

## RESEARCH SUBMISSIONS

# Matching-adjusted indirect comparisons of oral rimegepant versus placebo, erenumab, and galcanezumab examining monthly migraine days and health-related quality of life in the treatment of migraine

Evan Popoff MSc<sup>1</sup> | Karissa Johnston PhD<sup>1</sup> | Robert Croop MD<sup>2</sup> |  
Alexandra Thiry PhD<sup>2</sup> | Linda Harris MPH<sup>2</sup> | Lauren Powell MPH<sup>1</sup> | Vladimir Coric MD<sup>2</sup> |  
Gilbert L'Italien PhD<sup>2</sup> | James Moren MD<sup>3</sup>

<sup>1</sup>Broadstreet Health Economics & Outcomes Research, Vancouver, BC, Canada

<sup>2</sup>Biohaven Pharmaceuticals, New Haven, CT, USA

<sup>3</sup>The Headache Clinic, Island Hospital, Anacortes, WA, USA

## Correspondence

Evan Popoff, Broadstreet Health Economics & Outcomes Research, 201-343 Railway Street, Vancouver, BC, Canada, V6A 1A4.  
Email: [epopoff@broadstreetheor.com](mailto:epopoff@broadstreetheor.com)

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## Abstract

**Objective:** Rimegepant is an orally administered small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist, with demonstrated efficacy in the acute treatment of migraine. Recent estimates from a single-arm trial (BHV3000-201) have also shown evidence of long-term preventive effects in monthly migraine days (MMDs) and health-related quality of life (HRQoL). This study aimed to compare MMDs and HRQoL data for oral rimegepant to those obtained in placebo-controlled trials for injectable anti-CGRP monoclonal antibodies (mAbs) galcanezumab and erenumab.

**Methods:** Matching-adjusted indirect comparisons (MAICs) were conducted using rimegepant subject-level data and published aggregate-level results from mAb trials. Rimegepant baseline characteristics were matched to the pooled subject characteristics from EVOLVE-I/II (galcanezumab vs. placebo;  $n = 1773$ ) and STRIVE (erenumab vs. placebo;  $n = 955$ ) by reweighting the rimegepant subjects to more closely match the distributions observed in these trials. To align with inclusion criteria of the mAb trials, only the subset of rimegepant subjects with a history of 4–14 MMDs were included ( $n = 257$ ). Weighted mean differences were used to calculate adjusted change in MMDs, Migraine Disability Assessment Test (MIDAS) score, and Migraine-Specific Quality of Life Questionnaire version 2 (MSQv2) scores from baseline to week 12.

**Results:** When matched to the EVOLVE trials, rimegepant was superior to placebo with a mean difference in MMD change from baseline [95% confidence interval] of  $-1.16$  [ $-1.80, -0.52$ ] and was not statistically significantly different from galcanezumab  $0.59$  [ $-0.13, 1.32$ ]. When matched to the STRIVE trial, rimegepant was superior to placebo  $-1.59$  [ $-2.15, -1.03$ ] and was not statistically significantly different from

**Abbreviations:** CFB, change from baseline; CGRP, calcitonin gene-related peptide; CI, confidence interval; DD, disease duration; EF, emotional function; EOD, every other day; ESS, effective sample size; HRQoL, health-related quality of life; mAbs, monoclonal antibodies; MAIC, matching-adjusted indirect comparison; MIDAS, migraine disability assessment test; MMDs, monthly migraine days; MSQv2, Migraine-Specific Quality of Life Questionnaire version 2; NICE, National Institute for Health and Care Excellence; NR, not reported; PRF, role function-preventive; PRN, as needed; RCT, randomized controlled trial; RRF, role function-restrictive; SD, standard deviation.

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erenumab  $-0.06$  [ $-0.61, 0.50$ ]. Rimegepant showed superior MIDAS and MSQv2 results compared with placebo in both EVOLVE trials and in the STRIVE trial, no statistically significant differences from galcanezumab and erenumab regarding MIDAS, and favorable results compared with erenumab across all MSQv2 domains, while being generally similar to galcanezumab across all MSQv2 domains.

**Conclusions:** When adjustments were made to reflect baseline characteristics in published literature, supporting data from BHV3000-201 suggest that rimegepant every other day is an effective therapy in reducing disability and MMDs and enhancing migraine-specific HRQoL. These data support the preventive benefit observed in randomized trials of rimegepant and further validate its efficacy for both acute and preventive treatment of migraine.

#### KEYWORDS

health-related quality of life, matching-adjusted indirect comparison, migraine, monthly migraine days

## INTRODUCTION

Migraine is a common debilitating neurological condition that affects over one billion people worldwide.<sup>1</sup> In addition to severe headaches, patients with migraine may experience a range of symptoms including photophobia, phonophobia, nausea, and vomiting.<sup>2</sup> Many individuals with migraine experience a diminished health-related quality of life (HRQoL), reduction in workplace productivity, and limited enjoyment of social and leisure activities.<sup>3-5</sup> Migraine management consists of acute therapies taken during an attack to provide symptomatic relief and preventive treatments taken regularly to reduce the number of monthly migraine days (MMDs) for patients with  $\geq 4$  MMDs.<sup>6</sup> Historically, migraine therapies have been developed for either acute or preventive treatment, but not both.

