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THE 5HT1F RECEPTOR AS THE TARGET OF DITANS IN MIGRAINE – FROM BENCH TO BEDSIDE

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Abstract | Migraine is a leading cause of disability in more than one billion people worldwide, yet it remains universally underestimated, even by individuals with the condition. Among other shortcomings, current treatments, often repurposed agents, have limited efficacy and potential side effects, leading to low adherence. Following the introduction of agents targeting the calcitonin gene related peptide pathway, another new drug class, the ditans — a group of selective serotonin 5-HT1F receptor agonists — has just reached the international market. Here, we review preclinical studies from the late 1990s and more recent clinical research that contributed to the development of the ditans and led to their approval for acute migraine treatment by the US Food and Drug Administration and European Medicines Agency.

[H1] Introduction

Migraine is a polygenic brain disorder presenting with episodes of headache and accompanying symptoms that cause significant peri-ictal disability. As the second most prevalent neurological disorder, migraine affects more than one billion people worldwide and is the second leading cause of disability among all medical conditions and injuries.[1] Because migraine lacks validated medical or neuroimaging signs, its diagnosis is exclusively phenomenological,[2] and technical testing (e.g., neuroimaging, or lumbar punction) could be required to rule out mimics e.g., headache attributed to unruptured saccular aneurysm, or to increased cerebrospinal fluid pressure.[3] Typical features suggestive of migraine are repetitive attacks of moderate-to-severe, unilateral and pulsating headache, lasting 4–72 hours. Headache is often accompanied by nausea, vomiting, photophobia, phonophobia and osmophobia in some cases, resulting in a composite disabling profile that is worsened by even gentle physical activity, usually leading to a pause of mental and physical activities.[2] In approximately 30% of people with migraine, reversible focal neurological symptoms attributed to either cortex dysfunction, for example in the occipital lobe or somatosensory system, or brainstem dysfunction can precede migraine attacks; these symptoms include

visual signs such as zigzag lines, or flashes of light, or numbness in one hand or on one side of face, or speech disturbances and they are referred to as migraine aura, thus migraine is classified as either with or without aura. In addition, migraine is stratified based on its frequency as episodic (less than 15 days with headache per month) or chronic migraine (at least 15 days with headache per month).[2] Of note, people with migraine often overuse acute headache medications, leading to an increase in headache frequency and developing medication-overuse headache (MOH), a remarkably disabling condition difficult to treat.[2,4,5] Furthermore, in some individuals with migraine symptoms of anxiety and depression co-occur making the clinical presentation and treatment perplexing.[6,7]

Despite progress in understanding migraine pathogenesis over the past decade, many aspects of this complex disorder remain poorly understood. However, Michael Moskowitz's hypothesis in the late 1970s, that the trigeminovascular system (TVS) plays an important role, has provided a clearer pathophysiological basis of migraine.[8-10] The TVS is an excitatory pathway, with glutamate being the major neurotransmitter that activates second order neurons within the trigeminocervical nuclei.[11-15] Activation of the TVS is an early initiator of migraine pain and the accompanying symptoms. [8-10] The TVS consists anatomically of axonal projections from the trigeminal ganglion cells to the vasculature inside and outside the cranium. The peripheral and central projections of the TVS contain vasoactive peptides that, upon release, regulate vascular tone. Discharges within the brainstem caused by activated TVS and central transmission of noxious signals into thalamic and cortical structures alters sensory processing, which could generate headaches.[10] Whether the initial trigger of a migraine attack lies on the peripheral afferents of TVS or within the central parts of CNS remains debatable, however.[16]

Several receptor systems are expressed within the TVS and have been investigated as potential targets for anti-migraine drugs[11] (**Figure 1**). The serotonin receptors, also referred to as 5-hydroxytryptamine (5-HT) receptors, which control signal transduction related to pain transmission and attenuate calcitonin gene-related peptide (CGRP) expression, are among the most extensively studied.[17,18] Triptans — a class of selective agonists of the 5HT1 receptor — were the first anti-migraine specific drugs introduced in the early 1990s and have proven effective in treating acute migraine attacks.[19] However, triptan use is currently

limited by potential cardiovascular adverse events, the risk of developing MOH and their overall lower tolerability over non-triptan alternatives.[20] Ditans are a novel class of drugs that act as selective agonists of the 5-HT1F receptor, a target that is not expressed by human coronary arteries, unlike the triptan target receptor. [21] Ditans represent a promising mechanism-based approach for the treatment of migraine attacks and have gained importance in the past few years.[22-25] The role of 5-HT1F receptors in migraine has been extensively investigated for over three decades, with animal studies conducted in the late 1990s and a prolonged clinical program that was paused owing to concerns about hepatotoxicity in the early 2000s.[26-28] Subsequent data revealed that the hepatotoxicity was species-specific and not related to the ditans' mechanism of action. [26] In the interim, however, a second-generation agent without the indole core, which had, perhaps mistakenly, been targeted for potential hepatotoxicity, was developed and tested for efficacy in an extensive clinical program (see Development of Ditans below). This progress ultimately culminated in US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval of the first ditan, lasmiditan, for the acute treatment of migraine attacks in October 2019 and August 2022, respectively. Lasmiditan effectively complements the existing armamentarium for treating migraine (**Box 1**). This Review provides an overview of the ditan journey, discussing the rationale for their development and summarizing the findings of related experimental and clinical studies (**Figure 2**).

[H1] The serotonergic system and migraine
In human dura, several vasoactive neuropeptides have been identified within the trigeminal neurons, including substance P, neuropeptide Y, pituitary adenylate cyclase-activating peptide and CGRP . The functional importance of these peptides in migraine has been studied in depth.[11,29-35] A number of channels and receptors are present on trigeminal fibers, including the serotonergic receptors 5HT1B, 5-HT1D and 5-HT1F among others. [35-37] (**Figure 1**)

Serotonin, or 5-HT, is a monoamine neurotransmitter with complex brain functions, including modulation of mood, cognition, reward, learning, memory, biological rhythms, pain, motor activity and several physiological processes such as vomiting and vasoconstriction.[38] Approximately 90% of 5-HT produced in the body is located in the intestinal tract, 8% is found in platelets and only 1–2% exists in the CNS . The effects of 5-HT

depend on which cells and tissues express the receptors serotonin acts through. [39] (**Box 2**) The neurons of the raphe nuclei are the principal source of 5-HT release in the brain.[39] Axons from the neurons of the raphe nuclei form a neurotransmitter system reaching almost every part of the CNS: axons from the caudal raphe nuclei terminate in the cerebellum and spinal cord, and axons from the rostral nuclei spread throughout the entire brain.[40]

5-HT has long been implicated in the pathophysiology of migraine.[41,42] The role of 5-HT in migraine was supported by the findings that during a migraine attack, high quantities of 5-hydroxyindole acetic acid — the primary metabolite of 5-HT — are excreted [43] some monoamine-depleting drugs, such as reserpine, can provoke migraine attacks [44,45]; and that slow infusions of 5-HT might also provoke migraine attacks,[46] although not all studies verified this effect.[45] Given the various actions of 5-HT, it is not suitable as an antimigraine drug itself, because it would elicit many adverse effects, such as changes in heart rate, vasodilatation or vasoconstriction depending on the vascular bed, and gastrointestinal effects.[47,48] Although the aforementioned relationship between 5-HT and migraine pathophysiology is only circumstantial, the potential antimigraine efficacy of 5-HT, together with the proven antimigraine effect of ergotamine,[49] which also exhibits affinity for several 5-HT receptors, prompted the investigation aiming to mimic the positive effect of 5-HT on migraine, but with fewer side effects.[41,44,50]

Based on the vascular theory of migraine which explains the pain of migraine to be due to dilation of cranial vessels,[51] a search started for a selective vasoconstrictor compound that targets the extracerebral cranial circulation via a 5-HT receptor. This search led to the identification of the 5-HT1B receptor (then called 5-HT_1-like receptor), that mediated selective cranial vasoconstriction, with much less activity in other vascular beds.[41] Based on the identification of this receptor, sumatriptan was the first of the triptans to be developed,[50] initiating a novel generation of antimigraine drug with a greatly improved safety profile compared to the widely used ergot alkaloid therapies.[19,52,53] With advance in our knowledge, a pure vascular pathophysiology of migraine seems unlikely now, thus the effects of sumatriptan are probably explained, at least partly, by their presynaptic inhibition of CGRP release from the TVS,[54,55] which in turn prevents from neurogenic inflammation, and transmission of nociceptive information from intracranial blood vessels to the CNS.[56]

Triptans act as agonists of the 5-HT1B and 5-HT1D receptors, and several triptans, including sumatriptan, also display considerable affinity for the 5-HT1F receptor.[57,58]

Because triptans are capable of inducing vasoconstriction of coronary arteries through the 5-HT1B receptors,[48,58] triptans are contraindicated in people with cardiovascular risk factors,[59] although clinical experience for over 30 years with the triptans has proven that these drugs are clinically well-tolerated and safe. The undesirable vasoconstrictive function of 5-HT1B receptors has prompted studies that explored the other 5-HT1 receptor subtypes that are stimulated by the triptans. One research path led to investigate the efficacy of selective 5-HT1D receptor agonists, which are devoid of vasoconstrictor effects on either the cranial or the coronary circulation.[60-62] In addition, selective 5-5HT1D agonists were effective in inhibiting dural plasma protein extravasation, and capsaicin-evoked c-fos immunoreactivity within trigeminal nucleus caudalis in guinea pigs,[6,3,64] which are animal models of TVS activation and thus can be used to predict antimigraine drug efficacy.[65] However, PNU-142633, the selective 5-HT1D receptor agonist, failed to display antimigraine efficacy in a clinical trial. [66] Investigating the third receptor subtype that is stimulated by some triptans, the 5-HT1F receptor, demonstrated that selective stimulation of this receptor might indeed be associated with antimigraine efficacy.[22-25] This led to the development of the selective 5-HT1F agonists called ditans, which are devoid of activity at 5-HT1B/1D receptors when compared with triptans.[24,25,67]

[H1] Development of ditans

The 5-HT1F receptor, which shares the highest sequence homology with the 5-HT1E receptor (61%), was cloned and sequenced in 1992.[68,69] The receptor is composed of 366 amino acids in humans, rats, guinea pigs, and mice, and there are no splice variants.[70] The human 5-HT1F receptor gene, known as *HTR1F*, is located on chromosome 3p11-p14.1.[71] Interestingly, a recent genome-wide association study identified a risk locus for migraine containing the *HTR1F* gene.[72] The 5-HT1F receptor was originally discovered using a molecular cloning-based search for novel serotonin receptors, based on sequence homology with other 5-HT1 subtypes.[71,73-75] Like other 5-HT receptors except for 5-HT3, the 5-HT1F receptor is a metabotropic receptor and is coupled to the inhibition of adenylyl cyclase in transfected cells.[69,70] Unlike other 5-HT receptors, selective lesioning of 5-HT neurons does

not affect the density of 5-HT1F binding sites in all rat brain regions examined, indicating that 5-HT1F receptors do not act as autoreceptors.[75] (**Box 2**)

