Research Article

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Comparative effectiveness of erenumab versus rimegepant for migraine prevention using matching-adjusted indirect comparison

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Aim: To compare the efficacy of erenumab versus rimegepant as preventive treatment for patients with episodic and chronic migraine using an anchor-based matching-adjusted indirect comparison. **Methods:** Patients from two phase II/III trials for erenumab (NCT02066415 and NCT02456740) were pooled and weighted to match on the baseline effect modifiers (age, sex, race, baseline monthly migraine days [MMDs], and history of chronic migraine [CM]) reported in the phase II/III trial for rimegepant (NCT03732638). Four efficacy outcomes were compared between the two erenumab regimens (70 mg and 140 mg) and rimegepant, including changes in MMDs from baseline to month 1 and month 3, changes in Migraine-Specific Quality of Life Questionnaire role function – restrictive domain score from baseline to month 3, and change in disability from baseline to Month 3. **Results:** Compared with rimegepant, erenumab 70 mg was associated with a statistically significant reduction in MMDs at month 3 (-0.90 [-1.76, -0.03]; p = 0.042) and erenumab 140 mg was associated with statistically significant reductions in MMDs at month 1 (-0.94 [-1.70, -0.19]; p = 0.014) and month 3 (-1.28 [-2.17, -0.40]; p = 0.005). The erenumab regimens also had numerical advantages over rimegepant for other efficacy outcomes. **Conclusion:** In the present study, we found that erenumab had a more favorable efficacy profile than rimegepant in reducing MMDs at month 1 and month 3 for migraine prevention. These results may help with decision-making in clinical practice and can be further validated in future clinical trials or real-world studies.

Plain language summary: What was the aim of this research?: To compare the efficacy of erenumab with rimegepant as a treatment for prevention of episodic and chronic migraine.
How was the research carried out?: A matching-adjusted indirect comparison (MAIC) was conducted using clinical trial data for erenumab and rimegepant. The study assessed four efficacy outcomes: changes in MMDs from baseline to month 1 and month 3, changes in Migraine-Specific Quality of Life Questionnaire role function – restrictive domain score from baseline to month 3, and change in disability from baseline to month 3.
What were the results?: Compared with rimegepant, erenumab 70 mg was associated with a significantly larger reduction in monthly migraine days by month 3 and erenumab 140 mg was associated with significantly larger reductions in monthly migraine days by both month 1 and month 3. Additionally, both erenumab regimens demonstrated numerical advantages over rimegepant for all other efficacy outcomes.
What do the results of the study mean?: Compared with rimegepant, the erenumab regimens had a more favorable efficacy profile in reducing MMDs at month 1 and month 3 for migraine prevention.

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Keywords: erenumab • matching-adjusted indirect comparison • migraine prevention • rimegepant

Migraine is the second leading cause of disability affecting over 1 billion people worldwide [1]. Current treatment options available for migraine management can be categorized into acute and preventive therapies. Acute medications, such as triptans, ergots, opioids, paracetamol (acetaminophen) and nonsteroidal anti-inflammatory drugs aim to relieve symptoms during a migraine attack. However, the overuse of acute medications has been associated with migraine progression [2,3], medication overuse headache [2] and adverse events that included serious vascular events [4] and gastrointestinal-related events [5]. A consensus of expert opinions suggests that preventive therapies should be offered according to disease burden and when any one of the following is present: ≥4 headache days per month; attacks that significantly interfere with daily routines despite acute treatment; failure, contraindication or overuse of acute treatments; adverse events associated with acute treatments and patient preference. Patients with <4 headache days per month may also consider preventive therapies according to the level of disability associated with their migraine attacks [6,7].

In recent years, inhibition of the calcitonin gene-related peptide (CGRP) pathway has become the leading strategy of novel drug development for migraine prevention. Several monoclonal antibodies (mAbs) blocking CGRP or its receptor and small antagonists of the CGRP receptor (the gepants) have been approved by the US FDA and the European Medicines Agency for migraine prevention. Specifically, four mAbs (erenumab, fremanezumab, galcanezumab and eptinezumab) were approved for the prevention of chronic migraine (CM) and episodic migraine (EM) [8–11]; two gepants (rimegepant and atogepant) were recently approved for the prevention of EM [12,13].

