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DRUG EVALUATION

Lasmiditan for the treatment of migraine

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ABSTRACT

Introduction: Migraine is one of the most common diseases in the world, with high economical and subjective burden. Migraine acute therapy is nowadays based on specific and non-specific drugs but up to 40% of episodic migraineurs still have unmet treatment needs and over 35% do not benefit from triptans administration. Serotonin-1F receptors have been identified in trigeminal system and became an ideal target for anti-migraine drug development as potential trigeminal neural inhibitors. Lasmiditan, a novel serotonin1F receptor agonist, showed specific affinity in vitro for the receptor without any vasoconstrictive action and inhibited markers associated with electrical stimulation of trigeminal ganglion in migraine animal models.

Areas covered: This article reviews both preclinical and clinical studies on lasmiditan as a potential acute therapy for migraine, as well as pharmacokinetic and pharmacodynamic features. It also summarizes safety and tolerability data gathered in the various human studies.

Expert opinion: The absence of vasoconstrictive effects makes lasmiditan a promising novel migraine acute therapy. Although preclinical and Phase I and II studies established a significant efficacy, the limited knowledge about pharmacokinetics and metabolism, the high rate of non-serious central nervous system side effects and the lack of larger studies remain still a matter of concern that should be addressed in future studies.

1. Introduction

Migraine is one of the most common primary headache disorder, ranked as one of the most prevalent (3rd) and debilitating diseases worldwide as stated by the World Health Organization (WHO) [1–3]. Specifically, migraine affects over 14% of adults worldwide [4] with an estimated progression to the chronic form in about 1–4% of the population [5], especially between the age of 50 and 60 years [6]. Chronic migraine is characterized by headache occurrence at least 15 days per month for more than 3 months, and with the features of migraine headache on at least 8 days per month [7–9]. The total economic burden of migraine is estimated around €27 billion per year in Europe, and it is likely to be similar in USA [9].

Migraine is characterized by moderate–severe, unilateral, throbbing headache attacks lasting from 4 to 72 h, accompanied by additional symptoms such as nausea, vomiting, phonophobia, and/or photophobia. According to the ICHD-3-beta classification [7], two major subtypes are indicated for migraine: migraine without aura, which is characterized by headache with specific features and associated symptoms; and migraine with aura, primarily characterized by the transient focal neurological symptoms that usually precede or sometimes accompany the headache. A premonitory phase (from hours to days before the headache attack) and a resolution phase can additionally occur in some patients. Both phases include hyperactivity, hypoactivity, depression, cravings for foods, repetitive yawning, fatigue, and neck stiffness and/or pain [7]. In about one-third of the cases migraine headache is preceded by the aforementioned aura (i.e. short-lasting, fully reversible visual, sensory, or speech symptoms), which is less prevalent in women [10,11]. The cornerstones of migraine pharmacological treatment are represented by the acute therapy, aimed to abort attacks and provide a prompt relief from pain, and the preventive treatment, aimed to lower attacks frequency and severity [12]. Migraine acute therapy is nowadays based on specific (triptans and ergot derivatives) and nonspecific drugs (analgesics and nonsteroidal anti-inflammatory drugs – NSAIDs) that have shown efficacy in treating attacks. The choice between these two main classes might be based on a stratified care approach, i.e. depending on migraine severity and other clinical factors, or on the step care management, meaning that patients are primarily treated with analgesics but might receive specific drugs in case of poor response [12,13]. Both the ineffectiveness and the
overuse of acute drugs are two of the major risk factors for migraine chronification. Moreover, medication overuse is thought to be associated with a less-effective acute treatment that might lead the patient to increase drug intake and/or the dosages, which in turn leads to headache progression [9].

