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LASMIDITAN FOR THE TREATMENT OF ACUTE MIGRAINE: A REVIEW

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ABSTRACT

Migraine is a neurological and disabling disease and is ranked as the world's second leading cause of disability. The primary goal of therapy is to alleviate pain, restore normal functions, reduce headache frequency, and consequently eliminate migraine-related symptoms. Triptans (selective 5-HT1B/D agonists) are considered first-line therapy for acute migraine attacks. Although triptans are effective for acute migraine abortive treatment, a significant number of individuals do not respond, and these medicines are also contraindicated in cardiovascular (CV) conditions due to their vasoconstrictive effects. As a result, novel effective anti-migraine therapies with no cardiovascular adverse effects, such as selective 5-HT1F receptor agonists, are necessary (ditans). In recent years, there have been significant advances in migraine management and prevention. On October 11, 2019, the US FDA approved lasmiditan, the first serotonin (5-HT) 1F receptor agonist, for the acute treatment of migraine, with and without aura, in adults. It is the first neurally acting antimigraine drug, and has no vasoconstrictive activity. Several Phase II and III trials have demonstrated superiority over placebo as well as the absence of typical triptan-associated adverse events (AEs). In this review, we discussed the current knowledge about Lasmiditan and its pharmacological profile, as well as summarised safety and efficacy data from basic research and clinical trials.

KEYWORDS: Migraine, 5-HT1F, Lasmiditan, triptans, treatment.

INTRODUCTION

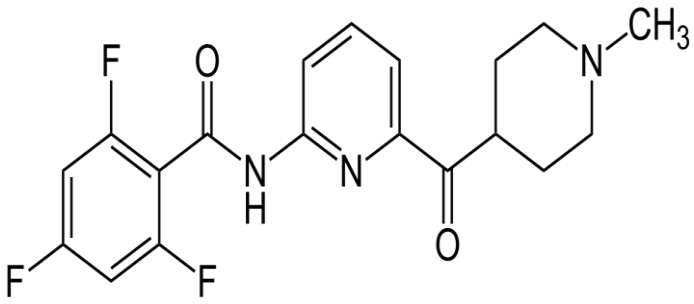
Migraine is a complex genetically influenced disorder characterised by episodes of moderate-to-severe headache, most often unilateral, and usually accompanied by nausea and increased sensitivity to light and sound.[1] Migraine is the second most common headache syndrome, affecting between 12 and 14% of the population.[2] According to a 2016 Global Burden of Disease (GBD) study, migraine is the world's second leading cause of disability.[3]

Acute migraine treatment includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, ergots, opioids, and triptans.[4] Most of these drugs are available over the counter(OTC), including some of the triptans. Triptans are considered first-line therapy for many patients with moderate to severe migraine.[4] Triptans work by binding selectively to the serotonin receptors 5-HT1B and 5-HT1D. Triptan binding to 5-HT1B receptors in the vascular system causes vasoconstriction of the cranial arteries, which painfully dilate during a migraine attack. Triptans prevent the release of vasoactive neuropeptides by inhibiting trigeminal nerve activation and blocking pain signal transmission to the brain when they bind to the neurogenic and central 5-HT1D receptors.[5] Triptans are specific drugs that have been shown to be effective and safe in several clinical trials; however, they can cause unpleasant side effects such as paraesthesias, flushing, tingling, neck pain, and mild transient chest pressure. Although uncommon, cardiovascular complications have been reported because triptans can activate the (5-HT2A) receptor in peripheral arteries and are thus contraindicated in patients with uncontrolled hypertension, coronary, cerebrovascular, and peripheral vascular disease.[6-8] These findings suggest that new acute anti-migraine drugs with a different adverse event (AE) profile are required. Drugs with no vasoactive properties are particularly sought after for use in subjects with cardiovascular disease and the elderly, who are naturally at a higher risk of vascular events.

