

Addressing an Unmet Need for Acute Treatment of Migraine

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Migraine Is a Debilitating and Recurrent, Chronic Neurologic Disease^{1,2}

History dictates that the first migraine, or hemicrania—from the Greek meaning “hemi and crania,” was diagnosed in 1597, though documentation of the pain and symptoms associated with this form of cephalalgia dates back to Hippocrates in the fourth century BC.^{3,4} In 2018, an estimated 1 in 7 Americans between the ages of 18 and 65 experienced some form of migraine pain in the previous 3 months.⁵

There are multiple types of migraine, but the most common are occasional migraine headaches that occur fewer than 14 days in a month and those that occur 15 days or more in a month with 8 or more migraine for over 3 months.⁶ The occasional migraine can progress over time or as a consequence of frequent use of acute medication.⁷

Regardless of migraine type, the primary goals of treatment have traditionally included relieving pain, restoring function, reducing frequency, and halting the progression to more frequent migraine.⁷

The earliest migraine treatments were acute, or abortive therapies, designed to provide relief from migraine pain and other symptoms after the attack occurs.⁸ Only in recent years have novel preventive treatments that were developed specifically for migraine entered the market. These preventive treatments help reduce the number and severity of migraine days; however, they do not stop all migraine attacks.¹ In fact, 2 out of 3 patients with migraine see only a 50% reduction in migraine frequency while using preventive treatments.⁸ Consequently, patients receiving preventive treatment will also require acute treatment. In fact, all patients with migraine need acute treatment.¹

Etiology/Pathophysiology of Migraine

In the early 1900s, migraine was thought to be primarily a vascular disorder, whereby headache and pain were caused by the dilation of blood vessels.⁴ The vascular theory gained credence among scientists and clinicians when the early vasoconstrictor therapies (ergotamines) successfully constricted dilated blood vessels and provided pain relief.⁹

There is growing evidence, however, that suggests vasodilation alone is insufficient to induce a migraine attack. While blood vessel dilation may be present during a migraine, there is no direct indication that it causes headache pain; rather, it is likely a consequence of the attack.^{9,10} Scientists now believe that migraine involves activated nerve pathways, imbalances in brain chemicals, inflammation, and artery dilation.¹¹

As a result, research attention turned to the activation of the trigeminovascular system, which scientists consider a primary pathway leading to the pain associated with migraine.¹²

Calcitonin gene-related peptide (CGRP) is a trigeminal sensory neuropeptide synthesized in nerve cells in the brain and spinal cord. CGRP and its receptor are expressed in both the peripheral and the central nervous system (CNS), including the trigeminovascular pathways.¹⁴ When trigeminal nerves are activated, neuropeptides such as CGRP are released, resulting in vasodilation, local inflammation in the meninges, and pain.^{11,12}

Prevalence/Burden of Illness

Migraine affects 39 million Americans, or approximately 15% of the US population, with the highest prevalence occurring during a person’s peak employment years of 25 to 55 years of age.^{5,16,17}



To date, there is

NO CURE for migraine, and while multiple treatment modalities exist, migraine remains a complicated disease to treat because scientists and physicians do not fully understand its precise pathophysiology.

In multiple clinical trials, researchers have discovered high levels of CGRP concentrations during migraine attacks. While the fundamental biology underlying migraine is still unknown, CGRP is now considered a key element in the pathogenesis of migraine. This has led to research and new treatment options for both preventive and acute migraine treatments.^{18,19}

Women are more likely to experience migraine than men, with 1 in 5 women experiencing migraine compared to 1 in 16 men.¹ The prevalence of migraine and severe headache has remained stable between 2006 and 2015. A 2015 National Hospital Interview Survey showed average prevalence rates of 15% overall, 20% for females, and 9.5% for males.⁵

Getting a correct diagnosis and treatment for migraine is often a hurdle. Studies have shown that more than half of all migraine sufferers do not seek care for their migraine pain and are therefore never diagnosed by, or prescribed treatment from, a licensed medical practitioner.¹⁶

Over half of those who receive an accurate diagnosis are not prescribed either acute or preventive treatment.²⁰ A national claims database review found that only 34% of patients with migraine received a prescription for triptans, while analysis of claims of more than 10,000 migraine patients showed that 50% of new triptan users did not refill their prescriptions over a 12-month period.^{21,22}

