (4.0, 16.2)
8 h	269 (63.1%)	327 (77.5%)*	14.9 (8.8, 20.9)	254 (59.8%)	308 (75.9%)*	16.4 (10.2, 22.6)	277 (66.4%)	363 (82.7%)*	15.8 (10.1, 21.5)
24 h	322 (75.6%)	361 (85.5%)*	10.5 (5.3, 15.7)	304 (71.5%)	337 (83.0%)*	11.8 (6.2, 17.3)	301 (72.2%)	367 (83.6%)*	10.5 (5.2, 15.8)
48 h	313 (73.5%)	358 (84.8%)*	12.1 (6.8, 17.4)	303 (71.3%)	337 (83.0%)*	12.2 (6.7, 17.7)	306 (73.4%)	370 (84.3%)*	10.2 (4.9, 15.4)

* P<0.05 (nominal) vs placebo.
[a] Rimegepant vs. placebo, CRD and associated 95% CI were calculated from Mantel–Haenszel test, stratified by use of prophylactic medication and country.
CRD=common risk difference

TIME COURSE EFFICACY – MBS

- The median time to first report of MBS freedom was significantly shorter for rimegepant vs placebo (119 vs 225 min; log rank P<0.0001).
- A higher proportion of participants in the rimegepant group achieved MBS freedom within 8 h compared with placebo (log rank P<0.0001; **Figure 2).**

Figure 2: Kaplan–Meier survival plot of time to first report of absence of MBS up to 8 h post dose of rimegepant or placebo – mITT population



MBS=most bothersome symptom; mITT=modified intent-to-treat

CONCLUSIONS

- Rimegepant 75 mg ODT treatment at the onset of a migraine attack of moderate to severe pain intensity provided rapid and sustained freedom from the accompanying symptoms photophobia, phonophobia, and nausea, as well as MBS, compared with placebo.
- Rimegepant provided freedom from phonophobia as early as 60 min, and photophobia and nausea as early as 90 min post dose.
- >80% of participants who received rimegepant were free of these accompanying migraine symptoms by 24 h post dose.

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DISCLOSURES

SY: Declares no conflicts of interest. **ZL, YL, QZ, SY, YZ:** Employees of Pfizer and may hold stock/stock options.

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