Evaluating and comparing the safety and efficacy of rimegepant versus lasmiditan in aborting acute migraine headaches in the adult migraineur.

by

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Abstract

Migraine headaches are one of the most common causes of primary headaches. Worldwide, migraines are one of the leading causes of disability and while the mechanism of migraines are not entirely understood, they result in significant disability for those who experience them. Dihydroergotamine was introduced for migraine treatment in the 1920s and in the 1990s triptans were introduced and have been the mainstay of acute migraine treatment since their introduction. In recent years, there have been several developments in the acute treatment and prophylaxis of migraine headaches. Some of the more widely studied and recently developed interventions include calcitonin gene related peptide (CGRP) receptor antagonists and 5-HT1F receptor agonists. These have been researched, developed, and approved by the FDA for acute migraine treatment.

The purpose of this literature review was to compare the efficacy and safety of rimegepant, a CGRP receptor antagonist and lasmiditan, a 5HT1F receptor antagonist in the treatment of acute migraine attacks. This comparison was accomplished by a thorough review of scientific articles available through various resources such as PubMed, Clinical Key and CINAHL Complete. The results from various clinic trials indicated that rimegepant and lasmiditan are both superior to placebo in aborting an acute migraine in addition to eliminating most bothersome associated symptoms. Rimegepant and lasmiditan were also proved to be safe in the tested populations although each pharmacological intervention does carry its own set of potential side effects. There have been no direct studies comparing both drugs or comparing the drugs to triptans, however several meta analyses showed triptans to still be superior in aborting acute migraine headaches.

Keywords: migraine disorders/drug therapy, double-blind method, calcitonin gene related peptide receptor antagonists/therapeutic use, 5-HT1F receptor agonists adult, oral administration, lasmiditan, rimegepant, safety, and triptan

Introduction

Statement of the Problem:

Migraine headaches continue to be a worldwide cause of disability. Patients do not always respond to current pharmacological interventions or treatment is contraindicated due to co-morbid medical conditions. The development of new pharmacological interventions for migraine headaches makes it imperative to evaluate and compare the safety and efficacy of these novel drug classes in the acute treatment of migraine headaches and how they can improve the quality of life of those who suffer from migraine headaches.

Research Question:

In adults, how do rimegepant and lasmiditan compare in safety and efficacy in the treatment of an acute migraine attack?

Background:

The International Headache Society (IHS) classifies a migraine as a primary headache disorder defined as a "Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characterisitics of the headache are unilateral position, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia." Migraines are generally classified by frequency (chronic versus episodic) and by associated symptoms (with or without aura). Migraines with aura have "fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms. Chronic migraine can be defined as a "headache occurring on 15 or more days a month for more than three months, which, on at least 8 days/month, the features of a migraine headache are present."

The above criteria is present in additional types of migraines but additional symptoms may be present or increased frequency may differentiate between episodic versus chronic (International Headache Society, 2019).

According to DynaMed, migraines typically affect middle aged adults with onset typically in late childhood or early adolescence and affect women two to three times more than men. The estimated cumulative lifetime incidence is 43% in women and 18% in men with a 15% prevalence in the United States and an 11.6% prevalence worldwide. This is an estimated 40 million people in the U.S. and 1.02 billion people worldwide. Burch et al (2019) compiled data from several large-scale migraine studies and presented the information in an article exploring the current disease burden of migraine headaches across the United States and worldwide. From an analysis of the 2016 Global Burden of Disease study it was estimated that 45.1 million years were lived with a disability due to migraines across the globe. Migraines were also found to be the second most disabling condition, following low back pain. In this study it was estimated that people with migraines experience increased direct (medical payments) and indirect (loss of productive time) costs compared to those without migraines. The difference was estimated at $9000 per year. That is potentially 360 billion dollars being spent or lost due to migraines annually. In addition to individual costs, it was estimated that it could cost an employer $2600 more per year to employ someone with migraine headaches due to short term disability, workers compensation and/or missed time from work. Episodic migraine has also been found to be comorbid with many other conditions such as psychiatric, cardiovascular and sleep disorders which overall contribute to the physical, emotional, and financial burden of this condition. Despite the many advances in medical science, technology and pharmacology, migraine

continues to be one of the most disabling conditions worldwide. From the figures presented above the economic and financial impact of migraines can also be appreciated.

According to Dr. Michael Cutrer (2023) in an article published in UpToDate, a migraine is most likely due to neuronal dysfunction which creates a cascade of intra and extra cranial changes. It was once thought that vasodilation was the cause of migraines, however recent studies have shown this not to be true. Although vasodilation may still occur during a migraine attack, it is not the cause of the migraine itself. A self-propagating wave of neuronal and glial cell depolarization has been observed in migraine attacks. This wave of depolarization has become known as cortical spreading depression. This depolarization is thought to cause the aura of a migraine, activation of trigeminal nerve afferents and alteration of blood-brain barrier permeability. Trigeminal afferent activation causes inflammatory changes within the meninges through a complex cascade of neuronal channels and the release of proinflammatory mediators. Vasoactive neuropeptides such as substance P, calcitonin gene-related peptide (CGRP) and neurokinin are released during the stimulation of the trigeminal ganglion and release of these peptides is linked to neurogenic inflammation. This inflammation leads to vasodilation and plasma protein extravasation. Elevated levels of the above-mentioned neuropeptides have been found in the cerebrospinal fluid of patients with migraines, possibly linking the presence of neuropeptides to migraines. The meninges are pain sensitive and generate the headache experienced in a migraine. This generation of pain is through the central and peripheral reflex mechanism. The trigeminovascular system consists of sensory neurons which originate from the trigeminal ganglion and upper cervical dorsal roots. These neurons are responsible for the innervation of the dura mater, large venous sinuses, large cerebral vessles and pial vessels. The pathway of the trigeminovascular system explains the usual distribution of migraine pain. The

inflammation caused by the release of these neuropeptides is thought to increase the responsiveness to nociceptive and non-nociceptive stimuli. This phenomenon is called sensitization and is likely responsible for signs and symptoms of a migraine and may play a role in the development of chronic migraines from episodic. Developing medications to block or enhance specific receptors or neurotransmitters has been the focus of acute migraine treatment over the past several decades. The role of serotonin in the generation of migraines is unclear, however there has been success with medications such as tricyclic antidepressants, which block serotonin reuptake and are effective at preventing migraine headaches. Activation of serotonin receptors has also been shown to be effective in the acute treatment of migraines. Additional evidence shows that low serotonin levels may facilitate activation of the trigeminovascular pathway and promote cortical spreading depression. The complete role of serotonin remains unclear but there is evidence that it does contribute to migraine headahces at some level. Another important peptide that has been investigated for its role in migraine headaches is CGRP. It is a 37 amino acid that is present in the trigeminal ganglia and is a potent vasodilator of cerebral and dural vessels. CGRP contributes to the vasodilation present in neurogenic inflammation and is possibly responsible for pain transmission through the trigeminovascular system through the intracranial vessels and into the central nervous system. Infusions of CGRP have been found to provoke a migraine in patients with migraines and stimulation of the trigeminal ganglion releases CGRP. Additional studies have found elevated CGRP levels in venous blood during an acute attack and normalization of levels following the administration of sumatriptan. There is a genetic component to migraines as well. One study found that relatives of patients with migraines were three times more likely to have migraines compared to those with relatives who did not have migraines. Inheritance may account for 40 to 50 percent of an individual's susceptibility to

migraine, however the identification of a specific gene has yet to be identified and it is a complex and multifactorial issue.

Acute migraines are treated in a step wise approach depending on severity. There are a variety of medications available that are effective in treating an acute migraine attack. The purpose of this paper is to explore two medications that have been approved within the past few years for the acute treatment of migraines. Safety and efficacy data will be analyzed and compared to see how the drugs compare to placebo, each other, and the current standard of care in providing safe and effective elimination of an acute migraine headache.

