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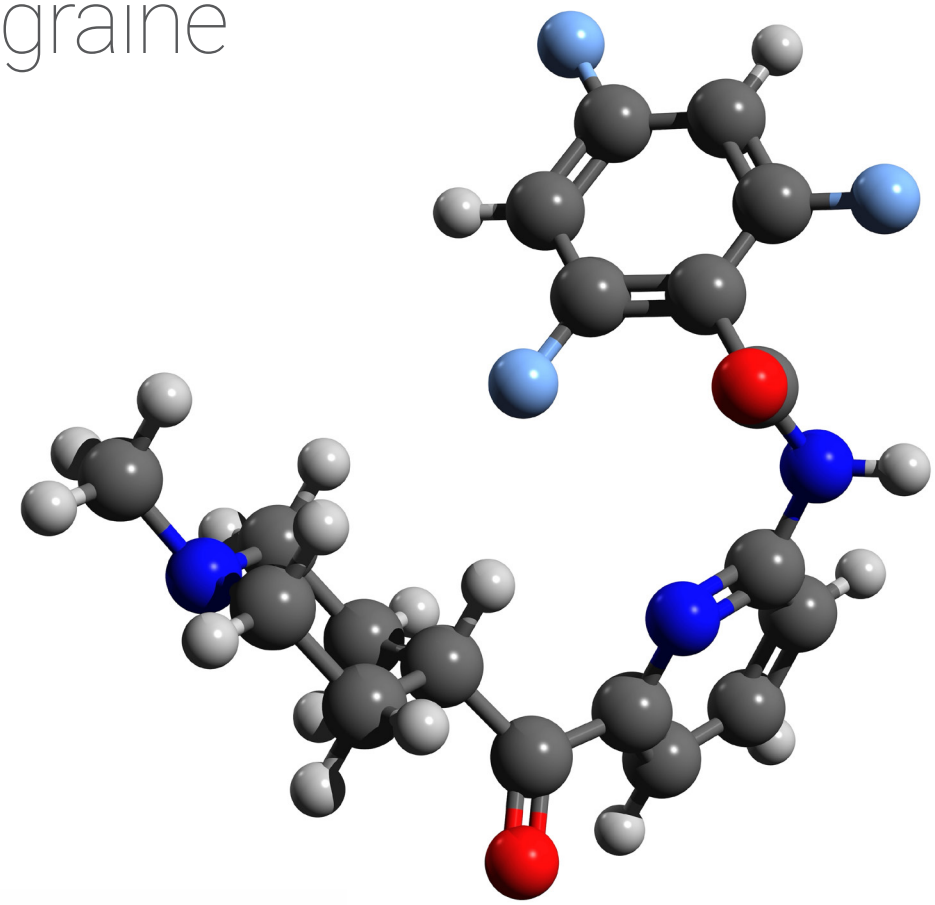
Lasmiditan for the Acute Treatment of Migraine



Shutterstock image: Lasmiditan (COL-144).

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Methods

These bulletins are not systematic reviews and do not involve critical appraisal or include a detailed summary of study findings. Rather, they present an overview of the technology and available evidence. They are not intended to provide recommendations for or against a technology.

Literature Search Strategy

A limited literature search was conducted by an information specialist on key resources including MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was lasmiditan. The initial search was conducted on September 27, 2019. Regular alerts updated the search until project completion; only citations retrieved before February 3, 2020, were incorporated into the analysis. No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Where possible, retrieval was limited to the human population.

Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was lasmiditan for the acute treatment of migraine. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

Peer Review

A draft version of this bulletin was reviewed by one clinical expert. The manufacturer was also given the opportunity to comment on an earlier draft.

