Long-term safety and discontinuation for rimegepant versus triptans: A matching-adjusted indirect comparison

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INTRODUCTION

- Rimegepant 75 mg (Vydura), is an orally administered calcitonin gene-related peptide (CGRP) receptor antagonist which offers a promising new treatment option for the acute and preventive management of migraines.[1-4]
- For several decades, triptans have been the standard of care for acute treatment, positioning them as the most relevant comparator to rimegepant.
- Although efficacy may be similar, rimegepant could offer tolerability advantages, given its favourable safety profile
- Comparative evidence on the long-term safety and tolerability of as needed (PRN) rimegepant versus triptans is lacking.

OBJECTIVE

- To compare rates of discontinuation and adverse events (AEs) over 12 months of open-label PRN use for rimegepant- and triptan-treated subjects using a matching-adjusted indirect comparison (MAIC).

METHODS

TARGETED LITERATURE REVIEW

- A targeted literature review was conducted on December 4, 2023, to identify open label extension (OLE) or long-term safety trials of sumatriptan, zolmitriptan, or rizatriptan.
- Comparability to PRN arms of a rimegepant trial (BHV3000-201; NCT03266588)[5] was assessed with respect to patient characteristics, outcome definitions, and data availability.
- A zolmitriptan long-term study (Cady et al., 1998)[6] was selected as it had the most comprehensive reporting of baseline covariates and similar safety outcome definitions
- However, this study had variable duration of follow up due to early termination. In addition, AEs from this study were only collected within 24 hours of taking the triptan treatment.

MATCHING-ADJUSTED INDIRECT COMPARISON

- A MAIC was performed in accordance with recommendations from the National Institute for Health and Care Excellence (NICE) Decision Support Unit, derived from the publication by Signorovitch et al. (2012).[7]

MATCHING-ADJUSTED INDIRECT COMPARISON CONT.

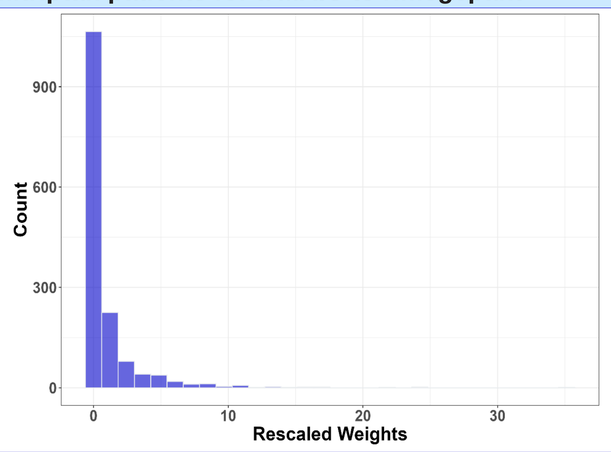
- Proportions of categorical fields and means of continuous fields were matched.
- Individual patient data (IPD) from the rimegepant trial, BHV3000-201,4 were weighted to match the baseline covariates in the Cady et al. (1998)[5] population (age, sex, history of aura, duration of migraine history, historical monthly migraine attacks, use of concomitant migraine preventive medications).
- Patient weights from the MAIC were used to calculate adjusted proportions of the outcomes examined: discontinuation and AEs
- Discontinuation was measured over 12 months for rimegepant and a variable timeframe for zolmitriptan (0-12 months; overall, due to AEs, or due to lack of efficacy). Specific AEs reported in both studies were compared (dizziness, somnolence, paresthesia, nausea, and asthenia).
- For each outcome, odds ratios (ORs), relative risks (RRs), and risk differences (RDs) were estimated with 95% confidence intervals (CIs).

RESULTS

RESULTS OF IPD WEIGHTING

- The MAIC weights were calculated for patients enrolled in BHV3000-201 (**Figure 1**).

