Comparative Efficacy and Safety of Rimegepant Versus Placebo in the Treatment of Acute Migraine: a Meta-Analysis With Sub-Group Analysis in the Asian Population

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ABSTRACT

Background

Acute migraine can be treated with rimegepant, an antagonist of the calcitonin gene-related peptide (CGRP) receptor. With a focus on the Asian population as a subgroup, this meta-analysis attempts to investigate the effectiveness and safety of rimegepant for individuals suffering from severe migraines.

Methods

PubMed, MEDLINE database and Cochrane Library were used to identify valid randomized controlled trials for this study. The primary endpoint investigated was freedom from pain and freedom from the most bothersome symptom 2 hours post dose. RevMan 5.4.1 software was used to perform a meta-analysis on each outcome measure.

Results

A total of five randomized controlled trials were incorporated, with two of them being conducted on Asian populations and published between 2014 and 2024. There were 2,516 cases in the rimegepant group and 2,668 cases in the placebo group out of the total 5,184 patients that were included. Rimegepant was found to significantly reduce the primary endpoints in acute migraine patients (RR 1.58, 95% CI 1.42-1.75, P-value 0.0001; RR 1.34, 95% CI 1.08-1.66, P-value 0.0001), and in the acute migraine Asian patients (RR 1.79, 95% CI 1.47-2.19, P-value <0.00001; RR 1.45, 95% CI 1.31-1.60, P-value <0.00001) but showed no significant difference in the risk reduction of any adverse event, nausea and urinary tract infection among acute migraine patients (RR 1.06; 95% CI, 0.93-1.21; RR 0.88; 95% CI, 0.57-1.35; RR 1.08; 95% CI, 0.64-1.84;).

Conclusion

The use of rimegepant is effective and safe for acute migraine patients, including the Asian subgroup.

Keywords: *CGRP - calcitonin gene-related peptide; Rimegepant; Acute Migraine*

INTRODUCTION

Background of the Study

A headache disorder is one of the most prevalent nervous system disorders, characterized by recurrent headaches.[7] In 2021, around 40% of the world's population, or 3.1 billion individuals, experience headache disorder; being more common in females than in males. From the age of five until the age of eighty, they are among the top three neurological conditions for the majority of age groups. Headache diseases afflict people of all ethnicities, financial

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levels, and geographic locations, despite minor regional variances.[7] One of the primary headache disorders is migraine and this is episodic in most cases, lasting between four to seventy-two hours, and sometimes accompanied by phonophobia, photophobia, nausea and/or vomiting. A brief, transient aura of unilateral, reversible visual, sensory, or other symptoms may occasionally precede it.

Those between the ages of 35 and 45 are typically affected by migraines, which typically start during adolescence. Perhaps due to hormonal effects, it is more common among women.[7]

Patients who often experience moderate to severe migraine attacks show up in emergency rooms, and frequently their standard acute migraine medication has not worked to relieve the pain.[5] Simple analgesics like nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen to triptans are the most frequently used as abortive or symptomatic therapy for migraines. Other options include antiemetics for patients who have experienced nausea or vomiting, relatively new calcitonin gene-related peptide (CGRP) antagonists, 5-HT1F receptor agonists like lasmiditan, and the ergot alkaloid dihydroergotamine.[3]

A calcitonin gene-related peptide (CGRP) antagonist called rimegepant has just been introduced to the Philippine market. Randomized clinical trials evaluating the effectiveness of rimegepant, a calcitonin gene-related peptide (CGRP) antagonist, against placebo have already been published.[1,4,9,8,2] These clinical trials had similar results showing that among patients with acute migraine headache, the use of rimegepant compared with placebo resulted in freedom from pain and freedom from the most bothersome symptom of migraine 2 hours post dose.

Considering the prevalence and the epidemiology migraine headaches affect the productive age group and the disabling symptoms that they cause, it is of interest to do a thorough review of the clinical trials providing evidence about the efficacy and safety of the new medications for migraine headache.

The purpose of this study is to provide more robust evidence regarding the results of the five randomized controlled trials through a meta-analysis and to do a subgroup analysis in the Asian population using the two trials done in Chinese and Korean population, which were both recently published in year 2023 and 2024.

METHODS

Search Strategy

Using the search phrases "rimegepant" AND "migraine," a thorough search was conducted in MEDLINE/ PUBMED, Cochrane Library, to find the relevant clinical trials. Only human studies and randomized controlled trials were allowed to be published in the articles. To see if there were any more research that would fit into this evaluation, the reference lists of each study were examined.

