


## Research Submission

# Onset of Efficacy Following Oral Treatment With Lasmiditan for the Acute Treatment of Migraine: Integrated Results From 2 Randomized Double-Blind Placebo-Controlled Phase 3 Clinical Studies

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**Objective.**—To expand on available information on the efficacy of oral lasmiditan for the acute treatment of migraine with particular focus on the timing of the effect and on its impact on migraine-associated symptoms.

**Background.**—Lasmiditan is a novel selective 5-hydroxytryptamine 1F receptor agonist that lacks vasoconstrictive activity. In 2 phase 3 studies, SAMURAI and SPARTAN, lasmiditan met primary and key secondary efficacy endpoints at 2 hours following initial dose.

**Methods.**—Integrated analyses were completed from 2 phase 3 clinical trials, SPARTAN and SAMURAI. Baseline data and data collected every 30 minutes up to 2 hours after taking lasmiditan (50, 100, or 200 mg) or placebo were analyzed to determine the onset of efficacy. A total of 5236 patients were randomized to be treated with placebo (N = 1493), lasmiditan 50 mg (N = 750), lasmiditan 100 mg (N = 1498), or lasmiditan 200 mg (N = 1495). Data were analyzed to determine the onset of improvement for the following efficacy measures: pain freedom, most bothersome symptom freedom, pain relief, freedom from associated individual symptoms (photophobia, phonophobia, or nausea), total migraine freedom (defined as pain freedom and freedom from associated symptoms), and freedom from migraine-related functional disability. Time to meaningful headache relief and time to first become pain free were also analyzed.

**Results.**—Significantly higher rates of pain freedom (100 mg, 10.0%,  $P = .012$ ; 200 mg, 15.5%,  $P < .001$ ; Placebo, 7.0%) and total migraine freedom (100 mg, 8.9%,  $P = .017$ ; 200 mg, 12.4%,  $P < .001$ ; Placebo, 6.1%) were achieved starting at 60 minutes in 100- and 200-mg lasmiditan-treated groups compared with placebo group. Rates of freedom from most bothersome symptom (100 mg, 11.1%,  $P = .015$ ; 200 mg, 13.0%,  $P < .001$ ; Placebo, 7.9%), and pain relief (100 mg, 17.5%,  $P = .007$ ; 200 mg, 19.1%,  $P < .001$ ; Placebo, 13.4%) were significantly higher starting as early as 30 minutes in lasmiditan 100- and 200-mg lasmiditan-treated groups. A significantly higher percentage of patients in the 200-mg lasmiditan-treated group achieved freedom from photophobia (13.7%,  $P = .005$ ; Placebo, 9.2%) and phonophobia (17.4%,  $P = .042$ ; Placebo, 13.4%) starting at 30 minutes. A significantly greater proportion of patients in the 200-mg lasmiditan-treated group achieved freedom from migraine-related functional disability starting at 60 minutes (16.4%,  $P < .001$ ; Placebo, 11.1%). All efficacy measures, except for freedom from nausea, were statistically significant after lasmiditan treatment (50, 100, or 200 mg) compared with

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placebo at 90 and 120 minutes. Finally, patients taking lasmiditan had a higher likelihood of achieving meaningful headache relief and becoming headache pain free within 24 hours compared with those taking placebo ( $P < .001$ ).

**Conclusions.**—Patients treated with lasmiditan for a migraine attack reported an earlier onset of efficacy compared with those treated with placebo. Some of the efficacy measures such as pain relief demonstrated improvement as early as the first assessment at 30 minutes after 100- or 200-mg lasmiditan treatment.

**Key words:** lasmiditan, migraine, onset of efficacy, onset of response, acute treatment, ditan class

**Abbreviations:** 5-HT 5-hydroxytryptamine, eDiary electronic diary, MBS most bothersome symptom, mITT modified ITT, OR odds ratio, TMF total migraine freedom

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## INTRODUCTION

Early relief of migraine symptoms and related disability are among the most important and widely measured benefits of acute migraine treatment.<sup>1-3</sup> This has been demonstrated in surveys of patients and their clinicians about treatment needs, multi-attribute decision modeling, and post hoc analysis of clinical trial data examining predictors of satisfaction with treatment and willingness-to-pay methods.<sup>3-5</sup> Studies assessing patients' preference for migraine medication efficacy highlight their desire to have an onset of response as early as 30 minutes after an orally administered treatment. Moreover, earlier freedom from migraine-associated symptoms (phonophobia, photophobia, nausea, and vomiting) after treatment is also desired.<sup>3,6</sup>

