Journal of Pain Research

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CLINICAL TRIAL REPORT

Long-Term Use of Rimegepant 75 mg for the Acute Treatment of Migraine is Associated with a Reduction in the Utilization of Select Analgesics and Antiemetics

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Purpose: To examine use of concomitant analgesics and antiemetics during treatment with rimegepant in adults with migraine.

Patients and Methods: This was a post hoc analysis of a long-term, open-label, safety study in adults with a history of 2–14 moderate or severe migraine attacks per month. Participants self-administered rimegepant 75 mg (1) up to once daily as needed (PRN) for 52 weeks or (2) every other day plus PRN (EOD+PRN) for 12 weeks. The PRN cohort was further divided based on baseline attack frequency, with PRN (2–8) and PRN (9–14) cohorts having a history of 2–8 or 9–14 attacks per month, respectively. Use of select analgesics and antiemetics was analyzed during a 30-day pre-treatment observation period (OP) and during rimegepant treatment.

Results: Overall, 1800 rimegepant-treated participants (PRN n = 1514, EOD+PRN n = 286) were included in the analysis. Select analgesics or antiemetics were used by 80.1% of participants during the OP. Among 1441 participants using analgesics or antiemetics during the OP, the proportion who did not use any analgesics or antiemetics following initiation of rimegepant treatment increased during weeks 1–4 (36.9%), 5–8 (52.6%), and 9–12 (56.5%). The mean number of days per month using analgesics or antiemetics was also significantly reduced over time in all cohorts beginning at weeks 1–4 ($P < 0.001$ vs OP). This pattern of reduced analgesic or antiemetic use was consistent for all rimegepant cohorts, but was most pronounced in the EOD+PRN cohort in which 74.8% of participants reported ≥50% reduction in analgesic/antiemetic days at weeks 9–12. Reduction in use was maintained over time, with 61.3% of participants not using any analgesics or antiemetics during weeks 49–52 of PRN treatment.

Conclusion: Long-term treatment with oral rimegepant was associated with reduced analgesic and antiemetic use. Clinicaltrials.gov: NCT03266588.

Keywords: rimegepant, migraine, analgesics, antiemetics, clinical trial

Introduction

Migraine is characterized by recurring, moderate-to-severe, pulsating, unilateral head pain.[1] Migraine may also be associated with other symptoms including photophobia, phonophobia, and nausea.[1,2] Though migraine is one of the most common causes of disability globally, it is still generally underdiagnosed and under-treated.[3,4] In response, migraine awareness campaigns have been carried out at both global and local levels to improve understanding, diagnosis, and treatment.[5,6] Non–migraine-specific therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, caffeinated analgesics, and antiemetics are widely used for the acute treatment of migraine.[7,8] However, the efficacy of these non-specific migraine therapies can be inadequate for more severe migraine pain.[8] These therapies are also associated with medication-overuse headache (MOH) and a variety of other adverse events.[7] Therefore, reducing the use of non-specific migraine medications may reduce total medication exposure, risk of adverse events, and medication overuse.[3,4] Further, replacing non-specific migraine medications with migraine-specific acute treatments could improve therapeutic response and enhance overall patient satisfaction with treatment.

Received: 21 December 2023
Accepted: 2 May 2024
Published: 15 May 2024

Rimegepant 75 mg, an oral small molecule calcitonin gene-related peptide receptor antagonist, is indicated in the United States, European Union, United Kingdom, and other regions for the acute treatment of migraine (taken as needed [PRN]) with or without aura and for the preventive treatment of episodic migraine (taken every other day [EOD]) in adults.[9,10] Previous clinical trials have demonstrated that acute treatment with oral rimegepant 75 mg provides rapid (within 2 hours post-dose) and sustained (over 48 hours post-dose) relief from pain and other symptoms associated with migraine (eg, nausea, photophobia, phonophobia), and is safe and well tolerated when dosed for periods of 1 year or more.[11–14] The purpose of this exploratory post hoc analysis was to assess the relationship between rimegepant administration and the use of select analgesics and antiemetics in adults with migraine.