The focus of new drug discovery programmes has shifted to the development of two classes of drugs: ditans, a class of antimigraine drugs that target 5-hydroxytryptamine1F (5-HT1F) receptors, and gepants, a class of calcitonin gene-related peptide (CGRP) receptor antagonists.[9] Rimegepant, Ubrogepant (CGRPs), and Lasmiditan (5HT1F) have recently been developed for the acute treatment of migraine.[10] Lasmiditan is a high-affinity, highly selective 5-HT1F receptor agonist that acts on the trigeminal system without causing vasoconstriction due to its low affinity for 5-HT1B receptors.[11] Lasmiditan is being

developed as an acute migraine treatment to address significant unmet needs in patients with cardiovascular risk factors, those with stable cardiovascular disease, or those who do not respond well to their current treatment.

Lasmiditan



Lasmiditan (COL-144 and LY573144) is a novel 5-HT receptor agonist with high affinity and selectivity for the 5-HT1F receptor. The IUPAC name for it is 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)pyridin-2-yl]benzamide.[12,13] This compound, which differs structurally from triptans, represents a new class of drugs known as ditans. Whereas triptans have an indole structure that is similar to the 5-HT receptor, ditans replace this indole group with a pyridine-piperidine scaffold.[12,14,15] Lasmiditan is superior to the other 5-HT1F receptor agonists such as LY-334370 due to its much higher selectivity for the 5-HT1F receptor, no activity at the 5-HT1B/D receptors, and extremely low affinity for the 5-HT1A receptor, with a 470-fold higher binding affinity for the 5-HT1F receptor than the 5-HT1B and 5-HT1D receptors.[16,17] Because the 5-HT1F receptor, unlike the 5-HT1B and 5-HT1D receptors, is primarily found in the trigeminal nerve rather than the vascular muscle, lasmiditan has no vasoconstriction effect.[13] Therefore, it is believed that it may be used in patients with cardiovascular diseases.[17,18]

Pharmacodynamic properties of Lasmiditan

Lasmiditan has a high affinity for the 5-HT1F receptor. 5-HT1F receptor agonists may be an alternate therapy option for those who do not react to triptans and/or have cardiovascular problems. Lasmiditan is thought to relieve migraines by acting as an agonist on the 5-HT1F receptor.[19] The exact mechanism of action of Lasmiditan is unknown. Effects of 5-HT1F receptor agonists that may contribute to activity in migraine include decreased plasma protein extravasation, decreased c-fos expression, suppressed neuronal firing within the trigeminal nucleus caudalis, inhibition of CGRP release from perivascular fibers, and direct antinociceptive modulation.[15] Agonists of the 5-HT1F receptor have been proven in

preclinical animal models and in vitro human models to cause no vasoconstriction.[20,21] The use of selective agonists to activate 5-HT1F receptors does not result in cerebral artery vasoconstriction. Furthermore, no vasoconstrictive effect of 5-HT1F receptor agonists was seen in peripheral arteries. In conclusion, the 5-HT1F receptor seems unlikely to be involved in the control of vascular tone in the human brain.[22] Lasmiditan is extremely lipophilic, allowing it to easily penetrate the blood-brain barrier; as a result, the most common side effects linked with lasmiditan are CNS-related.[15]