Figure 1. Histogram of weights (rescaled) given to zolmitriptan patients for a MAIC to rimegepant



Weight: zolmitriptan

- Weights were rescaled to sum to the original sample size allowing for the direct comparison of counts of zolmitriptan patients with given baseline characteristics before and after matching (**Table 1**).
- After scaling, the estimated weights of the patients in the IPD ranged from ~0 to 35.1.
- After weighting, the effective sample size was 220.6 (an 85.4% reduction from the original sample size), and the summary baseline characteristics of the rimegepant population matched those of the zolmitriptan population (**Table 1**).
- The proportion of patients in the rimegepant population with a history of aura and the proportion of females were reduced after matching.
- Matching also increased the proportions of rimegepant patients using concomitant preventative medications from 14% to 31%.
- Mean age at baseline decreased slightly in the rimegepant population after matching, as did the duration of migraine history.

Table 1. Rimegepant baseline characteristics before and after matching to zolmitriptan

Characteristic	Rimegepant		Zolmitriptan (n=2,058)†
	Before matching (n=1,514)	After matching (ESS=220.6*)	
History of aura (%)	40.4	30.5	30.5
Concomitant preventive medications (%)	14	31	31
Female sex (%)	90	86	86
Baseline age (mean)	43.0	40.9	40.9
Duration of migraine history in years (mean)‡	22.2	21.2	21.2
Monthly migraine attacks§ (mean)	6.7	2.9	2.9

Abbreviations: ESS = effective sample size
*85.4% reduction
†Estimates are displayed with the most precision (i.e., decimal places) with which they could be matched
‡Duration of migraine history estimated from age at baseline and age at migraine onset
§Monthly migraine attacks for rimegepant are historical moderate/severe migraines only

UNADJUSTED COMPARISON OF SAFETY ENDPOINTS

- Before IPD weighting, OR, RR, and RD for the unadjusted proportions of discontinuation and AE rates were compared (**Table 2**).
- The odds of discontinuation for any reason were similar between the two treatments (OR=1.01 [95% CI: 0.88, 1.16]) before adjustment.
- Before weighting, discontinuation due to AEs was lower for rimegepant (3.2%) compared to zolmitriptan (8.1%).
- In addition, within the unadjusted comparison of AEs, rimegepant had a significantly lower rate of all individual AEs compared to zolmitriptan.

Table 2. Unadjusted safety results for rimegepant versus zolmitriptan

	Rimegepant (n=1,514)	Zolmitriptan (n=2,058)*	Rimegepant versus zolmitriptan		
	n (%)	n (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
Discontinuation					
Any reason	560 (37.0)	755 (36.7)	1.01 (0.88, 1.16)	1.01 (0.92, 1.10)	0.3 (-3.0, 3.6)
Due to AE	48 (3.2)	167 (8.1)	0.37 (0.27, 0.51)	0.39 (0.29, 0.53)	-4.9 (-6.5, -3.4)
Due to lack of efficacy	72 (4.8)	226 (11.0)	0.40 (0.31, 0.53)	0.43 (0.33, 0.56)	-6.2 (-8.0, -4.4)
Adverse Events†					
Dizziness	39 (2.6)	288.1 (14)	0.16 (0.12, 0.23)	0.18 (0.13, 0.26)	-11.4 (-13.2, -9.7)
Somnolence	21 (1.4)	288.1 (14)	0.09 (0.06, 0.14)	0.10 (0.06, 0.15)	-12.6 (-14.3, -10.9)
Paresthesia	10 (0.7)	288.1 (14)	0.04 (0.02, 0.08)	0.05 (0.03, 0.09)	-13.3 (-15.0, -11.7)
Nausea	48 (3.2)	308.7 (15)	0.19 (0.14, 0.25)	0.21 (0.16, 0.28)	-11.8 (-13.7, -10.0)
Asthenia	2 (0.1)	370.4 (18)	0.01 (0.00, 0.02)	0.01 (0.00, 0.03)	-17.9 (-19.6, -16.1)

Abbreviations: AE = adverse event; OR = odds ratio; RR = relative risk; RD = risk difference.
*The n-values for specific adverse events in zolmitriptan were estimated from percentages, which were reported as a whole number.
†Adverse events for rimegepant are "on-treatment" adverse events defined as: events with a start date that is greater than or equal to first date of exposure to treatment and less than or equal to 7 days after the date of last exposure to treatment.