Summary

- Lasmiditan is a serotonin receptor agonist with high affinity to the 5-hydroxytryptamine 1F receptor. The intended use of lasmiditan is for the acute treatment of migraine.
- Two phase III randomized controlled trials have evaluated the efficacy and safety of lasmiditan for the acute treatment of migraine. In both trials, a greater number of patients who received lasmiditan achieved freedom from headache pain and freedom from the most bothersome symptom (from among these migraine-associated symptoms: photophobia, phonophobia, or nausea) at two hours when compared with placebo. The most frequently reported adverse event associated with lasmiditan was dizziness.
- There is potential for lasmiditan to be an alternative migraine treatment for patients who have failed, or have a contraindication, to triptans. Further studies are required to confirm the safety of lasmiditan in patients with cardiovascular or cerebrovascular disease.
- Due to frequent dizziness, the manufacturer recommends patients who take lasmiditan not engage in activities requiring mental alertness (e.g., driving) for at least eight hours. Lasmiditan is also associated with euphoria and hallucinations, suggesting abuse potential. The controlled substance schedule for lasmiditan is under review by the US Drug Enforcement Administration.
- On October 11, 2019, Lasmiditan was approved by the US FDA for the acute treatment of migraine with or without aura in adults. Lasmiditan is not approved in Canada.

Background

Migraine is a common, debilitating neurological disease.[1,2] Migraine is typically episodic, and recurrent attacks are characterized by headaches that are often one-sided and described as pulsatile or throbbing. Migraine is clinically diagnosed based on the frequency and nature of the headaches and the presence or absence of aura. Aura refers to a gradual onset of sensory or visual symptoms either before the onset of a headache or as part of the headache.[3] Migraine without aura, the most common type of migraine, is characterized by headache attacks lasting four to 72 hours. Attacks are usually accompanied by photophobia (light sensitivity), phonophobia (sensitivity to noise), and nausea, with or without vomiting. In addition to these symptoms, a migraine with aura is also characterized by reversible focal neurological symptoms, which usually precede the headache and last up to 60 minutes, or occasionally longer.[1]

According to the 2016 Global Burden of Disease Study, migraine is the second leading cause of years lived with disability globally.[4] In Canada, studies have shown the prevalence of migraine to be up to 26% in women, and up to 10% in men.[1] In 2010 to 2011, an estimated 8.3% of Canadians (2.7 million) were diagnosed with migraine. Among them, 42% took prescription medication for their condition. Migraine affects many aspects of daily life, including education, working, sleeping, and driving.[5] As such, migraine is costly, both in terms of direct and indirect costs.

The Technology

Lasmiditan (COL-144, LY573144; Eli Lilly Inc.) is a selective 5-hydroxytryptamine 1F receptor agonist intended for the acute treatment of migraine. Although the exact mechanism of action is unknown, it is suggested that lasmiditan acts on trigeminal pathways and inhibits the release of calcitonin gene-related peptide, a neuropeptide that mediates extracranial vasodilation that results in migraine pain.[6] Due to its high affinity for the 5-hydroxytryptamine 1F receptor, lasmiditan does not cause vasoconstriction, as reported with triptans. The vasoconstrictive properties of triptans are believed to be associated with 5-hydroxytryptamine 1B receptor activation in blood vessels.[6] Lasmiditan is not intended for use in migraine prevention.

Regulatory Status

Lasmiditan is not approved in Canada. On October 11, 2019, the US FDA approved lasmiditan (marketed as Reyvow) for the acute treatment of migraine with or without aura in adults.[7]

Cost and Administration

Lasmiditan is approved by the FDA for oral administration as one dose of 50 mg, 100 mg, or 200 mg taken as needed for the acute treatment of migraine.[7] The US product monograph states that no more than one dose should be taken in 24 hours. Lasmiditan is only available in the US as 50 mg and 100 mg oral tablets.[8] In the US, the cost of lasmiditan is US$80 per dose.[3]

Target Population

Lasmiditan is intended for the acute treatment of migraine in adults with or without aura. Patients who have failed other acute treatments or have contraindications to triptans may potentially be candidates for lasmiditan.

