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ORIGINAL ARTICLE

Lasmiditan efficacy in migraine attacks with mild vs. moderate or severe pain

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ABSTRACT

Objective: To evaluate the efficacy of lasmiditan (LTN) in treating migraine attacks of mild vs. moderate or severe pain intensity.

Methods: Pooled data from two single-attack, placebo-controlled studies (SAMURAI [NCT02439320] and SPARTAN [NCT02605174]), and a prospective, randomized, open-label study (GLADIATOR [NCT02565186]) were assessed. Efficacy measures included the proportion of attacks with 2-h pain freedom (PF), 2-h most bothersome symptom (MBS) freedom, and 24-h sustained pain freedom (SPF). Fisher's exact test was used to compare the proportion of PF, SPF, or MBS freedom outcomes among attacks treated at mild, moderate, or severe pain.

Results: In SAMURAI and SPARTAN, most treated attacks were of moderate ($N = 2768$) or severe ($N = 1147$) intensity, compared to mild ($N = 65$). Numerically greater 2-h PF and 24-h SPF response rates were observed in attacks treated at mild compared to moderate or severe pain. Analysis of GLADIATOR data included 273 (1.5%), 11,644 (65.1%), and 5948 (33.3%) attacks treated when pain was mild, moderate, and severe, respectively. In general, a significantly greater proportion of attacks treated at mild pain achieved 2-h PF and MBS freedom, as well as 24-h SPF. The incidence of treatment-emergent adverse events in LTN treatment groups were similar regardless of baseline head pain intensity.

Conclusions: Data from two placebo-controlled, single-attack trials, and an open-label study including treatment of multiple attacks, suggested a tendency to relatively better efficacy outcomes when LTN treatment was initiated at mild vs. moderate to severe pain. Further research is needed to better understand the relationship of lasmiditan outcomes to the time of administration in the course of a migraine attack.

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Introduction

Migraine is a chronic, disabling neurologic disease with an estimated global prevalence of 11.6%[1]. Among the vast list of migraine clinical manifestations, paroxysmal intense head pain accompanied by varying combinations of nausea, vomiting, photophobia, and phonophobia represents the archetype of this primary headache disorder.

In acute treatment of migraine attacks, early treatment has been found to be more effective[2]. The results from multiple studies on acute therapies for migraine, including nonsteroidal, anti-inflammatory drugs, ubrogepant, and triptans, suggested that efficacy outcomes were better when treatments were taken earlier in the course of an attack[3–11]. Higher headache pain intensity at the time of treatment is a significant predictor of inadequate 2-h headache pain freedom (PF) response to acute treatment, including triptans, according to the American Migraine Prevalence and Prevention study[12]. Tolerability of the treatment may impact the likelihood of early intervention, as patients reluctant to risk adverse events may be hesitant to treat a migraine attack when pain is mild. Although accumulating clinical trial data indicate that treating migraine early is more efficacious, there is little evidence to support that pain intensity at the time of dosing will impact the tolerability of a given treatment or class of treatment[3–11].

Lasmiditan (LTN), a novel, high affinity and selective 5-HT_{1F} receptor agonist[13], was superior to placebo in treating moderate to severe migraine attacks in two phase 3, randomized, placebo-controlled trials, SAMURAI[14] and SPARTAN[15]. Across both studies, LTN 200 mg, 100 mg, and 50 mg (SPARTAN only) were significantly more effective than placebo based on primary endpoint (PF at 2 h after dosing) and the key secondary endpoint (freedom from the most bothersome symptom [MBS] designated by the patient at 2 h) findings. In these trials, LTN was generally safe and well

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tolerated, with no deaths and a small number of serious adverse events reported. Common adverse events experienced with lasmiditan included dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, and muscle weakness. Safety and efficacy findings were similar in the subsets of study participants with known cardiovascular risk factors[16] or taking concomitant medications[17]. Additional information on the efficacy and tolerability of lasmiditan with intermittent dosing is available from analysis of GLADIATOR[18], a prospective, randomized, open-label study.

The objective of this post-hoc analysis was to evaluate the efficacy of lasmiditan in treating migraine attacks of mild vs. moderate or severe headache pain intensity using pooled data from SAMURAI and SPARTAN, and using data from GLADIATOR. Throughout this manuscript, attacks treated when pain was mild, moderate, or severe will be referred to as mild, moderate, or severe attacks, respectively.

Materials and methods

Study designs, participants, and treatment

The designs of SAMURAI (NCT02439320), SPARTAN (NCT02605174), and GLADIATOR (NCT02565186) studies were reported in detail previously[14,15,19].