Although clinical trials have compared each mAb and each gepant with placebo [14–20], the comparative efficacy of mAbs versus gepants remains unclear. Studies performing indirect comparisons between mAbs and gepants have drawn inconsistent conclusions, in part due to incomplete inclusion of clinical trials, differences in statistical methodologies, and failure to interpret the data in the context of respective limitations of the analyses [21,22]. For example, Popoff *et al.* indirectly compared rimegepant with erenumab and galcanezumab for the prevention of EM using an unanchored matching-adjusted indirect comparisons (MAIC) based on a single-arm trial for rimegepant and only one of the relevant clinical trials for erenumab [21]. Due to the lack of an anchor comparator arm, stronger assumptions of study comparability were required than with an anchored indirect comparison. The authors did not identify statistically significant differences between rimegepant and the two mAbs in terms of changes in monthly migraine days (MMDs) or Migraine Disability Assessment (MIDAS) scores. Rimegepant was associated with larger increases across all Migraine-Specific Quality of Life Questionnaire (MSQ) domains compared with erenumab, although no difference was observed in the comparisons with galcanezumab [21]. Silberstein *et al.* conducted a network meta-analysis (NMA) to indirectly compare fremanezumab with atogepant and rimegepant for the prevention of EM, which showed that fremanezumab was associated with larger reductions in average MMD than atogepant and rimegepant and a greater proportion of patients that achieved ≥50% reduction in average MMDs compared with rimegepant [22]. Patient-level effect modifiers, such as age, sex, race or ethnicity, days taking acute medication and number of previously failed preventive treatment [23], may be imbalanced across the trials and were not adjusted for in the NMA [22]. A population-adjusted indirect comparison approach can help ensure the robustness of the contrasts with potential effect modifiers balanced across studies.

To address the limitations in these previous studies, the present study applied an anchored MAIC to indirectly compare the efficacy of a mAb (erenumab) with a gepant (rimegepant) in migraine prevention.

Methods

Data source

The present study used (a) published aggregate data of the phase II/III clinical trial for rimegepant (NCT03732638) [14,24] and (b) individual patient data of the 295 (NCT02066415) and STRIVE (NCT02456740) trials for erenumab. The phase II/III trial for rimegepant was a randomized, double-blind, placebo-controlled trial that included adult patients with at least 1 year history of CM or EM. Eligible patients were required to have: (a) 4–18 migraine attacks of moderate or severe intensity per month and ≤18 headache days per month during the 3-month period before screening and; (b) ≥6 migraine days and ≤18 headache days during the 4 weeks prior to randomization. A total of 741 patients were randomized 1:1 to receive rimegepant 75 mg every other day (QOD; n = 370) or a matching placebo (QOD; n = 371) for the 12-week double-blind treatment phase. The primary efficacy end point was the change in MMDs from baseline to month 3 [14].

The 295 trial was a phase II, randomized, double-blind, placebo-controlled trial that included adult patients with a history of CM. Eligible patients were required to have (a) ≥5 migraine attacks, (b) ≥15 headache days per month of which ≥8 met criteria as migraine days during the 3-month period before the screening and the 4-week period prior to randomization. A total of 667 patients were randomized 2:2:3 to receive erenumab 70 mg every four weeks (Q4W; n = 191), erenumab 140 mg Q4W (n = 190), and placebo Q4W (n = 286) for the 12-week double-blind treatment phase. The primary efficacy end point was the change in MMDs from baseline to month 3 [16].

The STRIVE trial was a phase III, randomized, double-blind, placebo-controlled trial that included adult patients with a history of EM. Eligible patients were required to have ≥4 and <15 migraine days per month and <15 headache days per month on average during the 3-month period before screening and during the 4-week period prior to the randomization. A total of 955 patients were randomized 1:1:1 to receive erenumab 70 mg Q4W (n = 317), erenumab 140 mg Q4W (n = 319), or placebo Q4W (n = 319) for the 24-week double-blind treatment phase. The primary efficacy end point was the change in MMDs from baseline to months 4–6 [15].