Triptans are a class of serotonin 5-hydroxytryptamine 1B/1D (5-HT<sub>1B/1D</sub>) receptor agonists primarily prescribed for the acute treatment of migraine and represent 28-36% of prescribed medications for the acute treatment of migraine.<sup>7,8</sup> Triptans are not efficacious for all patients.<sup>9</sup> Rates of pain freedom at 2 hours after dose with triptans in a meta-analysis are between 20 and 40%.<sup>9</sup> Although the introduction of triptans improved the acute treatment of migraine, this class of medication

is not suitable for all patients with migraine. Triptans have been known to cause vasoconstriction; therefore, they are contraindicated in patients with cardiovascular disease and carry warnings and precautions for patients with the risk of cardiovascular disease.<sup>10</sup>

Lasmiditan (LY573144) is a novel therapeutic agent designated as a “ditan” in development for the acute treatment of migraine.<sup>11</sup> The chemical structure and 5-HT receptor-binding profile of lasmiditan are different from that of triptans, making lasmiditan a different class of treatment.<sup>12</sup> Lasmiditan has high affinity and selectivity for 5-HT<sub>1F</sub> receptors and lacks the vasoconstrictor activity inherent with triptans.<sup>13</sup> Lasmiditan efficacy and safety are supported by data from the phase 2 and phase 3 studies.<sup>14-18</sup> Both phase 3 studies, SAMURAI and SPARTAN, met primary and key secondary efficacy endpoints of statistically significantly higher percentage of lasmiditan-treated patients being migraine pain free and having freedom from their most bothersome symptom (MBS) at 2 hours following their initial dose compared with patients treated with placebo.<sup>16,17</sup>

Given the disability associated with the attacks and the patients' needs, it is important to evaluate all meaningful efficacy outcomes for acute treatment and

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the time to achieve those outcomes. To provide comprehensive assessment of lasmiditan efficacy in treating acute migraine attacks, we analyzed the integrated data to evaluate the onset of pain freedom, pain relief, freedom from migraine-associated symptoms (photophobia, phonophobia, or nausea), MBS freedom, total migraine freedom (TMF), patient reported freedom from migraine-related functional disability, and patient reported time to meaningful headache relief and time to first become headache pain free.<sup>19,20</sup> We hypothesized that oral lasmiditan would demonstrate earlier onset of efficacy than the prespecified 2-hour time point for all proposed endpoints.

## METHODS

**Study Design.**—Data from 2 phase 3 studies (SAMURAI [27 April 2015-12 August 2016] and SPARTAN [19 May 2016-29 June 2017]) were integrated for this report. Detailed descriptions of the study design for both studies have been reported separately.<sup>16,17</sup> Briefly, SAMURAI and SPARTAN were randomized, double-blind, placebo-controlled trials investigating a single migraine attack. SAMURAI evaluated 2 doses of lasmiditan (100 and 200 mg); SPARTAN evaluated 3 doses (50, 100, and 200 mg). Patients were randomized to either treatment or placebo (1:1:1 and 1:1:1:1, respectively). Patients were asked to treat a single migraine attack within 4 hours of onset of headache (if the headache severity was at least moderate at that time and not improving) within 8 weeks of enrollment.

**Trial Population.**—Studies SAMURAI and SPARTAN were conducted in patients aged 18 years or older, diagnosed with migraine based on the International Classification of Headache Disorders-II, with a history of migraine for at least 1 year, and with migraine onset before the age of 50. Eligible participants had to experience 3-8 migraine attacks per month (<15 headache days per month) during the baseline period. Participants were also required to have a Migraine Disability Assessment score  $\geq 11$ . Patients on stable doses of concomitant migraine preventive medications were allowed in the studies. Patients with cardiovascular risk factors were permitted in both the studies. Further inclusion and exclusion criteria have been discussed previously.<sup>16,17</sup> The participating sites for the studies were located in the United States, the United

Kingdom, and Germany. Subjects were randomized through a central randomization process by Interactive Response Technology during screening/Visit 1.

**Outcome Measures.**—Electronic diary (eDiary) was used to collect data at baseline and at 30-minute intervals up to 48 hours after treatment. The analyses presented used data collected at baseline, and data collected at 30, 60, 90, and 120 minutes after treatment. The intent-to-treat (ITT) population included all randomized patients who took at least 1 dose of study drug and had any post-dose headache severity or symptom assessments. The modified ITT (mITT) population included all ITT patients who treated a migraine attack within 4 hours of migraine attack onset. The mITT population data were used to perform all analyses, except for pain relief. Even though patients were asked to take the medication if their headache severity was at least moderate, 1.7% of patients who reported taking the medication while experiencing mild headache were also included in the analyses.