SAMURAI and SPARTAN were prospective, randomized, double-blind, multicenter, single-attack, phase 3 studies. In SAMURAI, participants were randomized (1:1:1) to a single dose of LTN 200 mg, LTN 100 mg or placebo. In SPARTAN, participants were randomized (1:1:1:1) to receive a single dose of LTN 200 mg, LTN 100 mg, LTN 50 mg or placebo.

Key inclusion criteria were fulfillment of International Classification of Headache Disorders, 2nd edition criteria 1.1 or 1.2.1 for migraine with or without aura[20], 3–8 migraine attacks per month with <15 monthly headache days, migraine onset before 50 years of age, and a Migraine Disability Assessment score of ≥ 11 (moderate or severe migraine-associated disability). While SAMURAI excluded individuals with known coronary artery disease, clinically significant arrhythmia, and uncontrolled hypertension, these individuals were eligible for SPARTAN.

GLADIATOR was a prospective, randomized, open-label, multicenter, phase 3 study enrolling eligible participants who had completed either SAMURAI or SPARTAN. The study was designed to evaluate the safety and efficacy of LTN for the acute treatment of migraine attacks for up to one year. In GLADIATOR, participants were randomized 1:1 to LTN 100 mg or 200 mg and stratified (yes or no) by use of concomitant migraine preventive medications.

While early treatment, when pain is mild, is clinically recommended, guidelines for conduct of clinical trials recommend administration of investigational treatment when pain is moderate to severe[2,21]. Consequently, in all three studies, participants were instructed to take study medicine when headache intensity was moderate or severe. The predefined analysis plan included all participants who dosed with study medicine in the analysis population, regardless of pain intensity. Relatively few participants dosed at mild pain in the single-attack, placebo-controlled studies ($n = 65$), but more attacks treated at mild pain were available for analysis in the 12-month, open-label study GLADIATOR ($n = 273$ attacks), which included a larger number of treated attacks, given intermittent dosing up to one year.

In SAMURAI and SPARTAN, participants were provided a second dose of either active study medication or placebo to use if needed for rescue or recurrence. In GLADIATOR, participants were able to take a second dose of lasmiditan, at the randomized dose, for rescue or recurrence. This manuscript focuses on outcomes after a single dose of LTN.

Studies informing this post hoc analysis were conducted in accordance with the International Council for Harmonisation principles of Good Clinical Practice and approved by each center's institutional review board of ethics committee. All participants provided written informed consent.

Efficacy and safety measures

Participants recorded the following efficacy-related data in an electronic diary at baseline and at 0.5, 1, 1.5, 2, 3, 4, 24, and 48 h after dosing: the current level of headache intensity according to the International Headache Society scale (none, mild, moderate, or severe),[21] presence or absence of associated symptoms of migraine (nausea, phonophobia, and photophobia—from the list of associated symptoms, participants selected the one they considered to be the MBS), presence or absence of vomiting, and the level of migraine-related disability. The reported level of migraine functional-related disability was rated with a 4-point scale: not at all; mild interference; marked interference; and completely needs bed rest.

In this post hoc analysis, efficacy outcomes included the proportion of participants who were PF and MBS-free at 2 h and the proportion of participants who had 24-h sustained headache pain freedom (SPF). PF was defined as a reduction in pain intensity from mild, moderate, or severe at baseline to none. MBS freedom was defined as the absence of the associated symptom of migraine that was identified pre-dose as the MBS. SPF was defined as headache PF at 2 h after first dose and 24 h, with no rescue medication used after the first dose.

Safety assessment included treatment-emergent adverse events (TEAEs). Any event that first occurred or worsened in severity within 48 h after treatment with the study drug was considered a TEAE.

Statistical analyses

Efficacy analyses for PF and SPF were performed on the intention-to-treat (ITT) population who had head pain of mild, moderate, or severe intensity at the time of dosing. Efficacy analyses for MBS freedom were performed on participants from the ITT population with an identified MBS at baseline. The ITT population was defined as all randomized participants who used ≥ 1 dose of study drug to treat the attack and had post-dose headache intensity level and/or symptom assessments. If a participant used rescue

medication prior to 2 h, then he/she was counted as a non-responder for that treated attack.

Data from the SAMURAI and SPARTAN studies were pooled (SAMURAI + SPARTAN) for the present analysis. Given the small number of mild attacks, no statistical comparisons between treatment groups were made and descriptive results regarding the proportion of participants with PF, SPF, or MBS freedom among mild, moderate, or severe attacks are reported.

In GLADIATOR, as individual participants treated multiple attacks, analyses are reported by the proportion of attacks in which they achieved each outcome. Fisher's exact test was used to compare the proportion of migraine attacks with PF, SPF, or MBS freedom among attacks with mild, moderate, or severe pain. The efficacy and safety of lasmiditan were also evaluated in a subset of participants ($N = 149$ [7.5%]) from the GLADIATOR study who treated $\geq$1 mild and $\geq$1 moderate or severe attack.