Current Practice

Pharmacologic options for the acute treatment of migraine include simple analgesics (acetaminophen and nonsteroidal anti-inflammatory drugs [NSAIDs]), triptans, and dihydroergotamine.[1] Opioids and barbiturates are not recommended due to their adverse effects and potential risk for abuse, their inability to stop a migraine attack, their lack of long-term efficacy, and the potential to worsen disease through medication overuse.[9] Treatments for migraine are recommended based on pain severity. According to the International Headache Society, severity can be measured using a four-point numerical rating scale (0 to 3) equal to no (0), mild (1), moderate (2), and severe (3) pain.[10] Acetaminophen or NSAIDs (e.g., diclofenac, naproxen) are recommended for the acute treatment of mild-to-moderate migraine attacks. Triptans are considered for moderate-to-severe attacks. For patients unresponsive to standard treatments, triptans may be combined with an NSAID; alternatively, dihydroergotamine may be used.[1]

Summary of the Evidence

SAMURAI and SPARTAN Studies

Study Design and Inclusion and Exclusion Criteria

Two phase III randomized placebo-controlled trials evaluated the efficacy and safety of lasmiditan for the acute treatment of migraine (Table 1). The patient population for the randomized controlled trials (SAMURAI and SPARTAN) included adults who had at least a one-year history of disabling migraines with or without aura (as per the International Headache Society diagnostic criteria) and three to eight attacks per month.[11,12] Patients with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension were excluded from SAMURAI; however, this population was included in SPARTAN. Both SAMURAI and SPARTAN excluded patients with chronic migraine, vestibular disorders causing dizziness and/or vertigo, and evidence of substance abuse within the past three years of study enrolment.[11,12]

Baseline Patient Characteristics

Patients enrolled in SAMURAI and SPARTAN were white females with a mean age of 41.4 years to 43.4 years (Table 2). Similarly, the majority of the patient population had at least one cardiovascular risk factor (CVRF), primarily due to age — CVRFs were identified using the American College of Cardiology/American Heart Association guidelines.[11-13] On average, patients experienced approximately five migraine attacks per month. Most patients (68% to 72%) had a headache of moderate severity prior to taking the study drug. A small number of patients (1% to 3%) took the study drug for mild attacks (Table 3).

Interventions and Comparator

SAMURAI and SPARTAN randomized patients to receive lasmiditan 50 mg (SPARTAN only), lasmiditan 100 mg, lasmiditan 200 mg, or placebo.[11,12] Patients were instructed to take their assigned study drug within four hours of migraine onset if the attack was moderate or severe and not improving. Patients were also permitted to take a second dose two to 24 hours following the first dose for rescue or recurrence of migraine. For the second dose, patients were randomized to receive the same active dose of lasmiditan or placebo — those initially assigned placebo received placebo for the second dose.[11,12] Other acute treatments for migraine (i.e., triptans, ergots, opioids, and barbiturates) were disallowed within 24 hours of study drug administration in SPARTAN.[11]

The treatment period for SAMURAI and SPARTAN lasted up to eight weeks and ended when patients treated a single migraine attack.[11,12] Patients who did not experience or treat a migraine attack were excluded from the efficacy and safety analyses.

Outcomes

Key outcomes of SAMURAI and SPARTAN included freedom from headache pain and freedom from the most bothersome symptom (MBS) (from among these migraine-associated symptoms: photophobia, phonophobia, or nausea) at two hours after the first dose of the study drug. Outcomes were reported by patients using an electronic diary.[11,12]

GLADIATOR: Long-Term Extension Trial

A phase III open-label extension trial (GLADIATOR) evaluated the long-term efficacy and safety of lasmiditan for the acute treatment of migraine (Table 1).[14] Patients who completed SAMURAI or SPARTAN were given the opportunity to enroll in GLADIATOR and were randomized to receive lasmiditan 100 mg or lasmiditan 200 mg. Patients were instructed to take the study drug within four hours of migraine onset. A second dose was permitted two to 24 hours following the first dose. Unlike SAMURAI and SPARTAN, patients enrolled in GLADIATOR treated multiple migraine attacks over a one-year period. The key outcome of GLADIATOR was to assess the safety and tolerability of lasmiditan.[14]