Inclusion and Exclusion Criteria

The papers analysed for this meta-analysis were randomized controlled trials (RCTs) where the medication administered was a 75 mg tablet of rimegepant as opposed to a placebo, and the participants were adult patients with acute migraine who had experienced headaches for at least a year. Individuals with the following characteristics were not allowed to participate in the included RCTs: (1) a history of any clinically significant or unstable medical condition; this includes alcohol or drug abuse and substance-use disorder; (2) a history of migraine with brainstem aura or hemiplegic migraine; and (3) a history of previously taking part in studies of investigational CGRP-antagonists (small molecule or biologic); or having been prescribed CGRP-antibodies within the last 6 months. The primary outcome measure analysed was

freedom from pain and freedom from the most bothersome symptom of migraine. While the secondary outcome measure analyzed the adverse effects of the said treatments.

Excluded studies included duplicate publications, inadequate or unretrievable raw data, and studies that did not fit the previously specified criteria.

Data Extraction and Analysis

The retrieval studies were evaluated by two independent reviewers using the Cochrane Collaboration's approved RoB 2 technique. The authors separately extracted and summarized the trial data. Before entering the data, summary statistics were calculated using the extracted data, if needed. At two hours after the dose, the main outcome of this meta-analysis was the freedom from pain and freedom from the most bothersome symptom. Every patient involved in the research was examined within the original randomized group (intention-to-treat analysis). Primary results between the groups were described using dichotomous outcomes. The fixed-effects model was used to modify the precision of the results using the statistical program Review Manager Analyses 5.4.1. The findings were presented as risk ratios with a 95% confidence level. Utilizing RevMan Analyses 5.4.1, chi square and I2 were used to evaluate the studies' heterogeneity.

RESULTS

Search Results

The search criteria in the Cochrane Library and MEDLINE/Pubmed databases yielded a total of 181 publications. Using the RCT filter, it reduced the number of items in the search to fourteen (14). Nine out of the fourteen studies were deemed ineligible for inclusion because they did not employ the intended research population, did not satisfy the inclusion criteria, were duplicates, or were not yet published trials. Five randomized controlled trials (RCTs) met the eligibility criteria for the meta-analysis. Full texts was retrieved for all the studies.

Characteristics of Included Trials

The five RCTs that were found were all randomized, placebo-controlled studies that assessed the effectiveness of rimegepant, a CGRP antagonist, as an acute migraine therapy. Adult patients who had experienced migraines for at least a year and were at least 18 years old were included in the research. A 75 mg oral dose of either rimegepant or a placebo was administered to trial participants.

This meta-analysis examined 5,184 participants in total from the five included studies. For patients who were included, either rimegepant or a placebo was used. While the remaining three trials examined a broad range of racial groups, including Whites, Black/African Americans, Asians, etc., two of the studies focused on the Asian population (South Koreans and Chinese). There were 2,417 patients in the Asian group and 2,767 in the mixed-race subpopulation.

Figure 1. PRISMA research flow diagram displaying the literature selection process and search outcomes

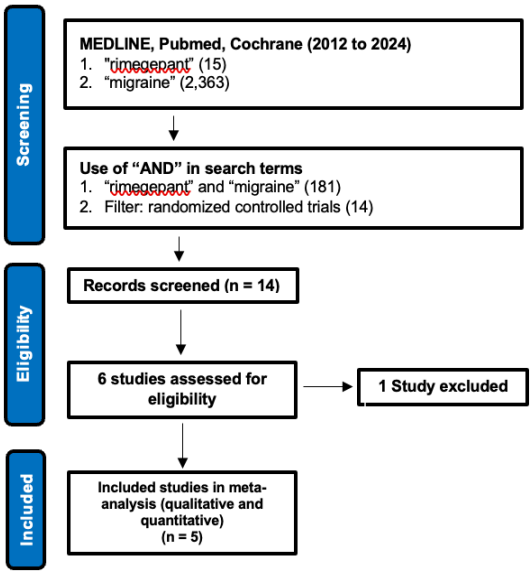

Table 1. Methodological Characteristics of the Eligible Studies.