Methods

A literature review was performed using the electronic databases of PubMed and Cochrane Library. In addition, Clinical Key was utilized to access full text articles that could not be accessed using the previously named resources. Clinicaltrials.gov was accessed to gather raw data from the identified studies. MeSH terms and keywords were identified to locate literature evaluating the use of rimegepant and lasmiditan in the acute treatment of migraine headaches in the adult population. Keywords/MeSH terms included: migraine disorders/drug therapy, double-blind method, calcitonin gene related peptide receptor antagonists/therapeutic use, 5-HT1F receptor agonists adult, oral administration, lasmiditan, rimegepant, safety, and triptan. Studies were limited to those completed within the past five years (although two studies were included outside of this range to evaluate the first published study on each medication). When searching PubMed for “rimegepant” between 2017-2022 an initial 105 results were queried. When filtered by “clinical” and “randomize controlled trial” this number decreased to eight results. Five articles from these eight were identified as suitable based upon the critera of “acute migraine treatment.” The same process was performed for lasmiditan with an initial search result of 143

articles. When filtered by “clinical” and “randomized controlled trial” the number decreased to 27 results. The final search resulted in 23 articles. After removal of duplicate studies and various post-hoc analyses, five studies were identified sufficient to meet criteria. A similar process took place when searching the Cochrane Library. The results from PubMed were compared to what was produced when searching the Cochrane Library and duplicate results were eliminated. Multiple studies were excluded because they were not clinical trials, focused on preventative migraine treatment instead of acute treatment, focused on other uses for rimegepant/lasmiditan other than migraine treatment and/or explored safety/efficacy outside of the identified population. Overall, ten clinical trials met criteria for inclusion. Three meta-analyses based upon data from clinical trials were included which compared rimegepant and lasmiditan directly as no clinical trials have been completed at the time of this writing directly comparing these to pharmacological therapies. Two post hoc analyses were included as they provided specific data presentation which helped to highlight tolerability and efficacy and presented data from one clinical trial that could not be found elsewhere. The articles reviewed in this paper do not represent an exhaustive exploration of the numerous articles and studies published on rimegepant, lasmiditan and triptans.

Literature Review

Mechanism of Action, Efficacy, and Safety Profile of Rimegepant

Rimegepant was approved by the FDA in 2020 for the acute treatment of migraine headache with or without aura in adults. Rimegepant is a calcitonin gene related peptide (CGRP) receptor antagonist. It is hypothesized to work by blocking CGRP receptors and not allowing CGRP to exert its vasodilatory and neurogenic inflammatory effects (American Headache Society, 2020).

Marcus et al. (2014) presented the data from a study performed from October 2011 to May 2012 to determine a safe and effective dose for BMS-92771 (rimegepant) in the acute treatment of a migraine. The design of the study was a double blinded, randomized, single dose comparison between placebo and rimegepant. In addition to placebo, oral sumatriptan was used as an active control for assay sensitivity. The primary endpoint was freedom from pain at two hours post administration of study medication. The study participants were randomly selected to receive one of the six doses of rimegepant (10, 25, 75, 150, 300 or 600 mg), 100 mg sumatriptan or placebo. Participants were informed to return to the study site within seven days after taking their assigned dose to go over the electronic diary, report any adverse events and receive safety monitoring (vital signs, ECG, and lab tests). Those who were eligible for this study included male and female participants between the ages of 18 and 65 who reported at least one year history of migraines (with or without aura). The reported migraines must have started before the age of 50 and must have had between two and seven attacks of moderate to severe intensity in each of the three months leading to the trial. Patients were allowed to use preventative medication if the dose was stable three months prior to beginning the study. Exclusions from this study included those with a history of basilar type or hemiplegic migraines, those who did not

receive relief from triptans, history of stroke, heart disease, coronary artery vasospasm, other significant heart disease, uncontrolled hypertension/diabetes, HIV, major depression, dementia, psychiatric conditions, or other significant neurological conditions that might interfere with study assessments. Women who were breastfeeding, currently pregnant or those of childbearing years who were unwilling or unable to use contraceptive during the study were also excluded (Marcus et al, 2014).

Patients who did not experience relief at the end of two hours after dosing were permitted to use rescue medication: aspirin, ibuprofen, acetaminophen, another NSAID, anti-emetics, or baclofen. The current standard of care prescription medication was allowed if it was 48 hours post dose of the study medication and if all the assessments were completed via the electronic diary. Pain intensity level was measured using a four-point scale at two hours post dose (no pain, mild, moderate, or severe). Secondary endpoint measurements were total migraine freedom, freedom from photophobia, phonophobia or nausea at two hours post dose and sustained freedom from pain between two to 24 hours (Marcus et al, 2014).

Of the 1026 participants that were enrolled in the study 812 (79.1%) completed the study. The most common reason for not completing the study was because the participant did not treat a moderate to severe migraine headache. Other causes for not completing the study included being lost to follow up and withdrawing consent. The 150 mg rimegepant group was the most effective at obtaining pain freedom at two hours post dose with 32.9% (28/85) of the participants from the group reporting freedom from pain which was significantly higher than placebo ($p<0.05$). The sumatriptan group reported 35% pain freedom ($p<0.05$). The 75/300 mg groups also reported superiority to placebo in obtaining freedom from pain at two hours with 31.4% and 29.7% ($p<0.05$). When evaluating secondary endpoints (total migraine freedom: no pain, nausea,

photophobia or phonophobia), the 75 mg dose was most effective with 28.2% of participants reporting total migraine freedom at two hours post dose when compared to placebo ($p<0.001$). The sumatriptan and 150/300 mg dose groups also reported superior outcomes when compared to placebo when providing freedom from pain at two hours post dose. When measuring other secondary endpoints (sustained pain freedom from 2-24 hours, sustained pain freedom from 2-48 hours, pain relief two hours and sustained pain relief from 2-24 hours post dose) the sumatriptan, 75, 150, 300 and 600 mg groups all performed better than placebo. When measuring freedom from migraine symptoms (nausea, phonophobia and photophobia) two-hours post dose, the sumatriptan, 75, 150, and 300 mg groups performed significantly better than placebo. By 48 hours post dose, 88.5% of patients reported pain relief and freedom from nausea, photophobia and phonophobia. Thirty-five- and one-half percent (288/811) of the participants used rescued mediations. Rescue medications were used most often in the placebo group (Marcus et al., 2014)

Marcus et al. (2014) reported the most common adverse event as nausea and was dose dependent. Two percent of the placebo participants reported nausea, whereas 3% of the 75 and 150 mg group, 4% of the 30 mg group and 8% of the 600 mg group reported nausea. Most adverse events were reported as mild to moderate, and no deaths occurred. Vital sign and ECG evaluation revealed no clinically significant adverse effects from the medication. There were only two reports of elevated liver enzymes, one in the 75 mg group and one in the placebo group. These elevations resolved on their own without major complication.

From the data and statistical analysis provided it can be concluded that the study medication (rimegepant) was superior to placebo in eliminating pain and associated migraine symptoms at two hours post dose and beyond. It is also safe to conclude that nausea was the most common side effect but there was no significant difference in the number who experienced

nausea at the 75 mg and 150 mg dose when compared to placebo. There was an increase in nausea as the rimegepant dose increased, however the increased doses did not always show an increase in efficacy when eliminating pain and migraine symptoms when compared to the 75 and 150 mg doses. There were no cardiovascular side effects reported when compared to placebo. The sumatriptan had two participants report chest discomfort. (Marcus et al., 2014).

Marcus et al. (2014) discussed one limitation is the single dose design of the study. This did not allow a long-term evaluation of repeated dosing or efficacy. The overall sample size was moderate; however, each group (compared to placebo) was relatively small. Also, this study excluded those with cardiovascular disease which is a major contraindication for those taking triptans (the mainstay of migraine treatment at this time). A study allowing those with significant cardiovascular disease would allow the evaluation of the safety of rimegepant in this specific population and determine if this is a better alternative for this group of patients.