Pharmacokinetic properties of Lasmiditan

The oral bioavailability of lasmiditan has been reported to be around 40%, and the time at which the maximal concentration of lasmiditan is obtained in serum ranges between 1.5 and 2.5 hours following oral administration of 50-400 mg.[23,24] The absorption or pharmacokinetics of lasmiditan in migraine patients did not alter during a migraine attack versus the interictal period.[13,19] Lasmiditan co-administration with a high-fat meal increased the mean Cmax and AUC values by 22% and 19%, respectively, and delayed the median tmax by 1 hour.[19] The human plasma protein binding of lasmiditan is around 55% to 60% and is independent of concentrations ranging from 15 to 500 ng/mL.[19] Lasmiditan was eliminated with a geometric mean t½ value of approximately 5.7 hours.[13,19] With daily dosage, no lasmiditan buildup was seen. Lasmiditan is predominantly removed by metabolism, with ketone reduction being the major pathway. Renal excretion is a minor pathway of lasmiditan clearance.[13,19] In 30 healthy volunteers, the maximum serum concentration (Cmax), Tmax, and area under the curve (AUC) of lasmiditan 200 mg were assessed under fasting and fed conditions. *C*max was, respectively, 322.8±122.0 and 394.7±167.8 ng/mL (mean±SD); Tmax was, respectively, 1.5±1.0 and 2.5±1.0 hours (mean±SD); and AUC0–t was, respectively, 1892±746.0 and 2244±926.2 ng×h/mL (mean±SD).[14,24] Lasmiditan is metabolized through hepatic and extra-hepatic metabolism, predominantly by non-CYP enzymes.[15,19] Lasmiditan oxidises on the piperidine ring to form M7 and M18 (M18 is a combination of M7 and M8 pathways). These two metabolites are considered to be pharmacologically inactive. A small proportion (3%) of the active medication is eliminated unaltered in the urine, whereas about 66% is excreted as the metabolite S-M8.[15,19]

According to a population pharmacokinetic (PK) analysis, age, gender, race/ethnicity, and body weight had no effect on the PK (Cmax and AUC) of lasmiditan. As a result, no dose

modifications are required based on age, gender, race/ethnicity, or body weight.[19] In a clinical pharmacology study, administration of lasmiditan to subjects 65 years of age or older had 26% higher AUC(0-) and 21% higher Cmax when compared to patients 45 years of age or less. This difference in exposure is not expected to be clinically significant.[13,19] The AUC and Cmax of lasmiditan were 18% and 13% higher in patients with severe renal impairment (eGFR 30 mL/min/1.73 m2, respectively). The Cmax and AUC for the major metabolite M8 were 1.2-fold and 2.5-fold greater, for (S,R)-M18 they were 1.4-fold and 2.6-fold greater, and for M7—1.2-fold and 1.7-fold greater, respectively.[13,19,24] The metabolites are considered to be inactive. Given the chronic-intermittent nature of lasmiditan dosing, increased metabolite exposure may not be clinically meaningful; consequently, no dose change based on renal function was indicated.[13,19] Patients with mild and moderate hepatic impairment (Child-Pugh Class A and B, respectively) had 11% and 35% higher exposure [AUC(0-)] to lasmiditan in a clinical pharmacology study, compared to subjects with normal hepatic function. Cmax was 19% and 33% higher in patients with mild and severe hepatic impairment, respectively. This exposure difference is not expected to be clinically meaningful. The use of lasmiditan in persons with severe hepatic impairment has not been studied.[19]

Therapeutic efficacy of Lasmiditan

Phase 1 clinical trials

There have been 14 completed Phase I clinical studies between 2003 and 2018, but there are currently no peer-reviewed publications.[14] There was no published data from the first Phase I study on intravenous administration of lasmiditan, which was conducted in 2003 with 40 patients to investigate safety, tolerability, and pharmacokinetics.[12,23] Two Phase I trials (COL MIG-102, COL MIG-103; Table 1) were conducted in 2008 to evaluate the bioavailability, safety, tolerability, and other pharmacokinetic parameters of different oral formulations (oral solution, oral tablet, and sublingual). Although full published data from these studies were not available, oral formulations were shown to achieve plasma levels previously associated with efficacy of intravenous administration without severe adverse effects.[12,22-24]

The cardiac safety of lasmiditan was studied in the Phase I trial COL MIG-105 in 2011. This randomised, double-blind trial evaluated the effects of oral lasmiditan (100 and 400 mg) on cardiac depolarization and repolarization duration, as well as other cardiac safety parameters,

versus those of the antibiotic moxifloxacin (400 mg) and placebo. When compared to moxifloxacin, which caused QT prolongation in other published studies, Lasmiditan at both doses did not produce QT prolongation.[14,16,23-24] Despite the lack of comprehensive published data, CoLucid reported no pro-arrhythmic effect of lasmiditan in cardiologist ECG examinations, with safety and tolerability similar to that observed in previous studies.[12] The bioavailability of oral lasmiditan (200 mg) in fed and fasted conditions was compared in a randomised, open-label research (COL MIG-104). The fed condition was associated with higher Cmax, Tmax, and AUC, as well as a lower rate of mild adverse effects (19 vs. 23). There were no major adverse effects, with somnolence being the most common.[12,23] Several Phase I clinical trials are now being conducted, while others have recently concluded but the findings are not yet accessible.[24]