Rimegepant is an orally administered small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist (gepant) and the first to show efficacy in both acute and preventive treatment of migraine.<sup>2,7-9</sup> Currently, rimegepant has been approved by the FDA for an acute indication. However, given the pharmacokinetic properties of rimegepant—namely its half-life of  $\sim 11$  h—and its ability to inhibit CGRP signaling, it was postulated that treatment may also confer preventive benefits when taken regularly. This hypothesis has been confirmed in a recent Phase 2/3 clinical trial that evaluated the efficacy and safety of rimegepant administered every other day (EOD) for up to 12 weeks.<sup>9</sup> Furthermore, the repeated use of rimegepant was not associated with increased risk of medication overuse headache,<sup>9,10</sup> which is a challenge for frequent use of other acute therapies including triptans and opioids.<sup>11,12</sup> Long-term (1-year) follow-up from this trial is ongoing.

The dual action of rimegepant (for both acute and preventive therapy) was initially observed by results from a long-term, 1-year, single-arm safety trial (BHV3000-201; NCT03266588), which explored the preventive effects of rimegepant in terms of MMD reduction and HRQoL measures.<sup>10,13</sup> BHV3000-201 evaluated long term as needed (PRN) dosing (analogous to repeated acute treatments) as

well as EOD dosing (analogous to treatment regimen in the pivotal prevention trial) in three enrollment groups further characterized by baseline MMDs (Group 1: 2–8 baseline MMDs receiving rimegepant PRN, Group 2: 9–14 baseline MMDs receiving rimegepant PRN, and Group 3: 4–14 baseline MMDs EOD plus PRN).<sup>10,13</sup> Interestingly, rimegepant showed evidence of MMD reduction for all three groups, demonstrating a mean reduction of 0.5 MMDs (2–8 PRN group), 2.9 MMDs (9–14 PRN group), and 3.3 MMDs (4–14 EOD/PRN group) over the trial duration.<sup>10,13</sup>

Although this single-arm trial (BHV3000-201) did not allow for direct calculation of a rimegepant treatment effect relative to a randomized comparator, the benefits observed across treatment regimens and baseline MMD frequencies warrant further consideration. In particular, how rimegepant compares with currently available preventive CGRP antagonists (the injectable monoclonal antibodies [mAbs], which were developed specifically for migraine prevention) is unknown and may help contextualize the value of rimegepant in the current preventive landscape. In these circumstances, a matching-adjusted indirect comparison (MAIC) can be used to compare the treatment effects indirectly across therapies that have not been studied head-to-head, while accounting for key differences in the trial populations.

The objective of this study was to compare MMD reduction and improvement in HRQoL (using the Migraine-Specific Quality of Life Questionnaire version 2 [MSQv2] and Migraine Disability Assessment Test [MIDAS] questionnaire) in subjects receiving oral rimegepant in trial BHV3000-201 with subjects being treated with injectable anti-CGRP mAbs (galcanezumab and erenumab) while accounting for any differences in the trial populations via MAICs. Given the magnitude of effects observed in BHV3000-201, and the relative similarities across trial populations, we hypothesized that after formally and quantitatively accounting for population differences, similar effects on MMDs and HRQoL would be estimated between rimegepant, galcanezumab, and erenumab.

## METHODS

### Motivation

The gold standard for obtaining relative treatment effects not directly compared in a randomized controlled trial (RCT) would be to conduct a network meta-analysis using a collection of RCTs linked through common comparators. Given the single-arm design of BHV3000-201, an MAIC is an alternative option to adjust for population differences when comparing results across trials. MAICs use subject-level data to balance baseline characteristics between trials, allowing for bias reduction in the estimation of relative treatment effect.<sup>14</sup> The methodology used to perform the MAICs presented here was based on the National Institute for Health and Care Excellence (NICE) Decision Support Unit's latest guidelines for population-adjusted indirect treatment comparisons.<sup>15</sup>

### Evidence base

MAICs were conducted using rimegepant subject-level data from BHV3000-201 [NCT03266588] and published aggregate-level results from mAb clinical trials (EVOLVE-I/II [galcanezumab vs. placebo; NCT02614183, NCT02614196;  $n = 1773$ ] and STRIVE [erenumab vs. placebo; NCT02456740;  $n = 955$ ]). BHV3000-201 was conducted in accordance with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation and in accordance with all applicable local regulations. The protocol was approved by centralized and local Institutional Review Boards, and participants provided written informed consent before they were screened for the study.

The mAb trials had inclusion criteria which allowed only subjects with 4–14 MMDs on average across the 3 months prior to screening and during baseline to participate. Since BHV3000-201 allowed for subject groups with a history of 2–8, 9–14, or 4–14 MMDs, in order to align with the inclusion criteria of the mAb trials, only the subset of rimegepant subjects with a history of 4–14 MMDs were included ( $n = 257$ ). Furthermore, these were the subjects in BHV3000-201

who were taking the EOD/PRN preventive regimen of rimegepant, which was most analogous with the pivotal prevention trial.<sup>9</sup> All included trials for this analysis were deemed to have a generally low to mild risk of bias in terms of randomization, blinding, and outcome reporting.