Migraine Attacks

Migraine attacks are painful and often disabling. The frequency, severity, and characteristics of a migraine attack vary among patients, and even within the same patient from attack to attack.¹ Along with the common symptoms of dizziness, nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia), migraine is frequently associated with anxiety, depression, and disturbances in sleep patterns.^{16,20,23}

The intense pain of a migraine can pose physical limitations, as well as significantly impair a person's cognitive performance and ability to function at work, school, home, or in social situations.^{7,24} More than 90% of patients with migraine are unable to work or function normally during a migraine attack, resulting in more than 157 million workdays being lost each year in the US due to migraine.¹⁶

Cause of health care interventions and costs

Migraine patients account for 1.2 million emergency department (ED) visits per year because patients require stronger treatment to resolve migraine pain.^{25,26} Data from a 2015 study indicated that approximately 25% of ED visits for migraine were followed by a second ED visit for headache in less than 6 months. A large percentage of patients seeking treatment in the ED were not instructed to follow up with their physician or left the ED without a prescription for treatment.²⁷

The costs of these ED visits can be considerable. In a study of over 850,000 patients with migraine, patients with 2 or more migraine-related ED visits incurred \$3125 more "total all-cause costs" compared to those with fewer than 2 visits.²

Other factors leading to increased healthcare resource utilization (HCRU) and costs among patients with migraine include more frequent primary care and neurologist visits, overuse of prescription opioids and triptans, as well as costs associated with comorbid conditions.^{2,16}

The economic burden of migraine is substantial

The American Headache Society (AHS) estimates the annual economic burden in the US associated with migraine is \$27 billion.¹ However, because a large percentage of patients with migraine are not diagnosed or misdiagnosed, and either not treated or under-treated, comprehensive estimates of migraine's clinical and economic burden cannot be accurately calculated.

Analysis of healthcare claims from more than 140,000 commercially insured patients with migraine between January 1, 2007 and June 30, 2013 found direct costs to be approximately 250% higher for the cohort of adult migraine patients than the cohort of adults without migraine.²⁸

Approximately 74% of the total incremental costs of migraine were direct costs, eg, payments for all healthcare services or products, including both payer-paid costs and patient-paid out-of-pocket costs. The remaining 26% were indirect costs, which included work absences and short- and long-term disability. Indirect costs were 21% higher on average in the migraine cohort than in the no-migraine cohort (\$11,294 vs \$8945, a difference of \$2350), due to an average of 9 more missed days of work per year.²⁸

Current Acute Treatments

Acute or abortive therapies are divided into 2 classes: specific (triptans and ergot derivatives) and nonspecific (non-steroidal anti-inflammatory drugs [NSAIDs] and analgesics).⁸

Triptans

Triptans are recommended as first-line prescription therapy in the acute phase of a migraine attack.²³ Sumatriptan was introduced as the first triptan in 1991; additional agents in this class include zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan.⁸ While these triptans are biochemically similar, each has different efficacy, tolerability, and pharmacokinetic/pharmacodynamic properties. Triptans can be administered nasally, by injection, or through orally disintegrating tablets.^{8,29}

Featuring a powerful vasoconstrictor mechanism of action (MOA), triptans are partial agonists of the 5-hydroxytryptamine (5-HT) receptors 5-HT_{1B} and 5-HT_{1D} that selectively constrict the blood vessels of the brain and inhibit neurotransmitter release at both the peripheral and central trigeminal sensory neurons terminals.^{8,30,31} Triptans increase the levels of 5-HT (serotonin) in the brain, constricting blood vessels and lessening inflammation and delivering pain relief.³²

Triptans are most effective when taken at the first signs of a migraine.²³ Patients with migraine using an oral triptan can take



Undiagnosed, misdiagnosed, untreated or under-treated migraine can result in **INCREASED** healthcare resource utilization (HCRU) and **COST**.^{33,34}