Phase 2 clinical trials

Two Phase II trials for the intravenous and oral formulations were conducted in 2007 and 2009, respectively.[25,26] The first study (ID NCT00384774, COL MIG-201) aimed to examine the efficacy of IV lasmiditan and determine the effective dose range.[14,25] The study was a multicenter, randomised, double-blind, placebo-controlled proof-of-concept and dose-finding trial that enrolled 130 migraine patients between the ages of 18 and 65 with a 1-year migraine history who were not taking prophylactic medication.[24,25] Doses ranging from 2.5 mg to 45 mg were administered to small cohorts (five or six participants) and were adjusted based on response rates or adverse events reported in the previous group. The primary end point was the reduction of a moderate to severe headache to mild or none after 2 hours of starting the trial dose.[14,25] Lasmiditan was administered to 88 patients, while 42 were given a placebo. When compared to the placebo group (45.2%), patients receiving 10, 20, 30, and 45 mg of lasmiditan had a better response (range from 54.2% to 75%). In addition, a substantial linear relation between dose levels and response rates was found. The 20 mg dose produced a headache response rate of 64%, with a therapeutic gain of 19% over placebo.[12,25] There were no significant adverse effects reported. The subjects did not report common triptan adverse effects such as chest pain or chest pressure. The most common adverse effects were parasthesias and dizziness, with no apparent dose-related response.[14,25]

The second Phase II clinical trial (ID NCT00883051, COL MIG-202) assessed the safety and efficacy of oral lasmiditan in acute migraine. In this randomised, double-blind, placebo-controlled, dose-ranging study, otherwise healthy patients aged 18 to 65 were randomly

assigned to either oral lasmiditan (50, 100, 200, or 400 mg) or placebo in a 1:1:1:1:1 ratio.[14,26] In total, 391 individuals were given lasmiditan and 86 were given a placebo. The primary end point was the headache response, which was defined as a moderate-to-severe attack that became mild or disappearing after 2 hours.[12,26] Every lasmiditan dose outperformed placebo for the primary efficacy measure (headache response at 2 hours), with a significant linear dose-response relationship. Except for the 50 mg dose, all doses were superior to placebo after 1 hour, while the 400 mg dose significantly reduced headache severity starting as early as 30 minutes, and all groups reached statistical significance vs. placebo after 90 minutes.[24,26] Interestingly, nausea, photophobia, and phonophobia decreased in all treatment groups within 2 hours of therapy, with the placebo group exhibiting the smallest reduction.[23,26] Lasmiditan was well tolerated, and there were no clinically significant changes in vital signs, ECG parameters, or haematological/clinical chemistry parameters. The most frequently reported adverse effects were paraesthesia, dizziness, or vertigo of mild to moderate degree.[23,26]

Phase 3 clinical trials

SAMURAI (ID NCT02439320, COL MIG-301)

Three Phase III clinical trials have been conducted on Lasmiditan. SAMURAI is the first Phase III clinical trial. The aim of this prospective randomised, double-blind, placebo-controlled, parallel-group study was to compare the efficacy of two doses of lasmiditan to placebo in the treatment of acute migraine with and without aura. Patients with vascular risk factors were included in the study, but those with a history of coronary artery disease, arrhythmia, uncontrolled hypertension, or seizures were excluded. The primary end point was headache freedom 2 hours after administration, while the secondary end points were headache relief, use of rescue medication, headache recurrence, and relief of the most unpleasant symptom (nausea, photophobia, phonophobia) 2 hours after administration.[27,28] Both doses achieved statistical significance for pain freedom at 2 hours versus placebo (P.001) and for freedom from MBS at 2 hours (P.001). When MBS was subdivided, there was no significant improvement in nausea and vomiting compared to placebo. The AEs appeared to be dose dependant and consistent with preceding trials. Palpitations in 5 patients and bradycardia in 1 patient were the only potentially drug-related cardiac AEs observed.[17,27-28]