In BHV3000-201 regarding baseline characteristics, no subjects had missing data for any variable used in the matching. In terms of outcomes, six subjects had missing data regarding change in MMDs at 12 weeks, two subjects had missing MIDAS data, and three subjects had missing data on all three MSQv2 domains.

The characteristics of subjects included in the MAIC analysis are shown in Table 1. For galcanezumab, MMDs, MIDAS, and MSQv2 outcomes were pooled across the 120 and 240 mg arms in the EVOLVE-I and EVOLVE-II trials. Similarly, the placebo arms were pooled across the two trials. For erenumab, the 70 and 140 mg arms from the STRIVE trial were also pooled for all outcomes. Discontinuation rates were higher in EVOLVE-I (18.1%) and EVOLVE-II (14.1%) compared with STRIVE (10.2%) and the subset of subjects from BHV3000-201 (5.4%).

### Endpoints

The endpoints of interest in this analysis were the change from baseline in MMDs, MIDAS, and MSQv2. Reduction in MMDs from baseline is a common measure used to show the efficacy of preventive migraine therapies. The MIDAS questionnaire is a patient-reported outcome developed to measure and quantify the impact headache-related disability has on a subject's life and captures information on disability in terms of number of days of missed work for pay, household work, social interactions, family interactions, and recreation.<sup>16</sup> The MSQv2 questionnaire evaluates the impact of migraine on the subject's HRQoL over the past 4 weeks across three dimensions: role function-restrictive (RRF), role function-preventive (PRF), and emotional function (EF).<sup>17</sup> Both mAbs and rimegepant (BHV3000-201) have been shown to have benefits in both MMD reduction and HRQoL outcomes.<sup>18,19</sup>

TABLE 1 Subject characteristics used in MAICs from included trials.

Trial	BHV3000-201	EVOLVE-I and EVOLVE-II pooled (Galcanezumab vs Placebo)	STRIVE (Erenumab vs Placebo)
Treatment	Rimegepant (4-14 MMDs subgroup)	All treatments pooled	All treatments pooled
<i>N</i>	257	1773	955
Age (years): mean (SD)	40.4 (12.1)	41.3 (11.3)	40.9 (11.2)
Female: <i>n</i> (%)	224 (87.2%)	1500 (84.6%)	814 (85.2%)
White ethnicity: <i>n</i> (%)	216 (84.0%)	1333 (75.2%)	851 (89.1%)
Monthly migraine days at baseline: mean (SD)	8.9 (3.7)	9.1 (3.0)	8.3 (2.5)
Disease duration (years): mean (SD)	20.3 (12.9)	20.3 (12.4)	NR
History of migraine with aura: <i>n</i> (%)	74 (28.8%)	938 (52.9%)	NR

Abbreviations: MMDs, monthly migraine days; NR, not reported; SD, standard deviation.

The grey represents the BHV3000-201 study. The greenish color represents the unmatched EVOLVE studies. The yellow represents the unmatched STRIVE study.

## Statistical analyses

Rimegepant subjects were each weighted by matching their baseline characteristics to the pooled subject characteristics from the mAb clinical trials such that the distributions of characteristics were equivalent across both. Variables used for matching, given in Table 1, include age, percentage female, percentage White, MMDs at baseline, disease duration, and percentage of subjects with a history of aura. Note that a limitation of the comparison against the STRIVE trial is that we were unable to match using disease duration and percentage with aura as they were not reported. Age, MMDs at baseline, and disease duration were treated as continuous variables, whereas all others were count variables and were included as percentages in the model. Continuous variables were matched by both their mean and standard deviation (SD). For BHV3000-201, frequencies, means, and SDs were all calculated after omitting missing data (only relevant for outcomes). For the EVOLVE and STRIVE trials, pooled frequencies, means, and SDs were extracted from the publications if available and were otherwise averaged across the arms of the respective trials. All analyses were conducted using R version V3.6.1.<sup>20</sup>

Subjects from BHV3000-201 were weighted using a logistic propensity score model, which is a method used to attempt to mimic randomization between the two treatment arms in a comparison.<sup>15,21</sup> Using the objective and gradient functions as described in Phillipppo et al.<sup>15</sup> the logistic model was optimized by using the *BFGS*<sup>22</sup> method using the *optim* (*stats* package) function in R. Performance of the optimization method was assessed by whether the algorithm successfully converged (i.e., a minimum of the objective function was found). In cases of nonconvergence, variables were removed from the model one at a time until the convergence criteria were met. Weights were rescaled to be relative to the original subject weight, so that a weight of >1 carries more weight in the comparison and likewise a weight of <1 carries less weight.<sup>15</sup> The effective sample size (ESS) is a function of these weights and is a measure of the remaining statistical power following matching. Matches with a small ESS are indicative of populations with little overlap and may result in

unstable, unreliable estimates.<sup>23</sup> Because it is not possible to match the population characteristics of both the EVOLVE and STRIVE trials simultaneously, separate MAICs were conducted. Note that no statistical power calculation was conducted prior to this study, and the sample sizes were based on data availability from these RCTs.