As the phase II/III trial for rimegepant included patients with CM or EM and reported limited data stratified by CM and EM, patients from the 295 and STRIVE trials were pooled to create a mix of CM and EM patients in order to be comparable with the study population of the phase II/III trial for rimegepant.

Treatments

The comparators in the present study included rimegepant 75 mg QOD, erenumab 70 mg Q4W, and erenumab 140 mg Q4W. The placebo arm was used as an anchor comparator.

Efficacy outcomes

The study focused on efficacy outcomes which met the following criteria: (a) outcomes were reported in both the phase II/III trial for rimegepant and the 295 and STRIVE trials for erenumab and; (b) outcomes were comparable in definitions across the three trials.

A total of 4 efficacy outcomes were eligible for evaluation based on these criteria: (a) change in MMDs from baseline to month 1; (b) change in MMDs from baseline to month 3; (c) change in MSQ role function – restrictive domain (MSQ-RFR) score from baseline to month 3 and; (d) change in disability as measured by MIDAS total score from baseline to month 3.

Statistical analysis

Pooling of data from 295 & STRIVE trials

Patients from the 295 and STRIVE trials were first pooled to create a population with both CM and EM patients. As the randomization ratios for placebo: erenumab 70 mg Q4W: erenumab 140 mg Q4W were 3:2:2 in the 295 trial and 1:1:1 in the STRIVE trial, directly pooling patients from these two trials would break the randomization between the placebo arm and the erenumab arms. Therefore, patients in each arm of the 295 trial were assigned a fixed weight to ensure that randomization was preserved across arms after pooling. Specifically, patients in the placebo arm of the 295 trial were assigned a weight of 0.78, and those in the erenumab arms of the 295 trial were assigned a weight of 1.17. This led to a 1:1:1 randomization ratio across the three weighted arms for the 295 trial, which became comparable to the randomization ratio for the STRIVE trial.

Matching of effect modifiers

Among the baseline characteristics reported in the clinical trials of interest, age, sex, race, baseline MMDs and history of CM were considered effect modifiers. These effect modifiers were selected based on clinical inputs, the potential effect modifiers per a physician survey in Fawsitt *et al.* [23], and the availability of variables reported for the rimegepant trial and collected in the two erenumab trials. Additionally, while age at disease onset was reported for the rimegepant trial and was available in the erenumab trials, we opted not to adjust for such a variable, because: (a) age at disease onset was reported as a median and; (b) patients may have tied age at disease onset. It is unclear how many patients had a tied age at disease onset in the rimegepant trial, and an adjustment in the presence of ties based on the median may introduce bias. We believe that population-adjusted indirect comparisons are more robust than an NMA or Bucher's indirect comparison, given the presence and potential imbalance of effect modifiers and the data availability to adjust for them. Network meta-regression is infeasible given the limited number of trials employed in the study. Therefore, an MAIC was carried out to indirectly compare erenumab with rimegepant.

Table 1. Baseline characteristics before and after matching.

	STRIVE & 295 pooled			STRIVE & 295 pooled			Phase II/III trial for rimegepant [14,23]	
	Before matching			After matching				
	Erenumab 70 mg Q4W n = 539.8	Erenumab 140 mg Q4W n = 540.7	Placebo n = 541.4	Erenumab 70 mg Q4W ESS = 405.5	Erenumab 140 mg Q4W ESS = 351.2	Placebo ESS = 466.5	Rimegepant 75 mg QOD n = 370	Placebo n = 371
Demographics								
Age (years), mean	41.2	41.4	41.6	41.3	41.3	41.1	41.3	41.1
Sex, %								
Female	85.7	84.8	83.0	81.1	81.1	84.4	81.1	84.4
Male	14.3	15.2	17.0	18.9	18.9	15.6	18.9	15.6
Race, %								
White	90.1	93.9	89.6	79.7	79.7	83.3	79.7	83.3
Non-White	9.9	6.1	10.4	20.3	20.3	16.7	20.3	16.7
Disease characteristics								
MMDs, Mean	12.2	12.2	12.3	10.3	10.3	9.9	10.3	9.9
History of chronic migraine, %	41.4	41.0	41.2	21.1	21.1	25.6	21.1	25.6

ESS: Effective sample size; mg: Milligram; MMDs: Monthly migraine days; QOD: Every other day; Q4W: Every four weeks.