Lipton et al. (2019) performed a phase three, multi-center, randomized, double blind study from July 2017 to January 2018 to evaluate the safety and efficacy of 75 mg of rimegepant compared to placebo in the acute treatment of a migraine headahce. A total of 1186 patients entered the trial at 49 locations across the United States. A total of 1080 participants completed the trial with 594 in the rimegepant group and 592 in the placebo. Men and women over the age of 18 were recruited to participate based on specific criteria which included having migraines with or without aura, having at least a one-year history of migraines, onset before the age of 50, two to eight attacks per month and if on preventative medication to been on a stable dose for at least three months prior to the study. Exclusion criteria included a history of any clinically significant or unstable medical conditions, alcohol or drug abuse or substance use disorder. The average age of the participant was 40.6 years with 88.7% of the participants being female. The

average migraines per month was 4.6 among the participants. Fifty one percent of the participants reported photophobia as their most bothersome symptom. Following a screening process, patients were randomized at a 1:1 ratio for rimegepant and placebo. Patients were either given a single 75 mg rimegepant or placebo tablet and told to take the pill upon onset of moderate or severe migraine. They were asked to document in an electronic diary before taking their study medication and at set intervals after the dose about their pain and any associated symptoms (nausea, phonophobia or photophobia). Patients were required to return to the testing center seven days after treatment for review of the diary and medical evaluation (Lipton et al., 2019)

Primary study endpoints were freedom from pain and freedom from most bothersome symptoms at two hours post dose. Secondary endpoints included freedom from photophobia and/or phonophobia, pain relief, freedom from nausea at two hours post dose, how likely the patient was to use rescue medication within 24 hours post dose, sustained freedom, and relief from pain from 2 to 48 hours, pain relapse and ability to return to normal function at two hours post dose. Safety evaluation included assessment of vital signs, adverse reactions, EKG, height and weight, routine lab testing and suicide screening (Lipton et al., 2019)

In assessing the primary endpoints, 19.6% of the participants in the rimegepant group reported pain freedom at 2 hours post dose compared to 12.0% in the placebo group (95% CI, 3.3 to 11.9; $p<0.001$). 37.6% of the rimegepant group reported freedom from their most bothersome symptom two hours post dose compared to 25.2% in the placebo group (95% CI, 6.9 to 17.9; $p<0.001$). The secondary endpoints which showed statistical significance were freedom from photophobia at two hours (37.4% vs 22.3% in placebo; $p<0.001$), freedom from phonophobia (36.7% vs 26.8% in placebo; $p= 0.004$), and pain relief at two hours (58.1% vs 42.8% in placebo;

$p<0.001$). All other secondary endpoints did not show significant difference and no statistical inferences were made based upon this data. When evaluating the safety of 75 mg of rimegepant, nausea was the most commonly reported adverse event (1.8% in rimegepant vs 1.1% in placebo). Another common adverse event that was reported was urinary tract infection (1.5% in rimegepant vs 1.1% in placebo). 2.4% of the rimegepant group reported increased liver enzymes compared to 2.2% of the placebo group but neither of the groups reported an increase in more than three times the upper limit of normal (Lipton et al., 2019)

From this study, the authors concluded that rimegepant 75 mg was superior to placebo in eliminating pain from an acute migraine headache at two hours post dose in addition to eliminating the most bothersome symptom. Rimegepant was also shown to be superior in pain reduction, eliminating phonophobia and photophobia at two hours post dose. Nausea and UTI were the most common side effects reported but these were similar in each group. Limitations that the authors noted were not having another migraine medication to compare rimegepant to. Also, this specific study did not examine or compare long term use or subsequent use of rimegepant and the possible efficacy and safety of continued use over a longer period. Finally, this trial did not evaluate the safety of rimegepant in patients with cardiovascular disease although no adverse cardiac events were reported (Lipton et al., 2019)

Croop et al. (2019) performed a study to evaluate the efficacy, safety, and tolerability of rimegepant orally disintegrating tablets for the acute treatment of migraine versus placebo in 2019. This was a double blinded, randomized, multicenter (69 trial centers across the U.S.), phase three trial. The study recruited adults over the age of 18 who had a history of migraines with or without aura for at least one year, migraine onset before the age of 50, at least two but no more than eight migraine attacks of moderate or severe intensity per month and fewer than 15

days per month with a migraine. The participants also had to be able to determine a tension type headache versus a migraine headache and those who were on preventative medications had to be on a stable dose for three months or more. Participants were excluded from the trial if they had any medical conditions that might interfere with study assessments of efficacy and safety or might expose the participant to unnecessary risk of an adverse advent, showed evidence or had been treated for alcohol abuse in the past 12 months, had a history of drug or other allergy that made them unsuitable for participation and/or had an ECG/lab test findings that raised safety concerns about tolerating the medication. 1446 total participants were enrolled and 732 were randomly assigned to the rimegepant group and 734 to the placebo group. 1375 participants received treatment (rimegepant = 682, placebo = 693) and 1351 participants were evaluated for efficacy of treatment (rimegepant = 669, placebo = 682). Of all the participants 85% were female, 70% identified as white, the mean age was 40.2, average BMI was 30.9, and 70% had migraines without aura. The demographics were evenly distributed across both groups.

After receiving group designation, participants were given a single dose of either the placebo or rimegepant and instructed to use it to treat a migraine attack with pain of moderate or severe intensity after answering eDiary questions about their current pain/symptoms, and identifying their current most bothersome symptoms of photophobia, photophobia, and nausea. They were instructed to enter information about their symptoms into their eDiary at set intervals over a 48-hour period. Pain intensity, presence or absence of associated symptoms and ratings of functional disability were assessed at the onset of the attack and at 15, 30, 45, 60 and 90 minutes and at 2, 3, 4, 6, 8, 24 and 48 hours post dose. Functional disability was rated on a four-point scale (0 was normal, 3 required bed rest). Participants were allowed to take rescue medications (aspirin, ibuprofen, acetaminophen), Naprosyn, antiemetics or baclofen after two hours post

dose. Within seven days of the treated attack, participants returned to their assigned study site for review of eDiary, assessment of medication compliance and monitoring of safety and tolerability. Participants that did not have a moderate to severe attack within 45 days were instructed to return study medication and eDiary to the study center (Croop et al., 2019)

Results were measured by freedom from pain and freedom from most bothersome symptoms associated with migraine (phonophobia, photophobia or nauseous) two hours post dose. Pain rated on four-point scale (0-none, 1-mild, 2- moderate, 3- severe). Most bothersome rated as 0-absent or 1- present. There were 21 endpoint measurements broken into three categories which were measured at two hours, 90 min and 60 min post dose. The endpoint measurements included relief of pain, freedom from photophobia/phonophobia/nausea and the ability to function normally. The study also measured durability of effect of drug which included assessment of treatment effects from 2 to 48 hours. Another point of evaluation was the use of rescue medications within 24 hours of dosing and pain relapse within 2 to 48 hours after taking the medication. Safety and tolerability assessment included adverse events, serious adverse events, ECG, vitals, physical measurements, routine lab tests and Sheehan Suicidality tracking scale (Croop et al., 2019)

Overall, rimegepant was shown to be superior two hours post dose to placebo in providing freedom from pain (21% vs 11% $p<0.0001$) and freedom from risk of most bothersome symptoms (35% vs 27% $p=0.0009$). Rimegepant was superior to placebo on all secondary endpoints as listed above. Nausea was the most reported adverse event (2% vs 1%), and UTI was the second most reported adverse event (1% vs 1%). One patient in each group presented with elevated transaminase concentration greater than three times the upper limit of

normal, however the was no signs of hepatotoxicity, no elevations of bilirubin at twice the upper limit of normal, and this was found to be statistically insignificant (Croop et al., 2019)

Strengths of the study include that this was the third study performed showing similar results when using rimegepant. The study had a large sample size and was a double blinded, randomized multicenter study performed at numerous centers across the United States. The study creators attempted to evaluate the effectiveness and safety across several endpoints and overall achieved results showing higher efficacy of rimegepant compared to placebo. The study has some areas of weakness including uneven distribution of gender and race, although each group had roughly the same distribution when compared to the total number of participants. The conclusion of efficacy was primarily based upon subjective data with no measurement of CGRP levels in relation to administration of medication and levels of pain. This may be hard to measure but would provide tangible evidence of effectiveness. This study also did not compare the safety/efficacy to other established migraine treatments. The fact that the study was a randomized, double-blind study allows for more reliability of the results. The study data was also made available to other researchers and organizations to evaluate thus providing another level of transparency (Croop et al., 2019)

BHV3000-201 was a phase 2/3 multi-center, open label, long term safety study performed to evaluate the safety of rimegepant 75 mg in the acute treatment of migraines (L'Italien et al., 2022). This study took place over 98 centers across the U.S. from August 2017 until August 2019. Three thousand nineteen participants were enrolled with 2867 entering the initial or observational period and 1908 participants enrolling in the long-term treatment period with 1800 receiving treatment during the long-term treatment phase and 1197 completing the long-term treatment phase. The most common reason for discontinuation was noncompliance

and withdrawal by participants. Inclusion criteria for this study included adults over the age of 18, a minimum of one year history of migraine with or without aura, at least 2-14 migraine attacks per month (moderate to severe in intensity) and preventive medication was allowed if the dose had been stable for three months. Exclusion criteria included those with a history of basilar/hemiplegic migraine, HIV, uncontrolled/unstable/recently diagnosed cardiovascular disease (ischemia heart disease, coronary artery vasospasm and cerebral ischemia), uncontrolled hypertension/diabetes, BMI > 30, or a history of gastric/small intestinal surgery or a disease-causing malabsorption. The study groups were divided into three separate categories based upon self-reported frequency of moderate to severe migraines within a one-month period. Each group was treated with 75 mg rimegepant and broken down as follows: 2-8 attacks per month taking rimegepant as needed for 52 weeks (683 participants), 9-14 attacks per month taking rimegepant as needed for 52 weeks (271), and 4-14 attacks per month taking rimegepant every other day with the option to take as needed for up to 12 weeks (243). Participants were expected to track the frequency, severity, and associated symptoms in an eDiary. Migraine days per month were defined as the number of migraines within a 4-week period. To complete the 52-week period, participants must have met certain criteria and remained compliant with eDiary entries during the initial phase of the study.