The efficacy outcomes evaluated were pain freedom, pain relief, freedom from MBS, freedom from other migraine-associated symptoms (photophobia, phonophobia, or nausea), patient-reported freedom from migraine-related functional disability, TMF, time to meaningful headache relief, and time to first become headache pain free. Patients recorded migraine headache pain using a 4-point International Headache Society pain severity rating scale (none, mild pain, moderate pain, and severe pain). Pain freedom was defined as a reduction in pain severity from mild, moderate, or severe at baseline to none at the specified time point. Pain relief was defined as experiencing moderate or severe pain at baseline that became mild or none, or mild pain at baseline that became none at the summarized time point.<sup>1,17</sup> The presence or absence of migraine-associated symptoms (photophobia, phonophobia, and nausea) was recorded at baseline. Freedom from these associated symptoms at summarized time points was analyzed in patients who reported the respective symptom at baseline. In addition, patients were instructed to record their selection of which of the accompanying symptoms (nausea, phonophobia, and/or photophobia) was the MBS. Freedom from MBS was defined as the absence of the selected MBS at subsequent time points. The patients were defined as having TMF at a

given time point if they were experiencing pain freedom and not experiencing any other migraine symptoms (ie, not experiencing nausea, photophobia, or phonophobia).<sup>21</sup> This measurement better addresses the patient's needs to be free from all migraine symptoms, not only headache pain. The degree of migraine-related functional disability was recorded in the eDiary as the response to "How much is your migraine interfering with your normal activities?". Responses were recorded on a 4-point numeric rating scale: not at all, mild interference, marked interference, and need complete bed rest.<sup>16</sup> Freedom from migraine-related functional disability was defined as having disability "None" at a given time point.

In addition, participants were asked to record in the eDiary the time at which headache relief became meaningful and time they became headache pain free. Patients were asked, "Has headache relief become meaningful?" (responded with "Yes" or "No"). If the patients responded "Yes" they were asked "Have you been headache pain free?" (responded with "Yes" or "No"). Patients censored were those that did not report experiencing the event of interest after treatment and did not use the eDiary within 24 hours after treatment. These patients were censored at their time of last-reported eDiary use. Finally, for these analyses, subjects were censored at 24 hours if they reported experiencing the event of interest more than 24 hours after taking the treatment or did not report experiencing this event.

**Statistical Analysis.**—Odds ratios (ORs) were used to quantify association between the efficacy measures of interest and lasmiditan treatment. For comparisons between treatment groups, the OR, its *P* value, and asymptotic confidence interval were calculated from a 2-sided test from a logistic regression model with treatment group, study, and background use of migraine preventive medication as covariates. Due to post hoc nature of these analyses, *P* values are reported without multiplicity correction. A *P* value <.05 was considered statistically significant. The sample size estimation for each study has been published previously.<sup>16,17</sup> Additionally, the number needed to treat (NNT) was calculated for several endpoints. NNTs were calculated as the inverse of the difference between the odds ratios of lasmiditan and placebo treatment arms at 2 hours post dose.

For pain freedom, pain relief, freedom from MBS, and freedom from other migraine-associated symptoms (photophobia, phonophobia, or nausea) endpoints denominators for calculating percentages are the counts of symptomatic subjects, defined as those experiencing the symptoms of interest at baseline. Denominators for calculating onset of TMF percentages are the counts of subjects with mild, moderate, or severe headache pain recorded at the time of dosing. Denominators for calculating migraine-related functional disability percentages are the counts of subjects in the mITT population for each treatment arm. Patients with missing data were treated as nonresponders for their missing time point values.

Output from SAS PROC LIFETEST Kaplan-Meier product limit method was used for plotting the cumulative probability curves in the time to meaningful headache relief, and time to first become headache pain-free figures. A stratified log-rank test for homogeneity of the curves stratified by treatment was conducted for each time to event endpoint.

SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC) statistical package was used for analyses.

All authors had full access to all study data and had final responsibility for the decision to submit for publication.

**Ethical Conduct of the Studies.**—These studies were reviewed and approved by appropriate institutional review boards and were conducted according to the Declaration of Helsinki. The participants signed an informed consent document approved by each study site's independent ethics committee or institutional review board before any study-related procedures were performed.

## RESULTS

**Patient Demographics and Baseline Disease Characteristics.**—The study population (all randomized patients) included patients with an average age of 42 years, mostly female (83%), and white (77%) (Table 1). The composition of the study population was similar to that of the U.S. population in terms of race and ethnicity (white, 77%; black, 19%; Hispanic, 18%). A total of 5236 patients were randomized to be treated with placebo (N = 1493), lasmiditan 50 mg (N = 750), lasmiditan 100 mg (N = 1498), or