Two selective ligands for the 5-HT1F receptor LY344864 (*N*-[(6*R*)-6-(dimethylamino)-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl]-4-fluorobenzamide) and LY334370 (4-fluoro-N-[3-(1-methylpiperidin-4-yl)-1H-indol-5-yl]benzamide) (**Figure 3**) have been used as pharmacological tools in different animal models of migraine to characterize the potential role of the 5-HT1F receptor in migraine pathogenesis. Increased expression of the immediate early gene *c-fos* or of its protein product Fos is a reliable biomarker of nociceptive stimulation, while inhibition of *c-fos* expression and trigeminal neuronal activity are suggestive of a CNS-mediated effect.[11,65] Likewise, the selective 5-HT1F receptor agonist LY344864 inhibited capsaicin induced *c-fos* expression within the spinal trigeminal nucleus caudalis in a dose-dependent manner both in rats and mice, indicating a central action within the CNS.[24,25] This effect was observed even after co-administration of a 5-HT1B receptor antagonist (SDZ 21-009), implying that like the 5-HT1B receptor, the 5-HT1F receptor is sufficient to modulate the activity of the trigeminal system.[24] (**Figure 4**) In cats, LY344864 inhibited superior sagittal sinus-evoked trigeminal activity — an effect unaltered by either 5-HT1B or 5-HT1D receptor antagonists (SB224289 and BRL-15572, respectively)[76] — indicating both a central and peripheral site of action for LY344864. In addition, LY344864 did not alter the carotid blood flow in cats, as naratriptan and alniditan did,[76] nor had a vasomotor response in bovine cerebral arteries.[60]

The selective 5-HT1F receptor agonist LY334370 showed efficacy in inhibiting plasma protein extravasation after electrical stimulation of the trigeminal ganglion, suggesting a peripheral site of action.[23,77,78] In other reports, LY334370 had no effect on neurogenic vasodilation of dural blood vessels, whereas the drug was effective in inhibiting evoked potentials within the spinal trigeminal nucleus caudalis, indicating that the drug most likely has a central site of action within the second-order neuron.[79,80] However, one study showed that the neurogenic vasodilation produced by electrical stimulation of the dura mater in rats was mediated via the Aδ fibers not the C-fibers.[81] The type of fiber on which the 5-HT1F receptors are located is not well characterized, but since LY334370 was effective in inhibiting plasma protein extravasation in other studies,[23,77,78] a peripheral site of action cannot be excluded. Furthermore, LY334370, like LY344864 but different to triptans, did not induce contractions in the rabbit saphenous vein either alone or in the presence of a

baseline vascular tone induced by PGF2α,[82] suggesting that activation of 5-HT1F does not induce vascular contraction, nor enhances contraction to other contractile agonists, and explaining why LY334370 had no effect on dural vasodilation induced by trigeminal stimulation, as triptans did.

LY573144 (2,4,6-trifluoro-*N*-[6-(1-methylpiperidine-4-carbonyl)pyridin-2-yl]benzamide) is another selective 5-HT1F receptor agonist without vasoconstrictor properties, which crosses the blood-brain barrier (BBB).[83] (**Figure 3**). LY573144 can modulate CGRP release from trigeminal afferents.[84] Ex vivo KCl-induced CGRP release from isolated mouse dura mater, trigeminal ganglion and trigeminal nucleus caudalis was similarly inhibited by both sumatriptan and LY573144.[84] In the rat closed-cranial window model, dural vasodilation induced by electrical stimulation or capsaicin, but not by CGRP, was significantly attenuated by intravenous LY573144 or higher doses of sumatriptan. These results suggest that LY573144 is a prejunctional inhibitor of CGRP release in peripheral and central trigeminal nerve terminals.[84] Furthermore, LY573144 dose-dependently reduced TVS activation, as demonstrated by reducing c-fos expression within the nucleus trigeminal caudalis and inhibiting plasma protein extravasation after electrical stimulation of the dura mater or the superior salivatory nucleus in anaesthetized rats.[83]

Since LY573144 is a lipophilic drug capable of crossing the BBB[84], the contribution of additional central sites of action remains to be determined. One study found low 5-HT1F receptor expression within the trigeminal neurons,[37] generating hypotheses for a potential central mechanism of action, e.g., by activating central TVS sites within the trigeminal caudalis; LY573144 might also attenuate glutamate release along with CGRP, preventing and possibly reversing the development of central sensitization, while activated thalamic 5-HT1F receptors could prevent central sensitization as well.[85] In addition, LY573144 induces mitochondrial biogenesis,[86] which is implicated in the pathophysiology of migraine,[87,88] representing another potential central mechanism of action.[85] Of the three ditans developed, only two have progressed to human trials for the acute treatment of migraine: LY334370 and LY573144/COLL-144. The latter was named lasmiditan, as it will be referred to in the text below. LY refers to Eli Lilly Co. who developed the synthetic agents and COLL refers to CoLucid Pharmaceuticals who relicensed the drug in 2006 and continued the clinical development with phase 2 and phase 3 trials. Finally, Eli Lilly Co. bought CoLucid in 2017 to obtain intellectual property of lasmiditan.

[H1] Clinical trials of ditans

[H2] LY334370

LY334370 was first tested in a randomized, placebo-controlled phase 2 trial that included 99 participants with moderate to severe migraine attacks.[89] The participants were randomly assigned to receive either 20 mg, 60 mg or 200 mg of LY334370 or a placebo. The primary endpoint of the trial was the 2-hour sustained response rate, which was defined as a reduction in migraine headache from moderate or severe pain, to mild or no pain at 2 h after treatment, without worsening or use of rescue medication within 2–24 h of treatment. The trial showed that the 60 mg and 200 mg doses of LY334370 were superior to the placebo in achieving pain relief at 2 h following treatment, with pain freedom rates of 19% and 29%, respectively, compared with 4% for the placebo.

The most frequent adverse events reported during the trial were asthenia, dizziness, and somnolence,[89] which occurred more frequently in the group receiving the active drug compared with the placebo group. Paresthesia was also reported, but its frequency was not significantly different between the two groups.[89] Despite demonstrating efficacy in a proof-of-concept trial, the further development of LY334370 was terminated owing to hepatotoxicity observed in beagle dogs exposed to the drug for over a month (data on file, Eli Lilly & Co.). Interestingly, hepatotoxicity was not observed in rats after treatment with LY334370. Furthermore, there were no recorded incidents of elevated liver enzyme in humans treated with LY334370 or any other triptan with a high affinity for the 5-HT1F receptor (such as naratriptan). These observations suggest that the liver dysfunction in dogs exposed to LY334370 was likely a result of species-specific, drug-related toxicity, rather than mechanism-related toxicity.[26] These findings, along with evidence of efficacy, have encouraged further human trials with second-generation 5-HT1F receptor agonists, which have a chemical structure that differs from the first-generation ditans by lacking the indole core. (**Figure 3**)

[H2] Lasmiditan

[H3] Phase 1

The development program for lasmiditan included several phase 1 trials and three phase 2 trials, followed by the initiation of three phase 3 studies.**(Table)** Early phase 1 trials assessed the safety, tolerability, bioavailability, and pharmacokinetics of lasmiditan, either orally or intravenously administered , but there are currently no peer-reviewed reports available on these phase 1 trials, only data-on-file.[90-94] Lasmiditan achieves peak plasma concentrations in a median of 1.8 h after oral administration, without differences between ictal and interictal periods. Food does not affect the absorption and pharmacokinetics, and the plasma protein binding rate ranges from 55% to 60%.[90-94]

A phase 1, single-center, open-label, fixed-sequence study evaluated the cardiovascular and pharmacokinetic effects of 200 mg lasmiditan in 44 healthy people who were receiving propranolol (160 mg/day). Co-administration of the drugs produced statistically significant short-lived (<4 hours) reductions in mean heart rate and increases in systolic blood pressure (8.3 mm Hg) and diastolic blood pressure (6.4 mm Hg), while the exposure to either drug was not affected by the coadministration.[95]

[H3] Phase 2

The first phase 2 trial (NCT00384774) was a dose-finding, proof-of-concept study for intravenous lasmiditan with a group-sequential, adaptive-treatment design that allowed up-and-down dose adjustment depending on the headache response and adverse events in previous participants.[96] The study enrolled 130 adults with 1–8 monthly migraine days and moderate to severe attacks. Participants received an infusion of 2.5–45 mg lasmiditan or placebo over 20 minutes. The primary endpoint of the study was headache response at 2 h, defined as improvement in pain intensity from moderate or severe to mild or no pain. 54.2–75% of participants who received 10–45 mg lasmiditan reached the primary endpoint with a linear dose-response relationship, compared with 45.2% of individuals in the placebo group. Pain freedom at 2 h following treatment was achieved by 21–25% of participants who received 10–45 mg lasmiditan, compared with 19% in the placebo group. Onset of efficacy occurred as early as after 20 minutes for lasmiditan doses ≥ 20 mg. Participants' satisfaction increased with increasing doses and the use of rescue medication decreased.

The most frequent adverse event was paresthesia (up to 43.8% of participants who received 30 mg lasmiditan compared with 0% in the placebo group), followed by dizziness, fatigue, and sensation of heaviness. There was no serious adverse event.[96] Interestingly,

participants treated with 10 mg intravenous lasmiditan also experienced adverse events, indicating that 5-HT1F receptors were activated, however headache relief was not achieved. This observation raises the question of whether activation of other 5-HT1 receptors is also required for lasmiditan to achieve an anti-migraine effect.[37] However the study was not powered to differentiate individual doses of lasmiditan from placebo, nor to detect effect differences for other migraine symptoms.

In the second double-blind phase 2 trial (NCT00883051), 512 individuals with episodic migraine were randomly assigned to receive 50 mg, 100 mg, 200 mg or 400 mg rapidly disintegrating lasmiditan tablets or placebo in response to a moderate to severe migraine attack.[97] All lasmiditan groups reported significantly more headache reductions from moderate or severe pain to mild or no pain at 2 h following treatment than the placebo group (43–65% versus 26%). The 400 mg lasmiditan group separated from placebo after only 30 minutes. In addition, the pain-free rates at 2 h were superior to placebo (7.4%) in both the 200 mg (11.7%) and 400 mg (21.9%) lasmiditan groups. The study showed a linear association between dose and response rates as well as participants' global impression of lasmiditan. Lasmiditan was generally tolerated well, with a dose-dependent occurrence of adverse events. Dizziness was reported by 37% of participants who received 400 mg Lasmiditan, compared with 0% of the placebo group. Other common adverse events were paresthesia, vertigo, fatigue, and somnolence. Moderate dizziness after taking 200 mg lasmiditan resulted in hospital admission of one participant, which was the only serious adverse event in the trial. Both phase 2 trials showed no clinically relevant change in vital parameters, ECG or laboratory values with lasmiditan treatment.[96,97]

Another phase 2 placebo-controlled study of oral lasmiditan (50 mg, 100 mg and 200 mg) (NCT03962738), also known as MONONOFU trial, enrolled 846 participants with migraine living in Japan.[98] The primary endpoint was headache pain freedom at 2 h posttreatment. The proportion of participants who achieved this endpoint were 23.5%, 32.4% and 40.8% for 50mg, 100mg, 200mg lasmiditan treatment respectively, compared with 16.6% in the placebo group; the linear dose-response relationship for pain freedom was statistically significant. The most common adverse events recorded in all lasmiditan groups were dizziness (39.4% versus 3.3% for placebo), somnolence (19.3% versus 5.1% for placebo) and malaise (10.5% versus 1.4% for placebo), without serious adverse events.[98]

[H3] Phase 3

The phase 3 clinical program of lasmiditan completed with three placebo controlled clinical trials and one randomised, open-label study.(**Table**) The first of these studies were the COLMIG-301 and COLMIG-302 trials, also known as SAMURAI and SPARTAN respectively.[99,100] Both trials were prospective, randomised, double-blind, placebo-controlled, outpatient studies that included individuals with disabling migraine, defined as a score of ≥ 11 on the Migraine Disability Assessment (MIDAS). In COLMIG-301, participants were randomly assigned 100 mg or 200 mg of oral lasmiditan or placebo to treat one migraine attack at home. Participants were also randomly allocated to a second dose of lasmiditan or placebo for rescue or recurrence of migraine, but all participants in the placebo group received placebo as the second dose. Notably, of the 1,856 participants who treated an attack, 1,445 (77.9%) had more than one cardiovascular risk factor in addition to migraine. At 2 h post-treatment, both lasmiditan doses significantly relieved participants from headache (primary endpoint) and their most bothersome symptom associated with migraine attacks (secondary endopoint) when compared to placebo. Participants who received lasmiditan as a first dose were less likely to use a second dose of study drug (31.9% of he lasmiditan 200mg group and 39% of he lasmiditan 100mg group took a second dose) than participants who received placebo as a first dose (59.9% took a second dose for rescue, or recurrence).[99](**Figure 5**)

The COLMIG-302 trial comprised 3,005 participants with disabling migraine.[100] In this trial most patients (79.2%) had more than one cardiovascular risk factor at baseline, in addition to migraine. As in COLIMG-301, a second dose of lasmiditan was permitted up to 24h after the first dose if the migraine did not respond at 2 h but no other rescue medication had been used. The primary endpoint of the study was to evaluate the safety and efficacy of 50 mg, 100 mg and 200mg oral lasmiditan compared with placebo, and the secondary enpoint was to evaluate the efficacy of these doses on freedom from the most bothersome symptom of migraine attacks. Both endpoints were met: the percentage of participants without pain was significantly higher in all three doses of lasmiditan compared with placebo. Moreover, lasmiditan significantly reduced the proportion of participants who became free from the most bothersome symptoms at 2 h after receiving the first dose.