Acute treatment of migraine attacks has been greatly improved for the last two decades, although treatment requirements of 40% of episodic migraineurs are not currently met, and headache-related disability (19%) and dissatisfaction with current drugs (15%) were stated in the American Migraine Prevalence and Prevention as the most frequent complaints from patients [14]. Likewise, over 35% of participants in clinical trials do not benefit from oral triptans administration [15,16]. Therefore, novel and more effective acute therapies are under active investigation and would hopefully improve migraine disability and clinical course. The pathophysiology of migraine remains still not completely understood, and most of the acute agents have been developed when a pivotal role in migraine headache was attributed to the abnormal vasodilation of intracranial vessels [17]. This hypothesis was reinforced by the effectiveness of triptans in migraine, a group of serotonin1B/1D (5-HT\textsubscript{1B/1D}) receptor agonists with vasoconstrictive effects. However, although the role of trigeminovascular system dysfunction has been widely described [10], it is still uncertain if it represents the primary nociceptive stimulus for migraine headache [18] and the neurogenic hypothesis has been proposed. According to this model, cranial vasodilation is a secondary event in migraine pathophysiology, and the primary cause is supposed to be the neuronal sensitization of the trigeminal system, i.e. the increased transmission of pain sensory information through the pathway [18].

This hypothesis implies the possibility of an alternative non-vascular antimigraine mechanism represented by the neural inhibition of trigeminal system [18,19]. In this view, serotonin-1F (5-HT\textsubscript{1F}) receptors, expressed by trigeminal neurons, trigeminal ganglion (TG), and trigeminal nucleus caudalis (TNC) with no vasoconstrictive effects (Figure 1), became an ideal target for antimigraine drug development. Lasmiditan, a novel 5-HT\textsubscript{1F} receptor agonist, showed in vitro specific binding affinity for the receptor without any vasoconstrictive action and inhibited markers associated with electrical stimulation of the TG in animal models of migraine [20]. Moreover, human clinical trials showed significant effectiveness with a favorable safety profile of lasmiditan oral administration as migraine acute treatment (Box 1).

2. Overview of the market

Currently, the so-called triptans family represents the mainstay of acute moderate-to-severe migraine therapy. Other first-line drugs for mild-to-moderate migraine include nonspecific agents such as NSAIDs, acetaminophen, caffeine [21,22]. Fixed combination of aspirin (250 mg), acetaminophen (200 mg), and caffeine (50 mg) showed a superior effectiveness than the same drugs administered alone [23–25].

Sumatriptan was the first triptan introduced in clinical use in 1991, followed by other six molecules belonging to this family (naratriptan, rizatriptan, zolmitriptan, almotriptan, eletriptan, and frovatriptan) that largely replaced ergot derivatives use for migraine acute treatment [26]. Collectively, they possess high affinity to three serotonin (5-HT) receptor subtypes (i.e. 5-HT\textsubscript{1B}, 5-HT\textsubscript{1D} and 5-HT\textsubscript{1F}) and their efficacy was demonstrated in large, randomized, placebo-controlled clinical trials. However, the vascular distribution of 5-HT\textsubscript{1B} receptors within the smooth muscle and in cerebral blood vessels endothelium mediates the vasoconstrictive properties of triptans, and, consequently, the
risk of coronary vasoconstriction [27]. For this reason, patients with cardio- and/or cerebrovascular disease, uncontrolled hypertension, and/or with particular forms of migraine-like hemiplegic migraine cannot use triptans [27,28]. Furthermore, other triptans-related side effects such as chest tightness, throat discomfort, muscle pain, and paraesthesia could lead some patients to avoid them [27]. Therefore, effective novel antimigraine treatments without a relevant vasoconstrictor activity remain a considerable area of unmet clinical need. In this view, lasmiditan represents a desirable option for the abortive therapy of migraine attacks. Calcitonin gene-related peptide (CGRP) receptor antagonists (gepants) and monoclonal antibodies against CGRP and CGRP receptors constitute promising alternatives [29,30], and different glutamate receptors antagonists as well [31].