From the above study, several post hoc analyses have been performed. One of particular importance was an analysis performed by L'Italien et al. (2022) which explored the number of monthly migraine days experienced by the participants throughout this long-term study. This post hoc analysis specifically looked at those participants who reported six or more monthly migraine days (MMD) per month and who were placed in the as needed treatment group (every other day plus as needed group was not included in the analysis). Primary outcome measures

were median time to 30% or greater and median time to 50% or greater reduction in MMD over the study period. Assessment of these endpoints was completed at four-week intervals until the 52-week endpoint. 1044 participants from the study were included in this analysis with a mean age of 43.2 years and 91.1% of the participants being female. The average MMD at the beginning of the study was 10.9 with 163 of the selected participants taking prophylactic migraine medication. Of the 1044 participants analyzed for this study, 635 completed the study. The participants were divided into three clusters depending on reported number of MMD. Cluster one was defined as the highest MMD over time with an average of 14.8 MMD, Cluster two was moderate with a mean of 11.8 MMD and Cluster three was the lowest MMD with an average of 8.7 MMD. Across all clusters the median time to 30% or more reduction in MMD was 12 weeks and 32 weeks for a 50% or more reduction in MMD. At the conclusion of the study, 78.6% of participants reported a 30% or more reduction in MMD and 63.3% reported a 50% or more reduction in MMD. Those participants with a higher reported MMD had a reduced rate of achieving 30% or 50% reduction of MMD. Cluster three achieved a 30% reduction in MMD more quickly than cluster two or one. Median time to 30% or greater MMD reduction was not reached in Cluster 1, 20 weeks in Cluster 2 and eight weeks in Cluster 3. On average, Cluster 3 reached 50% or more reduction within 16 weeks compared to Cluster 1 and 2 which did not achieve mean 50% or more reduction MMD within that timeframe. Greater reductions of MMD were noticed in the first weeks of treatment with a stable rate of reduction in MMD over the remainder of the study (L'Italien et al., 2019)

This study was performed over a substantial amount of time (52 weeks) and allowed for more realistic dosing as patients were allowed to take rimegepant as needed for acute migraine attacks however there was no control group, and this was an open label study. This study was

composed primarily of female participants. Although not definitive, this post hoc analysis shows that there might be a potential for rimegepant to reduce the number of monthly migraine days with as needed use.

Johnston et al. (2022) performed a post hoc analysis of a phase 2/3 safety study of rimegepant in the acute treatment of migraine (the same study that L'Italien analyzed for the evaluation of reduction in MMD). This analysis looked at the data from the open label part of the study which was an optional component of the study after the initial phase was completed. The study was conducted at 98 centers across the U.S. over approximately a two-year period. This analysis looked at data from 1044 subjects who reported six or more monthly migraine days. These subjects were part of the group taking rimegepant on an as needed basis. Eligibility consisted of being an adult with a minimum migraine history of one year and no history of hemiplegic or basilar migraines. Use of triptans was not allowed, however use of prophylactic migraine treatment was permitted if the dose was stable for three months prior to beginning the study. Subjects of this study were expected to treat an acute migraine with 75 mg of rimegepant orally once daily as needed for up to one year. Primary outcome measures were median time to reduction of greater than 30% and 50% in monthly migraine days. These were assessed at four-week intervals from start until week 52. In addition to measuring the number of monthly migraine headaches, this analysis also looked at long term health-related quality of life in the form of quality-adjusted life years (QALY). To measure QALY a migraine-specific quality of life instrument was used, and data was collected at set intervals over the 52-week period. By the end of the 52-week mark, the mean MMD decreased to 8.9 (starting point of 10.9). Also, during this time, mean monthly tablet use remained stable and slightly decreased from 7.9 tablets per month to 7.3. This statistic helps to support that prolonged and consistent use of rimegepant does

not lead to more headaches and stable dose of medication use over a prolonged period. Overall, this resulted in a 2.0 MMD reduction from baseline over the year that these subjects were taking rimegepant. A reduction in overall migraines per month also increases a patient's quality of life, which was reflected in the quality-of-life measurements obtained in this analysis.

The author lists some of their limitations to their study. This was an open label study with no comparison to placebo and how placebo might affect a monthly reduction in migraines. Another limitation they listed was that the analysis did not control the use of other preventive medications (Johnson et al., 2022) This could make it difficult to differentiate the true cause of the reduction in monthly migraines. The source of the reduction could be due to rimegepant, the preventative medication or a potentiating effect of both medications combined. This being a post hoc analysis opens to the possibility that the data might be skewed to present a certain point. Although the data certainly points towards a reduction in migraine headaches over the 52-week period, there was no established p value or confidence interval for each subgroup.

Mechanism of Action, Efficacy and Safety Profile of Lasmiditan

Lasmiditan was approved by the FDA in 2019 for the acute treatment of migraines with or without aura in adult patients. Lasmiditan is a serotonin receptor 5-HT1 agonist. It works by "decreasing the activation and sensitization of the trigeminal nerve system within the meninges by acting centrally on trigeminal neurons and peripherally on primary trigeminal afferents and cell bodies within the trigeminal ganglion. It does not activate 5-HT1B receptors in peripheral blood vessles, including coronary arteries and does not induce vasoconstriction" (ClinicalKey, 2022)

Farkkila et al. (2012) published the results of a randomized, double blind, placebo controlled, multicenter, parallel group, dose ranging study in 2012 to evaluate the efficacy and

tolerability of lasmiditan in the acute treatment of migraine headaches in the adult population. This study took place in five European countries across 43 migraine centers. Men and women between 18-65 with at least a one-year history of migraine with or without aura were included. Patients were excluded if they were taking prescription or herbal prophylaxis, vasoactive drugs, serotonin reuptake inhibitors or known C450 inhibitors. This study took place from July 8, 2009, to February 18, 2010. An initial 534 patients were screened and 512 were randomized. Three hundred ninety patients were reported to have finished the study. Patients were randomly assigned to a 50mg, 100mg, 200mg, 400 mg or placebo group. Patients were evaluated during a screening visit where a physical was performed along with ECG and labs. The groups were broken down as follows: 81 in the placebo group, 79 in the 50mg group, 81 in the 100 mg group, 69 in the 200 mg group and 68 in the 400 mg group. The average age of patients was between 38.7-42 years old. Eighty eight percent of the patients were female and 99% of patients were of white ethnic origin. On average, participants had approximately three migraines per month and most patients reported no aura before the migraine attack (Farkkila et al., 2012).

The patients were told to treat their next attack within four hours of onset if their headache was considered moderate or severe. Primary endpoint measurements where headache relief at two hours post dose and to evaluate safety over a 24-hour period after taking lasmiditan. Secondary endpoints included: pain freedom at two hours, headache response over time, associated symptoms, time to meaningful pain relief, headache recurrence within 24 hours, use of rescue medications between 2 to 24 hours, and clinical disability within 24 hours. A paper diary was used to report symptoms at onset and at set intervals after taking medication up to 24 hours after taking lasmiditan. Headahces were rated on a four-point scale (none, mild, moderate, or severe), associated symptoms (nausea, vomiting, photophobia, phonophobia) were marked as

either absent or present and global impressions was rated on a seven-point scale (very much better, much better, a little better, no change, a little worse, much worse and very much worse. Within 14 days of taking a dose of study medication, patients returned their diary, and a physical exam was performed along with a ECG and lab work (Farkkila, 2012).