Results were considered statistically significant if the p-value was $<.05$. Analyses were conducted using SAS Version 9.4 or higher.[i]

Results

SAMURAI + SPARTAN

Clinical characteristics of treated migraines

In SPARTAN and SAMURAI, 3980 participants treated a single migraine attack at mild ($n = 65$), moderate ($n = 2768$), or severe ($n = 1147$) pain with LTN 200 mg, 100 mg, and 50 mg (SPARTAN only). Average (mean) time from headache onset to treatment administration was 1.9 h (Table 1) and was lowest (0.4 h) for attacks of mild intensity compared to those of moderate (1.8 h) and severe (2.1 h) intensities. The reported presence of migraine-associated symptoms (photophobia, phonophobia, nausea and vomiting) generally increased with migraine attack pain intensity (Figure 1(A)). Migraine-associated functional disability worsened with increasing pain intensity (Table 1).

Efficacy

Pain freedom at 2 h. Response rates for 2-h PF were numerically greater in participants who treated mild attacks with all doses of lasmiditan vs. placebo. With one exception, response rates for 2-h PF were numerically greater in participants who treated mild attacks with LTN (50 mg [41.7%], 100 mg (26.7%), and 200 mg [45.5%]) compared to those in participants who treated moderate (28.3–37.6%) or severe (26.2–29.4%) attacks with LTN 50 mg, 100 mg, and 200 mg (Figure 2(A)). In those randomized to LTN 100 mg, the response rate for 2-h PF for those who treated mild attacks with LTN 100 mg (26.7%) was less than that seen for those treating moderate attacks (31.2%).

Most bothersome symptom freedom at 2 h. Response rates for 2-hr freedom from MBS were numerically greater in participants who treated mild attacks with all doses of lasmiditan versus placebo. Response rates for 2-h MBS Freedom were similar across participants who treated mild (40.0–42.1%), moderate (41.4–46.7%), or severe (38.7–39.2%) attacks with LTN 50 mg, 100 mg, and 200 mg (Figure 3(A)).

Sustained pain freedom at 24 h. Response rates for 24-h SPF were numerically greater in participants who treated mild attacks with all doses of lasmiditan versus placebo. Response rates for 24-h SPF were numerically greater in participants who treated mild attacks with LTN (50 mg [25.0%] and 200 mg [31.8%]) compared to those in participants who treated moderate (18.1–22.7%) or severe (14.5–15.0%) attacks with LTN 50 mg, and 200 mg (Figure 4(A)). In those randomized to LTN 100 mg, the response rate for 24-h PF for those

Table 1. Baseline treatment and attack characteristics (SAMURAI + SPARTAN).[a]

Characteristic	Pain intensity		
	Mild ($N = 65$)	Moderate ($N = 2768$)	Severe ($N = 1147$)
Attacks treated by dose, *n* (%)			
Placebo	16 (24.6)	782 (28.3)	331 (28.9)
50 mg	12 (18.5)	421 (15.2)	165 (14.4)
100 mg	15 (23.1)	794 (28.7)	324 (28.2)
200 mg	22 (33.8)	771 (27.9)	327 (28.5)
Time to dosing from attack start, hours, mean (SD)	0.40 (4.7)	1.8 (4.0)	2.1 (5.1)
Time to dosing from attack start, *n* (%)			
$\leq$1 h	41 (63.1)	1283 (46.4)	555 (48.4)
$\leq$2 h	13 (20.0)	632 (22.8)	240 (20.9)
>2 h	11 (16.9)	853 (30.8)	352 (30.7)
Associated symptoms, *n* (%)			
Nausea	16 (24.6)	1141 (41.2)	574 (50.0)
Photophobia	43 (66.2)	2076 (75.0)	940 (82.0)
Phonophobia	26 (40.0)	1646 (59.5)	815 (71.1)
Vomiting	3 (4.6)	36 (1.3)	55 (4.8)
None	8 (12.3)	209 (7.6)	56 (4.9)
Migraine-related functional disability, *n* (%)			
None	3 (4.6)	30 (1.1)	16 (1.4)
Mild	45 (69.2)	922 (33.3)	103 (9.0)
Marked	8 (12.3)	1563 (56.5)	587 (51.2)
Need complete bed rest	9 (13.8)	253 (9.1)	441 (38.4)

Abbreviations. h, hour; *n*, number of participants in specified population; *N*, total number of attacks treated; SD, standard deviation.
[a]$N = 1$ participant treated an attack when pain was categorized as "none."