Participants who received lasmiditan were less likely to use a second dose of study drug (21.2% of the 200mg lasmiditan group, 26.3% of the 100mg lasmiditan group, and 34.4% of the 50mg lasmiditan group received a second dose) versus participants treated with placebo (39.5% received a second dose).[100](**Table, Figure 5**)

In line with phase 1 and 2 studies, the most common adverse events reported after a single dose of lasmiditan in the COLMIG-301 and COLMIG-302 trials included dizziness, paresthesia, somnolence, fatigue, nausea and lethargy. Remarkably, the majority of adverse events recorded were mild or moderate in severity, treatment-related, and CNS driven in both trials.[99,100] Across both studies, the incidence of adverse events was higher in the lasmiditan treatment groups than in the placebo group, and was dose-related: 42.7–39.0%, 36.2–36.3%, 25.5% for 200, 100 and 50mg lasmiditan respectively compared with 11.6–16.4% with placebo. In addition, cardiovascular adverse events reasonably or possibly related to the testing drug, including palpitations and tachycardia, were reported by five (0.5%) and one participants (0.1%) in COLMIG-301 and by six (0.3%) and five (0.25%) participants in COLMIG-302, respectivelly. In general, lasmiditan was well-tolerated and there were no differences regarding cardiovascular adverse events in lasmiditan versus placebo groups.

The safety data from both COLMIG-301 and COLMIG-302 trials were integrated for two separate post hoc analyses. The first analysis focused on adverse events that occurred within 48 h posttreatment.[101] Adverse events were reported by 25.4% of 654, 36.2% of 1,265 and 40.6% of 1,258 participants who received 50 mg, 100 mg and 200 mg lasmiditan respectively, compared with 13.5% of 1,262 participants who received the placebo. In line with the initial trial results, the most common adverse events were dizziness, paresthesia, somnolence, fatigue, nausea, muscular weakness and hypoesthesia. There were no ischemic events and serious adverse events were reported by 0.2% of participants in all four treatment groups. Interestingly, the incidence of adverse events reported was numerically higher in those participants who took one versus two doses of study drug. The presence of dizziness, paresthesia, somnolence, or fatigue did not have a negative influence on primary endpoints, but nausea did.[101] The second analysis aimed to characterize dizziness after lasmiditan treatment,[102] finding a dose-dependent effect: the incidence of dizziness was 8.6% (0.3% severe), 14.9% (0.7% severe) and 16.8% (1.4% severe) in participants treated

with 50 mg, 100 mg and 200 mg lasmiditant respectively, compared with 2.9% (0.1% severe) in the placebo group. Among participants who received lasmiditan as their first dose, the risk factors for dizziness were: higher lasmiditan dosage; mild or moderate severity of migraine attack; and lower body mass index. The median time to onset of dizziness was 30–40 minutes posttreatment with a median duration of 1.5–2 h. Interestingly, the presence of dizziness did not change lasmiditan's effect on daily activity, participant global impression of treatment, or freedom from pain or most bothersome symptoms. A limited proportion of participants experienced vertigo, again in a dose-dependent manner.[102]

The COLMIG-303 trial, also known as GLADIATOR (**Table**), was a prospective, randomized, open-label study of participants from either COLMIG-301 or COLMIG-302 trials.[103] The trial was designed to evaluate the safety, efficacy and tolerability of long-term intermittent use of 100 mg and 200 mg oral lasmiditan, using patient-centered outcomes. The median duration of time particpants partook in the study was 288 days, with 814 (41.2%) participants completing one year at the first interim analysis. The most common reasons for treatment discontinuation were personal decision (21.8%), adverse event (12.8%) and lost to follow-up (9.2%). At least one adcerse event reasonably or possibly related to lasmiditan was reported by 48.6% of participants during the study, while nine patients (0.5%) reported 13 severe adverse events. The most common adverse events were CNS related and mirrored those seen in earlier phase 3 trials, with dizziness being the most common to lead to discontinuation. Notably, the incidence of adverse events decreased across the first five treated attacks (**Figure 5, panel C**). No cardiovasular adverse events was reported and no evidence of lasmiditan misuse, abuse or diversion was recorded.

Across all treated migrain attacks, the first interim analysis of the COLMIG-303 trial showed pain freedom at 2 h posttreatment in 26.9% of the attacks treated with lasmiditan 100 mg and 32.4% of the attacks treated with lasmiditan 200 mg; freedom from the most bothersome symptom in 37.5 0% of the attacks treated with lasmiditan 100 mg and 40.6% of the attacks treated with lasmiditan 200 mg; and pain relief in 54.8% of the attacks treated with lasmiditan 100 mg and 57.9.6% of the attacks treated with lasmiditan 200 mg (**Table**). In a subgroup analysis, the proportion of participants achieving pain freedom, most bothersome symptom freedom, and pain relief at 2 hours posttreatment was consistent across treated attacks 1 to 5 in participants who treated five attacks.[103] MIDAS scores were significantly lower at 3 months of treatment than at baseline **[Au: Addition of comparator**

OK? There was no comparator, comparison with baseline], which was maintained across 12 months for both doses of lasmiditan.[103] Moreover, approximately half of the participants achieved at least 50% reduction in MIDAS score with either dose at month 12 compared to baseline.[104] In addition, the number of absent days or days with substantially impaired productivity at work or school, monthly headache days and mean headache pain intensity were all significantly reduced by lasmiditan at all timepoints up to one year compared with baseline.[104]

More recently, the results of the CENTURION study — a randomised, double-blind, placebo-controlled trial — were published.[105] The trial assessed the efficacy and consistency of the response to lasmiditan in the acute treatment of migraine across four attacks with or without aura. Participants were randomly assigned to one of the three treatment groups: 100 mg lasmiditan, 200 mg lasmiditan and a control group that received placebo for the first three attacks and 50 mg lasmiditan for the fourth attack. Both doses of lasmiditan provided pain freedom at 2 h posttreatment for the first attack and in at least two out of three attacks, which were the primary endpoints (P = <0.001). The secondary endpoints — including pain relief, sustained pain freedom and disability freedom — were also achieved by both doses (**Table, Figure 5**). Adverse events were reported by 22%, 53% and 61% of participants receiving placebo, 100 mg and 200 mg lasmiditan respectively, and the proportion of participants who discontinued the study because of an adverse event was 1.2%, 7.4% and 7.8% respectively. In line with previous studies, the most common adverse events reported were mild to moderate and were CNS related, including dizziness, paraesthesia, nausea and fatigue.[105]

The safety data from CENTURION trial were integrated for a separate post hoc analysis to assess safety and tolerability of lasmiditan by attack treated.[106] The incidences of the adverse events including dizziness were decreased with repeated dosing. The time of onset of the common adverse events depended on the adverse event and ranged from 40 min to 60 min, but the onset of each adverse event was similar across attacks. Correspondingly, the duration of the common adverse events varied by the adverse event and attack but it was similar across the attacks. No evidence for increased motor vehicle accidents was recorded, while two participants experienced serotonin syndrome (see below).[106]

[H1] Current use of ditans

The phase 1–3 studies described above provide Class I evidence that lasmiditan is effective in the acute treatment of migraine, which led to its FDA approval in 2019, followed by approval from the EMA and Japan's Ministry of Health, Labor, and Welfare in 2022. Furthermore, in indirect comparisons lasmiditan shares similar efficacy with other currently available or emerging symptomatic migraine medications, such as aspirin, ibuprofen and sumatriptan.(**Figure 6**) Network meta-analyses also indicates that lasmiditan has comparable benefit-risk profile with the gepants — a class of novel synthetic small molecule CGRP receptor antagonists.[107,108]

Lasmiditan has several advantages over other medications, including: fast onset of action, consistency of efficacy and the lack of associated cardiovascular adverse events.[101-105, 109]

However, several tolerability issues have been highlighted, particularly CNS related adverse events, which raise concerns about widespread use of the drug. For instance, driving is not permitted for 8 h after lasmiditan use, following two randomized trials that showed driving impairment was dependent on lasmiditan blood concentration at 1.5 h but not at 8 h post-treatment.[110] Notably, the effectiveness of lasmiditan predicts the occurrence of CNS-related adverse events, such as dizziness; thus, those that might benefit from the treatment are more likely to experience an adverse event, although this does not affect the disability freedom, as revealed by a recent post-hoc analysis.[111] The incidence of adverse events seems to decrease with subsequent attacks, indicating a CNS habituation in serotonergic signals, which might increase treatment tolerance in an individual over time.[102] (**Figure 5**) So far, lasmiditan lacks real world evidence for long-term administration despite being commercialized for a few years now. This information would add value to the data of the long-term open study (GLADIATOR).[103,104] In contrast, there is a variety of post-hoc analyses for the use of lasmiditan in specific populations, as discussed below.

[H2] People with cardiovascular risk factors or cardiovascular disease

The use of lasmiditan in people with known cardiovascular disease (CVD) is of great importance because triptans are contraindicated for this subpopulation and ditans were developed to fill this gap. In addition to preclinical data, safety analyses of placebo-controlled studies that included a significant proportion of participants with CVD or with risk factors for CVD — such as, smoking, hypertension, diabetes, dyslipidemia and obesity — have also provided evidence for the safety of lasmiditan in these individuals. One post-hoc analysis pooled data from the SUMARAI and SPARTAN trials;[112] both trials included participants with risk factors for CVD, and, in SPARTAN, included participants with coronary artery disease, clinically significant arrhythmia or uncontrolled hypertension. From a total of 4,439 participants who received ≥1 dose of lasmiditan, 3,500 (78.8%) had ≥1 risk factors for CVD, and 1,833 (41.3%) had ≥2 risk factors for CVD at baseline. The presence of risk factors for CVD did not affect lasmiditan's efficacy results or the incidence of cardiovascular-related adverse events. Furthermore, the incidence of cardiovascular-like adverse events was similar among individuals with CVD risk factors treated with either placebo (0.5%) or lasmiditan (0.9%).[112] A second post-hoc analysis used data from the MONONOFU trial, comprising 691 participants with migraine, to compare individuals with ≤1 risk factors for CVD (54.3%) with those with ≥2 risk factors for CVD (45.7%).[113] The most frequent risk factors were family history of CVD, male gender, post menopause in women, obesity, age and hypertension. The most common CVDs recorded at baseline were hypertension, cardiac arrhythmias and CNS vascular disorders, all of which were equally distributed in all treatment groups (placebo: 10.7%; 50 mg lasmiditan: 5.7%; 100 mg lasmiditan: 9.6%; and 200 mg lasmiditan: 7.1%). The proportion of participants treated with lasmiditan who experienced at least one adverse event was not related to the number of CVDs that one individual had . Cardiovascular-related adverse events were reported by 1.4% of placebo-treated participants and 3.8% of lasmiditan-treated participants; the most frequently reported cardiovascular-related adverse event across all treatment groups was palpitation. All likely cardiovascular adverse events were non-serious, and all participants recovered without intervention. Lasmiditan efficacy did not differ between those participants who had ≤1 versus those who had ≥2 risk factors for CVD; in both participant subgroups, the proportion of participants who were pain-free, experienced pain relief, were most

bothersome symptom-free, or were disability-free 2 hours post-dose was higher with lasmiditan than placebo.[113] This data supports that of the post-hoc analysis from SUMARAI and SPARTAN, indicating that people with mild CVD or with risk factors for CVD can use lasmiditan to treat migraines safely.