Table 1: Characteristics of Lasmiditan Phase III Trials

Author (year), name of study (NCT number), country, manufacturer	Study design, study duration, sample size	Population	Interventions, comparator	Key outcomes
Kuca et al. (2018)[12] SAMURAI (NCT02439320) US Eli Lilly and Company	Randomized, double-blind, placebo-controlled, multi-centre study 8 weeks N = 2,231	Adults ≥ 18 years History of disabling migraine with or without aura ≥ 1 year (IHS diagnostic criteria 1.1 or 1.2.1) MIDAS[a] score ≥ 11 History of migraine onset before 50 years of age History of 3 to 8 migraine attacks per month	Interventions: Lasmiditan 100 mg (n = 744) Lasmiditan 200 mg (n = 745) Comparator: Placebo (n = 742)	Headache-pain freedom at 2 hours after first dose of study drug MBS freedom at 2 hours after first dose of study drug
Goadsby et al. (2019)[11] SPARTAN (NCT02605174) Germany, UK, US Eli Lilly and Company	Randomized, double-blind, placebo-controlled, multi-centre study 8 weeks N = 2,869	Adults ≥ 18 years History of disabling migraine with or without aura ≥ 1 year (IHS diagnostic criteria 1.1 or 1.2.1) MIDAS[a] score ≥ 11 History of migraine onset before 50 years of age History of 3 to 8 migraine attacks per month	Interventions: Lasmiditan 50 mg (n = 716) Lasmiditan 100 mg (n = 721) Lasmiditan 200 mg (n = 721) Comparator: Placebo (n = 711)	Headache-pain freedom at 2 hours after first dose of study drug MBS freedom at 2 hours after first dose of study drug

Author (year), name of study (NCT number), country, manufacturer	Study design, study duration, sample size	Population	Interventions, comparator	Key outcomes
Brandes et al. (2019)[14] GLADIATOR (NCT02565186) Germany, UK, US Eli Lilly and Company	Randomized, open-label, multi-centre study 1 year N = 1,978	Adults ≥ 18 years History of disabling migraine with or without aura ≥ 1 year (IHS diagnostic criteria 1.1 or 1.2.1) MIDAS[a] score ≥ 11 History of migraine onset before 50 years of age History of 3 to 8 migraine attacks per month	Interventions: Lasmiditan 100 mg (n = 963) Lasmiditan 200 mg (n = 1,015)	AEs

AE = adverse event; IHS = International Headache Society; MIDAS = Migraine Disability Assessment; NCT = National Clinical Trial.

[a] The MIDAS is a five-item questionnaire to measure headache-related disability. MIDAS scores are categorized into four grades: grade I (0 to 5), little or no disability; grade II (6 to 10), mild disability; grade III (11 to 20), moderate disability; and grade IV (≥ 21), severe disability.

Table 2: Baseline Characteristics of Patients[a] Enrolled in Phase III Randomized Placebo-Controlled Trials

