Review Article

Lasmiditan: A New Drug for Acute Migraine

Kallem Sharat Venkat Reddy*
Pharm-D, Bharat institute of technology, H-no.1-76, Shantinagar, Vanasthalipuram, Hyderabad, Telangana, India.
***Corresponding author's E-mail:** 97sharat@gmail.com

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ABSTRACT

Migraine is one of the leading and huge problems in most of the population whole worldwide. It is also a major disability in patients with most of the neurological diseases. With drastic increase in the number of patients with migraine headache, invention of new drugs with better therapeutic action and less side effects is the need of the hour. Lasmiditan sold under brand name Reyvow is the new oral drug approved for treatment of migraine by FDA and is already proving to have much better results in therapeutic action and pain relief in migraine patients compared to other triptans. Here our objective is to provide information about Lasmiditan and its results in terms of therapy so far.

Keywords: Migraine, Lasmiditan, Triptans, Reyvow, Anti-inflammatory, Ditan.

INTRODUCTION

Migraine is most common problem observed in vast population of all ages including the millenials. From a very long time triptans are the first line drugs used in the treatment of migraine and to relieve pain and symptoms. But there are increased cases of side effects of triptans in patients and also proving to be non therapeutic in some patients. Recent studies have shown that use of triptans leads to narrowing of the blood vessels (vasoconstriction) which causes chest pain, shortness of breath and sometimes also results in more serious conditions. Hence triptans are not prescribed to migraine patients with cardiovascular problems or any vascular diseases. As most of the migraine patients have common cardiovascular problems and also as most of the population shows nil therapeutic effect by triptans, a new medicine for acute treatment of migraine Lasmiditan comes into the picture. Fig 1 shows the molecular structure of Lasmiditan. [1, 2]

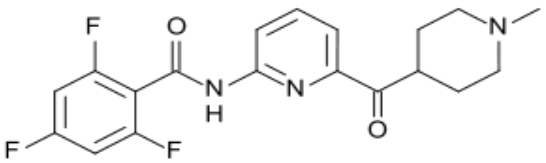

Figure 1: Structure of Lasmiditan

Formula: $C_{19}H_{18}F_3N_3O_2$

Common side Effects: Diziness, Sleepiness, Numbness [3,4]

TYPE: Serotonin receptor agonist[5]

History of Lasmiditan:

Lasmiditan was discovered by Elli Lilly and company in the year 2006.

Phase 2 clinical trials were completed for intravenous forms and oral forms in the years 2007 and 2010 respectively. It was submitted to FDA for approval in November, 2018. A phase 3 trial showed overall desired effects in the trail subjects and was approved by FDA on October, 2019.

Lasmiditan was placed under Schedule V in January, 2020. It became available in the United States from February, 2020. [6-9]

Mechanism of Action

Lasmiditan, a ditan is the first $5HT_{1F}$ (SEROTONIN) Receptor Agonist approved for treatment of acute migraine. It effectively targets the $5HT_{1F}$ receptors; it is centrally acting as it passes the blood brain barrier. It is superior when compared to the unsuccessful LY-334370, because of Lasmiditan's much higher selectivity for $5HT_{1F}$ receptor and no activity at $5HT_{1B/D}$ receptors and low affinity for $5HT_{1A}$ receptor.

Lasmiditan passes the blood brain barrier and therefore blocks the c-fos expression by activating the $5HT_{1F}$ receptors present centrally on the trigeminal neurons. Or also the $5HT_{1F}$ receptors outside the CNS which are present on primary trigeminal cell bodies within the trigeminal ganglion can mediate or promote the effect of Lasmiditan. There is even a possibility that both these mechanisms may be active at the same time. Ultimately, Lasmiditan is able to block the second order trigeminal neurons, which is the crucial part in the acute migraine patophysiology.

Having less affinity to receptors $5HT_{1B}$ and $5HT_{1D}$, relates to less side effects related to vasoconstriction as compared to Triptans, because Triptans have more affinity to these receptors. [9, 10, 11]

Figure 2: Brand Name of Lasmiditan and Product PHOTO by Lilly and Co.[9]

TRAIL RESULTS FROM OTHER STUDIES

Lasmiditan is an Effective Acute Treatment For Migraine: A Phase 3 Randomized Study [1]

Methods: Adult patients with migraine were randomized (1:1:1) to a double-blind dose of oral lasmiditan 200 mg, lasmiditan 100 mg, or placebo and were asked to treat their next migraine attack within 4 hours of onset. Over 48 hours after dosing, patients used an electronic diary to record headache pain and the presence of nausea, phonophobia, and photophobia, one of which was designated their most bothersome symptom (MBS).