Author / Year published	Trial	Subjects	Study centers / sites included	Total number of patients	Number of patients who had Rimegepant 75mg tablet	Number of patients who had placebo	Primary outcome	JADAD Score
Marcus, et al./2014	BMS-927711 for the acute treatment of migraine: A double-blind, randomized, placebo controlled, dose-ranging trial	Male and female subjects, 18 to 65 years of age, who had at least a one-year history of migraine with or without aura	41	320	91	229	Pain freedom at two hours post-dose	8
Croop, et al./2019	Efficacy, safety, and tolerability of Rimegepant orally disintegrating tablet for the acute treatment of migraine: a Rimegepant, phase 3, double-blind, placebo-controlled trial	Adults aged 18 years or older with history of migraine of at least 1 year	69	1375	682	693	Freedom from pain and freedom from the most bothersome symptom at two hours post-dose	8
Lipton, et al./2019	Rimegepant, an Oral Calcitonin Gene–Related Peptide Receptor Antagonist, for Migraine	Adults with at least a 1-year history of migraine and two to eight migraine attacks of moderate or severe intensity per month	49	1072	537	535	Freedom from pain and freedom from the most bothersome symptom (other than pain) identified by the patient, both of which were assessed 2 hours after the dose of Rimegepant or placebo was administered	8
Yu, et al./2023	Safety and efficacy of rimegepant orally disintegrating tablet for the acute treatment of migraine in China and South Korea: a phase 3, double-blind, randomised, placebo-controlled trial	Adults (≥18 years) with at least a 1-year history of migraine	86	1342	668	674	Pain freedom and freedom from the most bothersome symptom associated with migraine (ie, phonophobia, photophobia, or nausea) at 2 hours after dosing	8
Yu, et al./2024	Rimegepant orally disintegrating tablet 75 m for acute treatment of migraine in adults from China: a subgroup analysis of a double-blind, randomized, placebo-controlled, phase 3 clinical trial	≥ 18 years of age and had a ≥ 1-year history of migraine, with 2 to 8 attacks of moderate or severe pain intensity per month and < 15 headache days per month during the 3 months before screening	1	1075	538	537	Pain freedom and freedom from the most bothersome symptom (MBS) at 2 hours post-dose	7

*Modified Jadad scale interpretation: Studies with a score of 0-3 are considered as low-quality studies and studies with a score of 4-8 are considered as high-quality studies

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The methodological characteristics of the included studies are displayed in Table 1.

Risk of Bias Assessment

Risk of bias analysis was done on all five articles. As presented in Figure 2a and 2b, all the trial designs were done in a randomized, double blind, placebo-controlled fashion. All of the studies had low risk of bias as they made use of random sequence generation, with proper blinding of both the participants and the investigators. Attrition bias was low for all studies as all participants were followed up adequately with proper documentation.

Outcomes

The meta-analysis for the primary outcome freedom from pain and freedom from the most bothersome symptoms after 2 hours post dose showed that the intervention, which is rimegepant, showed a significant difference as compared to placebo. Also, the meta-analysis of the adverse effects of the intervention and placebo did not show a significant difference.

Figure 2a. Risk of Bias Summary of the Included Studies

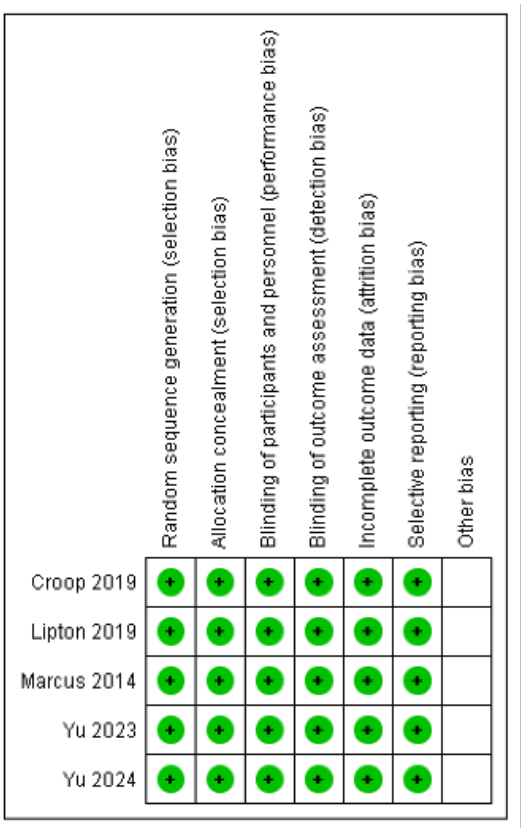


Figure 2b. Risk of Bias Graph: Review of Author's Judgement Across Different Studies.