One post-hoc analysis investigated the efficacy and safety of lasmiditan in participants with and without at least one triptan contraindication by pooling data from four phase 2/3 placebo-controlled trials: SAMURAI, SPARTAN, CENTURION, and MONONOFU;[114] among 5,704 participants, 207 (3.6%) had at least one contraindication for triptan use. The analysis revealed no difference in lasmiditan efficacy between participants with and without triptan contraindications. Similarly, the safety and tolerability of lasmiditan was comparable across both groups: 18.3% and 22.8% of individuals with and without triptan contraindications respectively reported dizziness, and 7.9% and 9.9%, respectively experienced somnolence. These results indicate lasmiditan as a treatment option for people with migraine who have contraindications to triptans.[114] Interestingly, lasmiditan's efficacy seems independent of prior triptan response.[115]

[H2] Women who are pregnant or breastfeeding

Special care is needed for migraines occurring in women during pregnancy and breastfeeding.[116] In these contexts, the preferred therapeutic strategy for migraine should be a non-pharmacological one, however this is not always sufficient and, therefore, there is a need to find safe treatments.[117] On a theoretical basis, because 5-HT1F receptors lack vasoconstrictive properties,[82,118] lasmiditan is an attractive potential treatment for migraine during pregnancy. However, as there are no data available so far for ditans' use either in pregnancy or breastfeeding, they should be avoided.

[H2] Women with perimenstrual migraine

One post-hoc analysis of pooled data from the phase 2/3 trials, MONONOFU and CENTURION, has assessed the efficacy and safety of lasmiditan in women with perimenstrual migraine.[119] The investigators identified 303 participants who had treated perimenstrual migraine attacks with 50 mg (N = 24), 100 mg (N = 90) or 200 mg of lasmiditan (N = 110), or placebo (N = 79). At 2 h posttreatment, 33.6% (P = <0.001), 16.7% (P

= 0.11) and 16.7% (*P* = 0.19) of participants treated with 200 mg, 100 mg or 50 mg lasmiditan respectively were pain free, compared with 7.6% in the placebo group. At two hours posttreatment, the proportion of participants with pain freedom was similar in perimenstrual and non-perimenstrual attacks with lasmiditan 200mg, but not with lower doses.[119] These results indicate that only a high dose of 200 mg of lasmiditan is effective for the treatment of this particular migraine subtype, which is more severe and difficult to treat than non-perimenstrual migraine.[120,121]

[H2] Children

The prevalence of migraine in children and adolescents (8-18 y old) has been estimated to be as high as 8% (95% confidence intervals 9–14%).[122] Whether lasmiditan is safe and efficient in children remains unclear. One phase 1, open-label, two-cohort study assessed the pharmacokinetics , safety, and tolerability of lasmiditan in individuals with migraine, aged 6-18 y old. No new safety or tolerability issues were identified in the trial and, as with other treatments, the pharmacokinetic results support weight-based dosing of lasmiditan in paediatric individuals.[123] A clinical phase 3, 12-month open-label trial of lasmiditan in individuals with migraine, aged 6-17 y old, is currently underway with an estimated study completion date of March, 2026 (NCT04396574, the PIONEER-PEDS2 study).

[H2] Older adults

In pivotal phase 3 studies, no upper age limit was defined for study participation and no dose adjustment is required in the elderly subpopulation.[99,100,103,105] In particular, no significant blood pressure changes were observed in healthy older (≥65 y) volunteers treated with lasmiditan compared with younger individuals (<65 y) receiving the same treatment or individuals of the same age receiving a placebo. The incidence and the severity of treatment-emerged adverse events were similar in both groups including cardiovascular adverse events in a post-hoc analysis of SUMARAI and SPARTAN studies assessing the incidence of adverse events in adults aged ≥65 y compared with those aged <65 y who were treated with lasmiditan. No deaths were reported in any of the studies and only one participant discontinued because of adverse events (dizziness and fatigue) in SPARTAN trial

(45 y of age). However, the number of participants in the higher age bracket was limited, corresponding to 4.2% approximately between both trials. [124] Notably, SAMURAI and SPARTAN trials were single-attack studies. Of 2,030 lasmiditan-treated participants in GLADIATOR trial in which multiple migraine attacks were treated (totaly 19,058 attacks), 85 (4.2%) were ≥65 y. The incidence of adverse events in GLADIATOR study was lower in people with older age (38% vs. 49% in younger participants) and discontinuations because of treatment related adverse events were similar in both age groups. In participants with age ≥65 y the most common adverse events led to treatment withdrawal were dizziness (10.6%), paresthesia (3.5%) and somnolence (2.4%).[124] Tolerability and safety data for participants ≥ 65 y of age in the CENTURION trial (four-attack study) are not yet available. In conclusion, the limited number of observations does not allow firm conclusions, which will likely be established by conducting long-term real-world studies.

[H1] **Future prospects**

Although there is a growing body of information on the use of ditans for the treatment of migraine, several questions remain unanswered, which will be the subject of future studies as this novel class of anti-migraine drugs continues to be developed. One crucial question is related to MOH, particularly because lasmiditan penetrates the BBB and therefore, has the potential of modulating central sensitization.[85] In a preclinical model of MOH, rats were administered repeated oral doses of either lasmiditan, or sumatriptan, or water, for two weeks. Both lasmiditan and sumatriptan displayed similar levels of drug-induced cutaneous allodynia in both the periorbital and hindpaw regions (which are models of peripheral and central sensitization), suggesting that lasmiditan, like sumatriptan, has the ability to induce MOH in people with migraine via peripheral and central sensitization mechanisms.[125] Furthermore, a phase 1, randomized, placebo controlled crossover study was conducted to evaluate the abuse potential of 100mg, 200mg, and 400 mg lasmiditan compared with 2mg alprazolam and placebo in adult recreational polydrug users by using the maximal effect score of the Drug- Liking Visual Analog Scale. Lasmiditan was not similar to placebo in drug-liking scores at all doses tested, but it exerted similar effects with alprazolam 2mg only at the supratherapeutic dose of 400 mg. However, the lower maximum

values and shorter duration of the subjective drug-liking effects induced by lasmiditan 400mg compared with those induced by alprazolam 2mg indicate that lasmiditan has a low potential for abuse.[126] There is some evidence to suggest a pathophysiological relationship between drug abuse and MOH,[127,128] but this association, if present, needs further investigation.[129] Recurrence rates of successfully treated migraine (relapse of pain within 2-24 h posttreatment) might predict an increased risk for MOH, but this has also not been established. The efficacy of repeated dosing in SUMARAI and SPARTAN trials

was evaluated in a separate post hoc analysis.A dose was considered a rescue dose if the participant did not achieve pain freedom at 2 h post-treatment and took a second dose at 2–24 h after the first dose; a dose was considered a recurrence dose if the participant did achieve pain freedom at 2 h after the first dose but took a second dose for a newly developed headache of any intensity at 2–24 h after the first dose. The analysis found no efficacy for a rescue dose but some efficacy for a recurrence dose, and there was no increase in treatment related adverse events for lasmiditan versus placebo after taking a second dose.[130] In conclusion, although the phase 3 trials did not confirm the potential risk of lasmiditan to induce MOH, this matter clearly calls for specifically targeted future studies.

Certain gepants, although designed for the acute treatment of migraine, have expanded into migraine prevention during their development, creating reasonable expectations for a smilar use of ditans. According to the product insert approved by the FDA, lasmiditan is indicated for the acute treatment of migraine with or without aura in adults.[90] No more than one dose should be taken within 24 hours and the safety of treating more than four migraine attacks in a 30-day period has not been established (https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-patients-migraine). To our knowledge, no studies have assessed the ability of lasmiditan to reduce the frequency of migraine. We can speculate that if a patient uses lasmiditan — a selective 5-HT1F receptor agonist — on a daily basis, they might develop MOH, as can be the case with daily triptan use. However, lasmiditan differs to triptans in that it is more lipophilic, can enter the CNS and lacks vasoconstrictive properties, which might make a difference for regular use, although this is currently unknown. Sumatriptan — a selective 5-HT1B/1D and 5-HT1F agonist — in combination with naproxen, did not reduce the monthly migraine days in a 3-month randomized clinical trial for the prevention of migraine, but naproxen alone did, indicating that activation of peripheral trigeminal 5-HT1B/1D/1F receptors is not sufficient

to prevent from migraine.[131] On the other hand, there is good evidence that triptans are effective, short-term preventive treatments for menstrual migraine;[132] but the duration of daily treatment in this case does not exceed five consecutive days. These data therefore cannot substantiate a prophylactic effect of triptans in migraine. Similarly, lasmiditan is unlikely to be used preventively, unless a prospective, double-blind trial provides solid evidence for safety and efficacy in this context.[133]

The potential interaction of concomitant use of a ditan along with a prophylactic treatment for migraine is still to be determined. According to US FDA approval, 22% of participants in phase 3 trials of lasmiditan were taking a preventive medication for migraine (https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-patients-migraine). In a post hoc analysis of SPARTAN and SUMARAI trials, 17.5% of participants used migraine preventive medications; the rates of adverse events were similar between participants using and not using preventive medications.[134] The incidence of serotonin syndrome occurring after excessive 5-HT receptor activity or neurotransmission and presenting with neuromuscular excitation, autonomic dysfunction and altered mental status [106,135] was very low (only six cases were identified), but among them one treatment related adverse event was severe[136] and met the Hunter criteria (presence of clonus, agitation, diaphoresis, tremor, hyperrefelixa, and/or fever).[137] Despite this evidence, in clinical practice most potential users of ditans will be under concomitant preventive treatment, highlighting the importance of future extensive investigation of lasmiditan in long-term, real-world studies.