Using the weights generated from the propensity score model, weighted means for each outcome were calculated using the BHV3000-201 individual subject-level data. Then, using these weighted means and the reported values from the EVOLVE and STRIVE trials, treatment differences between rimegepant and placebo, galcanezumab, and erenumab were calculated for change in MMDs, MIDAS, and the three individual MSQv2 domain (RRF, PRF, and EF) scores from baseline to week 12. A clinically meaningful difference in MIDAS score is recognized as a decrease of 5 points,<sup>24</sup> and clinically meaningful difference in MSQv2 domains are recommended as the following: RRF 3.2, PRF 4.6, EF 7.5.<sup>25</sup> A *p*-value of less than 0.05 coming from a two-tailed test was the criterion used for statistical significance.

## RESULTS

### Subject matching, model performance, and effective sample size

All subject characteristics reported in BHV3000-201, EVOLVE-I/II, and STRIVE were used for matching to improve comparability in the populations (Table 2, Figure 1). When matched to both EVOLVE-I/II and STRIVE, the optimization algorithm did achieve convergence with all available variables included.

Compared with an original sample size of 257, when matched to the pooled subject characteristics of the EVOLVE trials, the ESS for rimegepant was 169; whereas, rimegepant had a larger ESS of 214 when matched to STRIVE.

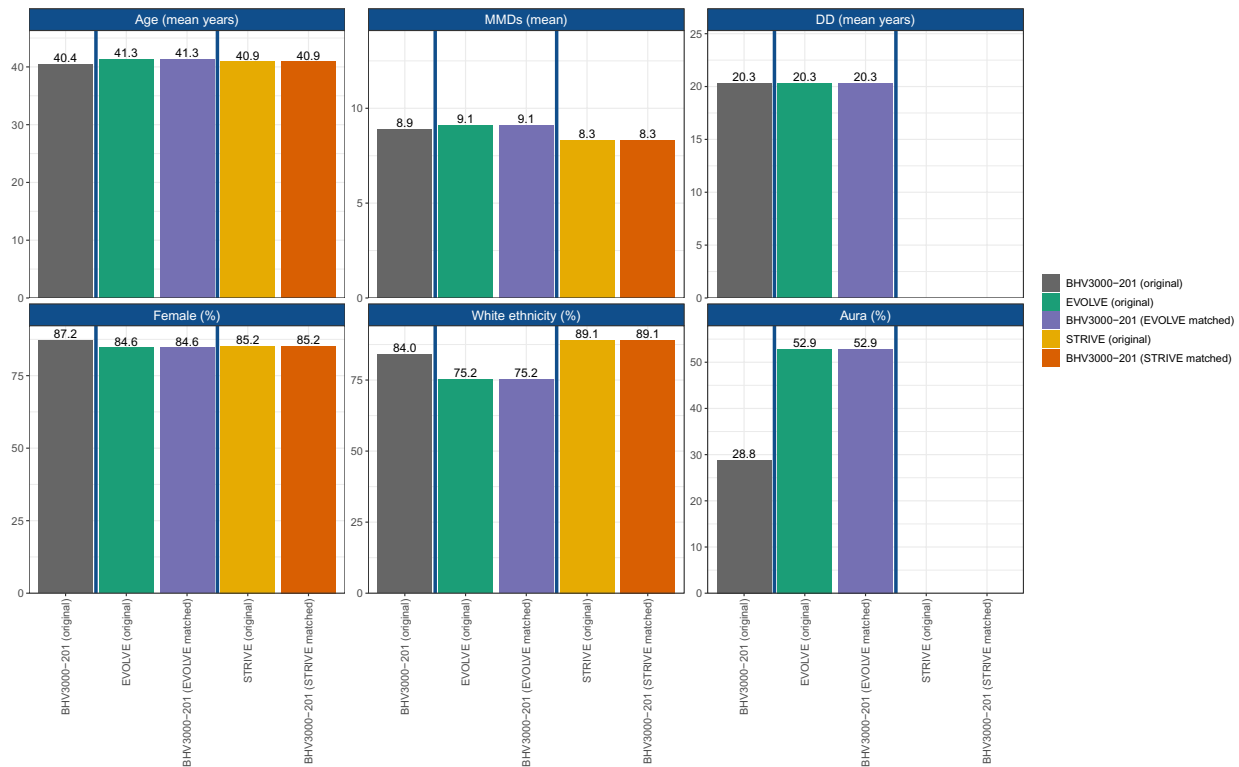
The relative BHV3000-201 subject weights when matched to the EVOLVE-I/II and STRIVE populations are shown in Figure 2. By design, the mean of the weights for each comparison was 1;

TABLE 2 Effective sample sizes and matched subject characteristics

	BHV3000-201 (4-14 MMDs subgroup)	BHV3000-201 matched to:	
		EVOLVE-I and EVOLVE-II pooled (Galcanezumab vs Placebo)	STRIVE (Erenumab vs Placebo)
Effective sample size	257 (original N)	169	214
Age (years): mean (SD)	40.4 (12.1)	41.3 (11.3)	40.9 (11.2)
Female: %	87.2%	84.6%	85.2%
White ethnicity: %	84.0%	75.2%	89.1%
Monthly migraine days at baseline: mean (SD)	8.9 (3.7)	9.1 (3.0)	8.3 (2.5)
Disease duration (years): mean (SD)	20.3 (12.9)	20.3 (12.4)	NR
History of migraine with aura: %	28.8%	52.9%	NR

Abbreviations: MMDs, monthly migraine days; NR, not reported; SD, standard deviation.