3. Introduction to lasmiditan

3.1. Chemistry

Lasmiditan, also known as COL-144 and LY573144, is a novel 5-HT_1F receptor agonist with high-affinity and selectivity for the 5-HT_1F receptor. Its chemical IUPAC name is 2,4,6-trifluoro-[6-[(1-methylpiperidin-4-yl)-carbonyl]pyridin-2yl]benzamide. The chemical structure of lasmiditan, as well as the pharmacological profile, is clearly different from triptans. In fact, the indole structure of triptans, identical to the neurotransmitter 5-HT, is replaced by a pyridinoyl-piperidine scaffold, which is not found in any other antimigraine classes. In addition, lasmiditan antimigraine efficacy is mediated through a non-vascular, primarily neural, mechanism, with a loss of the vasoconstrictor activity owned by triptans.

3.2. Pharmacodynamics

5-HT_1F receptor agonists represent a potential alternative treatment in patients not responding to triptans and/or with cardiovascular disorders. Selective 5-HT_1F receptor agonists do not involve blood vessel diameter or contractility, while 5-HT_1B/1D receptor agonists (such as triptans) do [32]. The first compound tested as selective for 5-HT_1F receptor has been LY334370 [17]. This compound, while preserving the indole-based chemical structure, showed a relatively high selectivity for 5-HT_1F (100-fold selective compared to SHT_1B and SHT_1D) and also for SHT_1A receptors [20]. However, its development had to be discontinued because of long-term safety concerns in animals [18]. Therefore, a new selective 5-HT_1F receptor agonist, lasmiditan, has been developed changing the chemical structure of LY334370 by deleting the indole moiety and is currently under clinical assessment. This new molecule showed a better receptor selectivity profile for 5-HT_1F and a reduced affinity for 5-HT_1A/1B/1D compared to LY334370. Lasmiditan selectivity has been evaluated using radioligand-binding techniques on a panel of over 50 ion channels, transporters, and receptors. It showed high selectivity for 5-HT_1F (450-fold higher affinity for 5-HT_1F than for 5-HT_1A/1B/1D receptors) and a significant low cross-reactivity with other members of the 5-HT receptor family, even if all of these receptors are structurally homologous. Moreover, lasmiditan showed no significant affinity with a group of receptors that regulate the vascular tone, the monoaminergic subtypes [20].

Lasmiditan chemical structure and activity profile are different from those of triptans and LY334370 and account for its inclusion in a novel drug class called ‘ditan’ [33]. 5-HT_1F receptors are present in different locations in the trigeminovascular system: in the peripheral TG and in the central TNC (Figure 1). Sited at peripheral and central ends of sensory trigeminal neurons, their function seems to be related to the hyperpolarization of nerve terminals and to the inhibition of trigeminal impulses [34]. Since it has been hypothesized that cranial vasodilation is not the primary nociceptive stimulus for migraine, the inhibition of trigeminal pathways could be a nonvascular antimigraine mechanism [19]. 5-HT_1F receptors are not expressed by endothelial or smooth-muscle cells of cerebral vessels; therefore, they are not implicated in the vascular tone regulation of the human brain.

Moreover, after electrical stimulation of the TG in rats, the administration of lasmiditan inhibited dual plasma protein extravasation and decreased c-Fos expression in the TNC [10,35]. Furthermore, unlike sumatriptan, lasmiditan also penetrates the blood–brain barrier (BBB) and could therefore trigger 5-HT_1F receptors centrally located on trigeminal neurons and reduce the c-Fos expression. Its effects could also be mediated by the action of 5-HT_1F receptors located outside the central nervous system (CNS), on primary trigeminal afferents or on cell bodies within the TG. Therefore, lasmiditan appears to be involved in the reduction of second-order trigeminal neurons activation that is considered an essential mechanism in the pathophysiology of acute migraine [30]. Moreover, 5-HT_1F receptors have been found in humans also in cortical layers 4 and 5 and in the granule cells of cerebellum [36] and lasmiditan actively penetrates the BBB (brain/plasma ratios of 1.08, 1.57, 1.30, and 1.33 at 0.5, 2, 4, and 6 h post-dosing, respectively) [37] without being a substrate of the efflux pump multidrug-resistance protein 1. Therefore, other central effects might be linked to 5-HT_1F agonism by lasmiditan, but we could find no data available on this topic. Furthermore, at the same concentrations, triptans caused a 50% vessel diameter constriction whereas lasmiditan had no vasoconstrictive effects. Moreover, lasmiditan low affinity for 5-HT_1B receptors produces no contractions of rabbit saphenous vein in doses up to 100 μM [33].