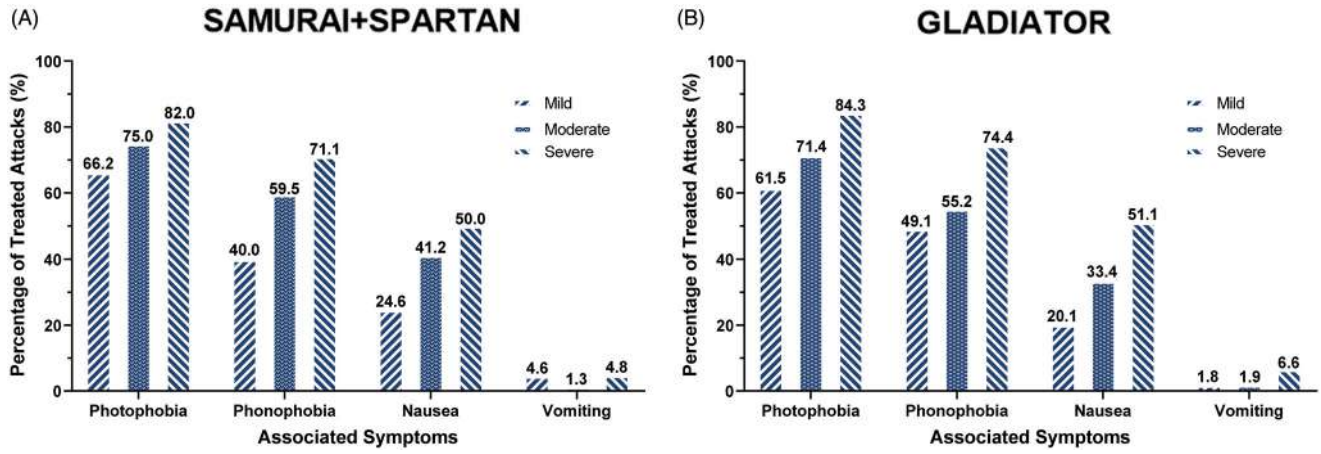

Figure 1. Experience of associated symptoms at attack baseline by pain intensity in (A) SAMURAI + SPARTAN and (B) GLADIATOR.