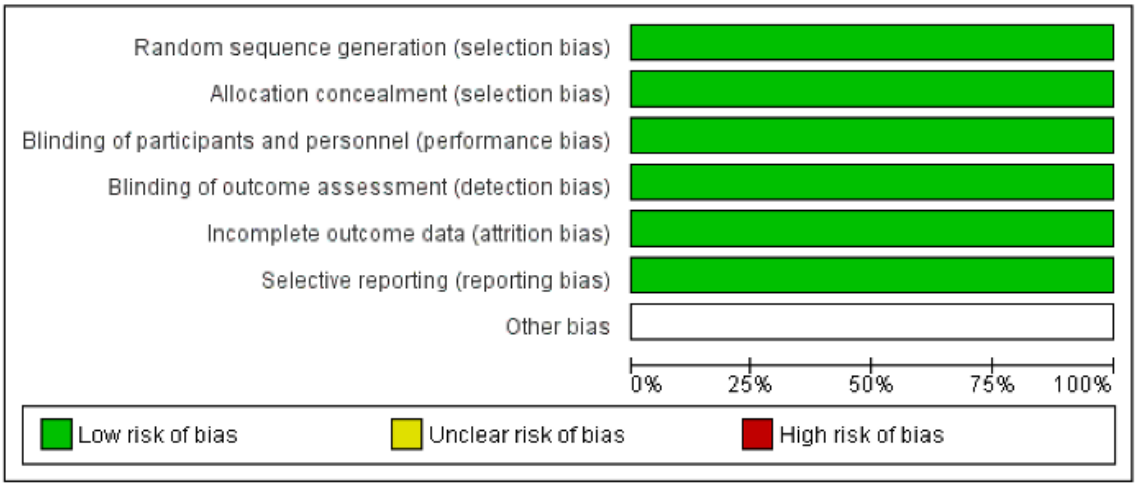
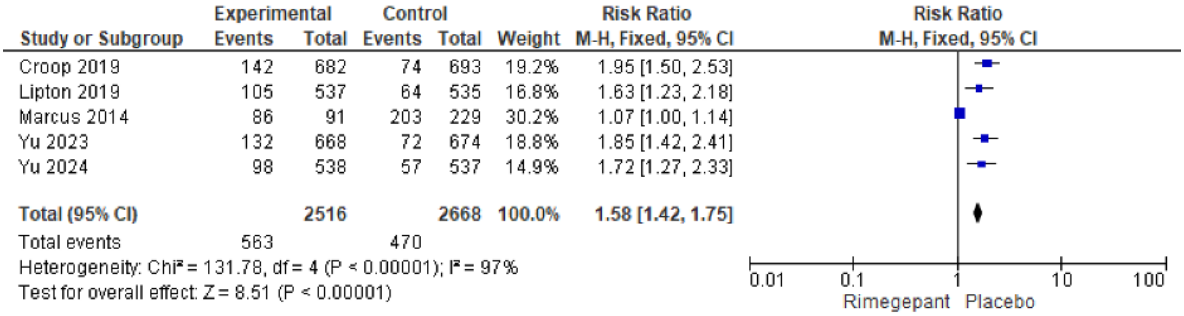
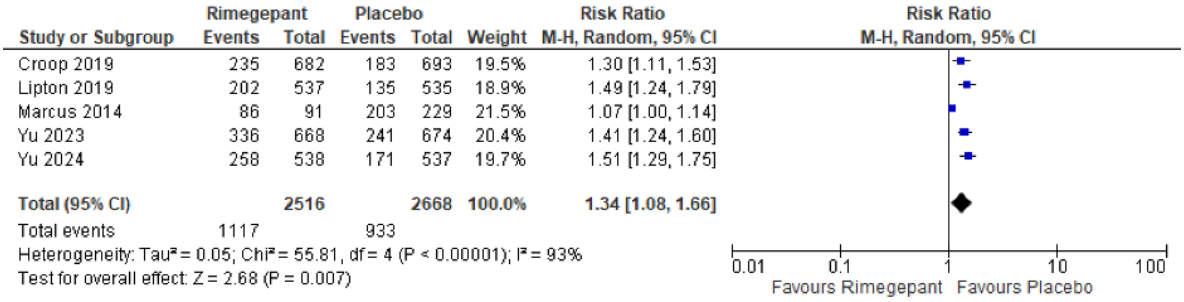


Figure 3.A Forest Plot for the Effect of Rimegepant vs Placebo on Freedom from Pain in Acute Migraine Patients Across Five Trials