Goals of Acute Treatments¹

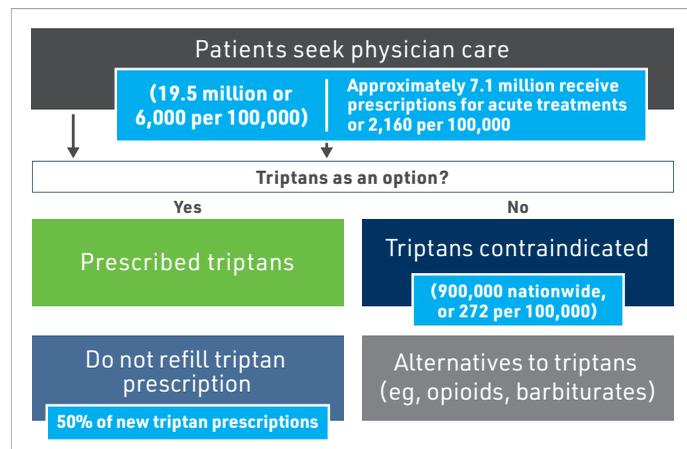
The 2018 AHS Consensus Statement reaffirmed the practice parameters developed by the American Academy of Neurology (AAN) for physicians to follow when diagnosing and treating migraine. The goals for acute treatment are:

1. Treat attacks rapidly and consistently while preventing recurrence
2. Restore the patient's ability to function
3. Minimize the use of backup and rescue medications
4. Optimize self-care and reduce subsequent use of resources
5. Have minimal or no adverse events (AEs)

a second dose after 2 hours if the migraine pain and symptoms have not completely abated.³⁵ Triptans should be used at most 3 times per week to treat migraine in order to decrease the risk of medication overuse headache (MOH).⁷

Only 25% of people with migraine who were surveyed reported that triptans controlled their migraine pain "very well," while almost 30% said they did not control them at all. These patients can choose an alternative triptan that may better match their personal headache profile, add an NSAID to the triptan, or use an NSAID alone. They may also be prescribed an opioid and/or butalbital to treat migraine pain [Figure 1].^{21,36,37}

Figure 1: Patient journey through triptan use^{1,21,22,38}



Triptans are contraindicated in more than 900,000 patients with migraine who have cardiovascular conditions, including untreated arterial hypertension and coronary heart disease [Figure 1].³⁸ All triptans are contraindicated in patients with Raynaud's disease, a history of ischemic stroke, severe liver or kidney failure, basilar or hemiplegic migraine, who are pregnant or breastfeeding, or who are 65 years or older. They should not be taken concomitantly with serotonin reuptake inhibitors (SSRIs).^{8,39}

The most common side effects of triptan use include fatigue, dizziness or vertigo, asthenia, and nausea.³⁶ Triptan users also frequently report experiencing 'triptan sensations,' which include paresthesia, flushing, tingling, and mild transient pressure of the chest, neck, or throat.⁸

NSAIDs

While triptans are the most frequently prescribed migraine treatment, NSAIDs (diclofenac, ketoprofen, flurbiprofen) are still the most commonly used over-the-counter (OTC) acute treatments for mild-to-moderate migraine attacks.^{8,41}

NSAIDs are non-specific antimigraine drugs with anti-inflammatory and analgesic properties that help reduce the inflammation associated with migraine and alleviate the pain.³² In the treatment of migraine, NSAIDs block the cyclooxygenase-2 (COX-2) enzyme, decreasing the synthesis and release of prostaglandins, a factor in the pathophysiology of migraine that promotes inflammation, pain, and fever.⁴¹

Many patients try NSAIDs and other OTC migraine relievers such as Excedrin[®] Migraine prior to seeing a physician.⁴² Patients who do not obtain migraine relief from NSAIDs or other OTC medications will typically be prescribed triptans as their first course of prescribed treatment. As noted earlier, however, NSAIDs can also be taken with triptans in patients who do not fully respond to triptans alone.^{37,41}

Adverse events associated with NSAID use are well documented; most notably they can cause adverse cardiovascular events and gastrointestinal side effects.^{1,41} NSAIDs are also contraindicated in patients with peptic ulcer and hemorrhagic diathesis.⁸ Common side effects include gas or bloating, heartburn, stomach pain, nausea, vomiting, diarrhea and/or constipation, dizziness, and lightheadedness, which can be avoided or lessened by taking NSAIDs with food.⁴³

Opioids, barbiturates

Opioids such as codeine, hydrocodone, meperidine, oxycodone, butorphanol, and hydromorphone, and the barbiturate butalbital are non-specific antimigraine drugs used to treat moderate-to-severe migraine. Opioids and butalbital are generally prescribed for short-term relief of migraine pain or as rescue medications and are not recommended for patients with chronic migraine as the risks may outweigh the benefits.⁴⁴⁻⁴⁶