Materials and Methods

Data were from a multicenter, open-label, long-term safety study of rimegepant for the acute treatment of migraine (NCT03266588). The study enrolled adults (≥18 years of age) with ≥1-year history of migraine attacks (with or without aura), 2–14 attacks of moderate or severe pain intensity per month during the 3 months prior to screening, and attacks that lasted an average of 4–72 hours if untreated. The primary aim of this trial was to evaluate the long-term safety and tolerability of rimegepant over a treatment period of up to 52 weeks. Full study details have been published.[14]

There was a total of 3 sequentially enrolled, non-randomized treatment cohorts based on dosing regimen and the participant-reported number of moderate-to-severe migraine attacks per month in the 3 months prior to screening. Participants self-administered oral rimegepant 75 mg up to once daily PRN upon the onset of migraine for up to 52 weeks to treat attacks of any pain intensity or EOD plus PRN (EOD+PRN) on non-scheduled days for up to 12 weeks. The PRN cohort was divided into those who had a history of 2–8 attacks per month, termed the PRN (2–8) cohort, and those who had a history of 9–14 attacks per month, termed the PRN (9–14) cohort. After enrollment of these PRN cohorts, the protocol was amended to add the EOD+PRN (4–14) cohort, which included participants who had a history of 4–14 attacks per month and who were assigned to rimegepant to be taken EOD (irrespective of migraine attacks) and additionally PRN on other non-scheduled days to acutely treat migraine attacks of any severity, up to a maximum dose of 75 mg per day.

Preventive migraine medications were allowed provided dosing was stable for ≥2 months prior to the baseline visit. Participants could take protocol-defined select standard-of-care analgesic (acetaminophen, ibuprofen, naproxen, or fixed combination of acetaminophen/caffeine/aspirin) and antiemetic (dimenhydrinate, meclozine, meclozine hydrochloride, metoclopramide, ondansetron, ondansetron hydrochloride, prochlorperazine, prochlorperazine edisylate, or promethazine) medications for migraine as needed. Triptan use was allowed during a 30-day observation period (OP) prior to treatment but was not permitted during the rimegepant treatment period.

The proportion of participants using select analgesics or antiemetics was assessed during the 30-day OP (prior to receiving rimegepant) and during the rimegepant treatment period. The mean number of days of analgesics or antiemetic use per month (ie, weeks 1–4, weeks 5–8, weeks 9–12, etc) was calculated during the rimegepant treatment period and compared with use in the OP using a paired *t*-test with a significance level of $\alpha = 0.05$. The number of drug days per 4 weeks was prorated to 28 days in the (1) OP and (2) last time interval for participants with <28 study days in their last time interval.

Results

A total of 1800 participants were treated with rimegepant 75 mg, which included 1033 in the PRN (2–8) cohort, 481 in the PRN (9–14) cohort, and 286 in the EOD+PRN (4–14) cohort. The participants' mean (standard deviation [SD]) age was 43.1 (12.2) years, the majority were female (89.4%), and most were White (81.9%) (Table 1). Baseline demographics were generally similar between cohorts, except for average body weight and body mass index, which were lower in the EOD+PRN cohort than in the 2 PRN cohorts.

Overall, 66.5% of participants completed the treatment period: PRN (2–8) = 66.1%, PRN (9–14) = 56.3%, and EOD +PRN (4–14) = 85.0%. Median time on rimegepant was 49.3 weeks for the PRN (2–8) cohort, 49.6 weeks for the PRN (9–14) cohort, 11.3 weeks for the EOD+PRN (4–14) cohort, and 47.3 weeks for the overall cohort (Table 2). As expected, based on baseline attack frequency in the PRN cohorts, the mean (SD) number of rimegepant doses taken per 4

Table 1 Participant Demographics and Baseline Clinical Characteristics

	Rimegepant 75-mg Dosing Cohort			
	PRN (2–8)[a]	**PRN (9–14)[b]**	**EOD+PRN (4–14)[c]**	**Overall**
n	1033	481	286	1800
Age, mean (SD), years	44.0 (11.8)	42.4 (12.4)	41.1 (12.7)	43.1 (12.2)
Sex, n (%)				
Female	917 (88.8)	444 (92.3)	248 (86.7)	1609 (89.4)
Male	116 (11.2)	37 (7.7)	38 (13.3)	191 (10.6)
Race, n (%)				
White	847 (82.0)	394 (81.9)	234 (81.8)	1475 (81.9)
Black or African American	149 (14.4)	66 (13.7)	35 (12.2)	250 (13.9)
Other[d]	37 (3.6)	21 (4.4)	17 (5.9)	75 (4.2)
BMI, mean (SD), kg/m^2	30.4 (7.8)	29.7 (7.7)	25.2 (3.5)	29.4 (7.5)
Primary migraine type, n (%)				
Without aura	674 (65.2)	311 (64.7)	215 (75.2)	1200 (66.7)
With aura	359 (34.8)	170 (35.3)	71 (24.8)	600 (33.3)
Used triptan, n (%)[e]	349 (33.8)	184 (38.3)	104 (36.4)	637 (35.4)
Used ≥1 prophylactic medication, n (%)[f]	136 (13.2)	76 (15.8)	32 (11.2)	244 (13.6)
No. of moderate or severe attacks per month, mean (SD)	4.9 (1.8)	10.8 (1.6)	6.8 (2.6)	6.7 (3.1)
Duration of untreated attacks, mean (SD), hours	33.7 (22.2)	34.5 (21.9)	33.5 (23.2)	33.9 (22.3)