	SAMURAI[12]			SPARTAN[11]			
	Lasmiditan 100 mg (n = 630)	Lasmiditan 200 mg (n = 609)	Placebo (n = 617)	Lasmiditan 50 mg (n = 654)	Lasmiditan 100 mg (n = 635)	Lasmiditan 200 mg (n = 649)	Placebo (n = 645)
Age, mean (SD), year	42.2 (11.7)	41.4 (12.0)	42.4 (12.3)	42.8 (13.2)	43.4 (12.6)	41.8 (12.4)	42.6 (12.9)
Female, n (%)	512 (81.3)	515 (84.6)	525 (85.1)	554 (84.7)	539 (84.9)	536 (82.6)	545 (84.5)
Caucasian, n (%)	471 (74.8)	450 (73.9)	479 (77.6)	524 (80.1)	509 (80.2)	522 (80.4)	516 (80.0)
MIDAS total score, mean (SD)	30.4 (21.2)	32.0 (21.7)	32.2 (23.7)	33.2 (25.2)	31.3 (20.7)	32.9 (23.5)	31.5 (23.1)
Duration of migraine history, mean (SD), year	19.7 (13.0)	18.9 (13.1)	19.3 (12.7)	18.6 (12.9)	19.2 (13.6)	17.6 (12.6)	17.9 (12.8)
Migraine attacks per month in the past 3 months, mean (SD), n	5.1 (1.8)	5.3 (2.3)	5.1 (1.8)	5.2 (2.0)	5.3 (1.9)	5.3 (1.9)	5.5 (2.4)
Patients with background use of migraine preventive medication, n (%)	97 (15.4)	111 (18.2)	103 (16.7)	125 (19.1)	122 (19.2)	121 (18.6)	126 (19.5)
Patients with ≥ 1 cardiovascular risk factor,[b] n (%)	489 (77.6)	471 (77.3)	485 (78.6)	508 (77.7)	510 (80.3)	528 (81.4)	517 (80.2)

MIDAS = Migraine Disability Assessment; SD = standard deviation.

[a] Included in the safety population.

[b] Cardiovascular risk factors include age of 40 years or older, diabetes, smoking, total cholesterol of 240 mg/dL (6.2 mmol/L) or higher, high-density lipoprotein cholesterol of less than 40 mg/dL (1.0 mmol/L) for men or less than 50 mg/dL (1.3 mmol/L) for women, and systolic blood pressure of 140 mm Hg and greater.

Table 3: Characteristics of Migraine Prior to Treatment With Lasmiditan in the Phase III Randomized Placebo-Controlled Trials

	SAMURAI[12]			SPARTAN[11]			
	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo	Lasmiditan 50 mg	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo
Severe headache pain, n/N[a] (%)	132/503 (26.2)	148/518 (28.6)	145/524 (27.7)	152/556 (27.3)	159/532 (29.9)	147/528 (27.8)	165/540 (30.6)
Moderate headache pain, n/N[a] (%)	366/503 (72.8)	355/518 (68.5)	370/524 (70.6)	392/556 (70.5)	364/532 (68.4)	374/528 (70.8)	369/540 (68.3)
Mild headache pain,[b] n/N[a] (%)	5/503 (1.0)	15/518 (2.9)	9/524 (1.7)	12/556 (2.2)	9/532 (1.7)	7/528 (1.3)	5/540 (0.9)

[a] Modified intent-to-treat population.

[b] Patients were instructed to take the study drug within four hours of migraine onset if the attack was moderate or severe; however, a small number of patients took the drug for mild attacks.

Efficacy

The key efficacy outcome results from SAMURAI and SPARTAN are summarized in Table 4.

The safety population was defined as all randomized patients who used at least one dose of the study drug. The intention-to-treat (ITT) population was defined as all patients in the safety population who recorded any post-dose headache severity or symptom assessments. The modified ITT population (also referred to as the full analysis set) was defined as all patients in the ITT population who treated a migraine attack within four hours of onset.[11,12] On average, patients in the modified ITT population took a dose of study drug within one hour of migraine onset.[11,12]

Several subgroup analyses were conducted using pooled data from SAMURAI and SPARTAN.[15,16]

Headache-Pain Freedom at Two Hours After The First Dose of The Study Drug

Headache-pain freedom was defined as a reduction in headache severity from mild, moderate, or severe pain at baseline to none using the International Headache Society four-point numerical rating scale.[11,12] Although patients were instructed to take the study drug within four hours of migraine onset if the attack was moderate or severe, a small number of patients took the study drug for mild attacks (Table 3) — these patients were included in the efficacy analysis.[11,12]