In evaluating response to medication at two hours post dose, 25.9% of the placebo group reported a decrease in pain compared to 43% in the 50 mg group ($p=0.022$), 64% in the 100 mg group ($p<0.0001$), 51% in the 200 mg group ($p=0.0018$) and 65% in the 400 mg group ($p<0.0001$). Pain freedom at two hours was only statistically significant in the 200mg and 400 mg group with 19% reporting freedom from pain in the 200 mg group and 28% reporting pain freedom in the 400 mg group compared to 7.4% in the placebo group. Overall, there was a higher decrease in associated migraine symptoms (photophobia, phonophobia, nausea and vomiting) in the lasmiditan groups as compared to placebo. Headache recurrence within 24 hours occurred at similar rates across all lasmiditan groups and placebo. Global impression was rated as very much better in 22.8-35.8% in the lasmiditan group compared to 16% in the placebo group (Farkkila, 2012).

When evaluating safety and tolerability of the lasmiditan versus placebo, adverse events were higher in the lasmiditan group when compared to placebo. Adverse events were defined as any abnormal symptoms up to 24 hours after taking the study medication. Sixty five percent of the 50 mg group, 72% of the 100 mg group, 86% of the 200 mg group and 84% of the 400 mg group reported at least one adverse event compared to 22% in the placebo group. Dizziness, fatigue, vertigo, and paresthesia were among the most reported adverse events. Most events were rated as mild to moderate but between 20%-44% of the adverse events were reported as serious in the lasmiditan groups while only 6% were classified as severe in the placebo group. One

patient was hospitalized due to dizziness after taking a 200 mg dose of lasmiditan. Her ECG showed sinus bradycardia up to four hours after the study medication was taken, however after receiving IV infusion of normal saline she completely recovered. No deaths were reported in the study. Vital signs, lab tests, ECG and physical exams performed at follow up after taking the study medication did not show any clinically relevant drug related changes (Farkkila, 2012).

Overall, the authors concluded that lasmiditan performed significantly better at pain reduction at two hours post dose across all groups when compared to placebo. The authors also concluded that for most of the other secondary endpoints that most treatment groups performed better than placebo. Based off the data from this study, it appears that adverse events are dose dependent and the higher the dose the more incidence and severity of adverse effects. There were little to no reports of any vasoconstrictive adverse events (chest, neck, or jaw heaviness/tightness or pain). The 100 mg dose appeared to perform the best when eliminating pain and reducing side effects. Limitations to the study were noted as sample size, single dose evaluation, it was a short-term study and possible cultural differences in evaluating side effect definitions/descriptions (dizziness versus vertigo). Another aspect to be aware of was that the funding was provided by the manufacturer of lasmiditan. The manufacturer also participated in data collection, analysis, interpretation and writing of reports (Farkkila, 2012).

Kuca et al. (2018) performed a phase three, double blind, randomized, multicenter trial (SAMURAI) between April 2015 and August 2016. The purpose of this study was to determine the efficacy and safety of 200 mg and 100 mg lasmiditan compared to placebo. The primary endpoint was pain freedom at two hours and the secondary endpoint was most bothersome symptom freedom at two hours. Study population included those that were male and female, 18 years or older, diagnosis with migraine with or without aura; a history of disabling migraine for

at least 1 year; MIDAS score of greater than 11; migraine onset before age 50 and a history of three to eight attacks per month. Exclusion criteria included those with a history of chronic migraine or other primary/secondary headache diseae within past 12 months, medication over use headache with a headache frequency of > 15 headache days a month; initiation or change in migraine prevention medication within three months before screening, known coronary artery disease, clinically significant arrhythmia, uncontrolled hypertension, or those at higher risk of seizures.

At the first visit, patients were assessed for eligibility and randomly assigned (1:1:1) lasmiditan 200 mg or 100mg and placebo. Patients were also randomly given a second dose of lasmiditan or placebo for reoccurring migraines or as a rescue medication. The lasmiditan group was either given an additional dose of lasmiditan or placebo and the placebo group was given another dose of placebo. Once eligibility was confirmed, patients were asked to treat their next migraine attack within four hours of onset if the attack could be described as moderate or severe and not improving. Rescue medication was not allowed until at least two hours post dose and could be taken up to 24 hours after the initial dose. An electronic diary was used to record the date and time of the migraine, pain level and any associated symptoms in addition to when the first dose was taken. Current level of pain, presence of associated symptoms, presence of vomiting, and level of disability were also recorded across several intervals starting at baseline and up to 48 hours post dose. Those reporting any adverse effects or anything unusual received a phone call from the from the study site. Additional assessments for safety were performed at the conclusion of the study and included a physical exam, lab work, vital signs, ECGs and a suicide assessment. Treatment emergent adverse event (TEAE) were defined as an event that started or

worsened after the first dose of the study medication and occurred within 48 hours of last dose (Kuca et al., 2018)

Of the 2231 patients randomized, 1856 used the first dose and 1805 completed the study. The groups were relatively equal with the 200mg group having 609 participants, 100mg 630 and placebo 617. Discontinuation rates were comparable across groups. Patient demographics: majority were female, white with a mean age of 42 years. 77.9% of the patients reported at least one cardiovascular risk factor. Average time of migraine history was 19.3 years with an average of 5.1 migraines within the previous three months. Migraine associated symptoms and the most bothersome symptom were comparable across all three groups (Kuca et al., 2018)

Lasmiditan 200 mg and 100 mg were significantly more effective at providing freedom from pain at two hours when compared to placebo. 32.2% of the 200 mg group ($p<0.001$) and 28.2% of the 100 mg group ($p<0.001$) reported pain freedom at two hours compared to 15.3% of the placebo group. The lasmiditan group also showed greater efficacy in eliminating the most bothersome symptom at two hours post dose (40.7%, $p<0.001$ for 200 mg, 40.8%, $p<0.001$ for 100 mg, 29.5% for placebo). The lasmiditan group also showed improved efficacy at headahce and other associated symptom relief at two hours. The placebo group was more likely to use a second dose of medication, 59.9% compared to 31.9% (200mg group) and 39.0% (100 mg group) (Kuca et al., 2018)

Kuca et al. (2018) reported that the lasmiditan group reported more adverse events than the placebo group. 42.7% of the 200 mg and 36.3% of the 100 mg group reported at least one adverse event compared to 16.4% in the placebo group. The adverse effects that occurred in greater than 2% of the lasmiditan groups were dizziness, fatigue, lethargy, nausea, paresthesia, and somnolence. No significant cardiovascular events occurred. Compared to baseline and across

all study groups, no clinically significant difference was noted on lab work, ECGs, vital signs, or physical exam.

From the study design and data presented it can be concluded that both doses of lasmiditan are effective are producing freedom from pain at two hours and even beyond. Lasmiditan is also effective at providing relief from phonophobia and photophobia compared to placebo. The lasmiditan group did report more adverse effects, mainly CNS effects, however these were reported as mild or moderate in severity. No serious adverse effects were thought to have occurred due to lasmiditan (Kuca et al., 2018)

Strengths of this study include a significant study size, double blind, and randomization. Tangible data points and attempt to make participant reporting as subjective as possible. Thorough follow up with patient after study and medication administration and adequate post administration health evaluation. Limitations: limited evaluation of male and people of other ethnicity, younger or older age, previous failure with triptans and other comorbid conditions. Study performed and funded by drug manufacture (bias), but data made available on clinical trials website.

Loo et al. (2019) performed a post hoc analysis of two randomized, double blind phase three studies of lasmiditan (SAMURAI and SPARTAN) to evaluate the safety and efficacy of concomitant use of migraine prevention medications. The purpose of the SAMURAI and SPARTAN studies were to evaluate how effective and safe lasmiditan was compared to placebo in eliminating headache pain and migraine associated symptoms (nausea, photophobia and phonophobia). Both studies were performed at multiple centers. SAMURAI took place in the United States and SPARTAN took place in the United States, United Kingdom, and Germany. When combining the two studies, the total study population came to 3,981 and out of these

patients, 17.5% were using migraine prevention medication. On average those using migraine prevention were four years older and had been diagnosed with migraines for three years longer compared to those who were not using migraine prevention. 82.5% of those using prevention only use one medication while 17.5% were using two or more medications. Anti-epileptic medications accounted for 35% of preventative medications, beta blockers 32.3%, antidepressants at 25.5% and botulinum toxin A at 5.7%. Those using preventive methods did not report severe migraine at baseline as frequently as the non-preventative group, but the two groups had similar distributions of migraine related disability. Both groups (preventative and non-preventative) had significantly higher percentages of pain freedom at two hours and most bothersome symptom relief post dose compared to placebo. The non-preventive group showed higher percentages for these primary endpoints when compared to the preventive group, however they were not statistically significant.