SPARTAN (ID NCT02605174, COL MIG-302)

This was a prospective, randomized, double-blind, placebo-controlled, multicentre phase 3 trial in patients with migraine with and without aura from 125 headache centres in the USA, UK and Germany.[29] SPARTAN used a similar trial design as SAMURAI, as well as primary and secondary outcomes, to compare three dosages of lasmiditan (50, 100, and 200 mg) to placebo in the treatment of acute migraine. In contrast to SAMURAI's healthy volunteers, SPARTAN did not exclude patients with coronary artery disease, cardiac arrhythmias, or uncontrolled hypertension.[14,29] They excluded a number of conditions, including epilepsy, hemorrhagic stroke, history of recurrent dizziness or vertigo, vestibular migraine, syncope/orthostatic hypotension, and drug/alcohol usage in the past three years.[17,29] The primary end points were pain freedom at 2 hours after dosing as well as freedom from MBS at 2 hours.[17,29] SPARTAN met its primary and secondary end objectives in all three doses evaluated in 2017.[14,29] Specifically, it was reported that 2 hours following therapy with lasmiditan, the percentage of migraine pain-free patients was significantly higher than placebo in all three oral doses: 28.6% for 50 mg (p= 0.003), 31.4% for 100 mg (p0.001), 38.8% for 200 mg (p0.001), and 21.3% for placebo.[23,29] Lasmiditan was also significantly effective in lowering the most bothersome migraine-associated symptom in patients 2 hours after their first dose: 40.8% for 50 mg (p= 0.009), 44.2% for 100 mg (p< 0.001), 48.7% for 200 mg (p< 0.001) and 33.5% for placebo. In line with previous studies, the most common side effects of lasmiditan were dizziness, paresthesia, somnolence, fatigue, nausea, and lethargy.[23,29]

GLADIATOR (ID NCT02565186, COL MIG-305)

This is a prospective, randomised, open-label trial in migraine patients who have completed COL MIG-301 or COL MIG-302 to assess the safety, tolerability, and efficacy of long-term intermittent use of oral lasmiditan 100 and 200 mg for the acute treatment of migraine.[23,30,31] The final GLADIATOR study results were consistent with the previously published placebo-controlled, phase 3, single-attack lasmiditan studies and the interim GLADIATOR results in terms of safety and efficacy.[27-31] Throughout the study, there was a relatively high dropout rate of 51.7%, with 12.8% of participants dropping out due to adverse events. The most common reason for discontinuation was dizziness (2.7% of patients in the 100 mg group and 4.3% of patients in the 200 mg group).[15] AE incidence and types were similar to those reported in the prior pivotal studies, with dizziness (18.6%) being most common, followed by paresthesias, fatigue, nausea, and asthenia. There were no cardiovascular AEs associated with

vasoconstriction, and no major AEs associated with the medication were observed.[17,30] Intermittent, repeated dosage of lasmiditan for up to a year was well tolerated and demonstrated consistent efficacy in the treatment of episodic migraine attacks.[31] The study's major limitation is that one year is not reflective of the disease state, and efficacy with lasmiditan over a longer period of time and to treat more than four migraine attacks in 30 days has yet to be established.[15]

CENTURION (ID NCT03670810)