Lasmiditan has been suggested to be useful in cluster headache (CH) treatment.[92] People with CH have an increased risk for CVD[138] which makes lasmiditan an attractive drug for the treatment of CH because it devoid of contractile properties.[60,118] In a preclinical model of CH, lasmiditan reduced superior salivatory nucleus-evoked activation of the TVS, but had no effect on cranial autonomic activation, suggesting that lasmiditan might be a candidate for treatment of CH.[139] Fast acting ditans that block CGRP have the potential to relieve CH attacks, but again the frequent use is not suggested even with faster acting formulations, such as intranasal sprays, in light of CNS-related adverse effects and MOH potential development. [133]

All the limitations discussed above highlight the need for the synthesis of a hydrophilic ditan that does not cross the BBB and therefore does not have CNS-related adverse effects. Migraine has been shown to be pharmaceutically controlled by agents that do not penetrate the BBB, including most triptans, anti-CGRP monoclonal antibodies and gepants; thus, a central action does not seem necessary for antimigraine medications. Novel molecules that activate 5-HT1F receptors within the TVS, but remain outside the brain, could therefore be the future of ditan. Efforts to improve the bioavailability, metabolic stability, and binding affinity of lasmiditan have been started and novel 5-HT1F receptor agonists have been already designed. A series of pyridinylmethylenepiperidine derivatives that display high affinity to 5-HTF receptors, without vasoconstriction effects and which inhibit dural plasma extravasation and c-fos expression within the trigeminal nucleus caudalis, like lasmiditan, have been announced, but their ability to cross the BBB and activate centrally located 5-HT1F receptors has not yet been studied.[140] Eventually, the journey has started.

[H1] Conclusions

Serotonin and its panoply of receptors have long been associated with migraine headache, especially its treatment. The relevant to migraine serotonin receptor subtypes, for example 5-HT1B, 1D and 1F, are expressed by trigeminovascular afferents; agonists that bind these prejunctional receptors inhibit neuropeptide release, explaining their abortive effects on acute migraine. Unlike the triptan receptor 5-HT1B, the 5HT1F receptor is not expressed by vascular smooth muscle, thereby dissociating neuropeptide release and relief of acute headache from blood vessel constriction. Moreover, as indicated by the success of triptans, acute migraine abortive drugs do not need to penetrate the BBB nor narrow the lumen of cranial blood vessels to relieve a migraine headache — a substantial departure from thinking over the last century. Assuming that centrally located 5-HT1F receptors are not essential for the therapeutic effect of ditans, the development of non-brain penetrant 5-HT1F receptor agonists could prevent centrally mediated unwanted effects. Finally, the 5-HT1F receptor was among the single-nucleotide polymorphism variants of migraine-associated gene loci identified in a 2022 genome wide association study.[72] Whether these variants point to a role for widely expressed 5-HT1F brain receptors in, for example,

migraine initiation, propagation or headache potentiation remains to be determined in future studies.

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Related links

https://clinicaltrials.gov/ct2/show/results/NCT02439320
https://clinicaltrials.gov/ct2/show/results/NCT02605174
https://clinicaltrials.gov/ct2/show/NCT02565186
https://clinicaltrials.gov/ct2/show/results/NCT03670810

Key points

- Various animal studies have shown that selective 5-HT1F agonists can reduce signals from an activated trigeminovascular system, thereby highlighting the receptor as an attractive target for symptomatic treatment of migraine.

- Long-term clinical studies involving two ditans — a group of 5-HT1F agonists — have provided class I evidence that lasmiditan, the first ditan, is both effective and safe in the symptomatic treatment of migraine.

- The 5-HT1F receptor is expressed by cells within the brain parenchyma, as well as by the trigeminal neurons, but not in vascular smooth muscle, suggesting ditans act via

neuropeptide release leading to acute headache relief, rather than potential vasoactive properties, such as vasodilatation.

- Dizziness is the most common adverse event of lasmiditan, thus driving an automobile is prohibited for eight hours after use of lasmiditan.
- Developing novel ditans that do not cross the blood brain barrier is expected to result in better tolerability and improved clinical use.

Table. The Phase 3–4 clinical program of lasmiditan in migraine symptomatic treatment.

Study design	Dose	Participants	Pain free 2PT (%)	MBS free 2PT (%)	Headache relief (%)	Most common AEs
SAMURAI (NCT02439320)[99,101,102]						
Randomized, placebo-controlled study to assess the efficacy of one dose of lasmiditan in one migraine attack.	100 mg lasmiditan	503	28.2	40.9	59.4	Dizziness, paraesthesia, somnolence, fatigue, nausea, and lethargy.
	200 mg lasmiditan	518	32.2	40.7	59.5	
	placebo	524	15.3	29.5	42.2	
SPARTAN (NCT02605174)[100]						
Randomised, placebo-controlled study to assess the efficacy of lasmiditan in one migraine attack.	50 mg lasmiditan	556	28.6	40.8	59.0	Dizziness, paraesthesia, somnolence, fatigue, nausea and lethargy.
	100 mg lasmiditan	532	31.4	44.2	64.8	
	200 mg lasmiditan	528	38.8	48.7	65.0	
	placebo	540	21.3	33.5	47.7	
GLADIATOR (NCT02565186)[103]						

Prospective, randomised, open-label study in participants who completed SAMURAI or SPARTAN to evaluate the safety, efficacy and tolerability of long-term intermittent use of 100 mg and 200 mg oral lasmiditan.	100 mg lasmiditan	991 (466 completed)	26.7	37.2	-	Dizziness, somnolence, fatigue, nausea, asthenia, and hypoesthesia
	200 mg lasmiditan	1,039 (503 completed)	32.2	40.8	-	
CENTURION (NCT03670810)[105]						
Randomised, double-blind study to assess the efficacy and consistency of lasmiditan response.	100 mg lasmiditan	419	25.8	14.4*	65.4	Dizziness, paraesthesia, fatigue, nausea, somnolence, and asthenia.
	200 mg lasmiditan	434	29.3	24.4	65.2	
	placebo	443	8.4	4.3*	41.3	

* Percentage of participants that are pain free at 2 h posttreatment in at least two out of three attacks

2PT: 2 hours posttreatment; AEs: Adverse events; MBS: most bothersome symptoms.

Figure 1 | The trigeminovascular system (TVS) and the receptors involved in cephalic pain neurotransmission. Primary afferent sensory innervation of the dura mater and cranial vessels that arise from neurons located in the trigeminal ganglia collectively form the TVS. Centrally, the pseudounipolar neurons of the trigeminal ganglia send axons that reach second order neurons within the trigeminal nucleus caudalis, which extends from the caudal brainstem to upper C2 spinal cord. Sympathetic fibers arising from the superior cervical ganglia, and parasympathetic fibers arising from the superior salivatory nucleus (SSN), the pterygopalatine (sphenopalatine) and otic ganglia were also shown to innervate dural vasculature.[141] Both the sensory and autonomic fibers that surround the cranial structures

contain a variety of vasoactive neuropeptides.[29] Receptors important for cephalic pain transmission expressed by the second order neurons within the brain stem include GABAa,[142] NMDA,[143] CGRP,[144] PAC1,[145] 5-HT1B[146] and 5-HT1F receptors.[57] Most of these receptors transmit information into the cell nucleus via AMP or Ca^{2+}.[11,34]

Figure 2 | Timeline of ditan development.

A chart showing the development of ditans, which began with animal studies investigating the pharmacological properties of 5-HT1F receptors in the 1990s, followed by the two-phase clinical program that led to the commercialization of lasmiditan in the US and Europe in 2019 and 2022, respectively. On the other hand, the development of selective 5-HT1D receptor agonists was terminated after a negative test in humans.

Figure 3 | Chemical formula of serotonin (5-HT) and ditans.

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter with an indole core consisting of a six-membered benzene ring fused to a five-membered pyrrole ring. LY344864 is a highly selective 5-HT1F receptor synthetic molecule, used as pharmacological tool for the characterization of 5-HT1F receptor.[22] LY334370 is an early prototype indole-based 5-HT1F receptor agonist[74] that has been tested in humans for symptomatic migraine treatment, but is not commercialized owing to liver toxicity in animals.[26] Both LY344864 and LY334370 share the same molecular formula (same number of atoms) and molecular weight (MW) but have different structural formula (order of bonding of the atoms). Lasmiditan is the first ditan compound to be commercialized as a clinical therapy for migraine. Lasmiditan has a pyridinoyl-piperidine scaffold and differs from first generation ditans and triptans by the absence of an indole core.[83]

Figure 4 | Capsaicin induced *c-fos* immunoreactivity within the trigeminal nucleus caudalis in rats.

a, The selective 5-HT1B/1D/1F agonist sumatriptan and the selective 5-HT1F agonist LY344864 dose-dependently decreased the capsaicin-induced c-*fos* immunoreactivity within the trigeminal nucleus caudalis of rats with an ID_{50} of 0.04 mg/kg and 0.6 mg/kg,

respectively. Data are presented as number of c-*fos* immunoreactive cells per section. Error bars represent standard error. These data indicate that activation of 5-HT1B, 5-HT1D and 5-HT1F receptors inhibit pain signals within the trigeminovascular system.[24] **b,** Sumatriptan and LY344864, which both have affinity to 5-HT1F receptor, inhibit the c-*fos* response within trigeminal nucleus caudalis of rats, compared with a vehicle control. The β-adrenoceptor blocker SDZ 21-009, which also displays high affinity for 5-HT1A/1B receptors, did not alter the number of cells showing positive c-*fos* immunoreactivity, compared with the control. The effect of sumatriptan, but not LY344864, was attenuated by SDZ 21-009, indicating that activation of 5-HT1F receptor is sufficient to inhibit *c-fos* immunoreactivity without synergistic effects of 5-HT1B receptor activity. Thus, activation of 5-HT1F receptor controls pain signals within the trigeminovascular system. Data are presented as weighted average of c-*fos*-like immunoreactive cells per section. (*) *P*= <0.05 compared with vehicle treated animals (n=6).

Figure 5 | Phase 3 clinical trials for lasmiditan in the acute treatment of migraine.
a, Efficacy results of the SAMURAI trial showing the proportion of participants acheaved pain free (PF), freedom from most bothersome symptoms (MBS) and headache pain relief (HPR), 2 h posttreatment.[99] **b,** Efficacy results of SPARTAN trial showing the proportion of participants who achieved PF and freedom from MBS 2 h posttreatment.[100] **c,** Proportion of participants reporting treatment-emergent adverse events (TEAEs) by migraine attack in the GLADIATOR study.[103] The incidence of TEAEs decrease across treated attacks 1 to 5 in the first interim analysis of GLADIATOR study; data from 1,126 participants who had treated at least five migraine attacks.[103] **d,** Consistency of lasmiditan efficacy in the CENTURION trial, showing 2 h posttreatment pain free rates across all four treated attacks.[105] **a–d,** Relief from the most bothersome symptom was defined as a change from 'yes' to 'no' for the presence of the patient's most bothersome symptom at baseline, including nausea, phonophobia or photophobia; headache pain relief was defined as a reduction in headache severity from moderate [2] or severe [3] at baseline to mild [1] or none [0] or a reduction in headache severity from mild [1] at baseline, to none [0]. (*) P= <0.01 compared with placebo.

Figure 6 | Number needed to treat (NNT) for symptomatic treatment of migraine with different drug classes.