Results: Results of the 1,856 patients who treated an attack, 77.9% had ≥1 cardiovascular risk factors in addition to migraine. Compared with placebo, more patients dosed with lasmiditan 200 mg were free of headache pain at 2 hours after dosing (32.2% vs 15.3%; odds ratio [OR] 2.6, 95% confidence interval [CI] 2.0–3.6, $p< 0.001$), similar to those dosed with lasmiditan 100 mg (28.2%; OR 2.2, 95% CI 1.6–3.0, $p< 0.001$). Furthermore, compared with those dosed with placebo, more patients dosed with lasmiditan 200 mg (40.7% vs 29.5%; OR 1.6, 95% CI 1.3–2.1, $p< 0.001$) and lasmiditan 100 mg (40.9%; OR 1.7, 95% CI, 1.3–2.2, $p< 0.001$) were free of their MBS at 2 hours after dosing. Adverse events were mostly mild or moderate in intensity.

Conclusions: Lasmiditan dosed at 200 and 100 mg was efficacious and well tolerated in the treatment of acute migraine among patients with a high level of cardiovascular risk factors.

Lasmiditan for Acute Treatment of Migraine In Patients With Cardiovascular Risk Factors: Post-Hoc Analysis Of Pooled Results From 2 Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trials [12]

Methods: SAMURAI and SPARTAN were similarly designed, Phase 3, randomized, double-blind, placebo-controlled trials in adults treating a single migraine attack with lasmiditan 50, 100, or 200 mg. Both studies included patients with CVRFs, and SPARTAN allowed patients with coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension. Efficacy and safety of lasmiditan in subgroups of patients with differing levels of CVRFs are reported. For efficacy analyses, logistic regression was used to assess treatment-by-subgroup interactions. For safety analyses, Cochran-Mantel-Haenszel test of general association evaluated treatment comparisons; Mantel-Haenszel odds ratio assessed significant treatment effects.

Results: In this pooled analysis, a total of 4439 patients received ≥1 dose of study drug. A total of 3500 patients (78.8%) had ≥1 CVRF, and 1833 patients (41.3%) had ≥2 CVRFs at baseline. Both trials met the primary endpoints of headache pain freedom and most bothersome symptom freedom at 2 h. The presence of CVRFs did not affect efficacy results. There was a low frequency of likely CV treatment-emergent adverse events (TEAEs) overall (lasmiditan, 30 [0.9%]; placebo, 5 [0.4%]). There was no statistical difference in the frequency of likely CV TEAEs in either the absence or presence of any CVRFs. The only likely CV TEAE seen across patients with ≥1, ≥ 2, ≥ 3, or ≥ 4 CVRFs was palpitations.

Conclusions: When analyzed by the presence of CVRFs, there was no statistical difference in lasmiditan efficacy or the frequency of likely CV TEAEs. Despite the analysis being limited by a single-migraine-attack design, the lack of differences in efficacy and safety with increasing numbers of CVRFs indicates that lasmiditan might be considered in the treatment algorithm for patients with CVRFs. Future studies are needed to assess long-term efficacy and safety.

Lasmiditan for the acute Treatment of Migraine: subgroup analyses by prior response to triptans[13]

Methods: Subgroups of patients reporting an overall response of "good" or "poor/none" to the most recent use of a triptan at baseline (defined as good or insufficient responders, respectively) and a triptan-naïve subpopulation were derived from combined study participants randomized to receive lasmiditan 50 mg (SPARTAN only), 100 mg or 200 mg, or placebo, as the first dose. Outcomes including headache pain-freedom, most bothersome symptom-freedom, and headache pain relief 2 hours post-first dose of lasmiditan were compared with placebo. Treatment-by-subgroup analyses additionally investigated whether therapeutic benefit varied according to prior triptan response (good or insufficient).

Results: Regardless of triptan response, lasmiditan showed higher efficacy than placebo (most comparisons were statistically significant). Treatment-by-subgroup analyses found that the benefit over placebo of lasmiditan did not vary significantly between patients with a good response and those with an insufficient response to triptans. Lasmiditan also showed higher efficacy than placebo in triptan-naïve patients.

Conclusions: Lasmiditan demonstrated comparable efficacy in patients who reported a good or insufficient response to prior triptan use. Lasmiditan also showed

efficacy in those who were triptan naïve. Lasmiditan may be a useful therapeutic option for patients with migraine.

Efficacy and Tolerability of Lasmiditan, An Oral 5-HT(1F) receptor agonist, for the acute treatment of migraine: A phase 2 Randomised, Placebo-Controlled, parallel-group, dose-ran: In this multicentre, double-blind, parallel-group, dose-ranging study in 43 headache centres in five European countries, patients with migraine with and without aura and who were not using prophylaxis were randomly assigned (1:1:1:1:1) to treat one moderate or severe attack at home with 50 mg, 100 mg, 200 mg, or 400 mg lasmiditan, or placebo. Study drug and placebo were supplied in identical numbered tablet packs. The randomisation code was generated by an independent statistician. Patients and investigators were masked to treatment allocation. The primary endpoint was dose response for headache relief (moderate or severe becoming mild or none) at 2 h. The primary analysis was done in the modified intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00883051.