Table 1.—Patient Demographics and Baseline Disease Characteristics

	SAMURAI (N = 2231)	SPARTAN (N = 3005)	Pooled (N = 5236)
Age, mean (SD)	42 (12.17)	42 (12.93)	42 (12.62)
% Female	82.6	83.7	83.2
% Caucasian	74.4	78.9	77.1
% Black	20.4	17.4	18.7
Ethnicity, n (%)			
Hispanic or Latino	303 (13.6)	610 (20.3)	913 (17.5)
Not Hispanic or Latino	1913 (85.70)	2373 (79.00)	4286 (82.0)
Not reported	13 (0.6)	10 (0.3)	23 (0.4)
Unknown	2 (0.1)	5 (0.2)	7 (0.1)
Duration of migraine history, years, mean (SD)	18.9 (13.02)	18.1 (12.97)	18.46 (13.0)
Migraines per month in past 3 months, mean (SD)	5.1 (1.89)	5.3 (2.06)	5.2 (1.99)
MIDAS total score, mean (SD)	31.3 (22.33)	32.5 (23.57)	31.94 (22.79)
Days with headache in past 3 months, mean (SD)	17.3 (10.76)	17.4 (10.46)	17.39 (10.41)
Baseline-associated symptoms, n (%)	N = 1545	N = 2156	N = 3701
Photophobia	1193 (77.2)	1649 (76.5)	2842 (76.8)
Phonophobia	952 (61.6)	1354 (62.8)	2306 (62.3)
Nausea	663 (42.9)	948 (44.0)	1611 (43.5)
Baseline-associated symptoms identified as MBS, n (%)	N = 1545	N = 2156	N = 3701
Photophobia	773 (50.0)	1090 (50.6)	1863 (50.3)
Phonophobia	317 (20.5)	447 (20.7)	764 (20.6)
Nausea	348 (22.5)	472 (21.9)	820 (22.2)

Duration of migraine history and frequency of migraine attacks in the last 3 months were measured from the date of Visit 1. MIDAS total score is calculated as the sum of the answers to the 5 questions on the MIDAS questionnaire.

MBS = most bothersome symptom; MIDAS = Migraine Disability Assessment; n = number of patients within each specific category; N = total number of patients; SD = standard deviation.

lasmiditan 200 mg (N = 1495). A total of 1301 patients treated with placebo and 3235 patients treated with lasmiditan completed the study. The baseline disease characteristics are presented in Table 1. All baseline disease characteristics had a similar percentage of patients in each study.

**Pain Freedom and Pain Relief.**—A significantly higher percentage of patients treated with 100- and 200-mg lasmiditan achieved pain freedom 60 minutes after treatment compared with the placebo group (Placebo, 7.0%; 100 mg, 10.0%,  $P = .012$ ; 200 mg, 15.5%,  $P < .001$ ; Fig. 1 and Table 2). Patients treated with 50-mg lasmiditan achieved pain freedom 90 minutes after treatment (Placebo, 11.9%; 50 mg, 18.0%,  $P = .012$ ). The NNT to achieve pain freedom 120 minutes after treatment and relative to placebo for 50 mg is 10, 9 for 100 mg, and 6 for 200 mg. As early as 30 minutes after treatment with lasmiditan 100 and 200 mg, a significantly higher percentage of patients achieved pain relief (Placebo, 13.4%; 100 mg, 17.5%,

$P = .007$ ; 200 mg, 19.1%,  $P = .001$ ; Fig. 1 and Table 2), while treatment with 50 mg of lasmiditan achieved pain relief at 60 minutes compared with patients in the placebo group (Placebo 30.6%; 50 mg, 37.3%,  $P = .023$ ). The NNT to achieve pain relief 120 minutes after treatment and relative to placebo for 50 mg is 7, 6 for 100 mg, and 6 for 200 mg.

There was a significant difference in onset of pain freedom and pain relief between lasmiditan dose groups. Patients treated with 200-mg lasmiditan experienced a significant pain freedom 60 minutes after treatment compared with 50- and 100-mg lasmiditan-treated groups (50 mg,  $P < .001$ , OR = 2.59 [1.78, 3.78]; 100 mg,  $P < .001$ , OR = 1.65 [1.26, 2.14]). Pain relief was experienced by 200-mg lasmiditan-treated patients 60 minutes after treatment compared with 50-mg lasmiditan-treated patients, whereas there was no difference with 100-mg lasmiditan-treated patients (50 mg,  $P < .001$ , OR = 1.46 [1.18, 1.81]).