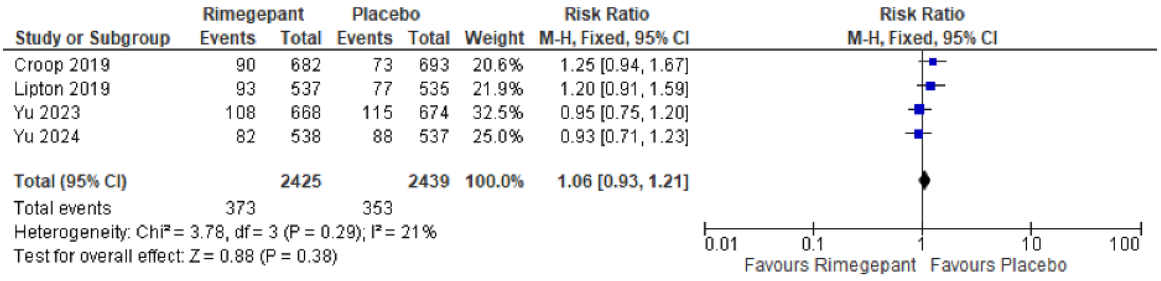
All of the five trials included patients with acute migraine, of which 2516 patients received rimegepant and 2668 patients received a placebo. Using fixed-effect model, rimegepant significantly reduced the risk of the primary outcome freedom from pain 2 hours post dose among acute migraine patients (RR 1.58, 95% CI 01.42-1.75, P-value 0.0001).

Figure 3.B Forest Plot for the Effect of Rimegepant vs Placebo on Freedom from the Most Bothersome Symptoms in Acute Migraine Patients Across Five Trials



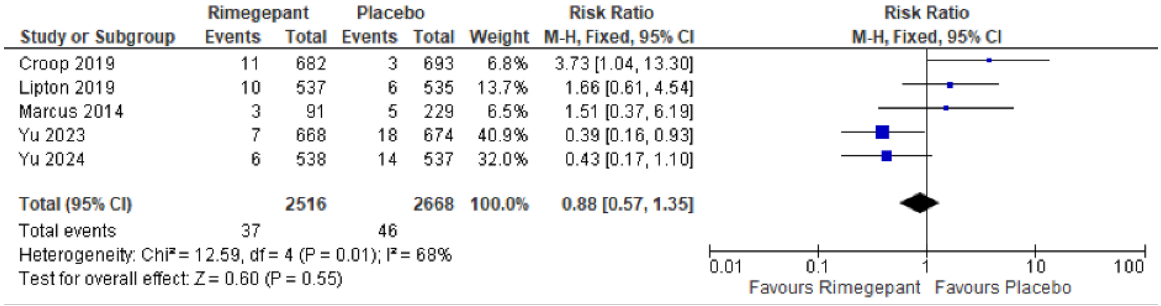
All of the five trials included patients with acute migraine, of which 2516 patients received rimegepant and 2668 patients received a placebo. Using fixed-effect model, rimegepant significantly reduced the risk of the primary outcome freedom from the most bothersome symptoms (MBS) 2 hours post dose among acute migraine patients (RR 1.34, 95% CI 1.08-1.66, P-value 0.0001).

Figure 4.A Forest plot of the effect of rimegepant versus placebo on any adverse event among acute migraine patients across four trials



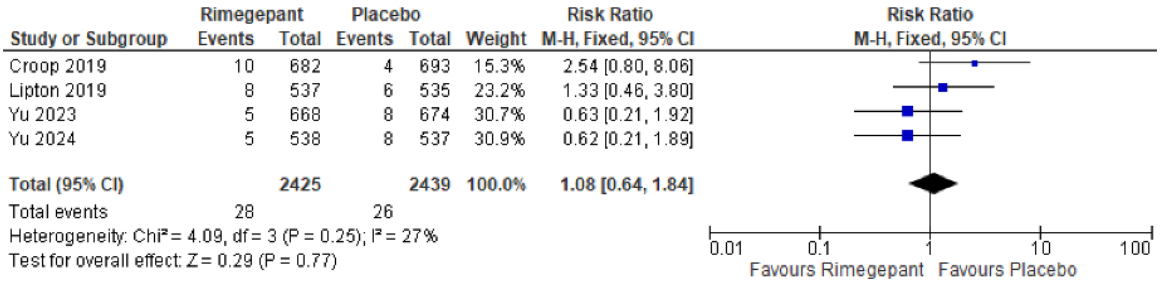
There were four trials in whom patients with acute migraine had any adverse event, of which 2425 patients received rimegepant and 2439 patients received a placebo. A subgroup analysis was done which showed a statistical heterogeneity between the studies (I^2=22%). Using fixed-effect model, there was no significant difference in the risk reduction of any adverse event among acute migraine patients (RR 1.06; 95% CI, 0.93-1.21).