The interaction with 5-HT_1F receptors and the absence of vasoconstrictive effects make lasmiditan the first molecule of a new drug category, the neurally acting antimigraine agents (NAAMAs) [33].

3.3. Pharmacokinetics and metabolism

Data on the pharmacokinetics of lasmiditan are scarce. We were able to find only information about lasmiditan oral bioavailability from a poster presentation [38], reported around 40%, and the time at which the maximum serum concentration of lasmiditan is attained (T_max), which ranges between 1.5 and 2.5 h after oral administration of 50–400 mg [33,35,39]. No data about the possible influence of age and gender on these parameters are available.

The results of a randomized, open-label study aimed to estimate lasmiditan relative bioavailability have been recently reported. The primary outcomes were the maximum serum
concentration ($C_{\text{max}}$), $T_{\text{max}}$, and the area under the curve (AUC) of lasmiditan 200 mg under fed and fasted conditions in 30 healthy subjects. $C_{\text{max}}$ was, respectively, 394.7 ± 167.8 (mean ± standard deviation) and 322.8 ± 122.0 ng/mL; $T_{\text{max}}$ resulted, respectively, 2.5 ± 1.0 (mean ± standard deviation) and 1.5 ± 1.0 h and AUC$_0-\infty$ was 2444 ± 926.2 (mean ± standard deviation) and 1892 ± 746.0 ng h/mL [40]. No data are available on lasmiditan half-life ($t_{1/2}$) and metabolism; therefore, the existence of active and/or inactive metabolites is not known.

4. Clinical efficacy

So far, two selective 5-HT$_{1F}$ agonists have been tested in human trials for migraine: LY334370 [9] and lasmiditan (LY573144; COL-144) [32]. LY334370 was effective in an early proof-of-concept, placebo-controlled, double-blind, parallel-group study on moderate-to-severe acute migraineurs [41]. Unfortunately, further clinical studies have been halted because of long-term-associated animal toxicity [18].

4.1. Preclinical data

The hypothesis of an antimigraine effect of 5-HT$_{1F}$ receptors agonists arose from the observation that sumatriptan was able to inhibit CGRP release by the activation of 5-HT trigeminal neurons presynaptic receptors [42]. Given the sumatriptan modest affinity for 5-HT$_{1F}$ receptors and their distribution on trigeminal neurons, it was hypothesized that selective 5-HT$_{1F}$ agonists might be useful in migraine [43,44]. Therefore, different 5-HT agonists were initially tested in the guinea pig dural plasma protein extravasation model and a strong correlation was found between the 5-HT$_{1F}$ receptors affinity and the ability to inhibit plasma protein extravasation, without vasoconstrictive effects [44,45]. The first 5-HT$_{1F}$ agonist developed, LY334370, showed promising efficacy with the inhibition of dural extravasation in guinea pig migraine models [46] with any vasoconstrictive effects, but it was not developed after the human proof-of-concept trials because of its significant affinity for 5-HT$_{1A}$ receptors and its possibility to activate 5-HT$_{1B}$ receptors at certain plasma levels [20]. Therefore, research has focused on the elaboration of a 5-HT$_{1F}$ agonist with a substantially different structure from triptans, and lasmiditan was generated. It was then tested for binding affinity to the 5-HT$_{1F}$ receptors in vitro, and in two rodent models of migraine [20]. Specifically, lasmiditan oral administration strongly inhibited TNC c-Fos induction and protein dural extravasation associated with the electrical stimulation of TG [20]. It is able to cross the BBB and its action might be both central on trigeminal neurons and peripheral on primary trigeminal afferents and cell bodies within the TG. The vasoconstrictive properties were also assessed in vitro using rabbit saphenous vein rings, and lasmiditan up to 100 μM concentrations showed no visible contractions [20]. Anyway, there are no data demonstrating the inhibition of CGRP release by lasmiditan and little is known about its binding sites in human brain potentially linked to adverse effects [10].