Notes: [a]PRN dosing (up to 52 weeks) in participants with 2–8 moderate or severe attacks per month in the 3 months prior to screening. [b]PRN dosing (up to 52 weeks) in participants with 9–14 moderate or severe attacks per month in the 3 months prior to screening. [c]EOD+PRN dosing (up to 12 weeks) in participants with 4–14 moderate or severe attacks per month in the 3 months prior to screening. [d]Includes American Indian or Alaska Native, Asian, Multiple, and Native Hawaiian or Other Pacific Islander. [e]Taken before 14 days prior to enrollment in the treatment period. [f]Taken on or after informed consent and before start of study drug.
Abbreviations: BMI, body mass index; EOD, every other day; PRN, as needed; SD, standard deviation.

Table 2 Summary of Rimegepant Exposure

	Rimegepant 75 mg Dosing Cohort			
	PRN (2–8)[a]	**PRN (9–14)[b]**	**EOD+PRN (4–14)[c]**	**Overall**
n	1033	481	286	1800
Time on rimegepant, weeks				
Mean (SD)	39.4 (16.9)	36.0 (19.0)	10.3 (3.0)	33.9 (19.2)
Median (range)	49.3 (0.1–55.3)	49.6 (0.1–53.4)	11.3 (0.1–16.9)	47.3 (0.1–55.3)
Number of doses per 4 weeks				
Mean (SD)	5.6 (3.5)	8.5 (4.2)	13.7 (2.9)	7.7 (4.6)
Median (range)	4.9 (0.2–27.6)	7.8 (0.7–26.6)	14.2 (0.3–22.0)	6.5 (0.2–27.6)
Cumulative number of doses				
Mean (SD)	59.9 (45.3)	80.8 (60.1)	39.6 (12.7)	62.2 (48.4)
Median (range)	52.0 (1.0–359.0)	73.0 (1.0–346.0)	43.0 (1.0–70.0)	50.0 (1.0–359.0)
Total number of doses (all participants)	61,837	38,841	11,336	112,014

Notes: [a]PRN dosing (up to 52 weeks) in participants with 2–8 moderate or severe attacks per month in the 3 months prior to screening. [b]PRN dosing (up to 52 weeks) in participants with 9–14 moderate or severe attacks per month in the 3 months prior to screening. [c]EOD+PRN dosing (up to 12 weeks) in participants with 4–14 moderate or severe attacks per month in the 3 months prior to screening.
Abbreviations: EOD, every other day; PRN, as needed; SD, standard deviation.

Table 3 Use of Select Analgesics or Antiemetics During the 30-Day Observation Period

n (%) of participants	Rimegepant 75 mg Dosing Regimen			
	PRN (2–8)[a]	PRN (9–14)[b]	EOD+PRN (4–14)[c]	Overall
n	1033	481	286	1800
Analgesics or antiemetics	828 (80.2)	388 (80.7)	225 (78.7)	1441 (80.1)
Analgesics	814 (78.8)	379 (78.8)	222 (77.6)	1415 (78.6)
Ibuprofen	418 (40.5)	199 (41.4)	122 (42.7)	739 (41.1)
Acetaminophen/aspirin/caffeine	368 (35.6)	184 (38.3)	104 (36.4)	656 (36.4)
Acetaminophen	162 (15.7)	95 (19.8)	52 (18.2)	309 (17.2)
Naproxen	141 (13.6)	61 (12.7)	38 (13.3)	240 (13.3)
Antiemetics[d]	52 (5.0)	40 (8.3)	14 (4.9)	106 (5.9)

Notes: [a]PRN dosing (up to 52 weeks) in participants with 2–8 moderate or severe attacks per month in the 3 months prior to screening. [b]PRN dosing (up to 52 weeks) in participants with 9–14 moderate or severe attacks per month in the 3 months prior to screening. [c]EOD +PRN dosing (up to 12 weeks) in participants with 4–14 moderate or severe attacks per month in the 3 months prior to screening. [d]Dimenhydrinate, meclozine, meclozine hydrochloride, metoclopramide, ondansetron, ondansetron hydrochloride, prochlorperazine, prochlorperazine edisylate, or promethazine.
Abbreviations: EOD, every other day; PRN, as needed.

weeks was higher in the cohort with 9–14 attacks per month (8.5 [4.2]) than in the cohort with 2–8 attacks per month (5.6 [3.5]).