Results: Between July 8 2009, and Feb 18, 2010, 512 patients were randomly assigned to treatment, 391 of whom received treatment. 86 patients received placebo (81 included in primary analysis) and 305 received lasmiditan (50 mg n=79, 100 mg n=81, 200 mg n=69, and 400 mg n=68 included in primary analysis). There was a linear association between headache response rate at 2 h and lasmiditan dose (Cochran-Armitage test p<0·0001). Every lasmiditan treatment dose significantly improved headache response at 2 h compared with placebo (lasmiditan 50 mg: difference 17·9%, 95% CI 3·9-32·1, p=0·022; 100 mg: 38·2%, 24·1-52·4, p<0·0001; 200 mg: 28·8%, 9·6-39·9, p=0·0018; 400 mg: 38·7%, 23·9-53·6, p<0·0001). The proportion of patients with treatment-emergent adverse events increased with increasing doses (53/82 [65%], 59/82 [72%], 61/71 [86%], and 59/70 [84%] for lasmiditan 50, 100, 200, and 400 mg, respectively vs 19/86 [22%] for placebo). Most adverse events were mild or moderate in intensity, with 16 of 82 (20%), 23 of 82 (28%), 28 of 71 (39%), and 31 of 70 (44%) of patients on lasmiditan 50, 100, 200, and 400 mg, respectively reporting a severe adverse event compared with five of 86 (6%) on placebo. The most common adverse events were CNS related and included dizziness, fatigue, vertigo, paraesthesia, and somnolence.

Conclusions: Oral lasmiditan seems to be safe and effective in the acute treatment of migraine. Further assessments in larger placebo-controlled and triptan-controlled trials are needed to assess the potential role of lasmiditan in acute migraine therapy.

Phase 3 Randomized, Placebo-Controlled, double-blind study of Lasmiditan for Acute Treatment of migraine[15]

Methods: This prospective, double-blind, phase 3 multicentre study randomly assigned patients with migraine with and without aura (1:1:1:1 ratio) to oral lasmiditan 200 mg, 100 mg, 50 mg, or placebo. Patients were instructed to dose at home within 4 h of onset of migraine attack of at least moderate intensity and not improving. The primary objective was to assess the proportion of patients' headache pain-free and most bothersome symptom-free at 2 h post-dose for each dose of lasmiditan versus placebo (NCT02605174). Patients (n = 3005) were assigned and treated (n = 2583, safety population): 1938 lasmiditan (200 mg n = 528, 100 mg n = 532, and 50 mg n = 556 included in primary analysis) and 645 placebo (540 included in primary analysis). Most patients (79.2%) had ≥1 cardiovascular risk factor at baseline, in addition to migraine.

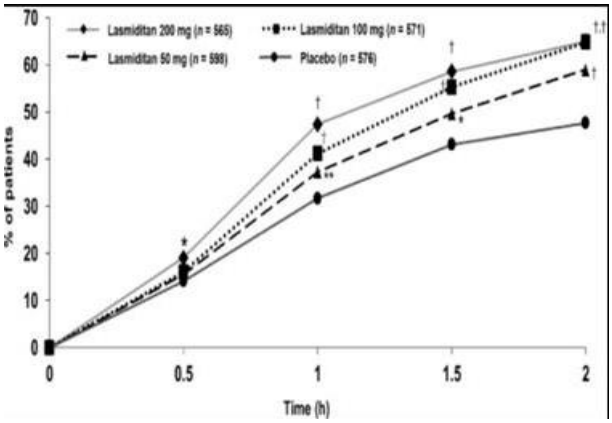

Figure 3: Headache Pain Relief in Patients Reported After First Dose[15]

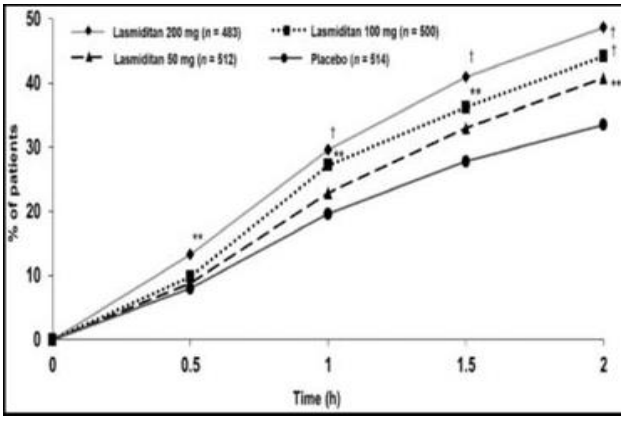

Figure 4: Most Bothersome Symptom Relief in Patients Reported After First Dose[15]