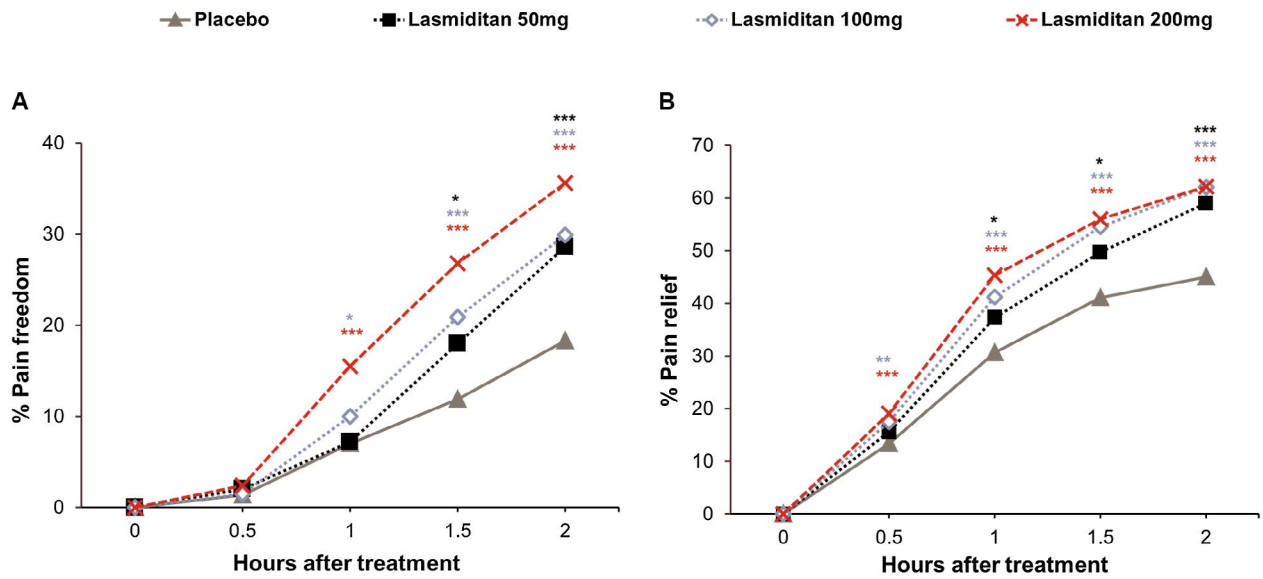


Fig. 1.—Percentage of patients experiencing (A) pain freedom and (B) pain relief. \*\*\* $P \leq .001$ ; \*\* $P \leq .01$ ; \* $P \leq .05$  vs placebo. [Color figure can be viewed at wileyonlinelibrary.com]

Table 2.—Odds Ratio of Patients Experiencing Pain Freedom and Pain Relief

	Time After Dose (min)	Placebo		LTN 50 mg		LTN 100 mg		LTN 200 mg	
		n	%	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Pain freedom		N = 1063		N = 556		N = 1035		N = 1046	
	30	15	1.4	11	1.38 (0.60, 3.15)	16	1.10 (0.54, 2.23)	25	1.71 (0.90, 3.27)
	60	74	7.0	40	0.94 (0.63, 1.43)	104	1.49 (1.09, 2.03)***	162	2.45 (1.83, 3.27)*
	90	127	11.9	100	1.46 (1.09, 1.97)***	216	1.94 (1.53, 2.46)*	280	2.70 (2.14, 3.40)*
	120	195	18.3	159	1.57 (1.22, 2.02)*	309	1.89 (1.54, 2.33)*	372	2.47 (2.02, 3.02)*
Pain relief		N = 1129		N = 598		N = 1133		N = 1120	
	30	151	13.4	93	1.21 (0.90, 1.62)	198	1.37 (1.09, 1.72)**	214	1.53 (1.22, 1.92)*
	60	346	30.6	223	1.29 (1.04, 1.61)***	467	1.59 (1.33, 1.89)*	509	1.89 (1.59, 2.24)*
	90	464	41.1	297	1.31 (1.07, 1.62)***	619	1.73 (1.46, 2.04)*	627	1.83 (1.54, 2.16)*
	120	508	45.0	353	1.58 (1.27, 1.95)*	704	2.01 (1.70, 2.38)*	697	2.02 (1.71, 2.40)*

\* $P < .001$ .

\*\* $P < .01$ .

\*\*\* $P < .05$  compared with placebo.

CI = confidence interval; LTN = lasmiditan; min = minutes; n = number of patients within each specific category; N = total number of patients; OR = odds ratio.

**Migraine-Associated Symptoms and Most Bothersome Symptom Freedom.**—The results for freedom from migraine-associated symptoms and MBS are presented in Fig. 2 and Table 3. As early as 30 minutes after dosing, patients treated with 200-mg lasmiditan achieved a significant photophobia freedom compared

with placebo (Placebo, 9.2%; 200 mg, 13.7%,  $P = .005$ ). Patients treated with 50- and 100-mg lasmiditan achieved photophobia freedom 60 minutes after dosing compared with placebo (Placebo, 18.0%; 50 mg, 23.7%,  $P = .045$ ; 100 mg, 28.7%,  $P < .001$ ). Patients treated with 200, and 100 mg achieved phonophobia