In the overall study population (n = 1800), 1441 (80.1%) participants received select analgesics or antiemetics during the OP (analgesics = 78.6%, antiemetics = 5.9%; Table 3). The proportion of participants using select analgesics or antiemetics during the OP was similar across all rimegepant treatment cohorts (78.7–80.7%). Ibuprofen was used by 41.1% of the overall population, a fixed combination of acetaminophen/aspirin/caffeine was used by 36.4%, acetaminophen was used by 17.2%, and naproxen was used by 13.3%.

In the overall study population (n = 1800), the proportion (95% confidence interval [CI]) of participants who did not use select analgesics or antiemetics (ie, 0 days of use, "analgesic/antiemetic free") increased from 19.9% (18.2%, 21.9%) during the pre-treatment OP to 44.6% (42.3%, 46.9%) during weeks 1–4 (the first time point assessed) and to 61.6% (59.2%, 63.9%) during weeks 9–12 (the latest time point available for the EOD+PRN cohort) following initiation of rimegepant treatment (Figure 1). This pattern of decreased use of select analgesics or antiemetics following initiation of rimegepant was evident in all treatment cohorts; however, the proportion of participants who were analgesic/antiemetic free was lower in the PRN (9–14) cohort relative to other cohorts (Figure 1). This pattern was mirrored by a slight increase in PRN rimegepant use; from a mean of 4.9 tablets in the PRN (2–8) cohort and 8.5 tablets in the PRN (9–14) cohort during weeks 1–4 of treatment to 5.6 and 9.2 tablets, respectively, during weeks 5–8 (Table S1). Rimegepant PRN dosing was relatively stable thereafter for the PRN (2–8) cohort and decreased somewhat for the PRN (9–14) cohort. Mean rimegepant tablet use during weeks 49–52 was 5.9 and 8.1 tablets for the PRN (2–8) and PRN (9–14) cohorts, respectively.

Among the 1441 participants using select analgesics or antiemetics in the OP, the mean (SD) number of days per month using these agents was 12.5 (10.7) and the median was 7.0. The median number of days of select analgesic or antiemetic use was higher in the PRN (9–14) cohort (10.0 days) compared with the PRN (2–8) cohort (6.0 days) and the EOD+PRN cohort (7.0 days). Following initiation of rimegepant, the mean (SD) and median number of days using these agents was reduced in all cohorts at all monthly time points through end of treatment (weeks 9–12 for the EOD+PRN cohort; weeks 49–52 for all PRN-alone cohorts; Table S2). In all treatment cohorts combined, the mean (SD) number of days per month using select analgesics or antiemetics was 7.4 (11.7) at weeks 9–12 and 7.5 (11.9) at weeks 49–52 ($P < 0.0001$ vs OP). Mean (SD) days of use of these agents at weeks 9–12 was highest in the PRN (9–14) cohort at 8.6 (12.1) days and lowest for the EOD+PRN cohort at 5.5 (10.5) days. At weeks 49–52, the mean (SD) utilization rate was 8.0 (12.1) days for the PRN (9–14) cohort and 7.2 (11.9) days for the PRN (2–8) cohort.