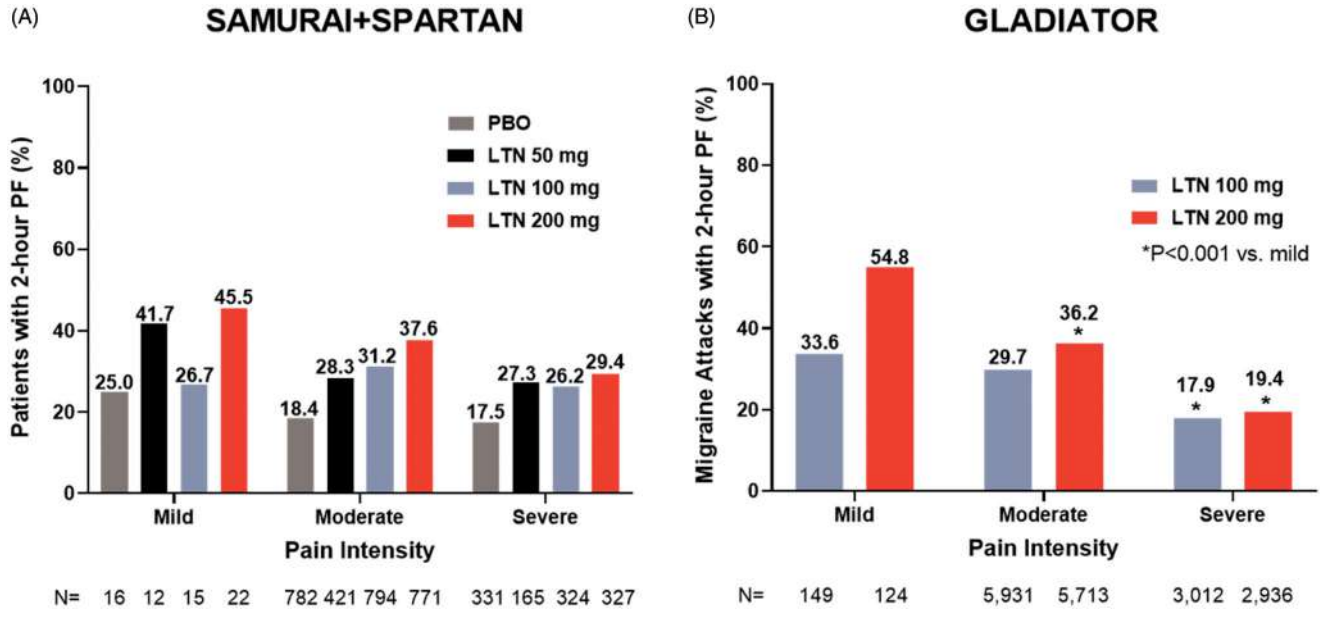

Figure 2. 2-H pain freedom: (A) percentage of study participants in SAMURAI + SPARTAN and (B) percentage of migraine attacks in GLADIATOR.
Abbreviations. LTN, lasmiditan; PF, pain free. Panel (A) shows the percentage of participants in SAMURAI + SPARTAN with 2-h PF, *N = number of study participants* included in the analysis; Panel (B) shows the percentage of migraine attacks in GLADIATOR for which there was 2-h PF, *N = number of migraine attacks* included in the analysis.

who treated mild attacks (13.3%) was less than for those treating moderate (17.3%) and severe attacks (14.2%).

Overall, there was no clear pattern or difference in the experience of TEAEs based on pain intensity at time of dosing, with ≥1 TEAE reported in 26.5%, 38.9%, and 30.8% of participants who were treated with LTN when pain was mild, moderate, and severe, respectively.

GLADIATOR

Baseline treatment and attack characteristics

Participants in GLADIATOR treated 17,878 migraine attacks; 273 (1.5%) mild attacks, 11,644 (65.1%) moderate attacks, and 5948 (33.3%) severe attacks (Table 2). Average (mean) time from headache onset to treatment administration was 1.3 h and did not differ across intensities. The occurrence of migraine-associated symptoms increased with migraine attack pain intensity (Figure 1(B)). Migraine-associated functional disability severity worsened with increasing pain intensity (Table 2).

A mean (standard deviation [SD]) of 9.0 (9.4) attacks was treated per participant during the study.

Efficacy

Proportion of migraine attacks with pain freedom, MBS freedom, and sustained pain freedom. Two-hour PF was achieved in a greater proportion of mild attacks (LTN 200 mg [54.8%], LTN 100 mg [33.6%]) compared to moderate (LTN 200 mg [36.2%], $p < .001$ vs. mild; LTN 100 mg [29.7%], $p = .318$ vs. mild) and severe attacks (LTN 200 mg [19.4%], $p < .001$ vs. mild; LTN 100 mg [17.9%]; $p < .001$ vs. mild) (Figure 2(B)).

Two-hour MBS freedom was achieved in 43.8% of mild attacks treated with LTN 200 mg and 31.5% treated with LTN 100 mg compared to 40.5% of moderate attacks treated with LTN 200 mg ($p = .456$ vs. mild) and 36.8% treated with LTN 100 mg ($p = .219$ vs. mild) and 29.4% of severe attacks