No increase in adverse events comparing preventive medication group to non-preventive group. Overall, no increased efficacy when using a preventive with lasmiditan but still more effective than placebo in acute migraine treatment. No increase in adverse events with preventative medication. Limitations as stated by study was population size did not allow proper subgrouping of each medication. The study does not evaluate long term effects of lasmiditan use and preventive use. Potential bias: studies performed by manufactured of lasmiditan. Study data has been made available to any who request it for evaluation (Loo et al., 2019)

The CENTURION study was a multicenter, double blind, phase three study performed to evaluate the efficacy and consistency of response to lasmiditan in the acute treatment of migraine across four attacks (Ashina et al, 2021). A total of 1613 patients were randomized, and 1049 patients provided enough data to assess consistency. Seventy percent of the patients were in

Europe, average attacks per month were 4.9, average age was 42, average duration of migraines was 17 years, and most participants were female. This study was performed in Europe, North America, and Asia. Inclusion for this study included those 18 and older, diagnosis of migraine with or without aura; history of disabling migraine, Migraine Disability Assessment Test (MIDAS) score of 11 or greater, onset of migraine prior to age 50, and three to eight migraine attacks per month but less than 15 headache days per month over the last three months. Patients were not excluded if they had known cardiovascular risk factors except those with a history of hemorrhagic stroke. Patients taking preventive migraine medications were allowed if they were stable on their dose for the previous three months. Those who had insufficient response to triptans were also predefined for evaluation during this study. Participants were assigned to one of the three treatment groups for four attacks: lasmiditan 100 mg, lasmiditan 200 mg, control group with a placebo and lasmiditan 50 mg for either attack three or four. Patients were asked to treat consecutive migraine attacks if possible and to treat their migraine within four hours of onset if the migraine could be described as at least moderate in severity and not improving and no other treatment had been taken. The period of treatment was four months or until all four attacks had been treated with study medications. The patients were contacted via phone at one month post randomization or after the first dose (depending on which one was sooner) and at three months post randomization. Participants were required to visit their designated site two months after randomization. If rescue medication was needed or if the patient experienced recurrent migraine, they were allowed to take their unexcluded medications at two hours post dose. Triptans, ergotamines, opioids and barbiturates were not allowed within 24 hours after taking the study medication (Ashina et al., 2021).

Primary endpoints for this study were pain freedom at two hours post dose during the first attack and pain freedom at two hours post dose in at least two out of the three other attacks. Seconday endpoints were pain relief at one and two hours, pain freedom at one-hour, sustained pain freedom at 24 and 48 hours, freedom from functional disability at two hours, pain freedom at two hours in patients with an insufficient reponse to triptans, most bothersome symptom free at two hours, rescue medication use between 2-24 hours and those who reported pain freedom at two hours with recurrence within 24 or 48 hours. Patients were asked to report the response to the medication in an eDiary at set intervals post dose up to 48 hours after administration. They were asked to specify pain, most bothersome symptoms, and level of interference of normal activities from the migraine and how those were impacted post dose. They were also asked to record any adverse effects they experienced post dose (Ashina et al., 2021)

Ashina et al. (2021) reported lasmiditan was superior to placebo at providing freedom from pain at two hours. 29.3% of the lasmiditan 200 mg group and 25.8% of the 100 mg group reported pain freedom at two hours compared to 8.4% in the placebo group ($P<0.001$). Lasmiditan also performed significantly better in the subsequent attacks with 24.4% of the 200 mg group and 14.4% of the 100 mg group reporting pain freedom at two hours in two of the three remaining attacks compared to 4.3% in placebo ($P<0.001$). Both doses of lasmiditan performed superior to placebo in most of the other secondary endpoints as well with at least a $p<0.01$ in all gated secondary endpoints. A total of 22 patients reported one or more serious adverse events and the incidence was similar across all groups. 53% of the 100 mg group and 61% of the 200 mg group reported at least one adverse event compared to 22.4% in the placebo group. The most common reported event was dizziness (22.3% in the 100 mg group, 26.5% in the 200 mg group and 4.6% in the placebo group).

In conclusion, this study presents data showing that lasmiditan is superior to placebo in providing freedom from pain at two-hour, freedom from most bothersome symptom at two hours, pain recurrence within 24 or 48 hours, migraine related disability was improved and those who had insufficient response to triptans reported superior pain freedom when compared to placebo. These results are consistent with the results of other phase three lasmiditan studies. The lasmiditan groups did report more adverse events (dizziness, paresthesia, fatigue, nausea, vertigo, somnolence, hypoesthesia, muscular weakness, asthenia and feeling abnormal) when compared to placebo, however these were reported to be generally mild to moderate and consistent with findings from other phase three trials. Limitations were that the control group took only three doses of placebo instead of four. The dose of lasmiditan in the control group could have added to adverse events. In evaluating insufficient reponse, the authors admit that there is not universally accepted definition of triptan insufficient response meaning this data should be interpreted and analyzed with more scrutiny (Kuca et al., 2021).

Brandes et al. (2020) performed a study coined GLADIATOR to assess the long-term safety and efficacy of 100 and 200 mg of lasmiditan in the acute treatment of migraine headaches. This study examined the use of lasmiditan on an intermittent basis for up to one year. The main objective was to determine the long-term safety and tolerability of the medication and seconday objectives were to evaluate how well the medicine provided freedom from pain and the most bothersome symptom associated with migraines. To be eligible for this study the participants had to complete one of the phase three single attack studies (SAMURAI or SPARTAN) or were lasmiditan naïve, met the International Headache Society (HIS) criteria for migraine with or without aura, had some degree of moderate disability from a migraine and had

three to eight migraines per month but less than 15 headaches per month. This study took place over 199 centers in the United States, United Kingdom, and Germany.

Patients were randomly assigned at a 1:1 ratio to either the 100 or 200 mg group. Initially, 2171 patients were randomized, and 2030 patients took at least one dose of lasmiditan (991 in 100 mg group and 1039 in 200 mg group). The mean participant age was 43.3 years with 85.3% of the patients being female and 78.5% identifying as white. 82% of patients stated they had at least one cardiovascular risk factor (hypertension, hypercholesterolemia, smoking, obesity, diabetes mellitus, men over 40 or postmenopausal women). The participants were instructed to use the assigned medication within four hours of moderate to severe pain onset for each new migraine attack. Participants were informed that if the pain persisted after two hours or came back after going away that they could take another dose of lasmiditan at the same dose or another migraine medication between two and 24 hours after the initial dose (triptans, ergots, opiods and barbiturates were not allowed). An eDiary was used to describe migraine and medication administration, including any unusual side effects. If any unusual effects were recorded in the eDiary, the participants received a phone call from the study site to determine if this was an adverse event. If the event was noted to start or worsen within 48 hours after taking lasmiditan it was concluded that it was from the study medication. All randomized patients who took at least one study dose were evaluated by physical exam, vital signs, laboratory tests and ECGs. Pain severity was rated on a scale of 0-3 (none, mild, moderate, severe) and evaluated at baseline and set intervals up to 48 hours post dose. Most bothersome symptoms (MBS) were evaluated as photophobia, phonophobia or nausea at baseline and post dose. The study also analyzed the Migraine Disability Assessment and number of headaches over the past three months (Brandes et al., 2020).

In total, 19, 879 migraine attacks were treated and a total of 970 (47.8%) patients completed the 12 months of study. 21.8% of patients discontinued at their own request, 12.9% discontinued due to adverse effects and 9.7% were lost to follow up. Overall, 45.1% of the 100 mg group reported at least 1 adverse event and 52.5% in the 200 mg group reported an adverse event. The most commonly reported event was dizziness and most other events were reported as mild to moderate. Adverse events tended to trend downward as more attacks were treated. Fourteen adverse events were categorized as severe however none were considered due to treatment and no deaths were reported. No reports of cardiovascular adverse events due to vasoconstriction were reported (Brandes et al, 2020)

In assessing long term efficacy, 26.7% of those in the 100 mg group reported pain freedom at two hours post dose and 32.3% of those in the 200 mg group reported pain freedom. Participants in both dosing groups also reported freedom from most bothersome symptom at two-hour post dose (37.2%, 100mg; 40.5%, 200 mg). Similar results were seen throughout all four quarters of the study in both dosing groups. There were also significant decreases observed in mean change from baseline to 12 months in MIDAS scores (27.0 plus/minus 19.73 to 14.35 plus/minus 17.10; $p<0.001$) and number of headache days in past three months (14.37 plus/minus 10.07 to 8.49 plus/minus 9.85; $p<0.001$) (Brandes et al., 2020).