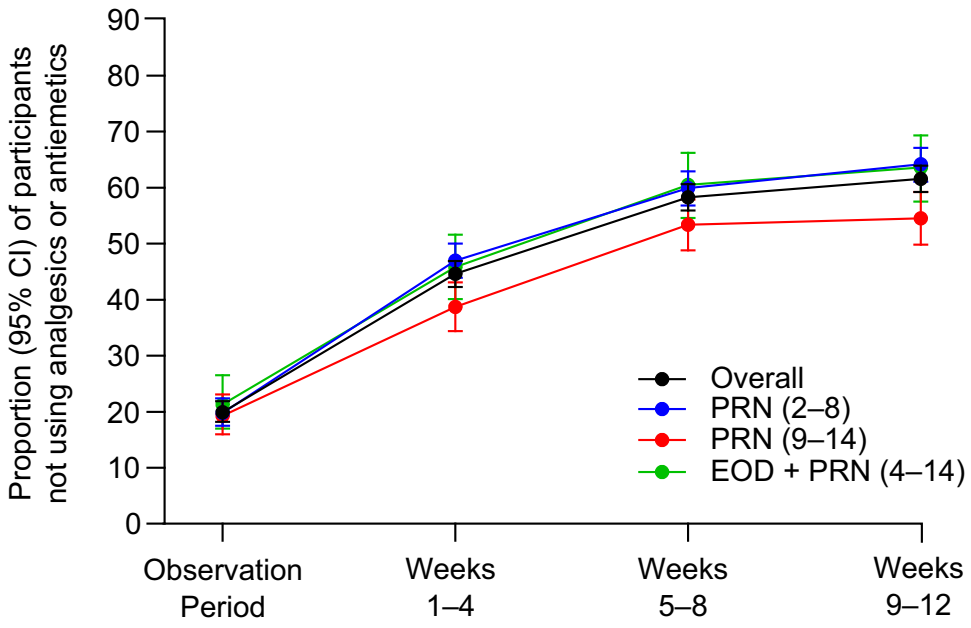

Figure 1 Proportion of all rimegepant-treated participants with no use of select analgesics or antiemetics. Overall cohort: observation period (n = 1800), weeks 1–4 (n = 1800), weeks 5–8 (n = 1725), and weeks 9–12 (n = 1645). PRN (2–8) cohort: observation period (n = 1033), weeks 1–4 (n = 1033), weeks 5–8 (n = 999), and weeks 9–12 (n = 963). PRN (9–14) cohort: observation period (n = 481), weeks 1–4 (n = 481), weeks 5–8 (n =455), and weeks 9–12 (n = 429). EOD + PRN (4–14) cohort: observation period (n = 286), weeks 1–4 (n = 286), weeks 5–8 (n = 271), and weeks 9–12 (n = 253). Confidence intervals were calculated using the Agresti–Coull method.
Abbreviations: CI, confidence interval; EOD, every other day; PRN, as needed.

Among participants using select analgesics or antiemetics during the OP (n = 1441), the proportion of participants who had a 100% reduction (ie, analgesic/antiemetic free) in the use of these agents following initiation of rimegepant treatment was 36.9% during weeks 1–4, 52.6% during weeks 5–8, and 56.5% during weeks 9–12 across the combined cohorts (Figure 2A). This pattern continued in the PRN cohorts beyond week 12, with 62.7% and 57.8% of participants not using select analgesics or antiemetics in the PRN (2–8) and PRN (9–14) cohorts, respectively, during weeks 49–52. The proportion of participants with a 100% reduction in the use of select analgesics or antiemetics was lower in the PRN (9–14) cohort compared with the PRN (2–8) cohort at all time points. More than half of all participants in each cohort had a ≥50% reduction in the mean number of days of select analgesic or antiemetic use per month at all time points following initiation of rimegepant treatment (Figure 2B). Slightly lower proportions of participants achieved ≥50% reduction in select analgesic and antiemetic use in the PRN (9–14) cohort compared with the PRN (2–8) cohort at time points up to week 12, with this trend diminishing beyond week 12. For both the ≥50% and 100% responder thresholds, the EOD+PRN group demonstrated a consistently higher response rate than both PRN cohorts throughout the initial 12-week treatment period in which the 3 cohorts were evaluated (Figure 2A and B).

A small proportion of all participants who used select analgesics or antiemetics during the OP demonstrated increased use of these agents following initiation of rimegepant (3.3–7.4% across all time points). In each cohort, the proportion (95% CI) of participants with increased use of select analgesics or antiemetics was highest at weeks 1–4; 7.4% (6.1%, 8.8%) in the overall cohort, 7.2% (5.7%, 9.2%) in the PRN (2–8) cohort, 7.0% (4.8%, 10.0%) in the PRN (9–14) cohort, and 8.4% (5.4%, 12.9%) in the EOD+PRN (4–14) cohort.

Select analgesics and antiemetics were examined as separate therapeutic classes (Figures S1 and S2, respectively). Findings for analgesics alone were comparable to the combined analgesic and antiemetic analysis, with substantial reductions in use observed following initiation of rimegepant overall and across all 3 cohorts. Reductions in antiemetic use were also observed following initiation of rimegepant and trended in a manner similar to select analgesics, with differences between cohorts qualitatively mirroring those observed in the combined analgesic and antiemetic group. However, conclusions are limited by the relatively small number of participants using antiemetics during the OP.