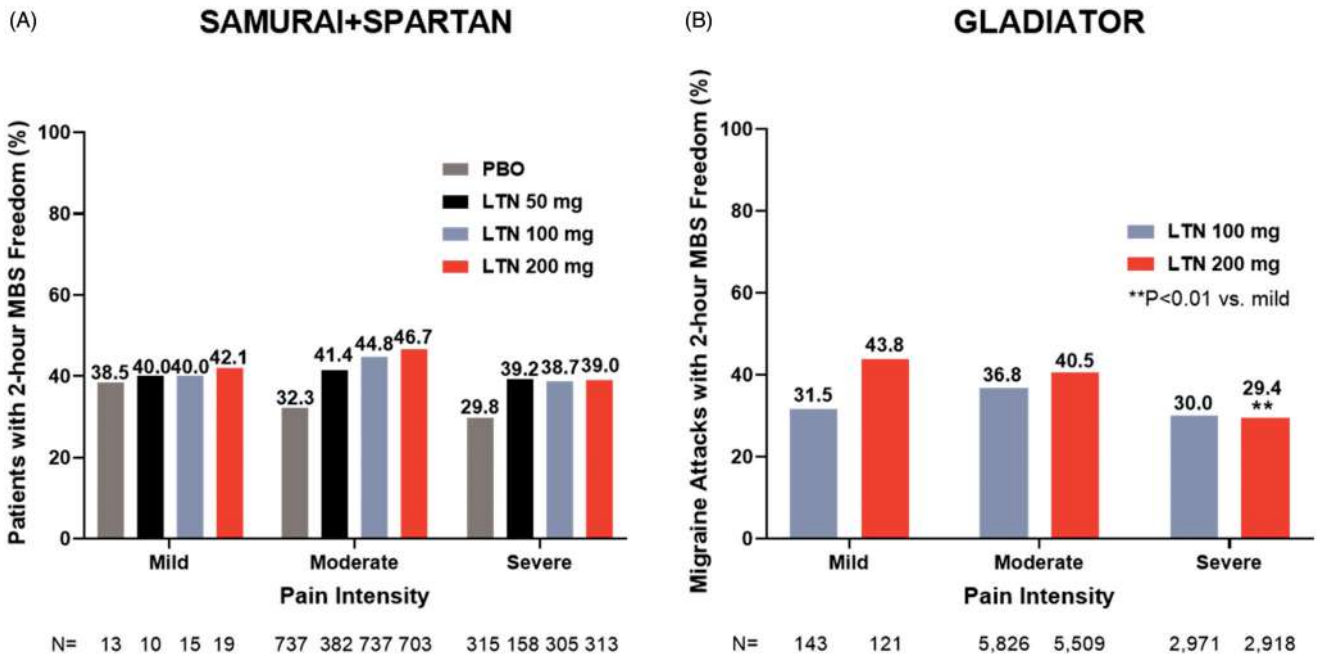

Figure 3. 2-H most bothersome symptom freedom: (A) percentage of study participants in SAMURAI + SPARTAN and (B) percentage of migraine attacks in GLADIATOR. Abbreviations. LTN, lasmiditan; MBS, most bothersome symptom. Panel (A) shows the percentage of participants in SAMURAI + SPARTAN with 2-h MBS freedom, *N = number of study participants* included in the analysis; Panel (B) shows the percentage of migraine attacks in GLADIATOR for which there was 2-h MBS freedom, *N = number of migraine attacks* included in the analysis.

treated with LTN 200 mg ($p = .001$ vs. mild) and 30.0% treated with LTN 100 mg ($p = .709$ vs. mild) (Figure 3(B)).

Twenty four-hour SPF was achieved in 33.1% of mild attacks treated with LTN 200 mg and 19.5% treated with LTN 100 mg compared to 23.6% of moderate attacks treated with LTN 200 mg ($p = .019$ vs. mild) and 19.1% treated with LTN 100 mg ($p = .916$ vs. mild) and 12.7% of severe attacks treated with LTN 200 mg ($p < .001$ vs. mild) and 10.5% treated with LTN 100 mg ($p = .002$ vs. mild) (Figure 4(B)).

Pain freedom, MBS freedom and sustained pain freedom in population who treated ≥1 mild and ≥1 moderate or severe attacks. Of the 1981 ITT participants in GLADIATOR, 149 treated ≥1 mild attack and ≥1 moderate or severe attack. Of the resulting 2016 attacks treated by this sub-population, Supplemental Figure 1 displays the proportion of mild, moderate, and severe attacks with PF, MBS freedom, and SPF. 2-h PF was achieved in a greater proportion of mild attacks (LTN 200 mg [55.3%], LTN 100 mg [32.6%]) compared to moderate (LTN 200 mg [38.9%], $p < .001$ vs. mild; LTN 100 mg [25.6%], $p = .097$ vs. mild) and severe attacks (LTN 200 mg [38.1%], $p = .008$ vs. mild; LTN 100 mg [15.9%]; $p < .001$ vs. mild). 24-h SPF was achieved in 33.3% of mild attacks treated with LTN 200 mg and 19.9% treated with LTN 100 mg compared to 24.5% of moderate attacks treated with LTN 200 mg ($p = .044$ vs. mild) and 15.8% treated with LTN 100 mg ($p = .264$ vs. mild) and 21.4% of severe attacks treated with LTN 200 mg ($p = .046$ vs. mild) and 10.1% treated with LTN 100 mg ($p = .012$ vs. mild). For 2-hr MBS freedom, the proportion of attacks was not statistically significant across pain intensity levels for either dose of LTN.

While participants reported fewer TEAEs in attacks treated at moderate and severe pain intensity, the relative occurrence of TEAEs was similar across groups. Overall, ≥1 TEAE was reported in 16.8%, 14.3%, and 10.2% of mild, moderate, and severe attacks, respectively.

Discussion

In this post-hoc analysis of pooled data from the SAMURAI and SPARTAN trials, response rates for 2-h PF and 24-h SPF were, in general, numerically greater in participants who treated mild attacks with LTN compared to those who treated moderate or severe attacks with LTN. Response rates for 2-h MBS Freedom were similar, regardless of baseline pain at the time of lasmiditan administration. No statistical comparisons between treatment groups were made, however, since a small number of attacks with mild pain were treated in these studies. Therefore, further analyses were conducted using data from the open-label trial, GLADIATOR, which included a larger number of attacks and sufficient power to make statistical comparisons. In GLADIATOR, a significantly greater proportion of mild attacks treated with LTN achieved 2-h PF and 24-h SPF, when compared to the proportion of moderate and severe attacks. These results were confirmed in a sub-population of participants who treated attacks both at mild and at moderate-to-severe pain intensity.