ADJUSTED COMPARISON OF SAFETY ENDPOINTS

- Rimegepant was associated with a lower overall discontinuation rate than zolmitriptan (31.7% versus 36.7%), and the difference was statistically significant (**Table 3**).
- The odds of discontinuation with rimegepant were lower than with zolmitriptan (OR=0.80 [95% CI: 0.70, 0.92]).
- Patients were less likely to discontinue rimegepant compared to zolmitriptan due to the following non-trial specific reasons: AEs (OR=0.14 [95% CI: 0.09, 0.23]) and lack of efficacy (OR=0.37 [95% CI: 0.28, 0.49]).
- Compared to zolmitriptan, rimegepant patients had a reduced risk of experiencing dizziness, somnolence, paresthesia, nausea, and asthenia.

ADJUSTED COMPARISON OF SAFETY ENDPOINTS CONT.

- The most frequently experienced of these AEs for rimegepant was nausea (3.5%), though the risk was lower than with zolmitriptan (15%; RD: -11.5 [95% CI: -13.3, -9.6]).

Table 3. MAIC safety results for rimegepant versus zolmitriptan

	Rimegepant (n=1,514, ESS=220.6)	Zolmitriptan (n=2,058)*	Rimegepant versus zolmitriptan		
	n (%)	n (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
Discontinuation					
Any reason	480.1 (31.7)	755 (36.7)	0.80 (0.70, 0.92)	0.86 (0.79, 0.95)	-5.0 (-8.2, -1.8)
Due to AE	18.5 (1.2)	167 (8.1)	0.14 (0.09, 0.23)	0.15 (0.09, 0.24)	-6.9 (-8.3, -5.5)
Due to lack of efficacy	65.7 (4.3)	226 (11.0)	0.37 (0.28, 0.49)	0.40 (0.30, 0.52)	-6.6 (-8.4, -4.9)
Adverse Events†					
Dizziness	29.9 (2.0)	288.1 (14)	0.12 (0.08, 0.18)	0.14 (0.10, 0.20)	-12.0 (-13.7, -10.3)
Somnolence	23.5 (1.6)	288.1 (14)	0.10 (0.06, 0.15)	0.11 (0.07, 0.17)	-12.4 (-14.1, -10.8)
Paresthesia	1.2 (0.1)	288.1 (14)	0.00 (0.00, 0.03)	0.01 (0.00, 0.03)	-13.9 (-15.5, -12.4)
Nausea	53.6 (3.5)	308.7 (15)	0.21 (0.15, 0.28)	0.24 (0.18, 0.31)	-11.5 (-13.3, -9.6)
Asthenia	0.3 (0.0)	370.4 (18)	0.00 (0.00, 0.03)	0.00 (0.00, 0.04)	-18.0 (-19.7, -16.3)

Abbreviations: AE = adverse event; ESS = effective sample size; OR = odds ratio; RR = relative risk; RD = risk difference.
*The n-values for specific adverse events in zolmitriptan were estimated from percentages, which were reported as a whole number.
†Adverse events for rimegepant are “on-treatment” adverse events defined as: events with a start date that is greater than or equal to first date of exposure to treatment and less than or equal to 7 days after the date of last exposure to treatment.

DISCUSSION & CONCLUSIONS

- **This MAIC suggests that when used long-term for the acute treatment of migraine, rimegepant is associated with lower rates of discontinuation and AEs (dizziness, somnolence, paresthesia, nausea, and asthenia) compared to zolmitriptan.**
- These results may be considered conservative for rimegepant due to the shorter follow-up time and briefer window of AE collection in Cady et al. versus the rimegepant BHV3000-201 trial.
- Given the similarities between triptans in terms of mechanism of action, efficacy, and safety, we would expect that these results are generalizable to triptans other than zolmitriptan (e.g., sumatriptan, rizatriptan).
- Future studies using real-world data can confirm these findings and assess the effectiveness, safety, and persistence of rimegepant when used in clinical practice.

REFERENCES

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CONFLICTS OF INTEREST

Lauren Powell, Ciara de Brún, and Basia Rogula are employees of Broadstreet Health Economics & Outcomes Research and received payment from Pfizer in the conduct of this study. Aaron Jenkins, Jo Atkinson, and Lucy Abraham are employed by and own stock or holds stock option in Pfizer.

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