4.2. Phase I clinical trials

Four Phase I studies have been conducted for lasmiditan oral formulations and one for the intravenous (Table 1) [47]. We were not able to find published data from the first Phase I study on intravenous administration of lasmiditan in 2003, where 40 subjects were challenged with lasmiditan with the aim of evaluate safety, tolerability, and pharmacokinetics. Nonetheless, a larger Phase II study was carried out in 2007 to assess intravenous lasmiditan efficacy and doses range in migraine patients (see next paragraph). Two Phase I trials were performed in 2008 (COL MIG-102, COL MIG-103; Table 1) and aimed to evaluate bioavailability, safety, tolerability, and other pharmacokinetic parameters of different oral formulations (oral solution, oral tablet, and sublingual). Although we were not able to find extensive published data from these studies, oral formulations were demonstrated to reach plasma levels previously associated with efficacy of the intravenous administration [38] without severe adverse effects associated. Reported side effects with the maximum dose of 400 mg were drowsiness, dizziness, and paraesthesia. The oral solution

<table>
<thead>
<tr>
<th>Study</th>
<th>Formulation</th>
<th>Phase</th>
<th>Patients on lasmiditan</th>
<th>Objectives</th>
<th>Results</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>COL-MIG 102</td>
<td>Oral solution and sublingual</td>
<td>I</td>
<td>44</td>
<td>Safety, tolerability, and pharmacokinetics</td>
<td>–</td>
<td>2008</td>
</tr>
<tr>
<td>COL-MIG 103</td>
<td>Oral solution and oral tablet</td>
<td>I</td>
<td>44</td>
<td>Bioavailability and pharmacokinetics</td>
<td>–</td>
<td>2008</td>
</tr>
<tr>
<td>COL-MIG 104</td>
<td>Oral tablet</td>
<td>I</td>
<td>30</td>
<td>Bioavailability under fed/fasted conditions</td>
<td>Ref [35]</td>
<td>2015</td>
</tr>
<tr>
<td>COL-MIG 105</td>
<td>Oral tablet</td>
<td>I</td>
<td>55</td>
<td>Thorough QT study</td>
<td>–</td>
<td>2011</td>
</tr>
<tr>
<td>No Name (intravenous infusion)</td>
<td>Intravenous</td>
<td>I</td>
<td>40</td>
<td>Safety, tolerability, and pharmacokinetics</td>
<td>–</td>
<td>2003</td>
</tr>
<tr>
<td>COL-MIG 202</td>
<td>Oral tablet</td>
<td>IIb</td>
<td>305</td>
<td>Efficacy and safety of a range of oral doses</td>
<td>Ref [32]</td>
<td>2009</td>
</tr>
<tr>
<td>COL-MIG 301 (SAMURAI)</td>
<td>Oral tablet</td>
<td>III</td>
<td>1.483</td>
<td>Efficacy</td>
<td>Closed</td>
<td>2016</td>
</tr>
<tr>
<td>COL-MIG 303 (SPARTAN)</td>
<td>Oral tablet</td>
<td>III</td>
<td>1.483</td>
<td>Efficacy</td>
<td>Ongoing</td>
<td>2016</td>
</tr>
<tr>
<td>COL-MIG 305 (GLADIATOR)</td>
<td>Oral tablet, open-label</td>
<td></td>
<td>2.200</td>
<td>Efficacy and long-term safety</td>
<td>Ongoing</td>
<td>2016</td>
</tr>
</tbody>
</table>