This was a multicenter, randomized, placebo-controlled; double-blind modified parallel Phase 3 study conducted in Europe, North America, and Asia. The trial was designed to evaluate lasmiditan's efficacy, including consistency of response, in the acute treatment of migraine attacks with or without aura.[32] The CENTURION study primary cohort publication contains a detailed summary of the study design and endpoints.[32] The study's duration was the treatment of four migraine attacks or four months, whichever occurred first. To measure prolonged pain freedom, patients were instructed to treat their migraine within 4 hours of an attack of moderate to severe intensity and not to repeat a dose until more than 48 hours after treatment of an attack.[15] All primary and secondary gated endpoints showed significant changes from placebo at any dose of lasmiditan ($p < 0.001$ in all cases).[32] Lasmiditan delivers consistent results across multiple migraine attacks. The most common treatment-emergent adverse events (TEAEs) with lasmiditan were dizziness, paresthesia, fatigue, and nausea, all of which were mild to moderate in intensity. The majority of TEAEs were recorded during the first treated attack.[32-33] By having participants treat multiple attacks rather than just one, CENTURION overcomes a major limitation of both the SPARTAN and SAMURAI. The efficacy and safety data remained consistent with the findings of the 3 prior Phase III studies.[15,32]

Safety and Tolerability of Lasmiditan

Lasmiditan was well tolerated, with no reports of triptan-like events (e.g., chest symptoms). Following the administration of lasmiditan, no clinically significant abnormalities in any safety measures, such as heart rate, blood pressure, 12-lead ECG, haematological, biochemistry, or urine analysis, were noticed.[12] The most commonly reported adverse effects of lasmiditan in phase II and III clinical studies were CNS-related, such as dizziness, fatigue, nausea, paresthesia, and somnolence. Adverse effects can also occur when lasmiditan is used with other CNS depressants, such as alcohol. Lasmiditan may cause substantial

driving impairment due to CNS adverse effects, and a single dose of lasmiditan delivered in a driving trial reduced patients' ability to drive. As a result, patients should avoid driving for at least 8 hours following each dose of lasmiditan.[15,34] No deaths were reported in any of the trials. Although the percentage of older patients who experienced at least one TEAE was identical in the SPARTAN+SAMURAI studies, it was lower in the GLADIATOR trial. TEAEs were observed in both old and non-elderly patients, although no tolerability concerns were noted in the elderly. Dizziness (10.6%), paresthesia (3.5%), and somnolence (2.4%) were the most common adverse effects that led to discontinuation in the elderly population. These same events frequently resulted in discontinuations in the nonelderly population.[35] In GLADIATOR, no cardiovascular events occurred in elderly patients during the lasmiditan treatment period, and no cardiovascular safety concerns were reported during long-term lasmiditan usage in the elderly or nonelderly population. These findings are compatible with data from SAMURAI and SPARTAN.[35] A recent study discovered that, while the incidence of TEAEs was rather high, the majority of TEAEs were mild in severity, occurred within 1 hour after therapy, and were transient and self-limiting. Dizziness, somnolence, and malaise were the most common TEAEs (affecting ≥10% of patients); the most influential risk factor for dizziness and somnolence was a higher lasmiditan dose.[36] Lasmiditan was well tolerated in pediatric migraine patients from the US and Japan when given as a single 100mg dose to patients 15kg to ≤ 40kg or as a single 200mg dose to patients > 40 to ≤ 55kg. There were no new safety findings in the paediatric population receiving lasmiditan doses comparable to the 200mg exposure in adults.[37]

CONCLUSION

Lasmiditan is a newly approved highly selective 5-HT1F agonist for the treatment of acute migraine. Individuals who were previously contraindicated for triptans due to cardiovascular disease or vascular risk factors are the target patients. Published studies clearly show that lasmiditan outperforms placebo in acute migraine. Lasmiditan is well-tolerated and has not been attributed to any major safety concerns, such as ischemic cardiovascular events, accidents, or injuries. The sole clinically meaningful predictor of common TEAEs was Lasmiditan dose, not any patient characteristic. Lasmiditan has not yet been studied in pregnant or nursing women.