Results: Lasmiditan was associated with significantly more pain freedom at 2 h (lasmiditan 200 mg: 38.8%, odds ratio 2.3, 95% confidence interval 1.8-3.1, P < 0.001; 100 mg: 31.4%, odds ratio 1.7, 1.3-2.2, P < 0.001; 50 mg: 28.6%, odds ratio 1.5, 1.1-1.9, P = 0.003 versus placebo 21.3%) and freedom from most bothersome symptom at 2 h (lasmiditan 200 mg: 48.7%, odds ratio 1.9, 95% confidence interval 1.4-2.4, P < 0.001; 100 mg: 44.2%,

odds ratio 1.6, 1.2-2.0, P < 0.001; 50 mg: 40.8%, odds ratio 1.4, 1.1-1.8, P = 0.009 versus placebo 33.5%). Treatment-emergent adverse events were reported in 253 of 649 (39.0%), 229 of 635 (36.1%), and 166 of 654 (25.4%) of patients on lasmiditan 200, 100, and 50 mg, respectively, versus 75 of 645 (11.6%) on placebo. Most adverse events were CNS-related and included dizziness, somnolence and paraesthesia.

Figure 3 and Figure 4 are Copied images from Ref Article[15] for better understanding of their results.

Conclusion: Lasmiditan was effective at 2 h post-dose for acute treatment of migraine at all oral doses tested. Efficacy and safety were consistent with the previous phase 3 study.

Effect of A Rescue or Recurrence Dose Of Lasmiditan on Efficacy And Safety in the Acute Treatment of Migraine: Findings from The Phase 3 Trials (Samurai And Spartan)[16]

Methods: Samurai and Spartan were double-blind, placebo-controlled Phase 3 studies in which individuals with migraine were randomized to oral lasmiditan 50 mg (SPARTAN only), 100 mg, 200 mg, or placebo. Study drug was to be taken within 4 h (h) of onset of a migraine attack (moderate or severe pain). A second dose of study drug was provided for rescue (patient not pain-free at 2 h and took a second dose 2-24 h post-first dose) or recurrence (patient pain-free at 2 h, but experienced recurrence of mild, moderate, or severe migraine pain and took a second dose 2-24 h after first dose). Randomization to second dose occurred at baseline; patients originally assigned lasmiditan were randomized to the same lasmiditan dose or placebo (2:1 ratio), and those originally assigned placebo received placebo. Data from SAMURAI and SPARTAN were pooled for efficacy and safety assessment of a second dose of lasmiditan.

Results: The proportion of patients taking a second dose was lower with lasmiditan versus placebo, and decreased with increasing lasmiditan dose; the majority who took a second dose did so for rescue. In patients taking lasmiditan as first dose, outcomes (pain free, most bothersome symptom [MBS] free) at 2 h after a second dose for rescue were similar whether the second dose was lasmiditan or placebo (p > 0.05 in all cases). In patients taking lasmiditan for first dose, outcomes at 2 h after a second dose for recurrence were as follows: lasmiditan pooled versus placebo - pain free, 50% vs 32% (p > 0.05); MBS free, 71% vs 41% (p = 0.02); pain relief, 77% vs 52% (p = 0.03). In patients whose first dose was lasmiditan, the incidence of treatment emergent adverse events (TEAEs) reported after the second dose was similar whether second dose was lasmiditan or placebo.

Conclusions: A second dose of lasmiditan showed some evidence of efficacy when taken for headache recurrence. There was no clear benefit of a second dose of lasmiditan for rescue treatment. The incidences of TEAEs were similar whether the second dose was lasmiditan or placebo.

INTERPRETATION AND CONCLUSION

From the past 20 years there has not been a single new inclusion in the list of drugs with anti migraine therapeutic efficacy. Triptans were proven to be efficient in therapy but still has limitations. Lasmiditan, a ditan is a new breakthrough with better therapeutic effect and also with no effects on the vascular system or any cardiac effects. It is showing desirable results in patients within 2 hours of administration and if it is taken at the very start of pain, Lasmiditan can prevent the progress of pain and patient may get back to normal as quick as possible. Also in patients who prior reported insufficient response to Triptans, this drug showed better efficacy.

However, it is not useful for prevention. As this a newly approved drug, it will take time to completely understand its pros and cons and maybe Ditan may emerge as a new class of drugs, which depends upon how Lasmiditan the first drug from ditan's, proves its worth.

For now, Lasmiditan seems to be safe and effective in treatment of acute migraine and maybe a useful therapeutic option for migraine patients.

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