Comprised of synthetic and naturally occurring opium derivatives, opioids attach to and activate opioid receptors on nerve cells in the brain, spinal cord, and other parts of the body to block pain messages sent to the brain.^{44,47} Opioids are narcotics frequently prescribed in the ED for relief of intense acute migraine pain.^{48,49} A health-records database analysis of 14,494 unique ED visits of people diagnosed with migraine between 2010 and 2016 found that opioids were ordered in 23% of visits within 12 hours of admission, and 58% of the prescriptions were first-line therapy.⁵⁰ Butalbital, a barbiturate, is a central nervous system (CNS) depressant that mimics the effect of the gamma-aminobutyric acid (GABA) inhibitor neurotransmitter in the brain by binding to a site on the GABA receptor. What results is an enhanced inhibitory effect of GABA that can reduce anxiety, depress respiration, and

The risk of physical dependence and/or psychological addiction leading to abuse or misuse of opioids is a serious and widely recognized **HAZARD** of opioid use.⁴⁹



produce sedation and euphoria. Butalbital may be combined with pain relievers such as acetaminophen, codeine, and/or caffeine.^{51,52}

Similarly, butalbital carries a risk of addiction, and the AHS and AAN do not recommend opioids or butalbital as first-line treatment for regular use in migraine treatment.⁵³⁻⁵⁶ Frequent use of butalbital can cause it to become less effective and can cause migraine to worsen and occur more frequently.^{46,51}

Long-term opioid use may affect gastrointestinal, respiratory, cardiovascular, and central nervous systems and can worsen migraine disease if overused.^{49,54} Side effects of opioids include sleepiness, constipation, and nausea; with butalbital, lightheadedness and shortness of breath can occur.^{47,52}

Other

Ergotamine, introduced in 1926, was the first drug used for acute treatment of migraine. Ergot derivative drugs (ergotamine tartrates and dihydroergotamine [DHE]) have the same vasoconstricting mechanism of action as triptans.^{8,11} In this class of drug, DHE is the most tolerated and most widely used.⁵⁷

Ergot derivatives are an appealing treatment for patients with migraine as they are inexpensive and have a long duration of action; however, they also have more side effects than other acute treatments, and frequent use carries a high risk of MOH.⁸ However, if patients with migraine do not achieve adequate response to triptans, ergotamines may be a viable alternative treatment option.¹¹

Additional acute treatment for migraine may include³²:

- Non-prescription analgesics or over-the-counter drugs such as ibuprofen, aspirin, or acetaminophen
- Combination analgesics such as acetaminophen plus caffeine and/or a narcotic for migraine
- Antiemetics

Similar to triptans, ergot derivatives are also contraindicated in patients with coronary artery disease, peripheral vascular disease, uncontrolled hypertension, impaired hepatic or renal function, and women who are pregnant.⁸

Shortcoming of Current Acute Treatments of Migraine

Many patients express dissatisfaction with triptans and discontinue treatment due to lack of efficacy and/or side effects.

Among the nearly 5600 triptan users in the web-based MAST Study, 57% discontinued use. The most common adverse events resulting in discontinuation were dizziness (37%), nausea (31%), and fatigue (25%).⁵⁸ A separate multi-center cross-sectional

survey found 44% of those who discontinued use cited a lack of effect as the reason, while 29% discontinued due to side effects.⁵⁹

All current acute treatments for migraine carry a risk of MOH. The ICHD-3 criteria for MOH are the use of triptans, ergotamines, opioids, or combination analgesics for 10 or more days a month for more than 3 months, or use of nonopioid analgesics, acetaminophen, and NSAIDs (including aspirin) for 15 or more days a month for more than 3 months.¹

Adverse events that impact function or safety

Side effects of acute treatment options (eg, triptans and opioids), such as drowsiness, mental confusion, dizziness or light-headedness can pose safety concerns when patients drive or can increase the potential for falls.^{37,52}

Symptoms of tiredness, difficulty concentrating, photophobia, neck pain, and increased somnolence can continue in the postdrome phase of a migraine. Often referred to as a "migraine hangover," these symptoms can occur even after successful acute treatment.^{11,60,61}