REFERENCES

1. Ruschel MA, De Jesus O. Migraine Headache. InStatPearls [Internet] Jul 6. StatPearls Publishing, 2022.
2. Schulte LH, May A. The migraine generator revisited: continuous scanning of the migraine cycle over 30 days and three spontaneous attacks. Brain, 2016; 139(7): 1987-93.
3. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet, 2017; 390(10100): 1211-59.
4. Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, *et al.* Triptans in the acute treatment of migraine: A systematic review and network meta-analysis. Headache: The Journal of Head and Face Pain, 2015; 55: 221-35.
5. Nicolas S, Nicolas D. Triptans. In: StatPearls. StatPearls Publishing, Treasure Island (FL), 2022. PMID: 32119394.
6. Antonaci F, Ghiotto N, Wu S, Pucci E, Costa A. Recent advances in migraine therapy. Springerplus, 2016; 5(1): 1-4.
7. Roberto G, Raschi E, Piccinni C, Conti V, Vignatelli L, D'Alessandro R, *et al.* Adverse cardiovascular events associated with triptans and ergotamines for treatment of migraine: systematic review of observational studies. Cephalalgia, 2015; 35(2): 118-31.
8. Dodick D, Lipton RB, Martin V, Papademetriou V, Rosamond W, MaassenVanDenBrink A, *et al.* Consensus statement: Cardiovascular safety profile of triptans (5-HT1B/1D agonists) in the acute treatment of migraine. Headache: The Journal of Head and Face Pain, 2004; 44(5): 414-25.
9. Yang CP, Liang CS, Chang CM, Yang CC, Shih PH, Yau YC, *et al.* Comparison of new pharmacologic agents with triptans for treatment of migraine: a systematic review and meta-analysis. JAMA Network Open, 2021; 4(10): e2128544-e2128544.
10. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache: The Journal of Head and Face Pain. 2021; 61(7): 1021-39.
11. Clemow DB, Johnson KW, Hochstetler HM, Ossipov MH, Hake AM, Blumenfeld AM. Lasmiditan mechanism of action–review of a selective 5-HT1F agonist. The journal of headache and pain, 2020; 21(1): 1-3.

12. Capi M, de Andrés F, Lionetto L, Gentile G, Cipolla F, Negro A, *et al.* Lasmiditan for the treatment of migraine. Expert opinion on investigational drugs, 2017; 26(2): 227-34.
13. Szkutnik-Fiedler D. Pharmacokinetics, pharmacodynamics and drug–drug interactions of new anti-migraine drugs—Lasmiditan, gepants, and calcitonin-gene-related peptide (CGRP) receptor monoclonal antibodies. Pharmaceutics, 2020; 12(12): 1180.
14. Oswald JC, Schuster NM. Lasmiditan for the treatment of acute migraine: a review and potential role in clinical practice. Journal of pain research, 2018; 11: 2221-2227.
15. Beauchene JK, Levien TL. Lasmiditan: Acute Migraine Treatment Without Vasoconstriction. A Review. Journal of Pharmacy Technology, 2021; 37(5): 244-53.
16. Reuter U, Israel H, Neeb L. The pharmacological profile and clinical prospects of the oral 5-HT1F receptor agonist lasmiditan in the acute treatment of migraine. Therapeutic Advances in Neurological Disorders, 2015; 8(1): 46-54.
17. Macone AE, Perloff MD. Lasmiditan: its development and potential use. Clinical Pharmacology in Drug Development, 2020; 9(3): 292-6.
18. Tsai M, Case M, Ardayfio P, Hochstetler H, Wilbraham D. Effects of lasmiditan on cardiovascular parameters and pharmacokinetics in healthy subjects receiving oral doses of propranolol. Clinical pharmacology in drug development, 2020; 9(5): 629-38.
19. Highlights of prescribing information - food and drug administration. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211280s000lbl.pdf.
20. Nelson DL, Phebus LA, Johnson KW, Wainscott DB, Cohen ML, Calligaro DO, *et al.* Preclinical pharmacological profile of the selective 5-HT1F receptor agonist lasmiditan. Cephalalgia, 2010; 30(10): 1159-69.
21. Cohen ML, Schenck K. 5-Hydroxytryptamine1F receptors do not participate in vasoconstriction: lack of vasoconstriction to LY344864, a selective serotonin1F receptor agonist in rabbit saphenous vein. Journal of Pharmacology and Experimental Therapeutics, 1999; 290(3): 935-9.
22. Neeb L, Meents J, Reuter U. 5-HT1F receptor agonists: a new treatment option for migraine attacks?. Neurotherapeutics, 2010; 7(2): 176-82.
23. Vila-Pueyo M. Targeted 5-HT1F therapies for migraine. Neurotherapeutics, 2018; 15(2): 291-303.
24. Negro A, Koverech A, Martelletti P. Serotonin receptor agonists in the acute treatment of migraine: a review on their therapeutic potential. Journal of pain research, 2018; 11: 515-526.