Specifically, individual patients in the pooled 295 and STRIVE population were further weighted such that (1) the weighted means of each effect modifier matched with those for the phase II/III trial for rimegepant (specifically, the erenumab 70 mg Q4W and 140 mg Q4W arms were both matched with the rimegepant 75 mg QOD arm; and the placebo arm of the pooled 295 and STRIVE population was matched with the placebo arm of the phase II/III trial for rimegepant); (2) the weight for each patient reflected the estimated propensity of being enrolled into the phase II/III trial for rimegepant relative to the pooled 295 and STRIVE population. Weights meeting these conditions were estimated by a logistic regression model that was weighted by the aforementioned fixed weights.

Before-matching and after-matching effect modifiers were described using means and standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables. The before-matching baseline characteristics were also compared using the z-test between: (1) the erenumab 70 mg Q4W arm versus the rimegepant 75 mg QOD arm; (2) the erenumab 140 mg Q4W arm versus the rimegepant 75 mg QOD arm and; (3) the placebo arm of the phase II/III trial versus the placebo arm of the pooled 295 and STRIVE population.

Comparisons of efficacy outcomes

The four efficacy outcomes associated with erenumab 70 mg Q4W and 140 mg Q4W were indirectly compared with those for rimegepant 75 mg QOD before and after matching, with placebo as the anchor. As all four efficacy outcomes were continuous, comparative results were described using mean differences and the corresponding 95% confidence intervals (*CIs*), with the standard errors estimated using the robust sandwich estimator [25].

P-value < 0.05 indicates statistical significance. All statistical analyses were conducted using R version 3.6.2 (R Foundation for Statistical Computing, Vienna).

Results

Study sample & patient characteristics

In the pooled 295 and STRIVE population, the sample sizes after weighting were 539.8, 540.7, and 541.4 for the erenumab 70 mg Q4W, erenumab 140 mg Q4W, and placebo arms, respectively. Compared with the phase II/III trial for rimegepant, the pooled 295 and STRIVE population had a higher proportion of white patients, higher baseline MMDs, and a higher proportion of patients with CM (Table 1). After matching, the effect modifiers were balanced between the pooled 295 and STRIVE population and the phase II/III trial for rimegepant. The effective sample sizes of the pooled 295 and STRIVE population became 405.5, 351.2, and 466.5 for the erenumab 70 mg Q4W, erenumab 140 mg Q4W and placebo arms, respectively, after matching (Table 1).

Direct treatment comparisons (versus placebo)

In the pooled 295 and STRIVE population before and after matching, patients in the two erenumab arms had larger reductions in MMDs by month 1 and month 3, a larger improvement in MSQ-RFR score and a larger reduction in MIDAS total score (all with $p < 0.05$) compared with patients randomized to the placebo arm (Figure 1). As reported elsewhere, rimegepant 75 mg QOD had larger reductions in MMDs by month 1 and month 3 and a larger improvement in MSQ-RFR score (all with $p < 0.05$) compared with placebo (Figure 1) [14,24]. However, the change in MIDAS total score by month 3 was comparable between the rimegepant arm and the placebo arm in the phase II/III rimegepant trial (Figure 1) [14,24].

Indirect treatment comparisons (erenumab vs rimegepant)

Before matching on the effect modifiers, patients in the erenumab 70 mg Q4W arm had a statistically significantly larger reduction in MMDs by month 3, compared with those in the rimegepant 75 mg QOD arm (-0.93 [-1.82, -0.04]; p = 0.040). Additionally, erenumab 70 mg Q4W had a numerically larger change in MMDs from baseline to month 1 (-0.61 [-1.36, 0.14]; p = 0.111), a numerically larger improvement in MSQ-RFR score from baseline to month 3 (1.53 [-2.54, 5.60]; p = 0.460), and a numerically larger reduction in MIDAS total score from baseline to month 3 (-4.79 [-10.71, 1.13]; p = 0.113). Moreover, compared with patients in the rimegepant 75 mg QOD arm, patients in the 140 mg Q4W arm had a statistically significantly larger reduction in MMDs by both month 1 (-0.85 [-1.61, -0.10]; p = 0.027) and month 3 (-1.22 [-2.12, -0.33]; p = 0.008) as well as a numerically larger improvement in MSQ-RFR score by month 3 (3.18 [-1.01, 7.36]; p = 0.137) and a numerically larger reduction in MIDAS total score by month 3 (-4.53 [-10.44, 1.38]; p = 0.133) (Figure 1).