Results of a migraine-related disability study found a high correlation between the disability of cognitive symptoms (worsening with mental effort and difficulty in thinking) related to acute treatment with triptans and analgesics (combination analgesics with codeine, caffeine or ergots). Analysis suggested one reason for the association could be a consequence of the treatment effects.²⁴

Safety concerns also exist among some acute treatments in development. Lasmiditan was developed as an alternative treatment for migraine for those with certain cardiovascular contraindications to triptans; and while lasmiditan does not have any known contraindications; it has been shown to cause increased dizziness/vertigo.^{8,62}

In a proof-of-concept and dose-finding study of 130 subjects in hospital during a migraine attack, patients taking lasmiditan (a 5-HT_{1F} agonist) reported significantly higher adverse events of dizziness, vertigo, paresthesia, and fatigue in a dose-dependent fashion than those taking placebo.^{61,63} In 2 simulated driving studies, lasmiditan was associated with impaired simulated driving performance in healthy volunteers at 1.5 hours postdose.⁶⁴ The product label for lasmiditan also advises patients "not to engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery, for at least 8 hours after each dose." As the first in a new class of serotonin receptor agonist, or "ditan," being studied, lasmiditan carries the same potential side effects and contraindications as other agents in this class.^{8,36,65}

Recurrence and redosing

Nearly a third of patients with migraine experience a recurrent attack after achieving initial pain and symptom relief.⁶⁶

The combined recurrence rate of migraine reported in studies of all triptans is between 20% and 45%, while 67% to 82% of



Non-scientific analysis of these unmet needs combined with the earlier retrospective claims-analysis results show a decade-long **INCREASE IN COSTS** associated with migraine that highlight a lack of optimal acute treatment options for patients with migraine.

triptan users experience migraine recurrence within 24 hours.^{67,68} Since most patients experience initial relief, recurrence does not mean the agent is ineffective; rather, it provides temporary relief, so that another triptan or an alternative acute treatment with a different MOA is needed.⁶⁶

A second dose is indicated for most triptans if the initial dose is ineffective 2 hours after initiating treatment. In the ACHIEVE 1 and ACHIEVE long-term use studies of ubrogepant, which is a small molecule CGRP-receptor antagonist in development, approximately 50% of patients required a second dose or used another form of rescue medication to achieve relief from 2 to 24 hours.^{35,69}

Quantity limits: pros and cons

Optimal management of frequent migraine attacks, recurrence and/or the need to redose can be obstructed by health plans placing quantity limits on acute medication prescriptions.

A review of one-hundred 2015 formularies from government and commercial plans found that all plans imposed quantity limits on 1 or more triptan formulations, with more than 80% imposing quantity limits on 14 of the 19 formulations studied.⁷⁰

Health plans typically impose quantity limits on triptans to ensure that physicians follow the current AAN guidelines for the prevention and treatment of migraine; triptans for acute therapy should be limited to no more than 2 headache days per week to prevent MOH. Prior authorization is then required if the patient exceeds the quantity limit whereby the physician may want to evaluate the patient for symptoms of chronic migraine or for MOH and/or determine whether switching to another acute treatment is appropriate.⁷¹

A New Treatment Modality Using New Technology

Researchers capitalized on the clinical study data showing the increase in CGRP concentrations during migraine attacks to develop acute therapies for migraine that decrease concentrations of this neuropeptide and/or block its receptors.⁷²

When CGRP was administered intravenously to patients with a history of migraine, migraine-like headaches ensued within hours, while the worst that subjects without migraine developed were mild headaches. Along with other evidence, this suggested that patients with migraine are sensitive to the CGRP neuropeptide and helped validate CGRP as a therapeutic target in migraine.^{31,73,74}

The resulting CGRP-receptor antagonists (also known as gepants) represent some of the first non-serotonergic, non-vasoconstricting therapies specifically designed for migraine in nearly 30 years.^{8,75}

Treatment with small molecule CGRP-receptor antagonists is believed to relieve migraine through the following mechanisms: blocking neurogenic inflammation, decreasing artery dilation (without active vasoconstriction), and inhibiting pain transmission.¹⁵

Differentiating CGRP Inhibitor Treatments

At the time of this printing, AIMOVIG® (erenumab-aooe), EMGALITY® (galcanezumab-gnlm), AJOVY® (fremanezumab-vfrm), eptinezumab, rimegepant, ubrogepant, and atogepant were under investigation and/or received FDA approval, offering clinically proven effective treatment options to patients suffering from migraine.⁷⁶ The 2 treatment categories include⁷⁶:

- 4 injectable monoclonal antibodies (mAbs), FDA approved for preventive treatment only
- 3 orally administered small molecule CGRP receptor antagonists (gepants), in development for acute and preventive treatment

The currently available CGRP mAbs, fremanezumab, and galcanezumab, and the CGRP receptor erenumab are FDA-approved for the prevention of migraine attacks. A fourth agent, eptinezumab, has its Biologics License Application (BLA) under FDA review.^{1,77} CGRP mAbs prevent the progression of migraine by binding to CGRP or the CGRP receptor and inhibiting its release. Because they do not cross the blood-brain barrier and are not metabolized by the liver, they have a more favorable side effect profile than other preventive treatments, with minimal organ toxicity and drug-drug reactions.^{13,72,73,78}

With a long duration of action that allows for less frequent use, they represent a new era of migraine prophylaxis treatment options for patients with migraine. These treatments represent new options for migraine sufferers who did not respond to standard treatments or experienced intolerable side effects.^{13,72}

The first small molecule CGRP agent to be studied was olcegepant in the early 2000s. Administered intravenously, olcegepant demonstrated proof of concept in clinical studies with the ability to block CGRP release; however, as an oral agent it had low bioavailability.^{79,80}

In the years since, with evidence to support the use of CGRP antagonists as an acute therapy for migraine, other pharmaceutical companies picked up the research mantle. The CGRP-inhibitor treatment rimegepant and other CGRP antagonists under investigation have been shown to be well tolerated, with fewer side effects than other migraine treatments like triptans.^{18,78,80}

Rimegepant Product Information

Rimegepant is one of the newest small molecule CGRP inhibitors studied for the acute treatment of migraine. Clinical studies have validated that the rimegepant orally dissolving tablet (ODT) formulation offers early onset of pain relief that lasts for 48 hours with a unique delivery mechanism.^{81,82}

Rimegepant uses the Zydys® lyophilized dosage technology, a unique, freeze-dried oral solid dosage form that disperses almost instantly in the mouth. The ODT formulation provides efficient drug delivery with increased bioavailability, enabling rapid absorption and onset of action.⁸³

Onset, duration of effect, and safety

In a Phase 3 clinical trial, rimegepant ODT-treated patients experienced pain relief response within 1 hour postdose that continued through 48 hours postdose. Both rapid onset and duration of effect offer potential advantages for rimegepant over triptans and other gepants.^{82,84}

With the ability to provide early and sustained relief of migraine pain and associated symptoms, rimegepant ODT acute treatment offers patients with migraine the ability to quickly return to normal function without the need for additional dosing or rescue medication.⁸²

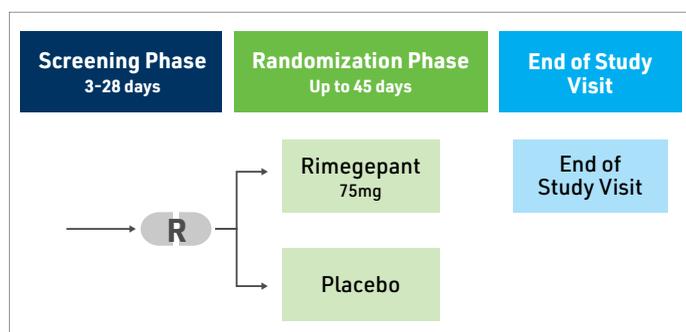
Throughout the clinical trials, rimegepant demonstrated a safety and tolerability profile similar to placebo, which was a welcome change for patients with migraine who either suffered through multiple adverse events with other acute medications or discontinued treatment as a result of those AEs.^{58,59,81,82}

Unlike triptans, rimegepant ODT is not a vasoconstrictor and is not contraindicated in patients with migraine with cardiovascular diseases and severe liver or kidney failure.^{8,81}

This Phase 3 randomized, double-blind, multicenter trial was designed to test the clinical efficacy, safety, and tolerability of rimegepant 75 mg ODT in the acute treatment of migraine.⁸²