25. Ferrari MD, Färkkilä M, Reuter U, Pilgrim A, Davis C, Krauss M, *et al.* European COL-144 Investigators. Acute treatment of migraine with the selective 5-HT1F receptor agonist lasmiditan–a randomised proof-of-concept trial. Cephalalgia, 2010; 30(10): 1170-8.
26. Färkkilä M, Diener HC, Géraud G, Láinez M, Schoenen J, Harner N, *et al.* COL MIG-202 study group. Efficacy and tolerability of lasmiditan, an oral 5-HT1F receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. The Lancet Neurology, 2012; 11(5): 405-13.
27. Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB, COL MIG-301 Study Group. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. Neurology, 2018; 91(24): e2222-32.
28. Loo LS, Plato BM, Turner IM, Case MG, Raskin J, Dowsett SA, *et al*. 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). BMC neurology, 2019; 19(1): 1-8.
29. Goadsby PJ, Wietecha LA, Dennehy EB, Kuca B, Case MG, Aurora SK, *et al.* Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. Brain, 2019; 142(7): 1894-904.
30. Brandes JL, Klise S, Krege JH, Case M, Khanna R, Vasudeva R, *et al.* Interim results of a prospective, randomized, open-label, phase 3 study of the long-term safety and efficacy of lasmiditan for acute treatment of migraine (the GLADIATOR study). Cephalalgia, 2019; 39(11): 1343-57.
31. Brandes JL, Klise S, Krege JH, Case M, Khanna R, Vasudeva R, *et al.* Long-term safety and efficacy of lasmiditan for acute treatment of migraine: final results of the GLADIATOR study. Cephalalgia Reports, 2020; 3: 1-5.
32. Ashina M, Reuter U, Smith T, Krikke-Workel J, Klise SR, Bragg S, *et al.* Randomized, controlled trial of lasmiditan over four migraine attacks: findings from the CENTURION study. Cephalalgia, 2021; 41(3): 294-304.
33. Yu T, He L, Yang X, Zhou J, Luo G, Wang H, *et al*. Efficacy and Safety of Lasmiditan as a Novel Acute Treatment in Chinese Patients with Migraine: A Subpopulation Analysis of the Randomized Controlled Phase 3 CENTURION Trial. Neurology and Therapy, 2022; 11(3): 1269-83.
34. Pearlman EM, Wilbraham D, Dennehy EB, Berg PH, Tsai M, Doty EG, *et al.* Effects of lasmiditan on simulated driving performance: results of two randomized, blinded,

crossover studies with placebo and active controls. Human Psychopharmacology: Clinical and Experimental, 2020; 35(5): e2732.

35. Martin VT, Ahmed Z, Hochstetler HM, Baygani SK, Dong Y, Hauck PM, *et al.* Tolerability and Safety of Lasmiditan Treatment in Elderly Patients With Migraine: Post Hoc Analyses From Randomized Studies. Clinical Therapeutics, 2021; 43(6): 1066-78.
36. Hirata K, Matsumori Y, Tanji Y, Khanna R, Ozeki A, Komori M. Safety profile of lasmiditan in patients with migraine in an Asian population. Expert Opinion on Drug Safety, 2022; 1-11.
37. Tsai M, Nery ES, Kerr L, Khanna R, Komori M, Dennehy EB, *et al.* Pharmacokinetics, safety, and tolerability of lasmiditan in pediatric patients with migraine. Clinical pharmacokinetics, 2021; 60(6): 819-28.