Authors of the study report similar safety and efficacy results from other placebo-controlled phase three trials performed prior to this long-term safety study. No new safety issues were identified, and conclusions were drawn that adverse events may decrease with long term use (this study specifically looked at those patients who treated five attacks or more to accommodate for patient attrition). The efficacy of MBS and pain freedom at two hours was consistent for the first five attacks and through each quarter assessed. The authors do identify

some limitations. First, they reported a high dropout rate compared to other migraine studies. This could have been due to study design or requirements. One of the most common reasons for study dropout was because of eDiary requirements and participants often complained about this requirement to site staff. Participants were required to make daily entries and during an attack entry at set intervals up until 48 hours after the attack. Another reason for the high drop rate was that participants were only allowed to treat when the pain was moderate and were asked to not drive for at least 12 hours after taking the medication. Conflicts of interest: Funding for the study was provided by the manufacture of lasmiditan and many of the authors are either employees or shareholders of the pharmaceutical company who makes lasmiditan (Brandes et al., 2020)

Comparison of Rimegepant and Lasmiditan

To date there have been no clinical studies performed directly comparing the safety and efficacy of rimegepant to lasmiditan, however a Cochrane review and literature search on PubMed revealed three meta-analysis which compared data from various clinical trials of these medications and how they compare in efficacy and safety. Two of these meta-analysis will be explored below.

The following meta-analysis was performed by Yang et al and published in October of 2021. This meta-analysis searched the Cochrane Register of Controlled Trials, Embase and PubMed from inception to March 5, 2020. Only double blind randomized clinical trials were included which focused on acute treatment of migraine attacks. A total of 261 articles were considered eligible and 62 articles met the inclusion criteria (64 total trials containing 46,442 participants). The primary outcomes which were analyzed were pain freedom at two hours post treatment. Secondary outcomes that were analyzed were pain relief two hours post treatment and treatment tolerability (assessed as adverse events or withdrawal due to adverse events). Two

authors assessed each article, data was extracted, and discrepancies were settled through discussion and consultation with a third author. Analysis was also restricted to medications and doses that were currently in widespread clinical use.

For the doses with widespread clinic use, all treatments were shown to have higher OR of achieving pain freedom at two hours when compared to placebo. Lasmiditan 50 mg was the lowest (OR, 1.65[95% CI, 1.08-2.50]) and eletriptan was the highest (OR 5.59 [95% CI, 4.50-6.94]). Triptans were also associated with higher OR of pain freedom compared to lasmiditan (OR, 1.72 [95% CI, 1.06-2.80] to OR, 3.40 [95% CI, 2.12-5.44]) and rimegepant (OR, 1.58 [95% CI, 1.07-2.33] to OR, 3.13 [95% CI, 2.16-4.52]). Comparisons between lasmiditan and rimegepant did not show significant difference in pain freedom or pain relief at two ours post dose. When assessing pain relief at two hours, triptans were associated with higher OR compared to lasmiditan (OR, 1.46 [95% CI, 1.09-1.96] to OR, 3.31 [95% CI, 2.41-4.55]) and rimegepant (OR, 1.33 [95% CI, 1.01-1.76] to OR, 3.01 [95% CI, 2.33-3.88]). When assessing adverse events reported in each study from medications with widespread clinical use lasmiditan 50 mg and 100 mg were associated with higher ORs for any adverse events than any other treatment (OR, 3.12 [95% CI, 1.86-5.24] and OR, 4.30 [95% CI, 2.80, 6.58]). Three triptans (rizatriptan, sumatriptan and zolmitriptan) were associated with higher OR for any adverse event compared to CGRP antagonists (OR, 1.96 [95% CI, 1.14-3.35] for rizatriptan; OR, 1.83 [95% CI, 1.09-3.09] for sumatriptan; and OR, 2.34 [95% CI, 1.39-3.95] for zolmitriptan. Overall, lasmiditan showed to have a 95.1% likelihood of causing an adverse event which was the highest OR out of all treatments (Yang et al., 2021).

Yang et al. (2021) were the first to perform a network meta-analysis comparing lasmiditan, rimegepant and Ubrogepant to other specific treatments for acute migraines. From

the analysis that was performed they found that the triptan group was more effective at providing pain freedom and relief at two hours when compared to the other three medications, however rimegepant, ubrogepant and lasmiditan performed like each other. They also concluded that certain triptans (rizatriptan, sumatriptan and zolmitriptan) had higher risks of adverse events and lasmiditan had the highest incidences of adverse events compared to any of the other treatments. Rimegepant and ubrogepant did not present with higher risk of adverse events when compared to placebo. The data analyzed from these studies infers that triptans are still superior to pain freedom and pain relief at two hours when compared to newer therapies, however there are now more options for those who have cardiovascular risk factors as triptans are often not used or contraindicated in those who have cardiovascular disease. As stated in the studies of lasmiditan and rimegepant above, these medications have been associated with higher ORs of pain relief and freedom at two hours compared to placebo. The adverse events associated with these medications have been shown to be well tolerated and non-serious, allowing for more treatment options in the care of acute migraines.

The authors of this study stated some limitations to their meta-analysis. They admit that this meta-analysis only focused on short term response and adverse events after a single dose and did not address the long-term safety and sustained efficacy of medication over a prolonged period. More studies and comparisons need to be performed evaluating the safety and efficacy of these medications over time and if the medications become effective over time. How these medications affect the number of migraines experienced per month should also be explored. The most important limitation was the fact that these were not direct comparisons studies and the data analyzed relies solely on how the data was analyzed and presented in each study. Performing a direct comparison of treatments will give the most accurate account of how these medications

perform in relieving pain from migraines and how safe they are for those taking them (Yang et al., 2021).

Polavieja et al. (2022) performed a network meta-analysis comparing the relative efficacy of lasmiditan versus rimegepant and ubrogepant and published their findings in 2022. They performed a general systematic literature review and identified phase 2-4 randomized control trials in the acute treatment of migraines. Abstracts and full text articles were reviewed independently by two authors and any issues were settled with a third reviewer. Those studies that were not in English and not randomized control trials were excluded from the analyze. An initial search identified 6240 records for review. Through an extensive process of eliminating duplicates and records that did not meet specific inclusion criteria a total of 12 studies were identified as adequate for the meta-analysis.

Polavieja et al. (2022) concluded from their network meta-analysis when evaluating pain freedom at two hours, all doses of lasmiditan (50, 100 and 200 mg), rimegepant and ubrogepant portrayed a higher likelihood of providing freedom from pain compared to placebo. Lasmiditan 200 mg showed a significantly higher likelihood at providing freedom from pain at two hours when compared to rimegepant (95% CI; OR 1.80 [1.49, 2.160] and ubrogepant. Lasmiditan 100 mg also showed a significant difference in providing pain freedom at two hours when compared to rimegepant 75 mg (95% CI; OR 1.39 [1.15, 1.67]) and Ubrogepant 25 and 50 mg. All doses of lasmiditan and rimegepant showed higher efficacy in reducing pain at two hours and one hour when compared to placebo. The 200 and 100 mg doses of lasmiditan showed a greater chance of reducing pain at 2 hours and 1 hour compared to rimegepant and ubrogepant. 50 mg of lasmiditan was comparable to rimegepant at achieving pain reduction at 2 hours and 1 hour. Both gepants and all doses of lasmiditan provided a higher likelihood of eliminating the most

bothersome symptom assocaited with a migraine at two hours when comparted to placebo. 200 mg of lasmiditan was assocaited with higher odds of eliminating most bothersome symptom when compared to the other medications however these results were not statistically significant and little difference was seen between the 100 mg dose of lasmiditan and rimegepant and ubrogepant. When evaluating sustained pain freedom at 24 hours, rimegepant, ubrogepant and all doses of lasmiditan performed superior to placebo. There was no statistical significance when comparing rimegepant and lasmiditan in providing sustained pain freedom at 24 hours. In evaluating adverse drug reactions, the most common that were reported with lasmiditan 50/100/200 mg were dizziness (9%/15%/17%), paresthesia (3%/7%/9%), sedation (6%/6%/7%), fatigue (4%/5%/6%), nausea/vomiting (3%/4%/4%) and muscle weakness (1%/1%/2%). In the trials of rimegepant, nausea was the most common adverse event reported (2%).