dose range at least effective as sumatriptan in acute migraine treatment was calculated with a population pharmacokinetic–pharmacodynamic model and resulted of 170 mg and above [48]. In 2011, the Phase I study COL MIG-105 [A Randomized, Double-blind, Placebo-controlled, 4-way Crossover Study to Compare the Effects on the Cardiac de- and Re-polarization Duration as well as other Cardiac Safety Parameters of Two Doses of Oral Lasmiditan (100 mg and 400 mg) with those of Moxifloxacin (400 mg) and Placebo in Healthy Subjects] deeply examined the QT/QTc changes in 55 subjects treated with lasmiditan and found no significant QT prolongation at either 100 or 400 mg, compared to moxifloxacin that showed its QT prolonging effect similar to that seen in other published studies [33,49]. Although we could not find extensive published data, CoLucid reported no pro-arrhythmic effect of lasmiditan in the cardiologist assessments of ECGs, with safety and tolerability similar to that observed in previous studies. The last Phase I study evaluated the effect of the fed and fasted state on pharmacokinetic parameters ($C_{\text{max}}$, $T_{\text{max}}$, AUC) and adverse effects. The fed state was associated with an increased $C_{\text{max}}$, $T_{\text{max}}$, and AUC and a lower rate of mild adverse effect (19 vs. 23) [40]. No serious adverse effects occurred and the most common side effect was somnolence.

4.3. Phase II clinical trials

Two Phase II trials were performed in 2007 and 2009 (Table 1). The first study tested the efficacy of intravenous lasmiditan for acute migraine treatment and to get information about the effective dose range [18]. It was a proof-of-concept, randomized, multicenter, double-blind, placebo-controlled trial with a group-sequential, adaptive-treatment design. One hundred and thirty patients with moderate-to-severe headache were allocated to a dose level of lasmiditan or placebo in small cohorts (five or six patients) and the dose used in the subsequent cohort was adjusted depending on the headache response and safety of the preceding group. Headache response was defined as improvement from moderate or severe headache to mild or no headache after 2 h from lasmiditan administration. The first intravenous dose was 2.5 mg and the highest was 45 mg. Lasmiditan was administered to 88 patients, whereas 42 received a placebo. Better response (ranging from 54.2% to 75%) was observed in the groups of patients receiving 10, 20, 30, and 45 mg of lasmiditan when compared to the placebo group (45.2%). Furthermore, a significant linear association between dose levels and response rates was identified [18]. The dose of 20 mg showed a headache response rate of 64%, with a therapeutic gain of 19% with respect to placebo [19]. This trial was not powered to demonstrate superiority of single doses of lasmiditan to placebo but gave the first larger human validation to the hypothesis that $5\text{-HT}_{1F}$ agonism is effective in migraine acute treatment.

The second Phase II trial aimed to assess efficacy and safety of lasmiditan oral formulation [35] for acute migraine treatment. This was a dose-ranging, double-blind, parallel-group, and multicenter study. Five hundred and twenty-one patients with migraine with or without aura who were not using prophylactic treatments were randomly assigned to treat a migraine attack with oral lasmiditan 50, 100, 200, 400 mg or placebo in a 1:1:1:1:1 ratio. Totally, 391 patients received lasmiditan and 86 were treated with placebo. The primary end point was the headache response, defined as a moderate-to-severe attack becoming mild or disappearing at 2 h. Every lasmiditan dose was superior to placebo at 2 h and a significant linear dose–response association was found. After 1 h, all the doses but the 50 mg were superior to placebo, and the 400 mg significantly reduced headache severity starting as early as 30 min with respect to placebo. For oral lasmiditan 400 mg, the therapeutic gain (38%) was higher than that of the intravenous 20 mg [19], probably because of the dose difference (oral 400 mg corresponds to the intravenous dose of about 160 mg) [19]. The headache responses in the 100- and 400-mg groups were similar (Figure 2), and 100 mg was superior to 200 mg in terms of headache relief. It remains to be clarified in larger clinical trials if it is related to the small sample sizes and random variation in migraine attacks severity and response. Safety and tolerability issues reported in these trials will be discussed in the appropriate section (see below).