The differences comparing the two erenumab regimens with rimegepant continued to be observed after matching on the effect modifiers. Specifically, compared with rimegepant 75 mg QOD, erenumab 70 mg Q4W was associated with a statistically significantly larger reduction in MMDs by month 3 (-0.90 [-1.76, -0.03]; p = 0.042) and erenumab 140 mg Q4W was associated with statistically significantly larger reductions in MMDs by both month 1 (-0.94 [-1.70, -0.19]; p = 0.014) and month 3 (-1.28 [-2.17, -0.40]; p = 0.005). Additionally, both erenumab regimens continued to have numerical advantages over rimegepant 75 mg QOD for all other efficacy outcomes (Figure 1).

Discussion

In the absence of head-to-head randomized clinical trials, the present study applied an anchored MAIC to compare the relative efficacy of erenumab 70 mg and 140 mg Q4W versus rimegepant 75 mg QOD for migraine prevention while adjusting for between-trial differences in effect modifiers. Compared with rimegepant 75 mg QOD, erenumab 70 mg Q4W was associated with a numerically greater reduction in MMDs by month 1 and a statistically significantly greater reduction in MMDs from baseline to month 3, while erenumab 140 mg Q4W was associated with a statistically significant reduction in MMDs from baseline to both months 1 and 3. In addition, both erenumab regimens had numerical advantages over rimegepant 75 mg QOD in terms of improving the MSQ-RFR score and reducing the MIDAS total score by month 3.

Compared with patients in the respective placebo arms, patients in the treatment arms (erenumab 70 mg, erenumab 140 mg, and rimegepant 75 mg) all had statistically significant reductions in MMDs by month 1 compared with baseline, indicating early onset of preventive effects of all three regimens. However, such an early benefit was 50.0% larger for erenumab 70 mg Q4W (-1.80 days relative to placebo) and 78.3% larger for erenumab 140 mg Q4W (-2.14 days relative to placebo), compared with rimegepant 75 mg QOD (-1.20 days relative to placebo). The time of onset of treatment effect may be a consideration when selecting a treatment.

Moreover, the treatment effect of the erenumab regimens persisted through month 3. Compared with rimegepant 75 mg QOD (-0.80 days relative to placebo), the reduction in MMDs by month 3 was 112.5% larger for erenumab 70 mg Q4W (-1.70 days relative to placebo) and 160.0% larger for erenumab 140 mg Q4W (-2.08 days relative to placebo).

Furthermore, both erenumab regimens had a greater effect than rimegepant (though not statistically significant) in improving the MSQ-RFR score and reducing the MIDAS total score. Specifically, Specifically, the increase in MSQ-RFR score by month 3 was 27.4% larger for erenumab 70 mg Q4W (+4.46 relative to placebo) and 76.3% larger for erenumab 140 mg Q4W (+6.17 relative to placebo) compared with rimegepant 75 mg QOD (+3.50 relative to placebo). Additionally, both erenumab regimens had statistically significantly higher reductions in the MIDAS total score by month 3 compared with placebo, while rimegepant 75 mg QOD was comparable to the