In SAMURAI, a greater proportion of patients achieved headache-pain freedom at two hours after the first dose of lasmiditan 100 mg (142 out of 503 patients [28.2%]; P < 0.001) and lasmiditan 200 mg (167 out of 518 patients [32.2%]; P < 0.001) when compared with placebo (80 out of 524 patients [15.3%]).[12]

In SPARTAN, a greater proportion of patients achieved headache-pain freedom at two hours after the first dose of lasmiditan 50 mg (159 out of 556 patients [28.6%]; P = 0.003), lasmiditan 100 mg (167 out of 532 patients [31.4%]; P < 0.001), and lasmiditan 200 mg (205 out of 528 patients [38.8%]; P < 0.001), when compared with placebo (115 out of 540 patients [21.3%]).[11]

MBS Freedom at Two Hours After The First Dose of The Study Drug

MBS freedom was defined as a change from "yes" to "no" for the presence of the patient's baseline MBS for one of the following: nausea, phonophobia, or photophobia.[11,12]

In SAMURAI, a greater proportion of patients achieved MBS freedom at two hours after the first dose of lasmiditan 100 mg (192 out of 469 patients [40.9%]; P < 0.001) and lasmiditan 200 mg (196 out of 481 patients [40.7%]; P < 0.001) when compared with placebo (144 out of 488 patients [29.5%]).[12]

In SPARTAN, a greater proportion of patients achieved MBS freedom at two hours after the first dose of lasmiditan 50 mg (209 out of 512 patients [40.8%]; P = 0.009), lasmiditan 100 mg (221 out of 500 patients [44.2%]; P < 0.001), and lasmiditan 200 mg (235 out of 483 patients [48.7%]; P < 0.001) when compared with placebo (172 out of 514 patients [33.5%]).[11]

Subgroup Analysis: Patients Requiring a Rescue Dose

A post hoc analysis of pooled data from SAMURAI and SPARTAN evaluated the efficacy of a second dose of lasmiditan.[15] The "rescue" population was identified from the ITT population (1,549 out of 3,981 patients [39%]) and included patients who did not achieve headache-pain freedom at two hours after the first dose of the study drug and subsequently took a second dose two to 24 hours following the first dose. For the second dose, patients initially randomized to lasmiditan were randomized to receive the same dose of lasmiditan (635 patients) or placebo (307 patients), whereas patients initially randomized to placebo received placebo for the second dose (606 patients).[11,12,15]

Efficacy results (i.e., headache-pain freedom and MBS freedom) at two hours after a second dose were similar between lasmiditan and placebo — this was consistent across all doses of lasmiditan (i.e., 50 mg, 100 mg, and 200 mg).[15]

Subgroup Analysis: Patients Taking Concomitant Medications for Migraine Prevention

A post hoc analysis of pooled data from SAMURAI and SPARTAN evaluated the efficacy of lasmiditan in patients taking concomitant medications for migraine prevention.[16] Of 3,981 patients, 698 patients (17%) were identified as taking concomitant medications (e.g., topiramate, propranolol) for migraine prevention.[11,12,16]

A greater proportion of patients taking concomitant medications for migraine prevention achieved headache-pain freedom and MBS freedom at two hours after the first dose of lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg when compared with placebo. There were no differences in outcome results between the patients taking preventive medications and patients not taking preventive medications.[16]

Subgroup Analysis: Patients With Prior Triptan Use

A post hoc analysis of pooled data from SAMURAI and SPARTAN evaluated the efficacy of lasmiditan in patients with prior triptan use.[17] A total of 1,786 patients (45%) from the ITT population had at least one triptan recorded as a current or prior migraine treatment. Patients with prior triptan use were further stratified to "good responders" or "insufficient responders" based on patient reports of their most recent triptan use. Insufficient responders represented 31% of patients with prior triptan use.[17]

A greater proportion of patients with prior triptan use achieved headache-pain freedom and MBS freedom at two hours after the first dose of lasmiditan 100 mg and lasmiditan 200 mg when compared with placebo. There were no differences in outcome results between good and insufficient responders to prior triptans.[17]