4.4. Ongoing trials

Two Phase III clinical trials and one long-term, open-label study are ongoing (Table 1). The first Phase III trial (COL MIG-301 or SAMURAI, Id number NCT02439320) has been completed with the enrollment of the last patient in June 2016 [50]. Detailed results are expected to be available in the third quarter of 2016. It is a prospective randomized, double-blind, placebo-controlled, parallel-group study of two doses of lasmiditan (100 and 200 mg) for the outpatient treatment of one migraine attack. Only patients with episodic disabling migraine (migraine disability assessment score $\geq 11$) have been included. Primary outcome measure was the proportion of headache-free subjects 2 h post-dose (defined as moderate or severe headache becoming none); secondary outcome was freedom from the most bothersome symptom associated with migraine, as identified by the subject, among nausea,
sensitivity to sound, and sensitivity to light. Other outcome measures were headache relief and use of rescue medication 2 h post-dose, headache recurrence within 48 h from dose, proportion of patients nausea free, photophobia and phonophobia free 2 h post-dose, safety up to 11 weeks (adverse events [AEs]), and health-care resource utilization 6 months prior to enter in the study compared with its use during the time of the study. The use of a second dose within 24 h was allowed for rescue or recurrence of migraine. The presence of cardiovascular risk factors did not exclude patients from the study whereas the initiation or change in concomitant preventive medication within 3 months was an exclusion criterion. Patients were randomized with a 1:1:1 ratio to lasmiditan 200 mg, lasmiditan 100 mg, or placebo.

The second Phase III trial (COL MIG-302 or SPARTAN, Id number NCT02605174) started in April 2016 and had a design similar to SAMURAI study. It evaluated with similar primary, secondary, and other outcomes three doses of lasmiditan compared to placebo (50, 100, 200 mg). It is expected to close the recruitment in June 2017 [35].

The long-term open-label trial of lasmiditan (COL MIG-305 or GLADIATOR, Id number NCT02565186) is a safety/efficacy study started in October 2015 and estimated to end in May 2018. The subjects who have completed COL MIG-301 and 302 will be eligible to participate in the study. Subjects will be randomly assigned with a 1:1 ratio to receive lasmiditan 100 mg or lasmiditan 200 mg for the first and the second dose, if needed for rescue or recurrence of migraine. All migraine attacks of the included subjects are treated with lasmiditan on an outpatient basis for up to 12 months. Two end points are established: first, the proportion of patients and the proportion of attacks associated with any AE and with specific AEs; and, second, the proportion of attacks treated with lasmiditan that respond 2 h after receiving a dose. The 12-month health-care resource utilization is additionally analyzed.

5. Safety and tolerability

The larger human safety and tolerability data were reported from the oral lasmiditan Phase II study [35]. Lasmiditan was well tolerated, as no triptan-like events (e.g. chest symptoms) were reported. No clinically significant abnormalities of any safety parameters, i.e. heart rate, blood pressure, 12-lead ECG, hematometry, biochemistry, and urine analysis following the administration of lasmiditan, were observed, and none of the subjects was excluded from the study due to the occurrence of side effects. However, this selective 5-HT1F receptor agonist showed a high incidence of adverse CNS-related events, such as dizziness, fatigue, vertigo, somnolence, and paraesthesia. AEs rate increased when increasing lasmiditan dose. Specifically, treatment-emergent adverse events (TEAEs) were reported by 65%, 72%, 86%, and 84% of subjects in the lasmiditan 50, 100, 200, and 400 mg groups, respectively [33]. In the placebo group, the 22% of subjects reported a TEAE. In lasmiditan 200 mg group, dizziness was reported by 38% of subjects, even if it has been rated as severe by 17% of subjects treated with 400 mg (compared to 15% in the 200-mg group). Lasmiditan 400 mg induced fatigue in 23% of subjects whereas the highest degree of severity (15%) was found with 200 mg (compared to 10% in the 400-mg group). Lasmiditan 400 mg was associated with vertigo in 23% of patients and scored as severe by 10% of them. Lasmiditan 100 mg produced somnolence in 12% of subjects, even if the 50-mg dose was related to the major severity of this AE (4% vs. 2% in 100-mg group). 20% of patients treated with lasmiditan 400 mg reported paraesthesia and scored as severe by 7%. Lasmiditan 100 mg caused nausea in 10% of the subjects, and was reported as severe in a higher percentage of patients treated with 50 mg (2% vs. 0%). Lasmiditan 200 mg induced sensation of heaviness in 10% of patients, although the 50- and the 400-mg groups reported the highest percentage of severe intensity (4% vs. 3%) [35].