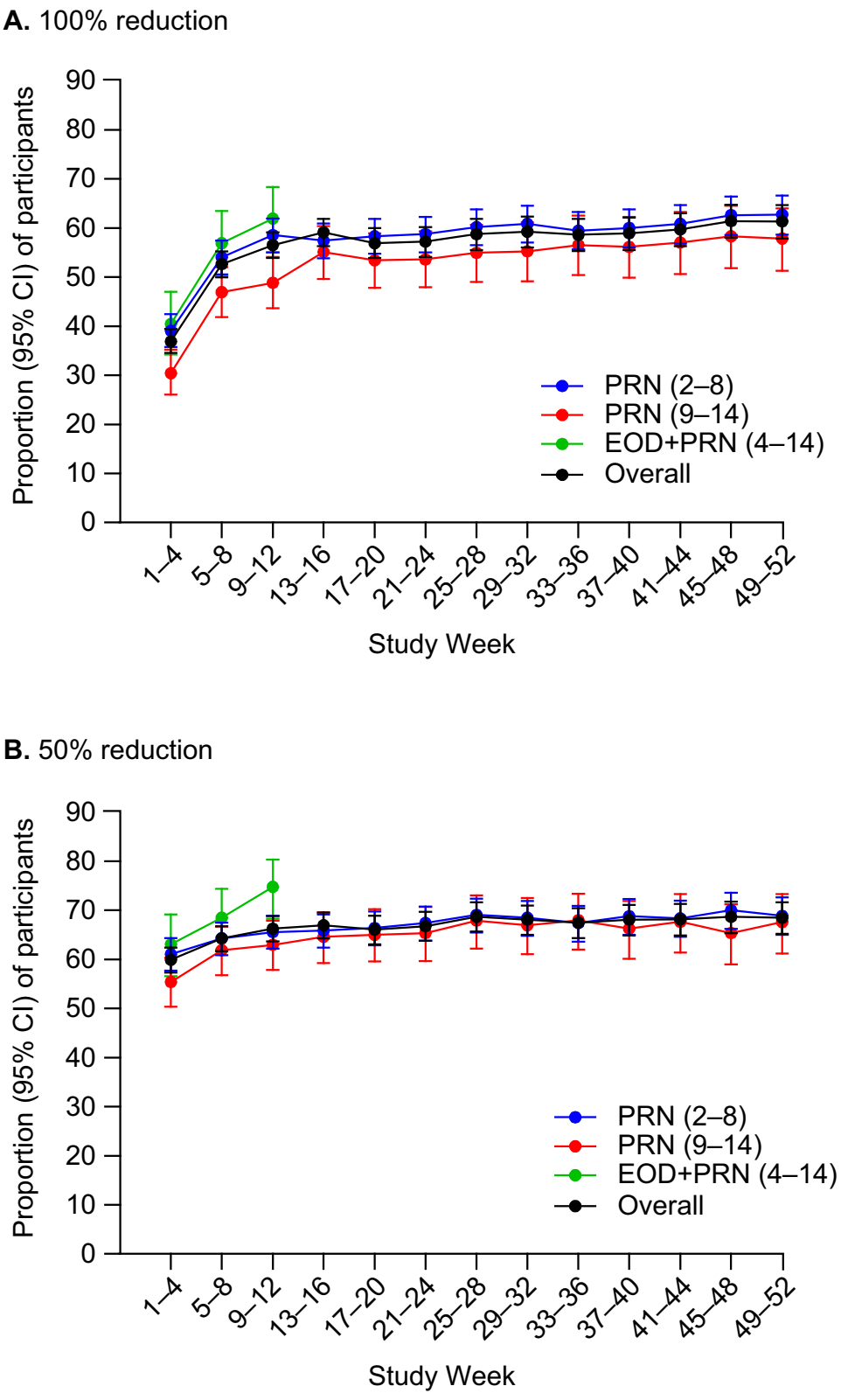

Figure 2 Proportion of participants with (**A**) 100% and (**B**) 50% reduction in the mean number of days per month using select analgesics or antiemetics following initiation of rimegepant treatment among participants using analgesics or antiemetics during the observation period: PRN (2–8), n = 828; PRN (9–14), n = 388; EOD + PRN (4–14), n = 225; Overall, n = 1441. Confidence intervals were calculated using the Agresti–Coull method.
Abbreviations: CI, confidence interval; EOD, every other day; PRN, as needed.

Among 359 participants (19.9%) who did not use select analgesics or antiemetics during the OP, 24.8% used ≥1 of these agents during weeks 1–4 of study treatment. However, the mean days of use among these 359 participants was <1 day (0.7 days) during this timeframe. The proportion of these participants using select analgesics or antiemetics during the treatment period decreased over time to 5.9% during weeks 49–52. Likewise, the mean days of use decreased over time to 0.3 days during weeks 49–52.