The NNT were calculated with the formula: NNT= 1/absolute risk reduction, which is the percentage reduction of the active treatment minus percentage reduction of the placebo treatment. NNTs are rounded up to the nearest whole number. Data were extracted from the following randomized placebo-controlled trials: lasmiditan, integrated data from SAMURAI and SPARTAN trials;[109] ubrogepant;[147] rimegepant;[148] sumatriptan;[149] and ibuprofen and aspirin.[150]

Box 1 | Migraine management

The management of migraine starts with patient education and the treatment decision depends on the disease severity, previous treatment outcomes, comorbidities and individual preferences.[151,152] In the symptomatic treatment of migraine, ergot alkaloids and caffeine derivates should be used with caution because of the high risk for medication overuse headache (MOH). High doses of simple analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are suggested as first line treatment for mild to moderate migraine attacks. For moderate to severe migraine attacks triptans are suggested as first choice treatment. Gepants and ditans share similar efficacy with triptans, but gepants have the advantage of low risk for MOH and ditans, unlike triptans, are not contraindicated in people with cardiovascular risk factors. To assess symptomatic treatment, the Migraine Treatment Optimization Questionnaire (mTOQ-4) is suggested.[153]

When migraine attacks continue to impair quality of life despite optimized acute therapy, additional prophylactic therapy should be considered.[151,152] Monoclonal antibodies targeting the CGRP receptor (anti-CGRP mAbs) and gepants share good scientific documentation and tolerability/safety profile.[154,155] Anti-CGRP mAbs, along with the traditional anti-migraine preventatives — anti-hypertensives, anti-epileptics, and antidepressants — are suggested as first prophylactic treatment options.[156] For the case of chronic migraine, onabotulinumtoxin A is also suggested as first line treatment.[157] Non-pharmacological approaches have low scientific documentation but high tolerability and should be considered alone or in combination with pharmacological treatments as alternative treatment options for people with migraine who avoid, do not tolerate or do not respond to medicines or are contraindicated.[151,152,158] To guide follow-up of migraine treatment in primary care the

Headache Under-Response to Treatment (HURT) questionnaire, or the Patients Global Impression of Change are suggested.[159]

Box 2 | Tissue distribution and functions of 5-HT receptors

5-HT receptors are classified into seven main types, exerting a wide variety of functions throughout the body. 5-HT1 receptors are subdivided into 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E and 5-HT1F subtypes.[160] In the human brain, 5-HT1F receptors are located in the limbic system,[161] in cortical layers 4–5, the subiculum and the cerebellar granule cell layer. Several brainstem regions, including the substantia nigra, spinal trigeminal nucleus and nucleus of the tractus solitarius, also display 5-HT1F sites.[57,75,146,161-164] Astrocytes express 5-HT1F mRNA, but the function of this expression is unclear.[163,165] 5-HT1F mRNA or immunoreactivity was detected in dorsal root,[166,167] trigeminal ganglion [18,22,23, 139,168-170] and trigeminal neurons, [171,172] although one study showed weaker expression in the latter neurons.[37] These observations suggest that 5-HT1F receptors have a role in both cranial and peripheral sensory processing. However, whether 5-HT1F receptor agonists have general analgesic properties is unclear.[18,23,172-175.]

5-HT1F receptors are found in reward-associated areas, such as the nucleus accumbent, where they attenuate methamphetamine relapse, suggesting that 5-HT1F agonists may be effective in preventing relapse in individuals with drug addiction.[176] 5-HT1F receptors in the arcuate nucleus might play a role in hypothalamic control of food intake and energy homeostasis.[177] 5-HT1F receptors also affect energy metabolism outside the brain, as glucose-dependent β-cell release of serotonin activates α-cell 5-HTR1F receptors, inhibiting glucagon secretion.[178] 5-HT1F activation induces stomach relaxation[179] and stimulates mitochondrial biogenesis in various tissues [86,180-182] — a response that could be targeted for the management of acute kidney injury, spinal cord injury, neuropathic pain or Parkinson disease. 5-HT1F receptor mRNA was also detected in human platelets,[183] rat hepatic stellate cells,[184] pig and human conjunctiva,[185] rat distal colon [186] and rat immune tissues.[187] Importantly, 5-HT1F receptors are not located within the vasculature,[21,60,163,169] in agreement with the lack of 5-HT1F-mediated vasoactive response [23,82,118,163,188-191,] although one study reported a strong 5-HT1F signal in human coronary artery.[192]

MIGRAINE TREATMENT

Pharmacological

Symptomatic

Migraine-specific
1. Ergot alkaloids
2. Triptans
3. Gepans
4. Ditans

Non-specific
1. Simple analgesics
2. NSAIDs
3. Caffeine
4. Combinations

Prophylactic

Migraine-specific
1. Anti-CGRP mAbs
2. Gepans

Non-specific
1. Anti-hypertensives
2. Anti-epileptics
3. Anti-depressives
4. Toxins (for chronic migraine only)

Non pharmacological

1. **Patient education**
2. Physical therapy
3. Cognitive therapy
4. Biofeedback
5. Acupuncture
7. Neuromodulation

The management of migraine starts with patient education; treatment decision depends on disease severity, previous treatments' outcomes, patient's comorbidities and patient's preferences.[23,24] In the symptomatic treatment barbiturates/opioids alone, or in combinations should be avoided because of the high risk of overuse. Similarly, ergot alkaloids should be used with caution. High doses of simple analgesics and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are suggested as first line treatment for mild to moderate migraine attacks. For moderate-to-severe migraine attacks triptans are suggested as first choice treatment. Gepants and ditans share similar efficacy with triptans, but gepants have the advantage of low risk for medication overuse headache and ditans are non-contraindicated in people with vascular risk factors. To assess symptomatic treatment the Migraine Treatment Optimization Questionnaire (mTOQ-4) is suggested.[25] When migraine attacks continue to impair quality of life despite optimized acute therapy, additional prophylactic therapy should be considered.[23,24] Monoclonal antibodies targeting the CRPP (anti-CGRP mAbs) and gepants share good documentation and tolerability/safety profile.[26,27] Anti-CGRP mAbs, along with the traditional anti-migraine preventatives (anti-hypertensive, anti-epileptics, and anti-depressives) are suggested as first treatment option.[28] For the case of chronic migraine, onabotulinum toxin type A is also suggested as first line treatment.[29] Non-pharmacological approaches share low scientific documentation but high tolerability and should be considered alone or in combination with pharmacological treatments, when people with migraine avoid, or contradict, or do not tolerate, or do not respond to medicines, as alternative treatment options.[23,24,30] To guide follow-up of migraine treatment in primary care The Headache Under-Response to Treatment (HURT) questionnaire is suggested.[31]

Box 2

Hindbrain

Trigeminal nucleus caudalis	Inhibition of trigeminal nociceptive processing
Vestibular nuclei	Function unknown
Spinal cord	Mitochodrial biogenesis

Sensory neurons

| Dorsal root ganglia | Nociception Itch |

Heart

| Atrium, ventricle wall, epicardium, | Function unknown |
| Coronary artery | No vasoactive properties |

Kidney

| Proximal tubules | Mitochondrial biogenesis |

Blood and immune tissues

Platelets	Function unknown
Lymphocytes	Function unknown
Thymus	Function unknown
Spleen	Function unknown

Forebrain

Cortex (Layers IV and V) Subiculum Substantia nigra Cerebellum (granule layer)	Central effects of lasmiditan (somnolence, dizziness, fatigue, and paresthesias)? Mitochondrial biogenesis
Nucleus accumbens	Attenuation of methamphetamine relapse
Arcuate nucleus	Hyperpolarization of rat insulin promoter (RIP)-expressing neurons