The grey represents the BHV3000-201 study. The purple represents the matched EVOLVE studies. The orange represents the matched STRIVE study.



**FIGURE 1** Matched and unmatched subject characteristics from analyzed trials. DD, disease duration; MMDs, monthly migraine days [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

whereas, the SD when matched to EVOLVE-I/II was 0.73 and 0.45 when matched to STRIVE. Using the published aggregate baseline characteristics from EVOLVE-I/II and STRIVE, the likelihood that each subject from BHV3000-201 belonged to a similar trial population was determined via a weight for each subject. In general, the more similar a BHV300-201 subject was to the external trial, the larger weight that subject would receive (i.e., upweighted). Conversely, outlying or dissimilar subjects would receive weights smaller than one (i.e., downweighted). When matched to the EVOLVE trials, there were more subjects with very large weights as well as more with weights less than 1, indicating the BHV3000-201 and EVOLVE populations were more dissimilar compared with the BHV3000-201 and STRIVE populations (which is indicative of the smaller ESS and larger SD of the weights). However, considering the ESSs were still relatively large compared with the original sample size, estimates compared with both trials were stable.

## Treatment comparisons

For the outcome of change in MIDAS from baseline to 12 weeks, rimegepant was found to be consistently superior to placebo, and not statistically significantly different from both mAbs. When observing the individual MSQv2 domains, rimegepant was associated with greater improvement from baseline across all three domains compared with placebo and erenumab, was not statistically

significantly different from galcanezumab in the PRF and EF MSQv2 domains, and was associated with less improvement compared with galcanezumab in the RRF domain. Finally, in terms of MMDs, rimegepant was favorably compared with placebo in both comparisons and not statistically significantly different compared with both mAbs. Figure 3 shows all unadjusted (triangles) and adjusted (squares) estimates across outcomes and comparisons. Purple indicates favorable results for rimegepant, whereas yellow indicates favorable results for erenumab or galcanezumab.

## Rimegepant versus galcanezumab and placebo in EVOLVE-I and EVOLVE-II

When matched to the pooled EVOLVE trials, rimegepant was superior to pooled placebo with a mean difference in MIDAS change from baseline [95% confidence intervals] of  $-7.37$  [ $-12.91$ ,  $-1.83$ ] and not statistically significantly different from pooled galcanezumab  $-0.09$  [ $-6.01$ ,  $5.83$ ]. For RRF, PRF, and EF, rimegepant also showed dominant results versus pooled placebo:  $4.08$  [ $0.92$ ,  $7.24$ ],  $4.76$  [ $1.88$ ,  $7.63$ ],  $4.94$  [ $1.30$ ,  $8.57$ ], and generally similar results compared with galcanezumab:  $-3.88$  [ $-7.40$ ,  $-0.35$ ],  $-1.45$  [ $-4.66$ ,  $1.77$ ]  $-3.01$  [ $-7.01$ ,  $0.98$ ]. Rimegepant was superior to pooled placebo with a mean difference in MMD change from baseline [95% confidence intervals] of  $-1.16$  [ $-1.80$ ,  $-0.52$ ], and not statistically significantly different from pooled galcanezumab  $0.59$  [ $-0.13$ ,  $1.32$ ].