Table 4: Key Efficacy Outcomes Results From Lasmiditan Phase III Randomized Placebo-Controlled Trials

	SAMURAI[12]			SPARTAN[11]			
	Lasmiditan 100 mg	**Lasmiditan 200 mg**	**Placebo**	**Lasmiditan 50 mg**	**Lasmiditan 100 mg**	**Lasmiditan 200 mg**	**Placebo**
Headache-pain freedom at 2 hours							
n/N[a] (%)	142/503 (28.2)	167/518 (32.2)	80/524 (15.3)	159/556 (28.6)	167/532 (31.4)	205/528 (38.8)	115/540 (21.3)
OR (95% CI)	2.2 (1.6 to 3.0)	2.6 (2.0 to 3.6)		1.5 (1.1 to 1.9)	1.7 (1.3 to 2.2)	2.3 (1.8 to 3.1)	2.2 (1.6 to 3.0)
MBS freedom at 2 hours							
n/N[a,b] (%)	192/469 (40.9)	196/481 (40.7)	144/488 (29.5)	209/512 (40.8)	221/500 (44.2)	235/483 (48.7)	172/514 (33.5)
OR (95% CI)	1.7 (1.3 to 2.2)	1.6 (1.3 to 2.1)		1.4 (1.1 to 1.8)	1.6 (1.2 to 2.0)	1.9 (1.4 to 2.4)	

CI = confidence interval; MBS = most bothersome symptom; OR = odds ratio.

[a] Modified intention-to-treat population.

[b] Not all patients in the modified intention-to-treat population reported an MBS at baseline.

Safety

Safety data from SAMURAI and SPARTAN were pooled.[18] A total of 4,439 patients were included in the safety analysis — 3,177 patients received lasmiditan and 1,262 patients received placebo. Adverse events that occurred within 48 hours of the first dose of the study drug were considered treatment-emergent.[18] No deaths were reported. Five patients (0.2%) who received lasmiditan reported a treatment-emergent serious adverse event, which included benign pituitary tumour, hypertension, hypotension, presyncope, and surgery. Due to its mechanism of action, a review was conducted to assess for possible cases of serotonin syndrome with lasmiditan. Five possible cases of serotonin syndrome were identified; however, none satisfied the Hunter criteria for serotonin syndrome. The proportion of patients who reported treatment-emergent adverse events (TEAEs) was greater in the lasmiditan group (1,134 out of 3,177 patients [35.9%]) when compared with placebo (174 out of 1,262 patients [13.8%]). The most frequently reported TEAEs were dizziness, paresthesia, somnolence, fatigue, nausea, muscular weakness, and hypoesthesia. One patient enrolled in SPARTAN withdrew from the study due to adverse events (dizziness and fatigue) of mild severity.[18]

Interim results from GLADIATOR reported long-term safety data associated with repeated use of lasmiditan. The safety population included 1,978 patients, of which 814 (41.2%) had completed 12 months of the study at the time of analysis.[14] Treatments were initiated within 1.2 hours of the attack. The mean total number of treated migraine attacks during the 12-month period was nine (standard deviation 9.2). No deaths were reported. Nine patients (0.5%) reported at least one treatment-emergent serious adverse event; however, these events were not described. A total of 962 patients (48.6%) reported at least one TEAE. The most frequently reported TEAEs included dizziness, somnolence, paresthesia, fatigue, nausea, asthenia, hypoesthesia, vertigo, and lethargy. The number of patients who withdrew from the study due to adverse events was 254 (12.8%). The most common adverse event leading to discontinuation was dizziness.[11,18]

Subgroup Analysis: Patients With Cardiovascular Risk Factors

A post hoc analysis of pooled data from SAMURAI and SPARTAN compared the frequency of likely cardiovascular TEAEs between lasmiditan and placebo in patients with or without CVRFs.[19] Of the 4,439 patients in the safety population, 3,500 patients were identified as having at least one CVRF. The number of patients with CVRFs who reported at least one likely cardiovascular TEAE was 30 (0.9%) in the lasmiditan group and five (0.4%) in the placebo group. There was no difference in the frequency of likely cardiovascular TEAEs between patients with CVRFs and patients without CVRFs.[19]

Study Limitations

The study population enrolled in SAMURAI and SPARTAN included a high proportion of white women compared with men, which is expected considering that migraine affects more women than men.