Discussion

Although non–migraine-specific analgesics and antiemetics are common acute treatments for migraine, they may not be fully effective for migraine attacks of moderate or severe pain intensity.[7,8] This could result in an insufficient initial response or the recurrence of pain or associated symptoms after an initial response, both common concerns of patients when considering acute migraine therapies.[8,15–18] For this reason, migraine treatment guidelines recommend offering patients migraine-specific acute treatment when there is a history of insufficient response to general analgesics.[8,19]

In this study, analgesics, including ibuprofen, acetaminophen/aspirin/caffeine combination, acetaminophen alone, and naproxen, were used by 78.6% of the study population during the baseline OP. Prolonged or frequent use of these agents, particularly the combination containing caffeine, may promote MOH.[1,20] Beyond the risk of MOH, there are other concerns regarding the long-term safety and tolerability of these analgesics. For example, while short-term treatment with NSAIDs such as ibuprofen and naproxen is generally well tolerated, prolonged use of such agents has been associated with gastrointestinal bleeding, cardiovascular events, and renal failure.[21,22] This is particularly relevant in patients who have comorbid risk factors for these events, such as older age or existing gastrointestinal, cardiovascular, or renal disease. Likewise, although short-term acetaminophen treatment at therapeutic doses is generally well tolerated, chronic treatment at a dose of 4 mg/day may cause transient elevations in serum aminotransferase and higher doses are associated with a risk of hepatotoxicity.[23–25] A total of 5.9% of participants used antiemetics during the OP. Common adverse events associated with these medications typically include sedation, drowsiness, or dizziness.[7,26]

In the current study, acute treatment of migraine with rimegepant 75 mg PRN or EOD plus PRN on non-scheduled dosing days was associated with a reduced requirement for select non-specific analgesics or antiemetics. In the overall study population, participants receiving analgesics or antiemetics during the OP used these agents 4 days less per month in the first month (weeks 1–4), on average, following initiation of rimegepant treatment. Similar or greater decreases from the OP were seen at all subsequent time points through weeks 9–12 in all 3 cohorts and through weeks 49–52 in the 2 PRN cohorts. Further, among participants using these agents during the OP, more than one-third were analgesic/antiemetic free in the first month (weeks 1–4) following initiation of rimegepant. The proportion of rimegepant-treated participants analgesic/antiemetic free increased to >50% during the second (weeks 5–8) and third (weeks 9–12) months in all 3 cohorts combined, and was increased to >60% after 1 year of treatment (weeks 49–52) in the combined PRN cohorts. These results suggest that a significant proportion of the study participants had satisfactory responses to rimegepant and did not require additional acute treatments for migraine.

There were notable differences between the 3 cohorts in baseline use of select analgesics and antiemetics and in the reduction of use of these agents during the treatment period. During the OP, the median number of days with use was 4 days higher in the PRN (9–14) cohort than the PRN (2–8) cohort and 3 days higher than in the EOD+PRN cohort. The mean number of days with select analgesic or antiemetic use remained higher in the PRN (9–14) cohort (8.6 days) than in the PRN (2–8) cohort (7.4 days) at weeks 9–12 despite a greater reduction (relative to the OP) in use in the 9–14 cohort (−5.6 days vs −4.3 days, respectively). The mean number of days of analgesic or antiemetic use over weeks 9–12 was also substantially higher in the PRN (9–14) cohort than the EOD+PRN cohort (5.5 days), despite a similar mean reduction from the OP in both groups (−5.6 days vs −5.8 days). Similarly, the proportion of participants with a 100% reduction in the use of select analgesics or antiemetics (ie, no days of use) was lower (2–10% less across time points) in the PRN (9–14) cohort than in the PRN (2–8) cohort, at all time points. Despite these observed differences in analgesic/antiemetic use during the rimegepant treatment period, all 3 cohorts demonstrated significant reductions from the OP with more than 30% of participants in each of the cohorts requiring no analgesics or antiemetics within the first month of treatment. This was associated with a commensurate increase in PRN rimegepant use (among all treated participants) in

the first 8 weeks of the treatment period, with relatively stable use or a slight reduction in use thereafter to 52 weeks of treatment.

The difference between the PRN (9–14) cohort and other cohorts in the frequency of use of select analgesics and antiemetics is not unexpected, as mean attack frequency at screening was more than double in the PRN (9–14) cohort (10.8 attacks per month) compared with the PRN (2–8) cohort (4.9 attacks per month). Participants with more frequent attacks would be expected to utilize more symptomatic treatment, including partial replacement by a specific abortive migraine therapy. Additionally, individuals with higher-frequency episodic migraine may be more refractory to acute treatments and require the use of rescue medication or treatment for recurrent attacks.[27] The proportion of participants with ≥50% reduction in the use of select analgesics or antiemetics was more similar in the 2 PRN cohorts (1% higher to 6% lower in the 9–14 cohort across all time points).