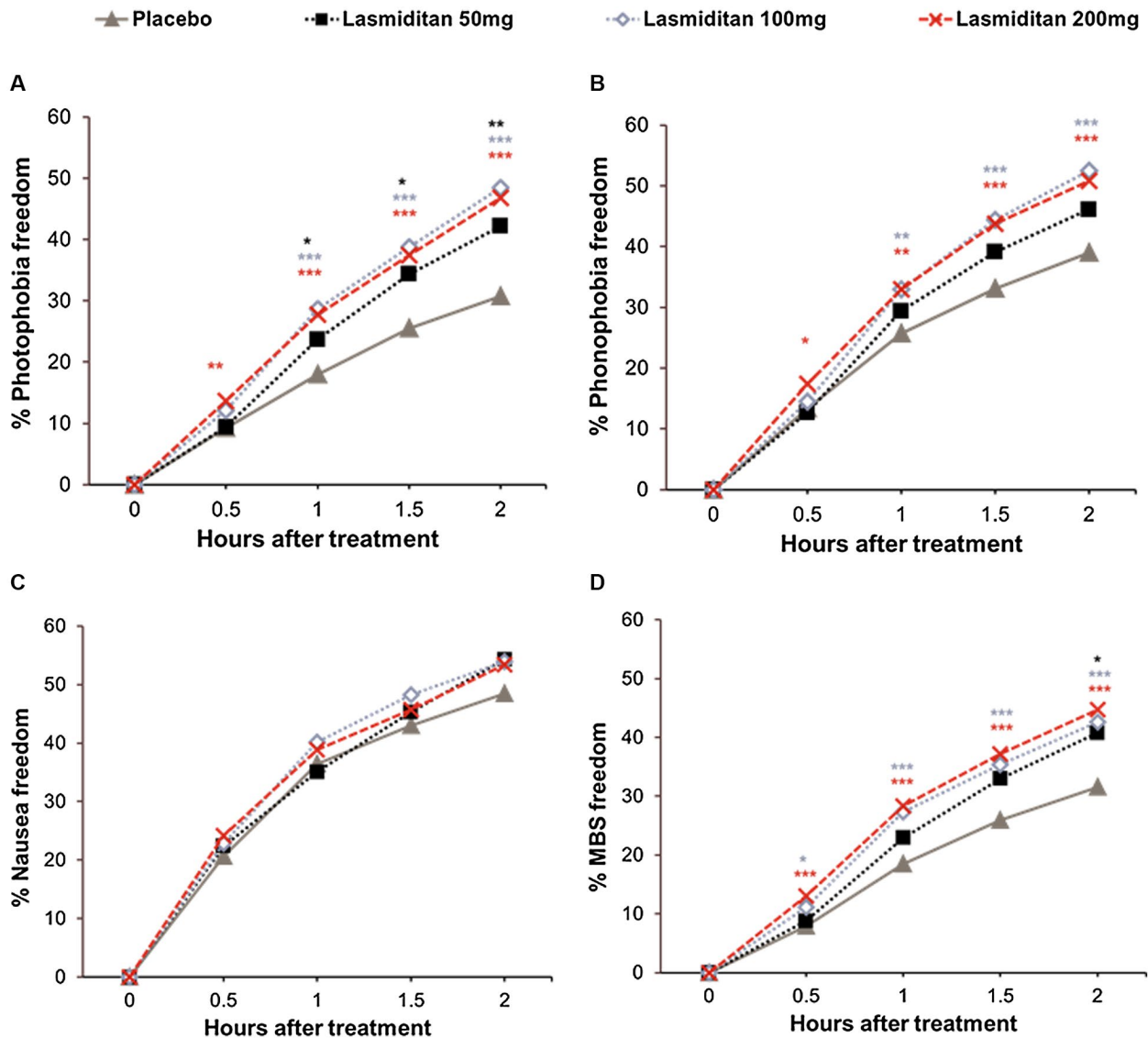


Fig. 2.—Percentage of patients experiencing freedom from (A) photophobia, (B) phonophobia, (C) nausea, and (D) MBS. \*\*\* $P \leq .001$ , \*\* $P \leq .01$ , \* $P \leq .05$  vs placebo. MBS = most bothersome symptom (nausea, phonophobia, and/or photophobia) selected by the patient. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

freedom 30 and 60 minutes after dosing, respectively, relative to placebo (Placebo 13.4%, 200 mg, 17.4%,  $P = .042$ ; Placebo 25.7%, 100 mg, 33.0%,  $P = .004$ ). None of the treatment groups achieved a significant freedom from nausea. Comparison among lasmiditan-treated groups showed a significance in achieving photophobia freedom in patients treated with 200- and 100-mg lasmiditan, compared with 50-mg treatment group, 30 and 60 minutes after treatment, respectively (200 mg,  $P = .015$ , OR = 1.65 [1.10, 2.46]; 100 mg,  $P = .044$ , OR = 1.34 [1.01, 1.79]). There was no

difference among lasmiditan-treated groups in regard to phonophobia freedom.