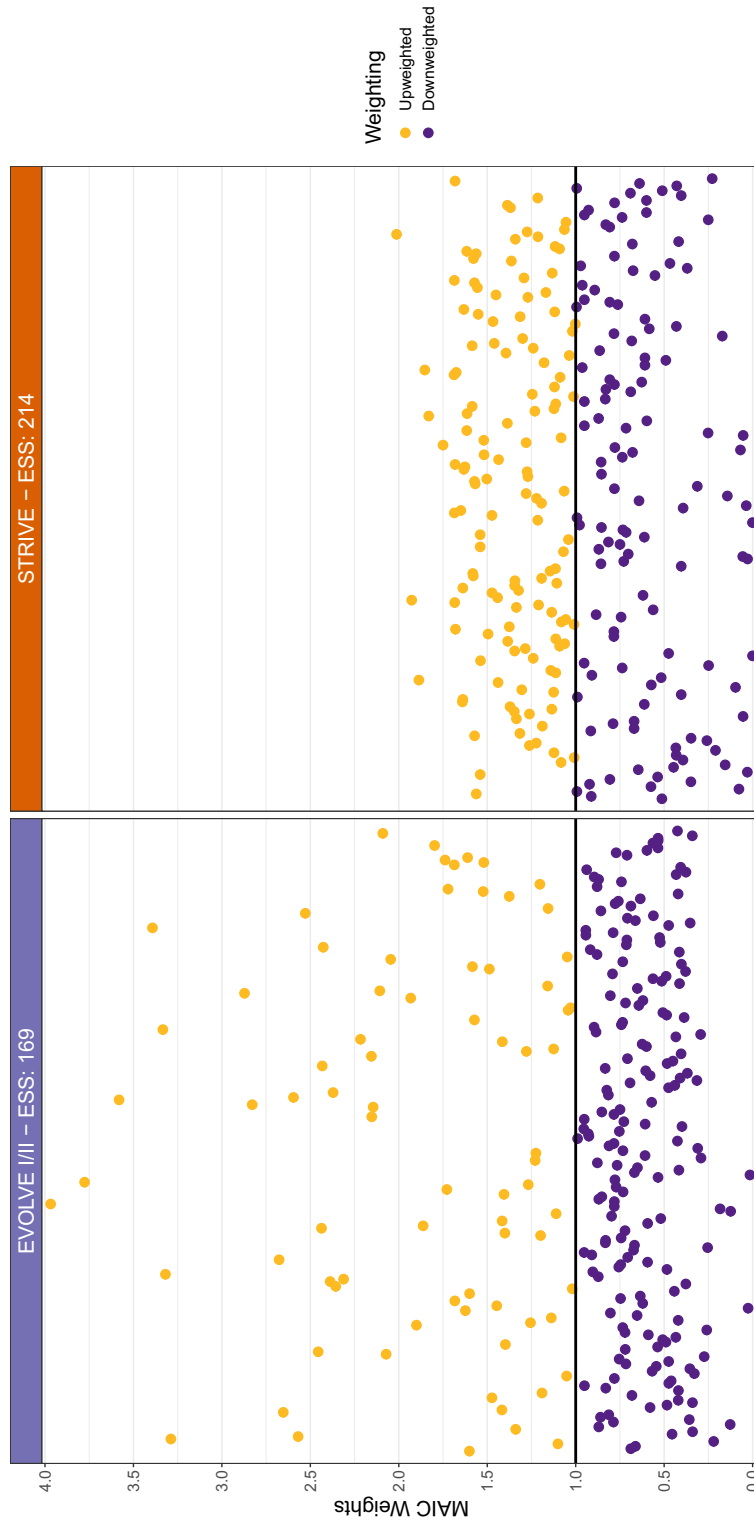
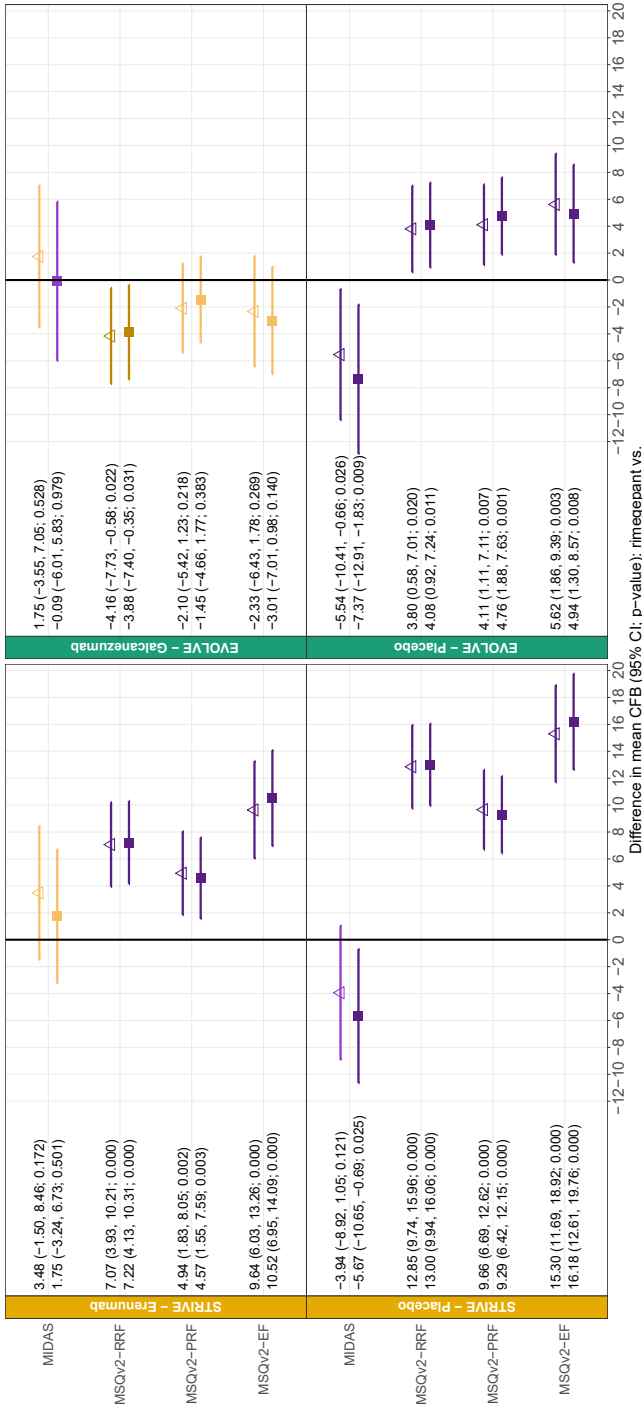
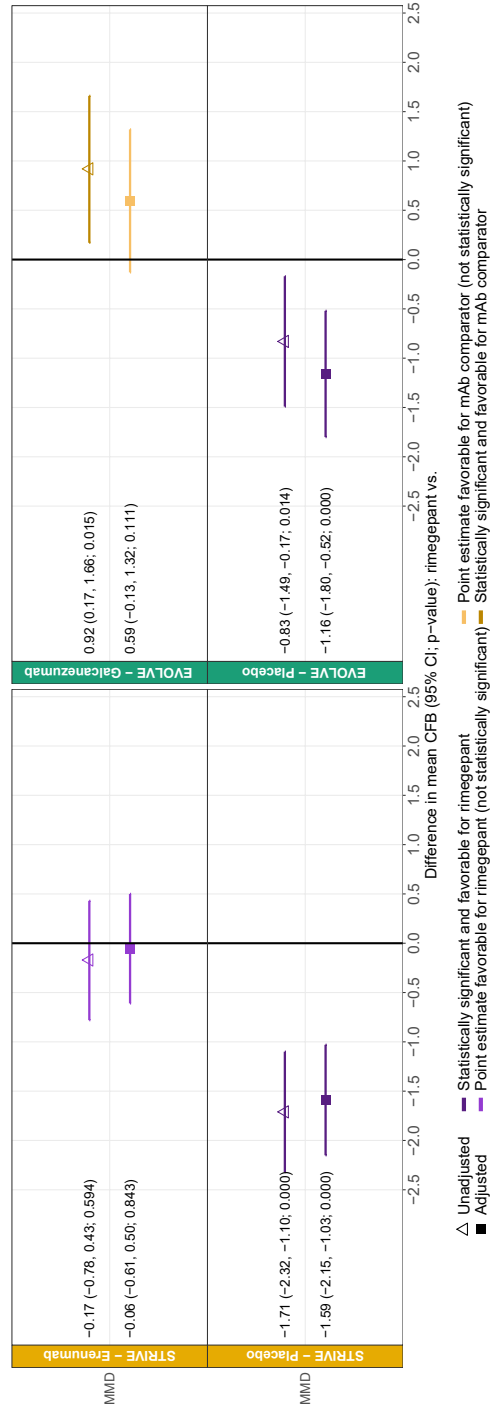