Additional analyses were performed in a group of 359 participants who were analgesic/antiemetic free during the OP, to evaluate whether use of these agents substantially increased during the treatment period. Approximately 25% of these participants used ≥1 of these agents during weeks 1–4 of study treatment, although mean days of use during this timeframe was low across the whole group (<1 day vs 8.1 days among those who used select analgesics and antiemetics during the OP). Further, the proportion of participants using these agents and the mean number of days of use consistently decreased over time (5.9% and 0.3 days at weeks 49–52). These results confirm that, among participants who did not use select analgesics or antiemetics during the OP, the use of these agents was low and sporadic during the treatment period. This initial increase in analgesic/antiemetic use could, in part, represent the switching from triptans, which were allowed prior to study treatment but not allowed during the treatment period, to alternate acute treatments permitted by the protocol. Triptans were taken by 35.4% and 36.0% of participants at screening and after enrollment during the OP but prior to study treatment, respectively. After the initial increase in analgesic/antiemetic use in weeks 1–4, a reduction in such use was observed over the remaining treatment period, an observation in line with the group using analgesics/antiemetics during the OP.

The results of this analysis suggest that a significant proportion of the study participants likely had satisfactory responses to rimegepant for the acute treatment of migraine and did not require additional treatments. Additionally, previously reported data from this study suggest a potential reduction in monthly migraine days even when rimegepant is used for the acute treatment of migraine.[14] This reduction in monthly migraine days is especially relevant for the EOD +PRN cohort, in which rimegepant was dosed in a manner consistent with the regimen approved for episodic migraine prevention. Indeed, the largest reduction from baseline in the mean number of days of analgesic or antiemetic use (−5.8) and the lowest mean number of days of such use (5.5) at weeks 9–12 were observed for this cohort relative to the other cohorts. Therefore, both the effective treatment of acute attacks and the potential prophylactic reduction in the number of attacks, which would also be reflected in the requirement for acute therapy, could explain the reduced utilization of select analgesics and antiemetics observed in this study.

Although this study demonstrated rimegepant was associated with a reduction in the requirement for additional analgesics or antiemetics when used for the acute treatment of migraine, some limitations should be noted. The study was designed primarily to evaluate the long-term safety of rimegepant and, as such, the open-label, uncontrolled design precludes drawing a definitive link between rimegepant administration and the reduction in select analgesic and antiemetic use. However, as an established effective agent for the acute and preventive treatment of migraine, the reduction in other medications used for acute treatment observed in this analysis would be expected, as previously discussed. Additionally, the analysis was based on the number of days per month that participants used analgesics or antiemetics. As such, the analysis does not assess drug dosage or dosing frequency during a single day. Therefore, it is possible that some participants took lower/higher or fewer/more doses of analgesics or antiemetics per day (on days where such agents were used) following rimegepant initiation, but this was not captured in our analysis. Also, the therapeutic responses to acute treatment with rimegepant or non-specific analgesics or antiemetics were not assessed and, therefore, it is not possible to examine the direct relationship between efficacy and use of analgesics or antiemetics in this study. Finally, given it was a long-term study, the participant population decreased over time and it is possible that those discontinuing were the participants who were more likely to require analgesics or antiemetics. This could potentially bias the remaining sample and artificially drive down the

proportion of participants who did not require analgesics or antiemetics at later time points. This is unlikely, however, since 88.9% of all treated participants completed at least 3 months of the treatment period and the proportion of participants with a reduction in the use of analgesics and antiemetics was at (or near) its peak value at this time.

Conclusion

Long-term treatment with oral rimegepant 75 mg, dosed as-needed for the acute treatment of migraine or every other day and as-needed, was associated with reduced analgesic and antiemetic use in adults with migraine.

Data Sharing Statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Pursuant to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Ethics Approval and Informed Consent

The study protocol was approved by an Institutional Review Board or Independent Ethics Committee for each participating investigational center. All participants provided written informed consent. The study was conducted in compliance with ethical principles of the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice Guidelines. Table S3 lists all ethics committees approving the protocol.

Acknowledgments

Medical writing support was provided by Matt Soulsby, PhD, CMPP, of Engage Scientific Solutions and was funded by Pfizer.

Funding

This study was sponsored by Biohaven, which was acquired by Pfizer in October 2022.

Disclosure

Terence Fullerton and Glenn Pixton are full-time employees of, and own stock/options in, Pfizer. Glenn Pixton owns stock in Abbvie. The authors report no other conflicts of interest in this work.

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