Both SAMURAI and SPARTAN evaluated the efficacy and safety of a single treatment of lasmiditan — the efficacy and safety of repeated doses or of regular use of the drug were not assessed. Lasmiditan was compared to placebo instead of standard treatment — no head-to-head studies have been conducted comparing lasmiditan to other acute treatments for migraine (e.g., triptans).

GLADIATOR evaluated the long-term efficacy and safety of lasmiditan; however, only interim results were available for this report. All patients at European sites received lasmiditan 200 mg due to lack of availability of lasmiditan 100 mg.[14] The proportion of patients who withdrew from GLADIATOR was 51.7%; thus, the study is at risk of attrition bias. Patients discontinued for various reasons, including lack of efficacy, dislike of electronic diary requirements, relocation, and scheduling conflicts; most withdrawals (21.8%) were due to "patient request."[14]

Results from the post hoc analysis evaluating the safety of lasmiditan in patients with CVRFs have limited external validity. Many of the patients identified with at least one CVRF were included due to their age (i.e., older than 40 years).[19] The proportion of patients within the safety population with a history of cardiovascular or cerebrovascular disease was 20.4%. In addition, only 85 patients were contraindicated for triptans.[19] Further studies are necessary to confirm the safety of lasmiditan in patients with cardiovascular or cerebrovascular disease.

Concurrent Developments

Ubrogepant and rimegepant are calcitonin gene-related peptide receptor antagonists for the acute treatment of migraine. Ubrogepant (Ubrelvy, previously MK-1602; Allergan) was approved for marketing by the US FDA in December 2019. Rimegepant (BHV-3000; Biohaven Pharmaceuticals) has not yet been approved to be marketed in any country and is under review by the US FDA. The application status to Health Canada is unknown for both drugs.

AXS-07 (Axsome Therapeutics) is an oral, fixed-dose combination of meloxicam and rizatriptan using Axsome's molecular solubility enhanced inclusion complex (MoSEIC) technology. Phase III trials evaluating AXS-07 in the acute treatment of migraine are currently ongoing (NCT03896009 and NCT04068051).[20]

M207 (proposed trade name Qtrypta; Zosano Pharma Corporation) is a zolmitriptan intracutaneous microneedle system for the acute treatment of migraine. Phase III efficacy and safety trials have been completed (NCT02745392 and NCT03282227). Zosano Pharma Corporation intends to file a New Drug Application for M207 in the fourth quarter of 2019.[21]

Implementation Issues

Dizziness and somnolence are frequently reported adverse events associated with lasmiditan.[14,18] The manufacturer recommends that patients who take lasmiditan not engage in activities requiring mental alertness (such as driving) for at least eight hours.[8] A randomized, double-blind phase I study evaluated the effect of lasmiditan on simulated driving performance in healthy subjects. Lasmiditan 100 mg and lasmiditan 200 mg were compared with diphenhydramine 50 mg as a positive control. Driving performance was measured using standard deviation of lateral position. Mean standard deviation of lateral position did not reach the threshold for driving impairment at eight hours or later following administration of lasmiditan 100 mg or lasmiditan 200 mg.[8]

A human abuse potential study reported higher "drug liking" scores with lasmiditan than with placebo, indicating abuse potential.[8,22] Adverse events such as euphoria and hallucinations have been reported with lasmiditan — the frequency of these events in phase II and phase III trials was less than 1%.[22] The controlled substance schedule for lasmiditan will be determined following review by the US Drug Enforcement Administration.[8]

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