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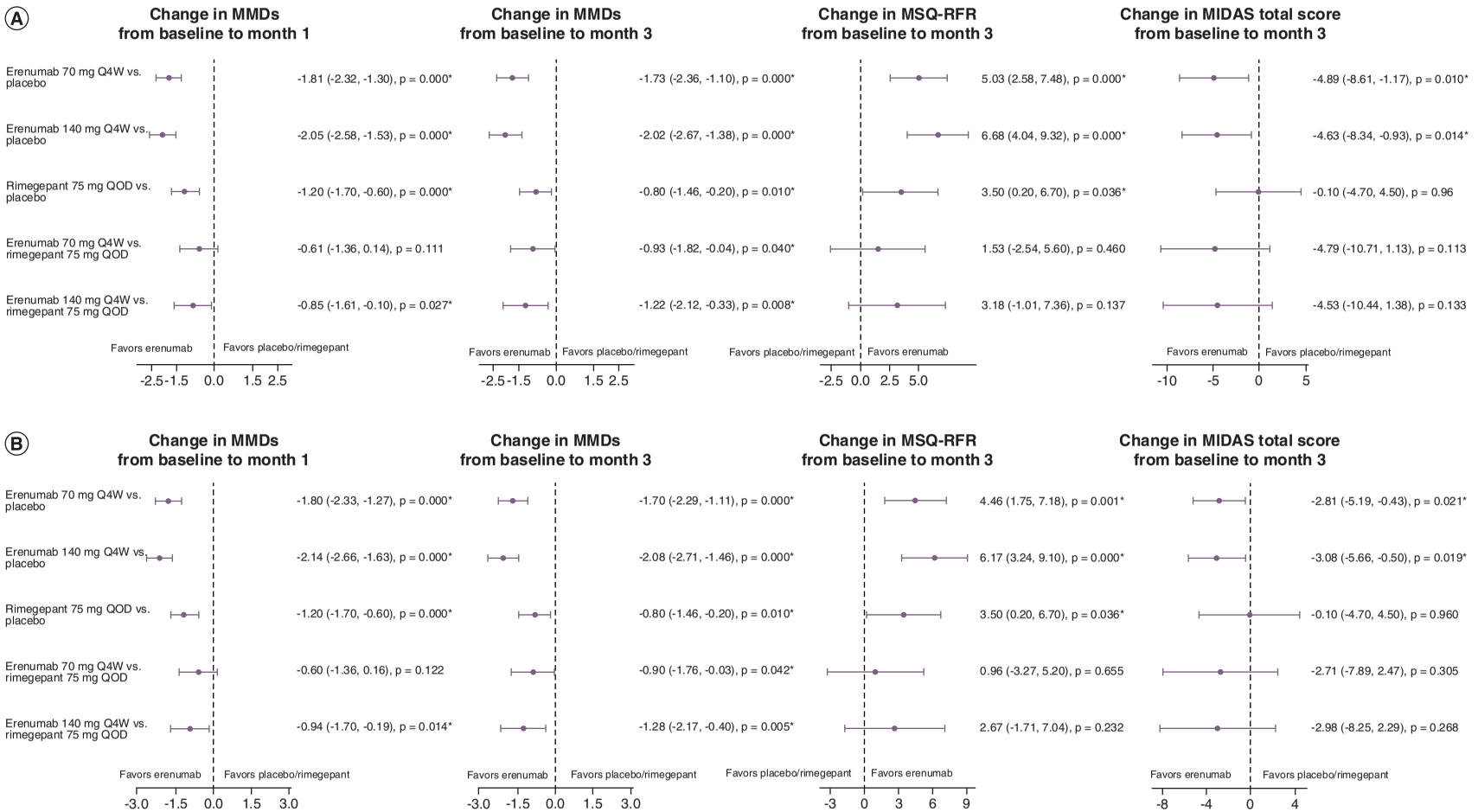

Figure 1. Summary of efficacy outcomes. (A) Before matching. **(B)** After matching. MSQ-RFR measures the impact of migraine on daily social and work activities. A higher score indicates less restriction or limitation in carrying out daily activities due to migraine. The between-group minimally important difference is 3.2 for MSQ-RFR [26]. MIDAS measures headache-related disability based on lost time in three domains: schoolwork or work for pay, household work or chores, and family, social, and leisure activities. MIDAS is scored as follows: 0–5 indicates minimal or infrequent disability, 6–10 indicates mild or infrequent disability, 11–20 indicates moderate disability, 21+ indicates severe disability [27].
*p-value < 0.1.
MIDAS: Migraine Disability Assessment; MMDs: Monthly migraine days; MSQ-RFR: Migraine-Specific Quality-of-life role function – restrictive domain score; QOD: Every other day; Q4W: Every four weeks.

placebo arm. Results of the present study are consistent with the European Headache Federation guideline and the Hellenic Headache Society Recommendations on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention [26,28], showing that erenumab is effective in migraine prevention.