Figure 4.B Forest plot of the effect of rimegepant versus placebo on nausea among acute migraine patients across five trials



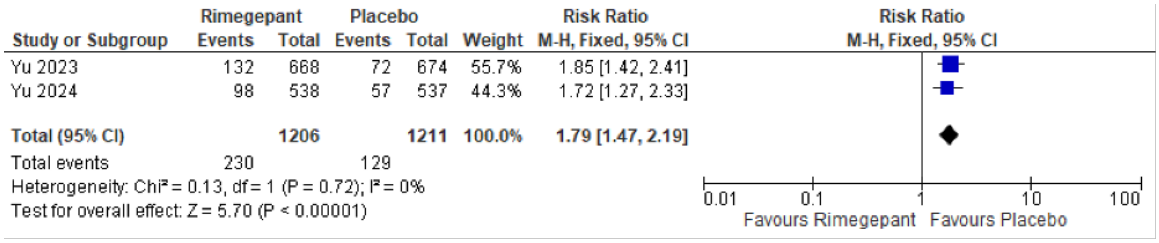
There were five trials in whom patients with acute migraine had nausea as an adverse event, of which 2516 patients received rimegepant and 2668 patients received a placebo. A subgroup analysis was done which showed a statistical heterogeneity between the studies (I^2=68%). Using fixed-effect model, there was no significant difference in the risk reduction of nausea among acute migraine patients (RR 0.88; 95% CI, 0.57-1.35).

Figure 4.C Forest plot of the effect of rimegepant versus placebo on urinary tract infection among acute migraine patients across four trials



There were four trials in whom patients with acute migraine had urinary tract infection as an adverse event, of which 2425 patients received rimegepant and 2439 patients received a placebo. A subgroup analysis was done which showed a statistical heterogeneity between the studies (I^2=27%). Using fixed-effect model, there was no significant difference in the risk reduction of urinary tract infection among acute migraine patients (RR 1.08; 95% CI, 0.64-1.84).

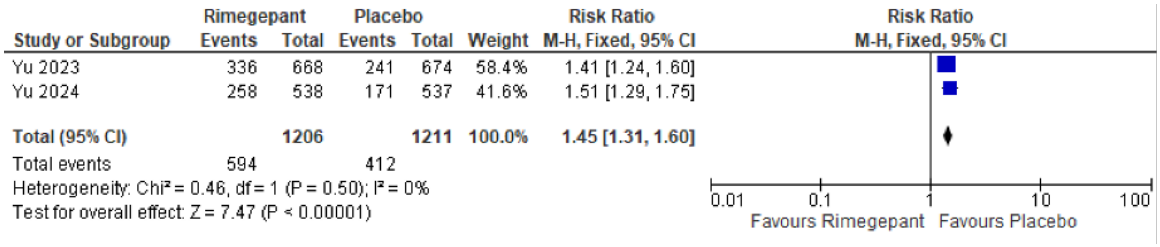
Figure 5.A Forest Plot of the Effect of Rimegepant vs Placebo on Freedom from Pain in Acute Migraine Patients Across the Asian Population



A sub-group analysis involving the Asian population, with the representative nationalities of Chinese and Koreans was done. It included a total of 2,417 patients with acute migraine wherein 1206 patients received rimegepant and 1,211 patients received placebo. It showed that the use of rimegepant was associated with a significant risk reduction of freedom

from pain 2 hours post dose (RR 1.79, 95% CI 1.47-2.19, P-value <0.00001) compared with placebo in patients with acute migraine across in both trials. There was no significant heterogeneity between the studies (I^2=0%).

Figure 5.B Forest Plot of the Effect of Rimegepant vs Placebo on Freedom from the Most Bothersome Symptoms in Acute Migraine Patients Across the Asian Population



In this figure, it showed that the use of Rimegepant was associated with a significant risk reduction of freedom from the most bothersome symptoms 2 hours post dose (RR 1.45, 95% CI 1.31-1.60, P-value <0.00001) compared with placebo in patients with acute migraine across in both trials. There was no significant heterogeneity between the studies (I^2=0%).