Eye

| Conjunctiva | Function unknown |

Digestive/endocrine system

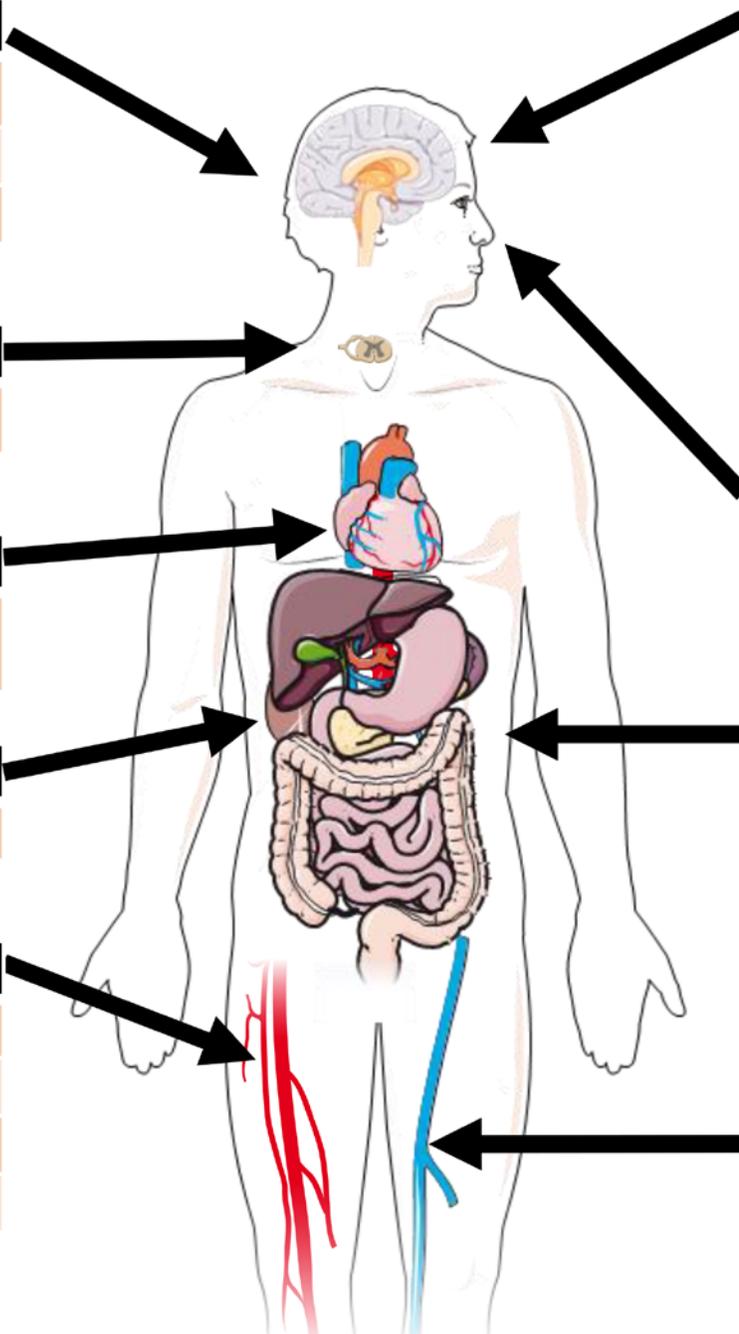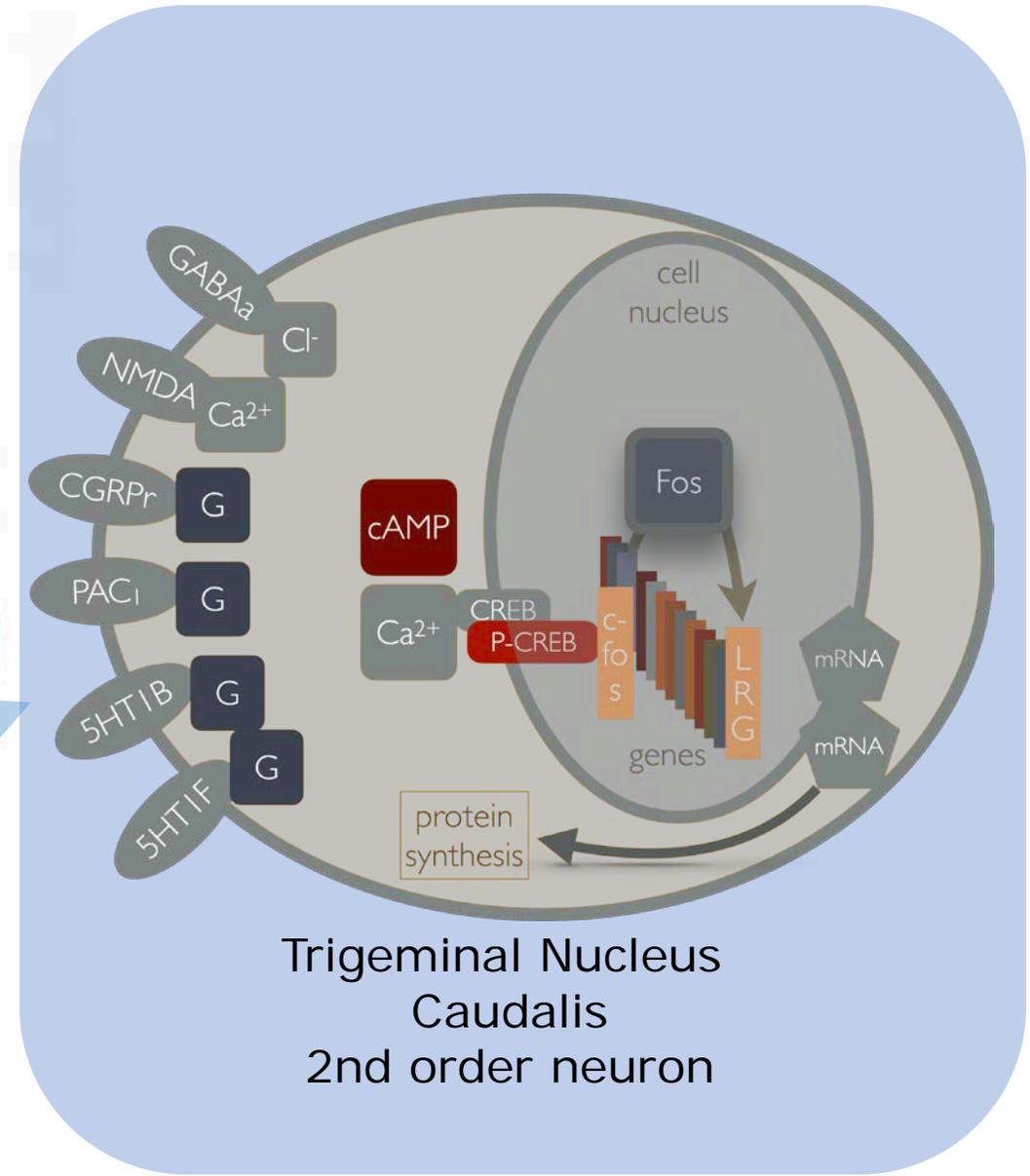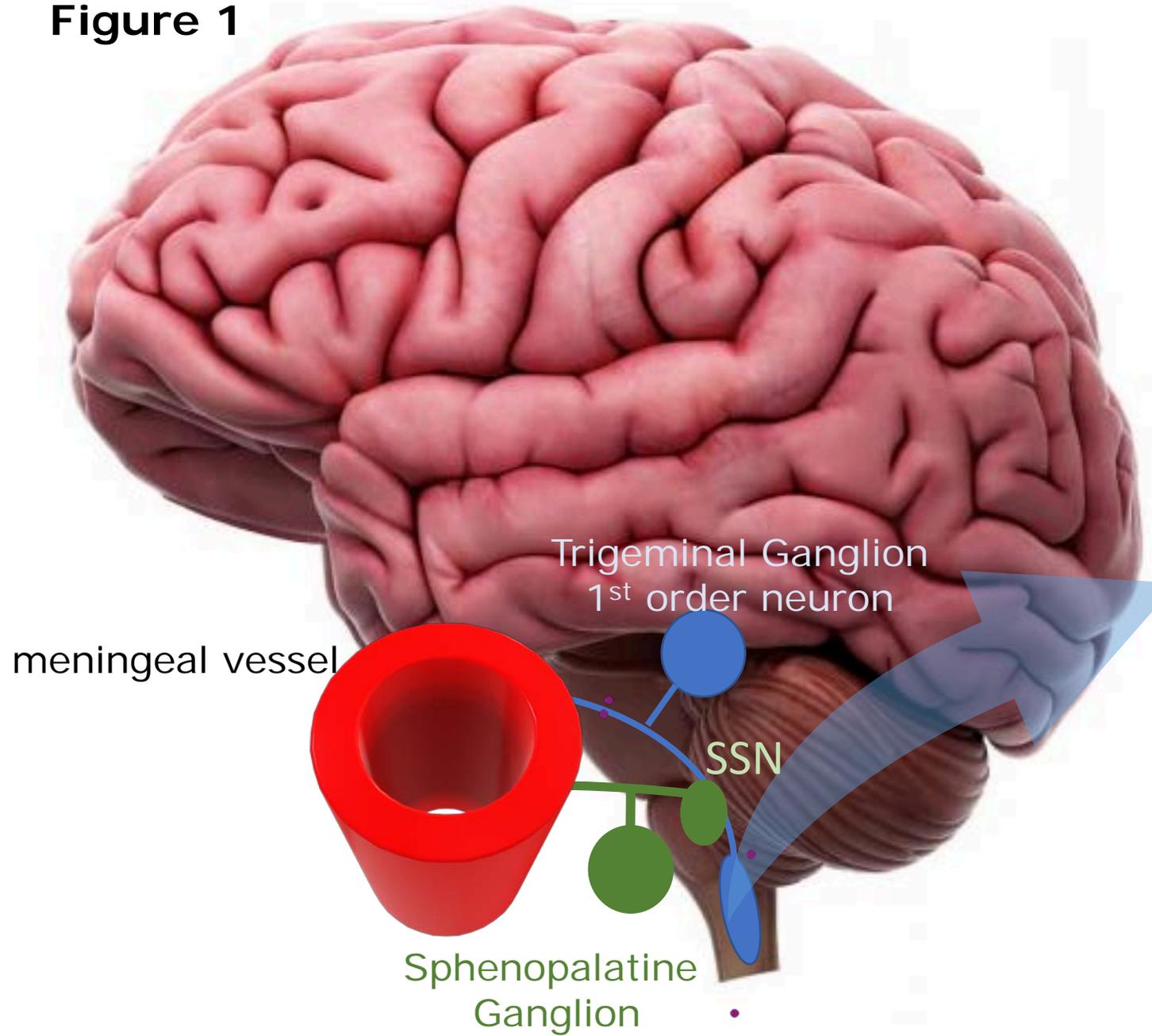| Pancreas (alpha cells) | Inhibition of glucagon secretion |
Stomach	Relaxation
Liver (stellate cells)	Function unknown
Distal colon	Function unknown

Saphenous vein

| No vasoactive properties |

Figure 1

meningeal vessel

Trigeminal Ganglion
1st order neuron

SSN

Sphenopalatine
Ganglion

GABAa
Cl-
NMDA
Ca2+
CGRPr
G
PACi
G
5HT1B
G
G
5HT1F

cAMP

cell
nucleus

Fos

Ca2+
CREB
P-CREB

c-fos
genes

L R G

mRNA

mRNA

protein
synthesis

Trigeminal Nucleus
Caudalis
2nd order neuron

Rationale
Triptans (5-HT1B/1D/1F agonists), relieve migraines but share high risk for vasoconstriction, via 5-HT1B receptor. Need to test whether selective 5-HT1D and 5-HT1F agonists display anti-migraine properties

1995

1996-2002

5-HT1F agonists Development
Positive tests of the selective 5-HT1F agonists LY344864 and LY344370 in animal models for migraine

1998-2001

Early clinical studies
Oral LY344370 was superior to placebo in human studies, but due to liver toxicity the program terminated.

2001-2021

Late clinical studies
Oral Lasmiditan was superior to placebo in human studies without liver toxicity

1995-1999

5-HT1D agonists development
Positive tests of 5-HT1D agonists PNU109291 and PNU142633 in animal models for migraine

2000

Clinical studies
PNU142633 failed to show efficacy over placebo in humans

2019-2022

FDA & EMA approval
Lasmiditan for the acute treatment of migraine with or without aura in adults
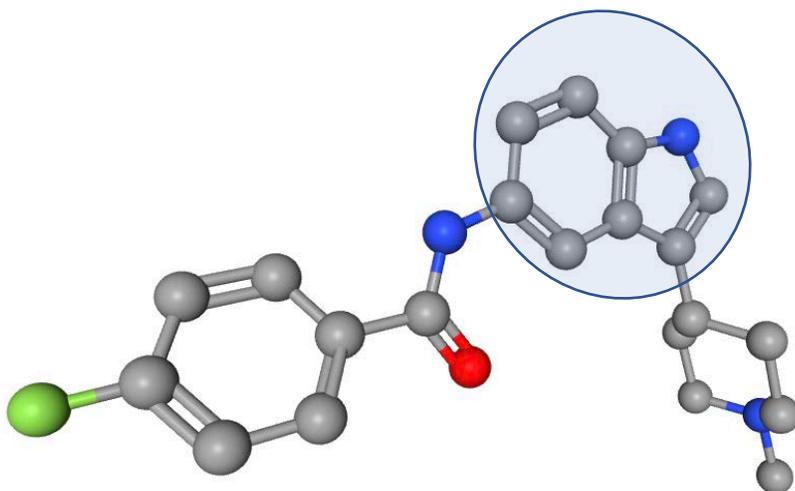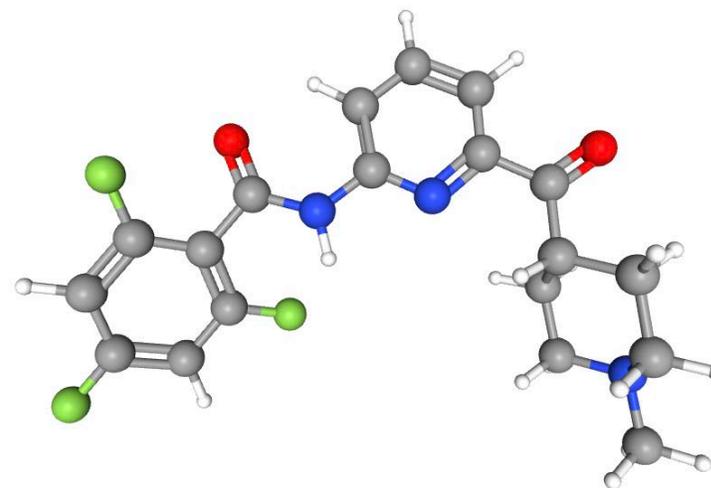
Figure 2

Figure 3

Indole core

Serotonin ($C_{10}H_{12}N_2O$)
MW=176.2
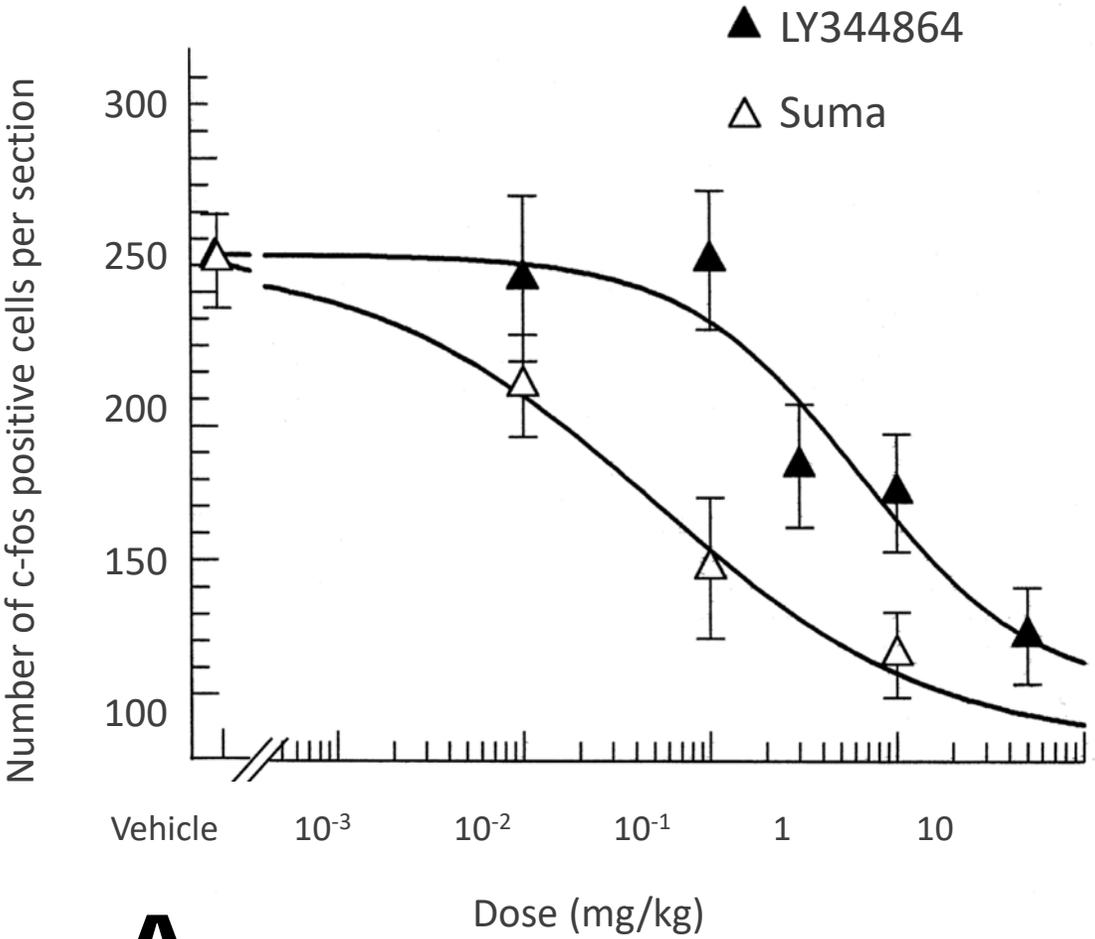
LY344864 ($C_{21}H_{22}FN_3O$)
MW= 351.4