Rimegepant ODT met both of the study's primary endpoints [Figure 2]. At 2 hours postdose, 21% of rimegepant-treated patients experienced freedom from pain and 35% had freedom from their most bothersome migraine symptom compared to placebo, 11% and 27%, respectively.⁸²

RIMEGEPANT Study 303



STUDY DESIGN: Eligible participants included men and women aged 18 years and older with at least a 1-year history of migraine with or without aura according to the criteria of ICHD-3 beta, migraine onset before age 50 years, at least 2 and no more than 8 migraine attacks of moderate or severe intensity per month, and fewer than 15 days per month with migraine or nonmigraine headache within the past 3 months. Patients received a single dose of rimegepant 75 mg or placebo to treat a single migraine attack of moderate or severe intensity.⁸²

Evaluation of onset activity demonstrated that beginning 15 minutes postdose, rimegepant showed better pain relief results than placebo, with the results statistically significant at 60 minutes postdose [Figure 3].⁸²

Rimegepant ODT was superior to placebo on 19 of the 21 secondary endpoints. Of note, rimegepant ODT-treated patients had lower use of rescue medications within 24 hours postdose (rimegepant, 14%; placebo, 29%) [Figure 4]. Rimegepant

ODT-treated patients also experienced greater sustained pain relief from 2 to 8 hours postdose (rimegepant, 58%; placebo, 48%) and 2 to 48 hours postdose (rimegepant, 42%; placebo, 25%).⁸²

Rimegepant ODT was also superior to placebo on the ability to function normally at 2 hours postdose (rimegepant, 38%; placebo, 26%) and from 2 to 24 hours postdose (rimegepant, 30%; placebo, 17%), and from 2 to 48 hours postdose (rimegepant, 26%; placebo, 15%).⁸²

Consistent safety profile

Rimegepant was generally well tolerated during the trial. The most common AEs ($\leq 1.6\%$) were nausea and urinary tract infection; liver function tests were similar to placebo.⁸²

The Rimegepant 303 Phase 3 study used a similar design as previous randomized controlled trials 301 and 302 (75 mg tablet). The pooled adverse event safety data and liver function tests were consistent across all trials, the results of which demonstrated an overall favorable tolerability and liver safety profile similar to that of placebo in patients with migraine.⁸²

Target Patient/Subpopulations

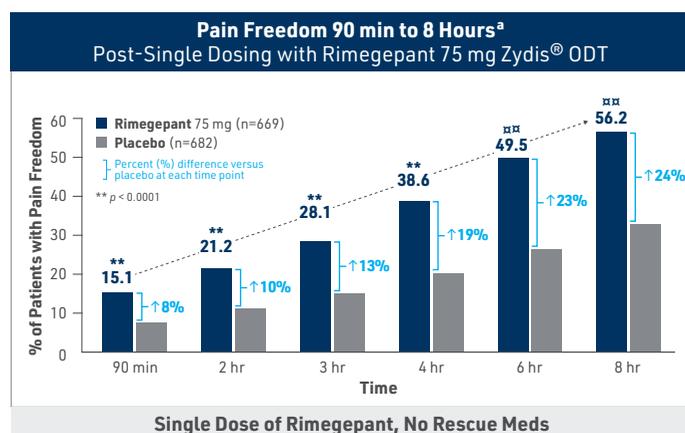
While 39 million Americans experience migraine, the number of patients with migraine with an unmet need for relief can be readily identified.¹⁶ The market entrance of CGRP inhibitors such as rimegepant ODT for the acute treatment of migraine pain can offer select subpopulations of migraine sufferers a viable option for effective, safe relief of their pain and symptoms.

Patients who cannot take triptans

Due to the nature of their vasoconstricting MOA, triptans are contraindicated in patients with a history of cardiovascular diseases and other vascular disorders and in patients who have severe liver or kidney failure or uncontrolled hypertension.^{8,40}

Because triptans act on the 5-HT (serotonin) neurotransmitters, the use of triptans with SSRIs should be avoided to avoid the potential for serotonin syndrome, a potentially life-threatening disorder.⁸⁶

Figure 2: Freedom from pain, co-primary endpoint at 2 hours postdose^{21,82}



^a Estimates computed using the mITT population and CMH methods. Subjects using rescue medications at or before the assessment, and subjects not providing data, are classified as failures. 3 to 8 hr are exploratory.