The literature includes data on the benefits of both treating a migraine attack early (utilizing time since the emergence of symptoms) and when pain is mild (which is presumably also "early" in the course of an attack). For example, individuals treated with rizatriptan, almotriptan, and sumatriptan in multiple clinical trials were more likely to report a pain-free response when treatment was administered early in a migraine attack, when pain was mild, rather

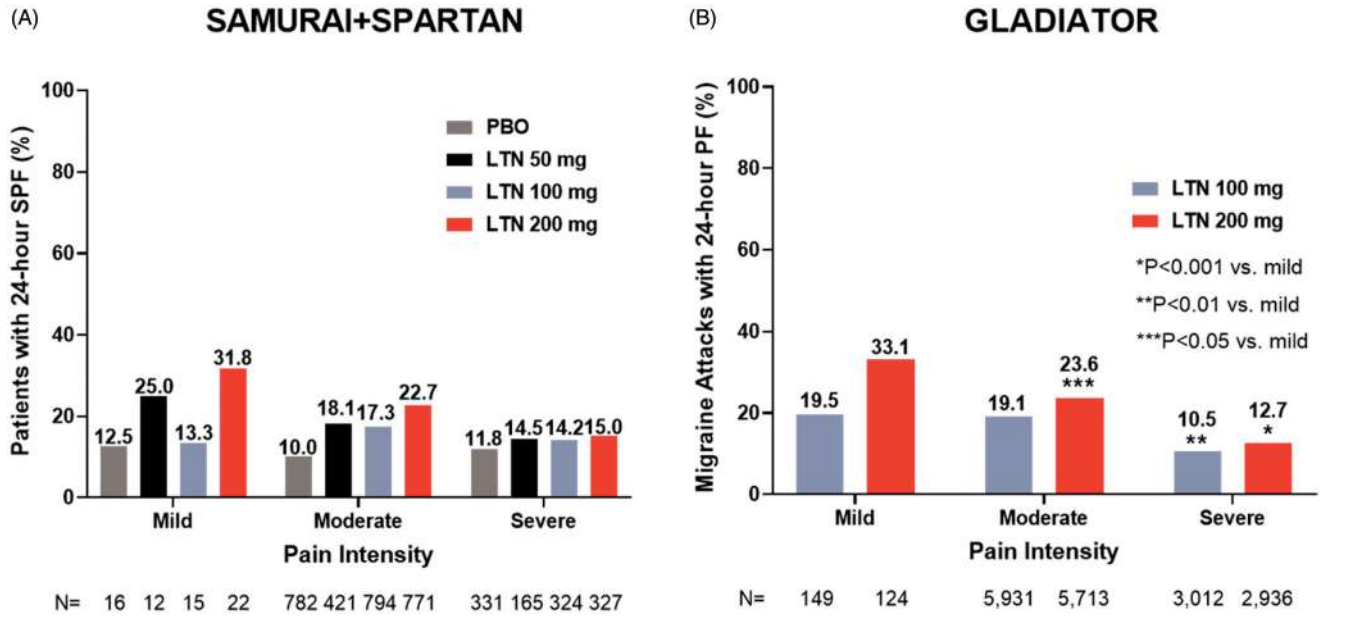

Figure 4. 24-H sustained pain freedom: (A) percentage of study participants in SAMURAI + SPARTAN and (B) percentage of Migraine Attacks in GLADIATOR. Abbreviations. LTN, lasmiditan; SPF, sustained pan freedom. Panel (A) shows the percentage of participants in SAMURAI + SPARTAN with 24-h SPF, *N = number of study participants* included in the analysis; Panel (B) shows the percentage of migraine attacks in GLADIATOR for which there was 24-h SPF, *N = number of migraine attacks* included in the analysis.

Table 2. Characteristics of all migraine attacks (GLADIATOR).[a]

Characteristic	Pain intensity		
	Mild (*N* = 273)	Moderate (*N* = 11,644)	Severe (*N* = 5948)
Attacks treated by dose, *n* (%)			
100 mg	149 (54.6)	5931 (50.9)	3012 (50.6)
200 mg	124 (45.4)	5713 (49.1)	2936 (49.4)
Time to dosing from attack start, hours, mean (SD)	1.2 (3.5)	1.2 (2.4)	1.3 (3.1)
Time to dosing from attack start, *n* (%)			
≤1 h	196 (71.8)	6767 (58.1)	3658 (61.5)
≤2 h	40 (14.7)	2700 (23.2)	1160 (19.5)
>2 h	37 (13.6)	2177 (18.7)	1130 (19.0)
Associated symptoms, *n* (%)			
Nausea	55 (20.1)	3893 (33.4)	3042 (51.1)
Photophobia	168 (61.5)	8317 (71.4)	5014 (84.3)
Phonophobia	134 (49.1)	6431 (55.2)	4425 (74.4)
Vomiting	5 (1.8)	217 (1.9)	391 (6.6)
None	51 (18.7)	1461 (12.5)	272 (4.6)
Migraine-related functional disability, *n* (%)			
None	30 (11.0)	126 (1.1)	30 (0.5)
Mild	201 (73.6)	2716 (23.3)	142 (2.4)
Marked	29 (10.6)	8091 (69.5)	1979 (33.3)
Need complete bed rest	13 (4.8)	711 (6.1)	3797 (63.8)