Several CNS symptoms were observed, probably because of the CNS permeability to lasmiditan. 5-HT1F receptors are mainly located in the cerebellum and the lateral vestibular nucleus, where they can be activated when lasmiditan is administered, thus contributing to these aforementioned unwanted effects.

Although it was proven to be effective, little is known regarding the binding sites of lasmiditan in human brain. This could predict a potential wide range of central side events that may delay lasmiditan further development [39]. The high incidence of moderate or severe AEs after oral lasmiditan 100 and 400 mg could, if confirmed in a Phase III trial, limit the clinical use [19].

6. Conclusions

Lasmiditan has much higher affinity for 5-HT1F receptors than for vasoconstrictor 5-HT1B receptors [20] and seems to be safe and effective in the acute treatment of migraine when orally administered. Both preclinical and clinical studies showed promising efficacy data with no severe AEs. Although these data remain to be confirmed in Phase III clinical trials, it might offer an alternative to treat acute migraine with no cardiovascular risk associated.

7. Expert opinion

Acute migraine pharmacological treatments aim to abort the attacks effectively in order to improve patients’ burden and functioning. Moreover, an effective acute therapy might prevent migraine chronification and drug abuse. Although effective, currently specific and unspecific acute drugs are not able to satisfy patients’ needs in a substantial percentage of subjects. In particular, triptans administration is limited in patients with cardio- and/or cerebrovascular disease, uncontrolled hypertension, and with particular forms of migraine like hemiplegic migraine due to their vasoconstrictive effects. Therefore, a novel, nonvascular, and effective acute antimigraine drug would probably improve quality of life, social and role functioning, and disease course in a significant number of patients. Lasmiditan, a novel 5-HT1F agonist with no vasoconstrictive action demonstrated in vitro and in vivo, has
been developed with these aims and showed a significant efficacy both in animal models of migraine and in human Phase I and II trials. The absence of cardiovascular side effects might offer a new and effective therapeutic alternative in patients affected by both episodic and chronic migraine with contraindications or nonresponsive to triptans. Although it has not been compared yet to triptans in clinical studies, it has been demonstrated effective with respect to placebo in two Phase II clinical trials and other three Phase III trials are ongoing. Nevertheless, lasmiditan ability to cross the BBB might be the pharmacological substrate not only of its efficacy but also of the high rate of CNS side effects described in Phase II clinical trials. In fact, dizziness, drowsiness, vertigo, somnolence, and paraesthesia were reported from a substantial number of participants, across all the different oral lasmiditan doses groups. Although no serious AEs occurred, CNS side effects might affect both quality of life and functioning and should be balanced, in future clinical use, with the benefits given by headache relief in migraine patients. Moreover, pharmacokinetic data are still limited in literature, with only oral bioavailability, Cmax, Tmax, and AUC reported. Therefore, further studies are needed to clarify additional pharmacokinetic data (t1/2) and metabolism parameters of lasmiditan before its clinical use could be suggested.

The absence of vasoconstrictive effects make lasmiditan the first molecule of a new drug category, the NAAMAs, with a promising future in acute migraine treatment. Moreover, lasmiditan efficacy demonstrated in migraineurs strengthens the neural hypothesis of migraine that places vasodilation as a secondary event to the central sensitization of trigeminal system. Therefore, lasmiditan 5-HT1F agonist activity, both centrally on trigeminal afferents and peripherally on trigeminal cell bodies within the TG, might represent a considerable advancement in migraine acute therapy. Although preclinical and human data are promising and established a significant efficacy for acute migraine treatment, the limited knowledge about pharmacokinetics and metabolism, the high rate of nonserious CNS side effects, and the lack of large studies remain still a matter of concern that should be addressed in future studies.

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**Declaration of interest**

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**References**

Papers of special note have been highlighted as either of interest (-) or of considerable interest (--) to readers.


- The most important global study on disability related diseases, including for the first time medication overuse headache alongside migraine and tension-type headache.


- An updated picture on harmful chronic migraine.