FIGURE 2 Weighted BHV3000-201 subjects when population matched to EVOLVE and STRIVE trials, weights were rescaled to be relative to the original subject weight, so that a weight of >1 carries more weight in the comparison (upweighted) and likewise a weight of <1 carries less weight (downweighted). ESS, effective sample size; MAIC, matching-adjusted indirect comparison [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**(A) MIDAS and MSQv2**



**(B) MMD**



**FIGURE 3** Summary of all outcomes based on unadjusted and population adjusted estimates; differences in mean CFB (95% CI; p-value), CFB, change from baseline; CI, confidence interval; EF, emotional function; mAb, monoclonal antibody; MIDAS, migraine disability assessment; MMDs, monthly migraine days; MSQv2, Migraine-Specific Quality of Life Questionnaire version 2; PRF, role function-preventive; RRF, role function-restrictive [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



While results were generally consistent pre- and postmatching, the treatment effect of rimegepant versus galcanezumab showed improvement after matching to the population of the EVOLVE trials.

### Rimegepant versus erenumab and placebo in STRIVE

When matched to the STRIVE trial and looking at the change in the MIDAS score, rimegepant was superior to placebo  $-5.67$  [ $-10.65$ ,  $-0.69$ ] and not statistically significantly different from pooled erenumab  $1.75$  [ $-3.24$ ,  $6.73$ ]. For RRF, PRF, and EF, rimegepant also showed dominant results versus pooled placebo:  $13.00$  [ $9.94$ ,  $16.06$ ],  $9.29$  [ $6.42$ ,  $12.15$ ],  $16.18$  [ $12.61$ ,  $19.76$ ] and erenumab:  $7.22$  [ $4.13$ ,  $10.31$ ],  $4.57$  [ $1.55$ ,  $7.59$ ],  $10.52$  [ $6.95$ ,  $14.09$ ], respectively. For MMDs, rimegepant was superior to placebo  $-1.59$  [ $-2.15$ ,  $-1.03$ ] and not statistically significantly different from pooled erenumab  $-0.06$  [ $-0.61$ ,  $0.50$ ].

## DISCUSSION

Oral rimegepant taken EOD/PRN was found to be associated with a similar reduction in MMDs compared with the established mAb-injectable therapies erenumab and galcanezumab, based on MAIC analyses. In addition, rimegepant demonstrated superior results compared with erenumab in terms of MSQv2, no statistically significant differences in terms of MIDAS, and no statistically significant differences compared with galcanezumab in these outcomes.

Rimegepant is currently approved in the United States for the acute treatment of migraine and is the first novel therapy to demonstrate efficacy for both acute and preventive therapy in phase 3 clinical trials.<sup>2,8,9</sup> The current analysis helps to contextualize the additional supporting evidence from a single-arm safety trial, in which a preventive benefit of rimegepant was observed.<sup>10</sup> Although, at the time of writing, rimegepant is not approved for preventive use in migraine, this indirect comparison suggests no statistically significant differences in efficacy outcomes between rimegepant and the established anti-CGRP mAbs in terms of both MMD reduction and improvement in HRQoL.