Abbreviations. *n*, number of participants in specified population; *N*, total number of attacks treated; SD, standard deviation.
[a]*N* = 13 attacks were treated when pain was categorized as "none."

than moderate or severe[22–26]. In accordance, in the SAMURAI and SPARTAN trials, mild attacks were treated earlier (time to dosing from attack start: mean of 24 min) than moderate (110 min) or severe (127 min) attacks. In contrast, mild and moderate attacks in GLADIATOR were treated on average within 72 min and severe attacks within 78 min from attack start. It is more likely that the difference found in GLADIATOR was not due to early treatment, but exclusively to attack intensity.

While studies documenting the natural progression of migraine attack pain intensity are scarce, there is likely a strong correlation between time since onset of symptoms, and pain intensity. These post hoc analyses with LTN provided evidence that, consistent with observations in other treatments, treating early, when pain is mild, is more effective[9]. Thus, observing better efficacy outcomes when treatment was initiated at mild vs. moderate to severe pain is most likely not related to a particular property of LTN and may likely be migraine dependent.

Nearly half of patients delay acute medication intake following an attack onset despite evidence suggesting that treating migraines when pain is mild can result in relatively better outcomes[27]. In this study, participants completed a follow-up questionnaire about the tendency to avoid or delay treatment with a single question, "Do you often avoid or delay taking your migraine medication when you start to experience a migraine attack?". The two most common reasons for avoiding or delaying treatment were "wanting to

wait and see if it is really a migraine attack" (69%) followed by "only want to take medications if it is a severe attack" (46%). A patient's ability to predict a migraine attack "early" may represent an educational opportunity for physicians to advise patients with migraine on how to differentiate migraine from other headache types and about when to use acute migraine medications.

In SAMURAI, SPARTAN, and GLADIATOR, the tolerability of LTN was similar regardless of whether attacks were treated at mild, moderate, and severe pain intensities. In GLADIATOR, there was a trend for a greater proportion of TEAEs reported when pain was mild, but the overall rate of TEAEs was similar across groups. Results from studies that examined the incidence of TEAEs and reporting at mild vs. moderate or severe pain intensities are varied. In a triptan therapy analysis, a reduced incidence of TEAEs was observed when attacks were treated early compared to when treated when pain was moderate or severe[28] and no difference in the incidence of TEAEs for mild vs. moderate or severe attacks was reported in a post hoc analysis of an almotriptan open-label study[25]. This discrepancy may be due to the small sample size included in this analysis. In addition, TEAEs were reported across pain intensity levels at the time of LTN dosing, and independent of pain response. Participants may not have differentiated TEAEs from their migraine-related symptoms. Additional studies would be required to address this further.

There are limitations to consider when interpreting the results of this post-hoc report. All analyses were completed post hoc and the studies were not powered to assess outcomes by baseline pain intensity. As a result of protocol direction (participants were instructed to treat attacks of moderate or severe intensity), the mild intensity pain subgroup was small. This was particularly apparent for SAMURAI and SPARTAN (pooled data), such that statistical comparisons were not feasible in this case. GLADIATOR, a multiple attack study, employed an open-label study design that lacked a placebo control for comparison of both safety and efficacy results. The lack of information as to why participants decided to take medication while pain was mild, despite study instructions, is a possible limitation; reasons may have influenced the efficacy and tolerability results. The focus of this analysis was pain intensity, while in a real world setting, migraine severity is influenced by symptoms beyond head pain, for example photophobia, phonophobia, and nausea.

In conclusion, previous studies have shown a greater benefit of LTN over placebo in treating moderate to severe migraine attacks. The present results add to the understanding of LTN's efficacy by demonstrating that treating migraine attacks of mild pain intensity with LTN resulted in relatively better efficacy outcomes, suggesting that earlier dosing (when pain is mild) is beneficial. Further research is needed to better understand the relationship of LTN outcomes to the time of administration in the course of migraine attacks.

Note

i. SAS Institute, Cary, NC, USA.

Transparency

Declaration of funding

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