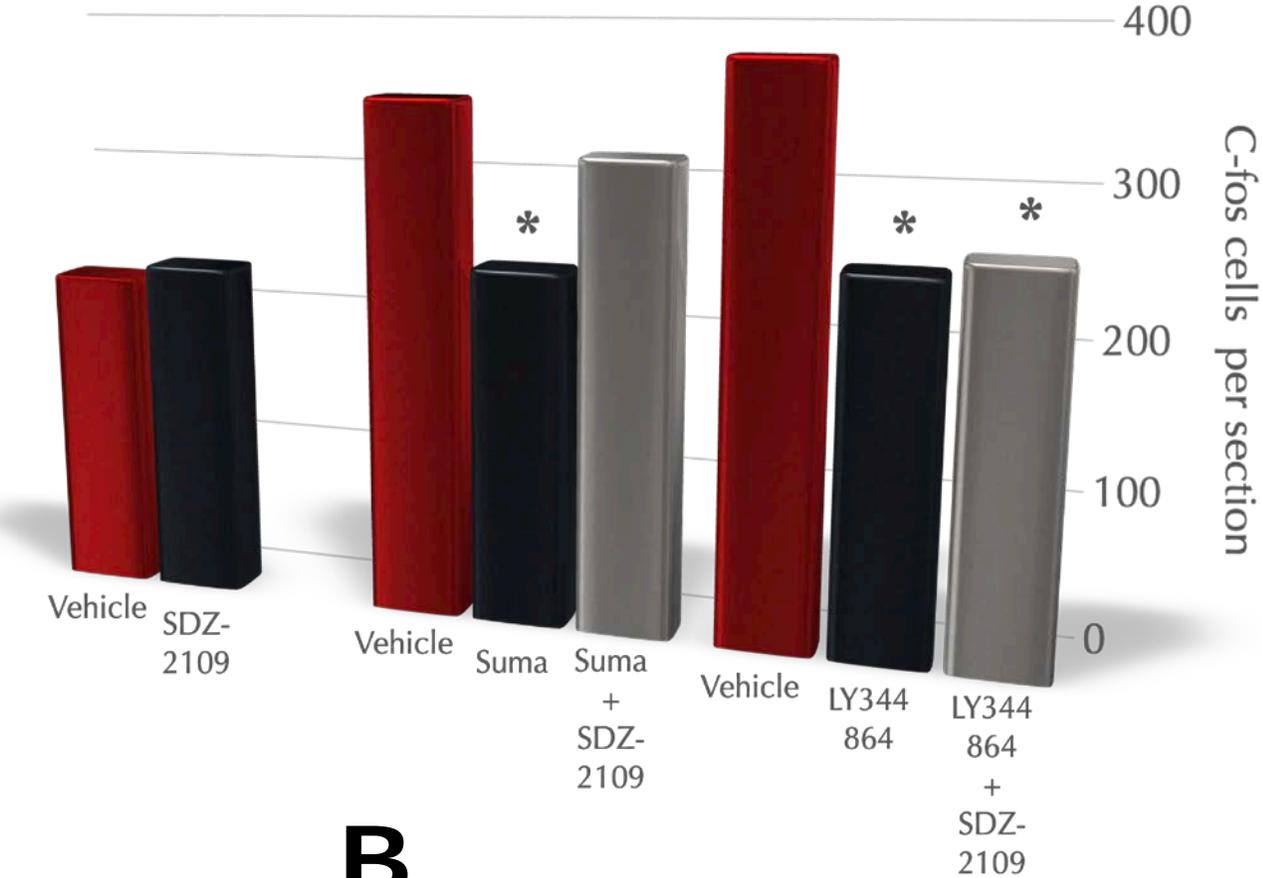LY334370 ($C_{21}H_{22}FN_3O$)
MW=351.4

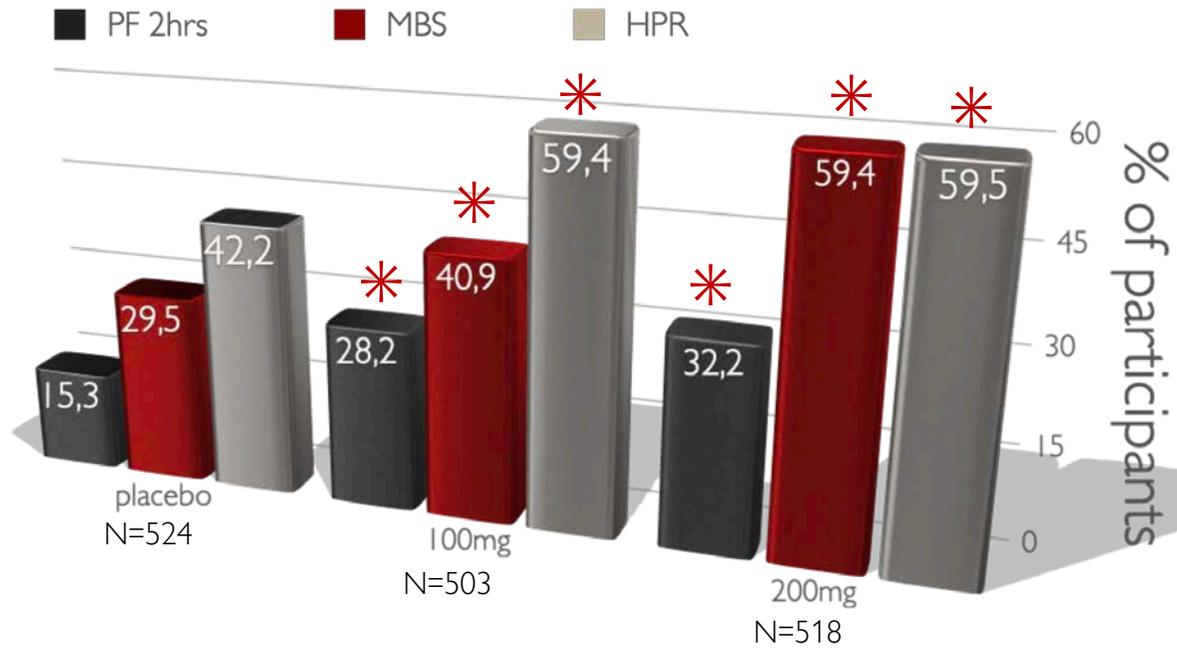LY573144 or COL-144 ($C_{19}H_{18}F_3N_3O_2$)
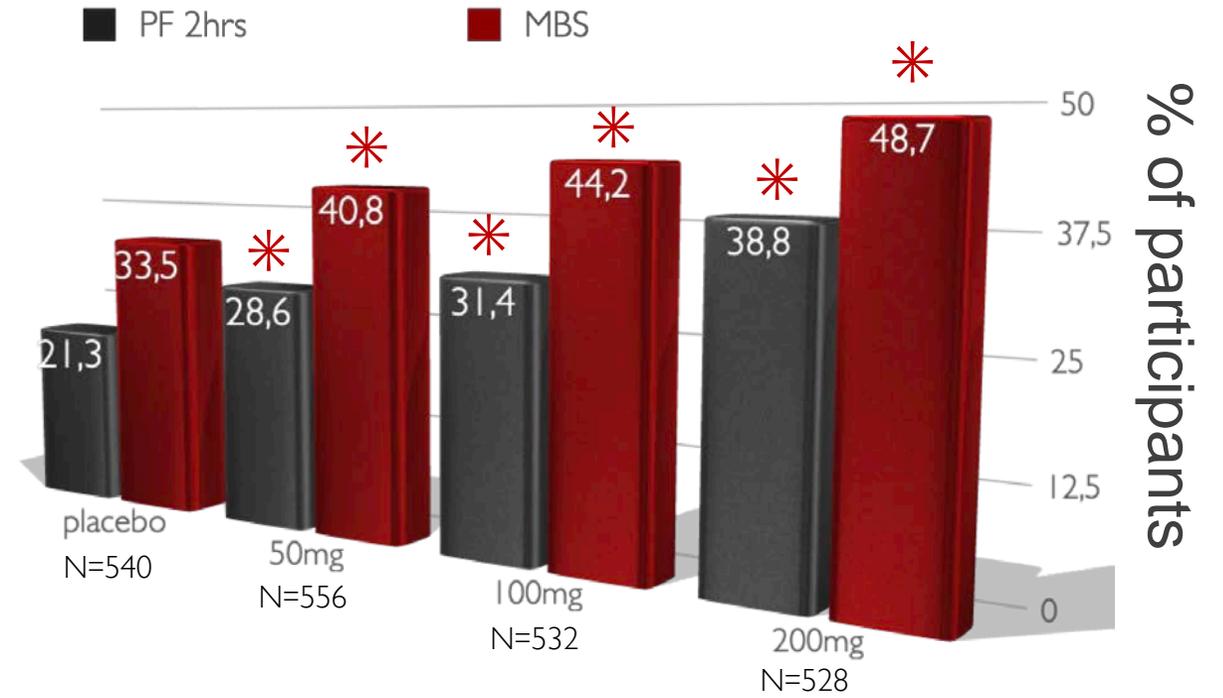Lasmiditan MW= 377.4

Figure 4

Figure 5

Figure 5

C

Legend: 100mg (n=560), 200mg (n=566)

% of participants

	Attack 1	Attack 2	Attack 3	Attack 4	Attack 5
200mg	27,4	19,4	17,5	15,5	14,5
100mg	20,9	13,3	13,2	10,7	11,3

D

Legend: Placebo, 100mg, 200mg

% of participants

	Placebo	100mg	200mg
Attack 1	8,4	25,8 *	29,3 *
Attack 2	7,4	19,4 *	29 *
Attack 3	13,6	19,5 *	25,7 *
Attack 4	9,4	21 *	27,7 *

Figure 6

NNT

Drug	NNT
Lasmiditan 200mg	6
Ubrogepant 100mg	11
Rimegepant 75mg	10
Sumatriptan 100mg	5
Ibuprofen 400mg	5
Aspirin 1000mg	7