A significantly higher percentage of patients treated with 100- and 200-mg lasmiditan achieved freedom from MBS 30 minutes after treatment relative to placebo (Placebo 7.9%; 100 mg, 11.1%,  $P = .015$ ; 200 mg, 13.0%,  $P < .001$ ). Patients treated with 50-mg lasmiditan achieved freedom from MBS at 120 minutes (Placebo 31.5%; 50 mg, 40.8%,  $P = .012$ ). The NNT to achieve freedom from MBS 120 minutes after

Table 3.—Odds Ratio of Patients Experiencing Freedom From Photophobia, Phonophobia, Nausea, and MBS

Time After Dose (min)	Placebo		LTN 50 mg		LTN 100 mg		LTN 200 mg	
	n	%	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
	N = 835		N = 427		N = 648		N = 788	
Freedom from photophobia								
30	77	9.2	40	0.95 (0.62, 1.44)	96	1.36 (0.99, 1.86)	108	1.57 (1.15, 2.14)**
60	150	18.0	101	1.36 (1.01, 1.83)***	227	1.82 (1.44, 2.31)*	219	1.75 (1.39, 2.22)*
90	213	25.5	147	1.40 (1.07, 1.83)***	307	1.84 (1.49, 2.27)*	295	1.75 (1.41, 2.16)*
120	256	30.7	180	1.51 (1.17, 1.95)**	384	2.12 (1.73, 2.59)*	369	1.98 (1.62, 2.43)*
	N = 680		N = 330		N = 648		N = 648	
Freedom from phonophobia								
30	91	13.4	42	0.91 (0.60, 1.37)	94	1.09 (0.80, 1.49)	113	1.37 (1.01, 1.84)***
60	175	25.7	97	1.12 (0.82, 1.52)	214	1.41 (1.11, 1.79)**	214	1.42 (1.12, 1.80)**
90	225	33.1	129	1.18 (0.88, 1.57)	288	1.61 (1.29, 2.01)*	284	1.58 (1.26, 1.98)*
120	265	39.0	152	1.18 (0.89, 1.56)	340	1.72 (1.38, 2.14)*	329	1.62 (1.30, 2.02)*
	N = 470		N = 245		N = 445		N = 451	
Freedom from nausea								
30	97	20.6	55	1.06 (0.71, 1.57)	102	1.15 (0.84, 1.57)	109	1.23 (0.90, 1.68)
60	171	36.4	86	0.85 (0.60, 1.19)	179	1.17 (0.90, 1.54)	175	1.12 (0.86, 1.46)
90	202	43.0	111	0.96 (0.69, 1.33)	215	1.24 (0.95, 1.61)	206	1.13 (0.87, 1.47)
120	228	48.5	133	1.07 (0.78, 1.49)	240	1.24 (0.96, 1.61)	241	1.24 (0.95, 1.61)
	N = 1002		N = 512		N = 969		N = 964	
Freedom from MBS								
30	79	7.9	45	1.16 (0.78, 1.74)	108	1.46 (1.08, 1.98)***	125	1.74 (1.29, 2.34)*
60	185	18.5	117	1.25 (0.95, 1.64)	265	1.66 (1.34, 2.05)*	273	1.74 (1.41, 2.15)*
90	260	25.9	169	1.27 (1.00, 1.62)	343	1.56 (1.28, 1.89)*	359	1.69 (1.40, 2.05)*
120	316	31.5	209	1.34 (1.07, 1.70)***	413	1.61 (1.33, 1.93)*	431	1.76 (1.46, 2.11)*

\*  $P < .001$ .

\*\*  $P < .01$ .

\*\*\*  $P \leq .05$  compared with placebo.

CI = confidence interval; LTN = lasmiditan; MBS = most bothersome symptom; min = minutes; n = number of patients within each specific category; N = total number of patients; OR = odds ratio.