To date, migraine therapies have been targeted to either acute or preventive treatment. Of the novel CGRP antagonists, specifically, four mAbs are indicated for migraine prevention (erenumab, galcanezumab, fremanezumab, and eptinezumab),<sup>26-29</sup> two gepants are indicated for acute therapy (rimegepant and ubrogepant),<sup>2,7,30,31</sup> and two gepants have demonstrated efficacy for prevention (rimegepant and atogepant).<sup>9,32</sup> The dual therapy action of rimegepant, which has demonstrated both acute and preventive benefits, represents a paradigm shift for migraine treatments and their evaluation. A therapy with these characteristics may offer advantages for some patients, allowing for a simplified medication regimen, increased treatment flexibility, and greater patient autonomy. However, in the current landscape, which is built on the dichotomy of acute and preventive therapies, the adoption of an oral agent with dual therapy action could run into

several obstacles, including those related to cost and reimbursement limits. This could hinder treatment flexibility at the patient level if, for example, only a limited number of doses are approved for reimbursement at any given time, and will require further consideration.

It is possible that the oral prevention dosing schedules of the gepants (daily for atogepant and EOD for rimegepant) could be associated with lower compliance in clinical practice compared with the once-monthly mAbs. This could factor into their relative effectiveness; however, to date, this has not been studied and warrants future investigation. Nonetheless, rimegepant is associated with several favorable attributes relative to anti-CGRP mAbs. For example, one study reported that half of headache patients prefer oral versus injectable treatments for prevention, largely due to familiarity with orals and an aversion to needles.<sup>33</sup> The half-life of anti-CGRP mAbs (27–31 days compared with ~11 h for rimegepant) limits the ability for immediate cessation of treatment in the event of pregnancy, hypersensitivity reaction, or serious adverse events. Given that migraine disproportionately affects women of childbearing potential, there is particular value in a preventive treatment that provides this flexibility.<sup>34</sup> Furthermore, MMDs have been shown to fluctuate over time (in both decreasing and increasing frequency),<sup>35</sup> and the future ability to tailor treatment based on current disease status could be highly valuable to some patients. Other potential areas of unmet need with anti-CGRP mAbs—which could be addressed by a novel therapy—are only now emerging with real-world evidence of effectiveness and patient satisfaction. For example, a recent study of erenumab in chronic migraine patients suggests that there could be challenges with erenumab persistence and evidence of a potential wearing-off effect toward the end of each treatment cycle, both of which warrant further investigation.<sup>36</sup>

In the absence of head-to-head comparisons between mAbs and rimegepant, the current analysis provides evidence of not statistically significant differences in terms of key efficacy outcomes and supports further investigation into rimegepant as a preventive migraine therapy. An unanchored population adjustment (i.e., population adjustment without a common comparator) is an established analytic option to incorporate data from single-arm trials. An underlying assumption of an MAIC is that all relevant population characteristics are accounted for.<sup>15</sup> A limitation of this analysis is that we were limited to the availability of published aggregate data for the competing trials, so it was not possible to adjust for variables that were not reported in trial publications. Important prognostic factors including migraine comorbidities and history of acute medication use were not accounted for in the propensity model,<sup>37-39</sup> which may affect the validity of the findings. Another factor that we were unable to control for in the MAIC was the potential difference in expectation of treatment benefit between subjects in the double-blind treatment trials (erenumab and galcanezumab) and those in the open-label trial (rimegepant). If the expected treatment benefit was indeed greater in the open-label trial, the results may be biased in favor of rimegepant. Future work that incorporates the results of the pivotal prevention trial for rimegepant will be of interest and would add to this growing body of knowledge.<sup>9</sup>



## CONCLUSIONS

Oral rimegepant taken EOD/PRN was found to be superior to placebo and not statistically significantly different from injectable galcanezumab and erenumab in reducing MIDAS, superior to placebo and erenumab in improving MSQv2, generally similar to galcanezumab in improving MSQv2, and superior to placebo and not statistically significantly different from injectable galcanezumab and erenumab in reducing MMDs. When adjustments were made to reflect baseline characteristics in the published literature, current data suggest that rimegepant is an effective therapy in reducing disability and MMDs and enhancing migraine-specific HRQoL. These data support the preventive benefit observed in randomized trials of rimegepant and further validate its efficacy for both acute and preventive treatment of migraine.

## CONFLICT OF INTEREST

EP, KJ, and LP are employees of Broadstreet HEOR, which received funds from Biohaven for this work. RC, AT, LH, VC, and GL are employees of Biohaven. JM has been a speaker for Amgen/Aimovig, Ubrelvy/ubrogepant-Allergan, and TEVA/Ajovy.

## AUTHOR CONTRIBUTIONS

*Study concept and design:* Evan Popoff, Karissa Johnston, Linda Harris, Lauren Powell, Gilbert L'Italien. *Acquisition of data:* Robert Croop, Alexandra Thiry, Linda Harris, Vladimir Coric, Gilbert L'Italien. *Analysis and interpretation of data:* Evan Popoff, Karissa Johnston, Linda Harris, Lauren Powell, Gilbert L'Italien. *Drafting of the manuscript:* Evan Popoff, Karissa Johnston, Robert Croop, Alexandra Thiry, Linda Harris, Lauren Powell, Vladimir Coric, Gilbert L'Italien, James Moren. *Revising it for intellectual content:* Evan Popoff, Karissa Johnston, Linda Harris, Lauren Powell, Gilbert L'Italien, James Moren. *Final approval of the completed manuscript:* Evan Popoff, Karissa Johnston, Robert Croop, Alexandra Thiry, Linda Harris, Lauren Powell, Vladimir Coric, Gilbert L'Italien, James Moren.

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