Another analysis of the Asian population with acute migraine who had any adverse event and urinary tract infection as adverse event was done. It showed no statistical heterogeneity between the studies (I^2=0%). Using fixed-effect model, there was no significant difference in the risk reduction of any adverse event and urinary tract infection as an adverse event among acute migraine patients (RR 0.94 and 0.63, 95% CI 0.78-1.13 and 0.29-1.38) as shown in Appendix A.

Also, in the two trials with Asian patients with acute migraine who had nausea as an adverse event was done, the subgroup analysis showed no statistical heterogeneity between the studies (I^2=0%). Using fixed-effect model, placebo showed a significant risk reduction of nausea among acute migraine Asian patients (RR 0.41, 95% CI 0.22-0.77) as shown in Appendix B.

DISCUSSION

In this meta-analysis, a total of five randomized controlled trials were included wherein two are recent trials published in year 2023 and 2024. The included literatures were of excellent quality and comparability, and the baseline parameters of the five trials were comparatively similar. In order to examine the effectiveness and safety of rimegepant, 5,184 patients with acute migraine attacks were included in the trial. Additionally, the Asian patients who experienced an acute migraine attack underwent a subgroup analysis. The analysis of the five RCTS revealed that, two hours after taking a dose of rimegepant, a considerably higher number of patients than those in the placebo group reported being significantly free of pain and free from the most bothersome symptom of migraine. When the Asian population subgroup was examined independently, it had the same results. However, upon analysis of the adverse events, it was shown that nausea, urinary tract infection, and other unspecified adverse events were caused by both rimegepant and placebo. Furthermore, a comparison of these side effects revealed that among Asian patients with acute migraines, placebo significantly reduced the likelihood of nausea.

Considering the results of this study about rimegepant in the treatment of acute migraine headache, it showed that this new drug is effective and safe as compared to placebo. And this study showed that through

the mechanism of action of this calcitonin gene-related peptide receptor antagonist, it is a good treatment option for acute migraine headache especially for patients who have contraindications to the other treatments for acute migraine headache like the triptans. And though rimegepant has already been approved by the US Food and Drug Administration (FDA) for the preventive treatment of migraine[2], this study can also be used as an evidence of the efficacy and safety of rimegepant as a treatment for acute migraine headache.

There are some limitations in this analysis. The trials included only compared rimegepant with placebo and not with the other abortive treatments for acute migraine like nonsteroidal anti-inflammatory drugs, triptans and ergot alkaloids. This study also did not include analyses of the other secondary outcomes from the five trials included like the symptom relief at 2-24 hours, symptom relief at 2-48 hours, and the other adverse events of the drug.

It would be of interest to see the comparative efficacy as well as the safety of rimegepant as compared to the other medications usually used for acute migraine through a meta-analysis.

CONCLUSION

Overall, this meta-analysis confirmed that the CGRP antagonist rimegepant is effective and safe for patients with acute migraine relieving from acute pain within 2 hours of headache onset including the Asian subgroup. Rimegepant was effective as well in reducing other most bothersome symptoms (i.e., phonophobia, photophobia, or nausea). Further, rimegepant is safe and well tolerated with minimal adverse effect such as nausea and urinary tract infection.

REFERENCES

1. Croop, R., Goadsby, P. J., Stock, D. A., Conway, C. M., Forshaw, M., Stock, E. G., Coric, V., & Lipton, R. B. (2019). Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. *The Lancet*, *394*(10200), 737–745. https://doi.org/10.1016/s0140-6736(19)31606-x
2. Hoffman, M. (2021, May 28). *Rimegepant Approved for Preventive Treatment of Migraine, Adding to Acute Indication*. Neurology Live. https://www.neurologylive.com/view/rimegepant-nurtec-odt-approved-preventive-acute-migraine-indication-biohaven
3. Kelley NE, Tepper DE. Rescue therapy for acute migraine, part 1: triptans, dihydroergotamine, and magnesium. Headache 2012; 52:114.
4. Lipton, R. B., Croop, R., Stock, E. G., Stock, D. A., Morris, B. A., Frost, M., Dubowchik, G. M., Conway, C. M., Coric, V., & Goadsby, P. J. (2019). Rimegepant, an Oral Calcitonin Gene–Related Peptide Receptor Antagonist, for Migraine. *New England Journal of Medicine*, *381*(2), 142–149. https://doi.org/10.1056/nejmoa1811090
5. Marcus, R., Goadsby, P. J., Dodick, D., Stock, D., Manos, G., & Fischer, T. Z. (2013). BMS-927711 for the acute treatment of migraine: A double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia*, *34*(2), 114–125. https://doi.org/10.1177/0333102413500727
6. Schwedt, T., & Garza, I. (2019). *Acute treatment of migraine in adults*. Uptodate.com. https://www.uptodate.com/contents/acute-treatment-of-migraine-in-adults
7. Steinmetz, J. D., Katrin Maria Seeher, Schiess, N., Nichols, E., Cao, B., Chiara Servili, Cavallera, V., Cousin, E., Hagins, H., Moberg, M. E., Mehlman, M. L., Yohannes Habtegiorgis Abate, Abbas, J., Madineh Akram Abbasi,