Figure 3: Secondary endpoint: Pain relief at 2 hours postdose^{82,85}

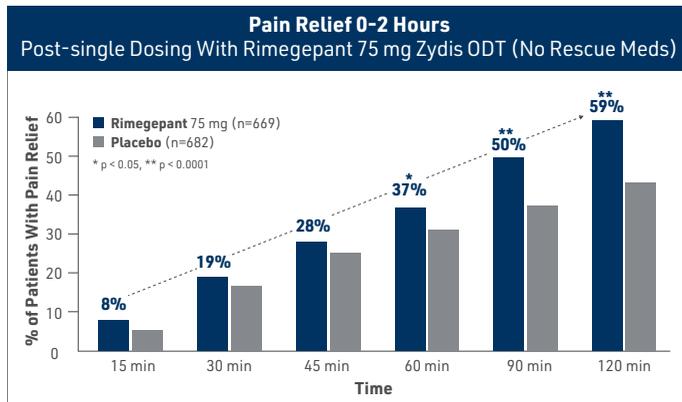
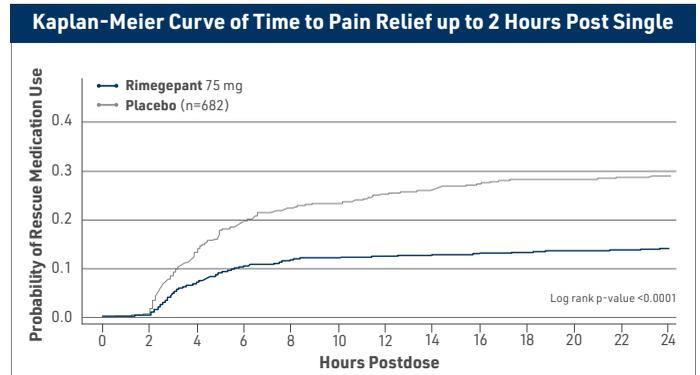


Figure 4: Secondary endpoint: Time to rescue medication use up to 24 hours post single dose⁸⁵



Graph is an approximate representation of the data. See the Clinical Study Report for specific point values.

Patients who had poor experiences with triptans

While the biochemistry of the different triptans is relatively the same, the pharmacokinetics and pharmacodynamics differ. Patients with migraine may cycle between triptans to find the agent that best treats their migraine profile, which is a frustrating process that may not provide migraine relief.^{87,88}

A lack of effect was cited as the reason why 44% of people with migraine discontinued triptan use.⁵⁹ Studies have shown that headache recurrence can occur in up to 40% of patients taking oral triptans.⁸ Patients with migraine who need to redose and treat recurring migraine are at greater risk of MOH if they use triptans more than 3 times a week.³⁵

Patients who currently are not using triptans due to AEs

All migraine treatments have been shown to have side effects. While many are mild and manageable, others are severe and can lead to discontinuation of treatment; survey results indicate nearly 30% of patients with migraine who discontinued triptans cited side effects as the reason.⁵⁹ The web-based MAST study found dizziness, nausea, and fatigue were the most common reasons that led to the discontinuation of oral triptans.⁵⁸

Conclusion

Migraine is a complex disease with considerable patient and societal impact. To date, a cure is elusive, and the pathophysiology is still largely uncertain.

Acute treatments for migraine have been available since 1946, when the first ergot derivative, dihydroergotamine was introduced. The first triptan, sumatriptan, was introduced in 1991. Preventive therapies specifically designed for migraine began entering the market in 2018.⁸⁹ Collectively, these agents have provided some measure of relief to the millions of Americans suffering from migraine pain. However, there remains a clear unmet need for alternative, novel, acute treatment options for patients with migraine who have cycled through existing acute therapies due to ineffectiveness, intolerability, or contraindications.³⁵



The recognition of the role of CGRP in the pathophysiology of migraine has led to the development of several new therapy options: injectable mAbs for preventive treatment and oral small molecule CGRP agonists for acute treatment.^{1,73}

Rimegepant represents a new treatment option that is clinically proven to be fast acting and long lasting. This can result in early pain relief and return to function, with a positive safety profile comparable to placebo in patients not satisfied with or contraindicated to current therapies.⁸² The 2018 AHS consensus statement suggests that patients with contraindications to triptan use or who have failed to respond to or are intolerant of triptans are eligible for rimegepant or other CGRP inhibitor treatments currently available.¹

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