Harris *et al.* conducted a real-world database analysis in the US, showing that the average 6-month migraine-related specialty care costs were $509 for patients with grade I MIDAS, $532 for patients with grade II MIDAS, $597 for patients with grade III MIDAS, $849 for patients with grade IVA MIDAS and $885 for patients with grade IVB MIDAS [27]. This may suggest treatments that can more effectively reduce disability associated with migraine have the potential to mitigate the economic burden related to migraine. Furthermore, López-Bravo *et al.* showed in the real world setting that reductions in MIDAS were associated with patients' global satisfaction with an anti-CGRP pathway mAb treatment for migraine prevention [29].

Based on an unanchored MAIC, Popoff *et al.* reported that erenumab and rimegepant had a comparable effect on reducing MMDs by month 3 (erenumab 70 mg and 140 mg Q4W pooled vs rimegepant 75 mg QOD: 0.06 [-0.50, 0.61]; p = 0.843) [21]. By comparison, the present study showed that both erenumab 70 mg and 140 mg Q4W were associated with a significantly larger reduction in MMDs than rimegepant 75 mg QOD (erenumab 70 mg Q4W vs rimegepant 75 mg QOD: -0.90 [-1.76, -0.03]; p = 0.042; erenumab 140 mg Q4W vs rimegepant 75 mg QOD: -1.28 [-2.17, -0.40]; p = 0.005). Additionally, Popoff *et al.* found that erenumab had a numerically larger reduction in MIDAS total score by month 3 (erenumab 70 mg Q4W and 140 mg Q4W pooled vs rimegepant: -1.75 [-6.73, 3.24]; p = 0.501) and that rimegepant was associated with a larger numerical improvement in MSQ-RFR score by month 3 compared with erenumab (erenumab 70 mg and 140 mg Q4W pooled vs rimegepant: -7.22 [-10.31, -4.13], p < 0.01) [21]. In contrast, we found that both erenumab regimens were associated with a numerically greater improvement in the MSQ-RFR score and a numerically larger reduction in the MIDAS total score by month 3 than rimegepant 75 mg QOD. Differences in these findings can be potentially attributed to the following two factors. First, as the BHV3000-201 trial is a single-arm trial, Popoff *et al.* [21] had to rely on an unanchored MAIC approach, requiring adjustment for not only all effect modifiers but also all prognostic variables to obtain an unbiased comparison of erenumab with rimegepant. However, this is a strong assumption especially given the limited number of baseline characteristics available for adjustment. Additionally, as observed in the present study, despite the adjustment for the effect modifiers, patients in the placebo arm of the phase II/III trial for rimegepant continued to experience larger improvements in all four efficacy outcomes compared with those in the placebo arm of the pooled 295 and STRIVE population, suggesting the necessity of accounting for the differences in the placebo arms when indirectly comparing erenumab versus rimegepant. Such a difference may be in part attributable to unadjusted prognostic factors, underscoring the importance of leveraging the anchor placebo arm in the MAIC. Second, the (effective) sample sizes in the present study were larger than Popoff *et al.* [21], which may lead to a more statistically powered comparison. Since the publication of the phase II/III rimegepant trial, an MAIC using the placebo arms as the anchor has become feasible. Compared with an unanchored MAIC, the anchored MAIC relaxes the assumption that all prognostic variables need to be adjusted for. Moreover, population-adjusted indirect comparisons, compared with indirect comparisons without population adjustment, are more appropriate for the present study given the differences in the key effect modifiers between the pooled erenumab trials and the rimegepant trial (particularly sex, race, MMDs and history of CM in Table 1).