From this meta-analysis, the authors concluded that lasmiditan 200 mg performed better than rimegepant, ubrogepant and placebo in providing freedom from pain at two hours, and pain relief at two hours and one hour. Lasmiditan 100 mg also performed better than rimegepant in the above stated evaluation endpoints. Lasmiditan was shown to be associated with higher incidences of neurological side effects whereas rimegepant was associated with nausea (Polavieja et al., 2022). When comparing to other meta-analyses they report similar findings to the other studies performed with some variation in method and outcomes evaluated. This study also had data available from more recent clinical trials performed. This study also included 200 mg of lasmiditan for evaluation whereas one of the other larger studies did not. Another difference in this study is that it examined and compared pain outcomes prior to the two-hour mark. A limitation that the authors stated was that the actual number of studies for each outcome was relatively small and there was little evidence of long-term safety and efficacy. They also

reported a poor model fit for accurately evaluating and comparing adverse events and therefore could not quantify safety profiles. Finally, they reported some estimation of the data sources due to actual patient counts not always being published, and they estimated from the percentages provided, this might lead to slight variation from true values (Polavieja et al., 2022).

Discussion

Based on the thorough literature review formed in the prior section of this paper it can be concluded that rimegepant (when compared to placebo) has been shown to be statistically superior in providing freedom from pain at the two-hour mark. This was demonstrated through several trials with significant sample sizes. Rimegepant 75 mg was also shown to be statistically superior in providing freedom from most bothersome symptoms when compared to placebo. Rimegepant did show some superiority in other metrics, however freedom from pain and most bothersome symptoms were the primary endpoints of all the studies. Rimegepant has also demonstrated safety in short term, long term (up to 12 months) and repeated use when compared to placebo. Nausea and gastrointestinal upset were the most common side effects with reports in approximately 2-3% of the sample population. Although there have been concerns in the past with other first generation CGRP receptor antagonists causing liver enzyme elevations and paresthesias, these side effects were not reported with the use of rimegepant. There has been some concern raised about vasoconstriction since CGRP promotes vasodilation and rimegepant blocks these receptors. There were no serious cardiovascular events reported during any of the clinical trials where rimegepant was the main study medication, however the long-term effects of CGRP blockade are still being investigated. Several of the studies allowed patients with preexisting cardiovascular conditions that were stable to participate and there were no reports of rimegepant exacerbating these conditions. As of this writing, there have been no direct efficacy studies of rimegepant compared to another specific migraine abortive medication however there have been several meta-analyses comparing safety and efficacy of rimegepant and other abortive medications. Rimegepant was not shown to be the most effective oral agent in migraine abortion but was still superior to placebo. There has also been some data to suggest that repeated use of rimegepant correlates with a decrease in monthly migraine days without an increase in

rimegepant use or decreased effectiveness. Rimegepant has also been recently approved (May of 2021) for the use in migraine prevention, expanding upon the clinical use of its ability to reduce monthly migraines with limited side effects. Overall, from the data presented it can be concluded that rimegepant is effective in the acute treatment of migraine headaches and associated symptoms with a relatively low side effect profile. Further studies are needed to evaluate the long-term effect of CGRP blockade, safety in those with established cardiovascular co-morbidities, efficacy, and safety in the elderly (over 65) and pediatric populations (less than 18) and direct comparisons to other acute migraine treatment medications.

From the data provided throughout this paper, it is evident that lasmiditan is superior to placebo in eliminating acute migraines. Lasmiditan was also shown to be superior in eliminating the most bothersome symptoms associated with migraine. When compared to placebo, the side effects of lasmiditan were more prominent, especially effects on the CNS. Lightheadedness, dizziness, paresthesia, and fatigue were some of the most reported side effects. These side effects appeared to be more intense with the higher doses and there were some indications that these side effects lessened over time as the medication was used more. There is currently a caution listed under the medication side effects to not drive or operate heavy machinery within eight hours of taking lasmiditan. This could potentially limit or discourage some people from taking this medication; however, some migraines can be debilitating to the point where people cannot perform daily functions regardless. Lasmiditan works on a different 5HT receptor, so in theory it should not cause some of the chest heaviness or additional cardiovascular complications that have been theorized with the triptans. Cardiovascular or vasoconstrictive adverse events were not reported in trials where lasmiditan was the primary medication being studied. As stated above, there have been no direct comparisons performed between lasmiditan and any other abortive

therapies for migraine, however several meta-analyses have been performed. Lasmiditan was shown to be superior to placebo and CGRP receptor antagonists and some triptans, but overall, still inferior to the triptan class at providing pain freedom at the two-hour mark. Overall, it has been shown that lasmiditan is effective at aborting migraine headaches and reducing the most bothersome symptoms, however it has a higher side effect profile when compared to placebo and some of the other available migraine mediations. Lasmiditan has also been listed as a Schedule V substance (low abuse potential). Further studies are needed to evaluate the safety in those with established cardiovascular co-morbidities, efficacy, and safety in the elderly (over 65) and pediatric populations (less than 18), direct comparisons to other acute migraine treatment medications and the safety of long-term use when it comes to CNS suppression and abuse potential.

Rimegepant and lasmiditan have been shown to be effective in aborting migraine headaches and helping with most bothersome symptoms. Although not routinely used first line, these medications are another option for patients who have migraines that have not responded to traditional therapy or who have comorbid health conditions that prevent them from using traditional abortive therapies. According to the American Head Society's updated consensus on integrating new migraine treatments into clinical practice, Ailani et al state that up to 30% of those who are given a triptan for acute migraine treatment experience an insufficient response. These guidelines go on to explain criteria for initiating treatment with a gepant, ditan or neuromodulator device:

- The intervention must be prescribed/recommended by a licensed clinician
- The patient must be at least 18 years old,

- A diagnosis meeting the criteria set forth by the ICHD-3 migraine with/without aura or chronic migraine must be present
- A contraindication and/or inability to tolerate triptans or inadequate response to two or more oral triptans must have been proven

According to this guideline update, triptans should be avoided or used with caution in those with coronary artery disease, peripheral vascular disease, uncontrolled hypertension, and other vascular factors/disorders and gepants/ditans/neuromdulator devices should be explored as alternative in this patient population (Ailani et al, 2021). The studies analyzed throughout this paper did not specifically explore the safety/efficacy of triptans when compared to placebo or other migraine medications, but they are currently one of the first line medications indicated for moderate to severe migraine attacks. Several meta-analyses show that triptans are superior to placebo and other abortive therapies for migraines. Despite their first line indication, not all patients respond sufficiently and there is a theoretical risk of increased vasoconstriction. Rimegepant has also not be shown to cause medication overuse headaches and does not cause an increase in medication use over a prolonged period (a common problem with traditional therapy). Studies of these medications and medication classes continue and many more are expected to be conducted. There will likely be more data and discoveries made for their use in the acute management of migraine headaches and additional indications. Rimegepant and lasmiditan have been shown to be effective and safe in the acute treatment of migraine headaches. These medications are not yet first line treatments for moderate to severe migraines according to the American Headache Society, however they are safe and effective second line options when failure or contraindications exist for triptans or additional first line abortive therapies.

Conclusion

To summarize, rimegepant and lasmiditan have been shown through numerous clinical trials to be effective pharmacological interventions in the abortion of acute migraine headaches in the adult patient. The safety data also gathered from these studies has shown safety in short- and long-term use in addition to repeated use of the medication. Lasmiditan was shown to have a higher side effect profile when compared to placebo, but these side effects appeared to be mild/moderate in nature and no serious adverse events were observed. Rimegepant has a relatively low side effect profile when compared to placebo with nausea being the most prominent side effect.

Applicability to Clinical Practice

The American Headache Society recommends starting with NSAIDs, acetaminophen, non-opioid analgesics and/or caffeine combination products in the acute treatment of mild to moderate attacks and migraines specific treatments (triptans or ergots) for moderate to severe attacks. Treatment is recommended at onset to ensure effective pain management. In current clinical practice, lasmiditan and rimegepant are not recommended as first line abortive treatments by the American Headache Society. A patient must have a contraindication to using a triptan or have failed two oral triptans before coverage will be approved. These guidelines are important to keep in mind when dealing with patients who present with an initial onset of migraines or are dealing with refractory migraines. Although these medications are new and have been shown to be effective and safe, they are not always the most cost-effective option for the patient. On the other hand, if there is a patient who has tried several different medications with no improvement, rimegepant and/or lasmiditan are potential second line therapies.

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