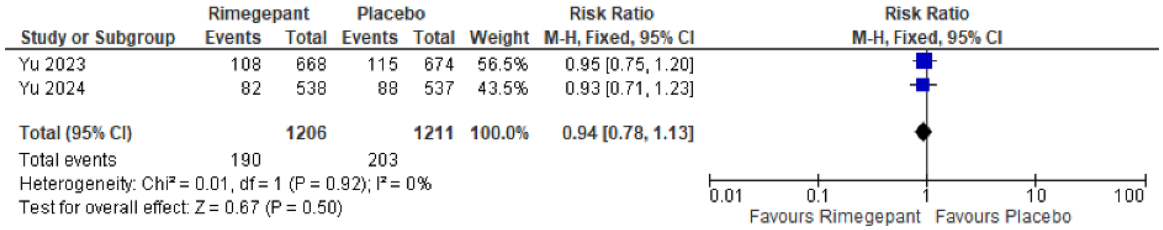
Mohammadreza Abbasian, Hedayat Abbastabar, Abdelmasseh, M., Abdollahi, M., Abdollahi, M., & Mohammad-Amin Abdollahifar. (2024). Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet Neurology*, *23*(4). https://doi.org/10.1016/s1474-4422(24)00038-3

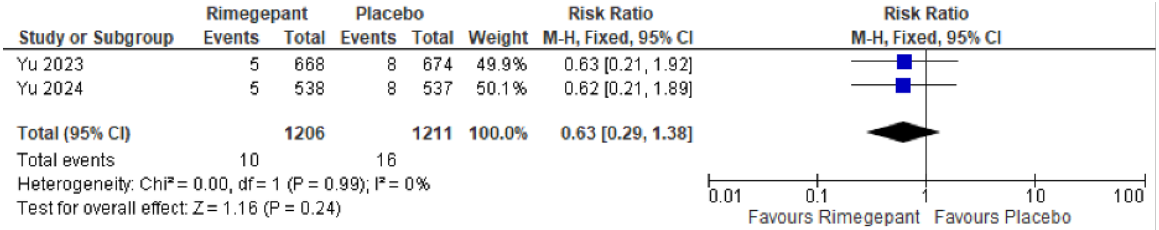
8. Yu, S., Guo, A., Wang, Z., Liu, J., Tan, G., Yang, Q., Zhang, M., Hasiyeti Yibulaiyin, Chen, H., Zhang, Y., Croop, R., Sun, Y., Liu, Y., Zhao, Q., & Lu, Z. (2024). Rimegepant orally disintegrating tablet 75 mg for acute treatment of migraine in adults from China: a subgroup analysis of a double-blind, randomized, placebo-controlled, phase 3 clinical trial. *The Journal of Headache and Pain*, *25*(1). https://doi.org/10.1186/s10194-024-01731-4

9. Yu, S., Kim, B.-K., Guo Aihong, Kim, M., Zhang, M., Wang, Z., Liu, J., Moon, H.-S., Tan, G., Yang, Q., McGrath, D., Hanna, M., Stock, D. A., Gao, Y., Croop, R., & Li, Z. (2023). Safety and efficacy of rimegepant orally disintegrating tablet for the acute treatment of migraine in China and South Korea: a phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Neurology*, *22*(6), 476–484. https://doi.org/10.1016/s1474-4422(23)00126-6

APPENDICES

Appendix A. Forest plot of the effect of rimegepant versus placebo on any adverse event and urinary tract infection as an adverse event among Asian patients with acute migraine





Appendix B. Forest plot of the effect of rimegepant versus placebo on nausea as an adverse event among Asian patients with acute migraine