The results of this study should be interpreted within the context of the following limitations. First, the effect modifiers for adjustment were limited by the data published for the phase II/III trial for rimegepant and the variables collected in the 295 and STRIVE trials. As such, it was not feasible to adjust for unreported or unmeasured effect modifiers. Second, other important efficacy and safety outcomes cannot be compared given the between-trial differences in their definitions. For example, the proportion of patients achieving ≥50% reduction in MMDs can be more clinically meaningful than the absolute reductions in MMDs over time. However, the phase II/III trial for rimegepant examined ≥50% reduction in moderate or severe MMDs, which was not comparable with ≥50% reduction in MMDs collected in the erenumab trials. Additionally, safety outcomes cannot be compared across 295, STRIVE, and the phase II/III trial for rimegepant due to the variable lengths for safety data collection (295: 12 weeks; STRIVE: 24 weeks; the phase II/III trial for rimegepant: 12 weeks). Third, the definition of migraine days differed slightly across 295, STRIVE, and the phase II/III trial for rimegepant. Specifically, in the 295 trial, a migraine day was defined as a day with migraine without aura lasting for ≥4 continuous hours or a day with migraine with aura, while in the STRIVE trial and the phase II/III trial for rimegepant, a migraine day was defined as a day with migraine with or without aura lasting for ≥30 minutes [15,16]. Fourth, additional differences in study designs (e.g., concomitant treatments; intensity of migraine attacks) may undermine the comparability between

the three clinical trials. Fifth, the placebo arms for the erenumab trials were administered through subcutaneous injection, while the placebo arm for the rimegepant trial was administered orally. As pointed out by Deligianni *et al.* [30], the placebo response in clinical trials for migraine may vary by route of administration, which may undermine the comparability of the placebo arms and the transitivity assumption of the present anchored MAIC. Sixth, the current study only compared erenumab versus rimegepant. As a growing number of mAbs and gepants are approved, future studies are warranted to indirectly compare a comprehensive set of approved migraine therapies. Lastly, since the present study used clinical trial data, results may not necessarily be generalizable to the real world. Additionally, as patients enrolled in the trials are those who had failed 1–2 classes of medications for migraine, the results of the present study may not be generalizable to all patients with resistant and refractory migraine [31]. Future studies for a broader difficult-to-treat population are needed.

Conclusion

In the present study, we found that erenumab had a more favorable efficacy profile than rimegepant in reducing MMDs at month 1 and month 3 for migraine prevention. These results may help with decision-making in clinical practice and can be further validated in future clinical trials or real-world studies.

Summary points

- Erenumab and rimegepant are both approved therapies for migraine prevention in adults that target the calcitonin gene-related peptide (CGRP) pathway.
- No head-to-head clinical trials have been conducted to compare the efficacy of erenumab versus rimegepant in migraine prevention.
- The present study conducted an anchored matching-adjusted indirect comparison (MAIC) of the efficacy of erenumab 70 mg and 140 mg every four weeks (Q4W) versus rimegepant 75 mg every other day (QOD).
- Patients from two phase II/III clinical trials for erenumab (295 and STRIVE) were pooled and assigned weights, such that the weighted mean effect modifiers at baseline (age, sex, race, baseline monthly migraine days [MMDs], and history of chronic migraine) matched those reported for the phase II/III trial for rimegepant (NCT03732638).
- Erenumab 70 mg Q4W was associated with a significantly larger reduction in MMDs at month 3 compared with rimegepant 75 mg QOD.
- Erenumab 140 mg Q4W was associated with a significantly larger reduction in MMDs at month 1 and month 3 compared with rimegepant 75 mg QOD.
- Further clinical trials or real-world studies could offer additional evidence to confirm findings from the present study.

Author contributions

KA Betts, Y Wang and S Gao designed and performed the analyses. All the authors participated in data interpretation, contributed to the development of the manuscript and provided final approval for the submission.

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Competing interests disclosure

R Mahon, S Tiwari, M Koch and M Ferraris are employees of Novartis and may own Novartis stock or stock options. KA Betts, Y Wang and S Gao are employees of Analysis Group, Inc., which received payment from Novartis for participation in this research. The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Data sharing statement
The authors certify that the present study conducted a secondary analysis of clinical trial data utilizing the deidentified patient-level data from the 295 and STRIVE trials and the published data from the phase II/III trial for rimegepant (NCT03732638). The 295 and STRIVE trial data were provided by Novartis to the authors. The use of the shared data is in accordance with the terms agreed upon receipt.

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