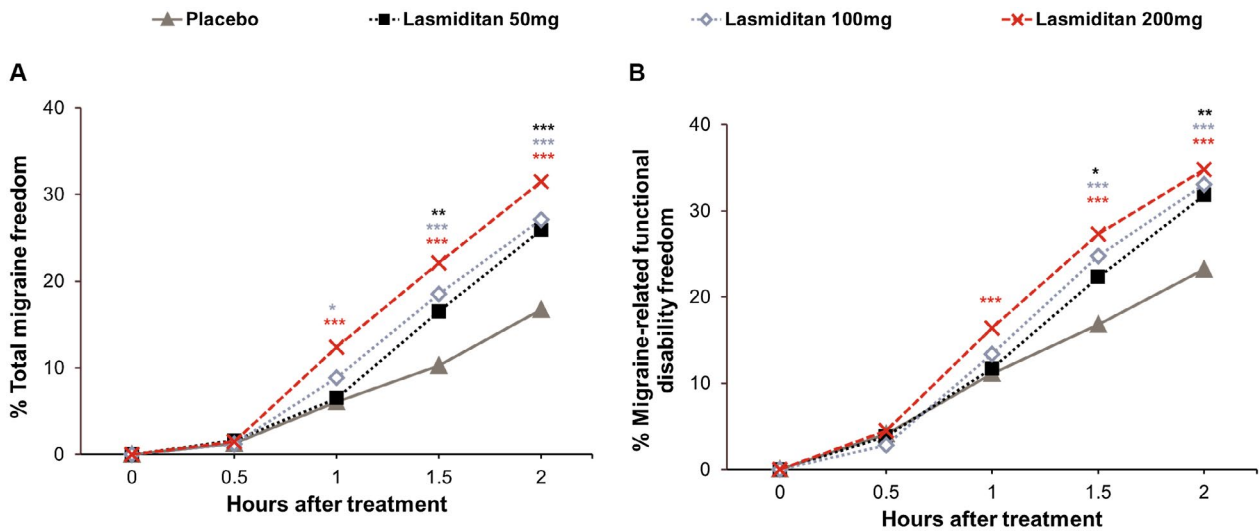


Fig. 3.—Percentage of patients (A) Experiencing total migraine freedom and (B) Freedom from migraine-related functional disability. \*\*\* $P \leq .001$ , \*\* $P \leq .01$ , \* $P \leq .05$  vs placebo. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

treatment and relative to placebo for 50 mg is 11, 9 for 100 mg, and 8 for 200 mg.

**Total Migraine Freedom.**—TMF was achieved by patients receiving 100- and 200-mg lasmiditan 60 minutes after treatment compared with patients in the placebo group (Placebo, 6.1%; 100 mg, 8.9%,  $P = .017$ ; 200 mg, 12.4%,  $P < .001$ ; Fig. 3 and Table 4). Patients treated with 50-mg lasmiditan achieved TMF 90 minutes after treatment (Placebo 10.3%; 50 mg, 16.5%,  $P = .002$ ; Fig. 3 and Table 4). The NNT to achieve TMF 120 minutes after treatment and relative to placebo for 50 mg is 11, 10 for 100 mg, and 7 for 200 mg. Comparison among lasmiditan-treated groups showed that patients treated with 200 mg of lasmiditan were more likely to achieve TMF at 60 minutes after treatment compared with patients treated with 50- and 100-mg lasmiditan (50 mg,  $P < .001$ , OR = 2.23 [1.49, 3.33]; 100 mg,  $P = .009$ , OR = 1.46 [1.10, 1.93]).

**Freedom From Migraine-Related Functional Disability.**—Patients treated with 200 mg of lasmiditan achieved freedom from migraine-related functional disability 60 minutes after treatment (Placebo, 11.1%; 200 mg, 16.4%,  $P < .001$ ; Fig. 3 and Table 4), while patients treated with 50- and 100-mg lasmiditan achieved freedom from migraine-related functional disability 90 minutes after treatment compared with patients who received placebo (Placebo, 16.8%; 50 mg, 22.3%,  $P = .031$ ; 100 mg, 24.8%,  $P < .001$ ; Table 4).

Comparison among lasmiditan-treated groups showed that patients treated with 200 mg of lasmiditan were more likely to achieve freedom from migraine-related functional disability 60 minutes after treatment compared with the 50-mg treatment group ( $P = .019$ , OR = 1.47 [1.07, 2.03]).

**Time to Meaningful Headache Relief and Time to Become Headache Pain Free.**—The cumulative probability of achieving meaningful headache relief was higher for patients in all lasmiditan-treated groups compared with placebo 24 hours after treatment (Fig. 4,  $P < .001$ ). The time to become headache pain free after treatment was reduced in lasmiditan-treated patients compared with placebo within 24 hours after treatment for all lasmiditan-treated groups (Fig. 5,  $P < .001$ ). A dose-response was observed with a greater probability of reaching meaningful headache relief and becoming headache pain free when treated with higher doses of lasmiditan.

## DISCUSSION

In this integrated report of efficacy from 2 clinical studies, we have presented data showing that patients treated with lasmiditan for a single migraine attack reported an earlier onset of efficacy compared with patients who received placebo in measures of pain freedom, freedom from MBS, pain relief, photophobia freedom, phonophobia freedom, TMF, freedom from

**Table 4.—Odds Ratio of Patients Experiencing Total Migraine Freedom and Freedom From Migraine-Related Functional Disability**

Time After Dose (min)	Placebo		LTN 50 mg		LTN 100 mg		LTN 200 mg	
	n	%	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
	N = 1063		N = 556		N = 1035		N = 1046	
Total migraine freedom	14	1.3	9	1.25 (0.51, 3.07)	12	0.88 (0.40, 1.91)	16	1.17 (0.57, 2.40)
	65	6.1	36	0.98 (0.63, 1.51)	92	1.49 (1.07, 2.08)***	130	2.18 (1.60, 2.97)*
	110	10.3	92	1.62 (1.19, 2.22)**	191	1.96 (1.52, 2.52)*	231	2.45 (1.92, 3.14)*
	177	16.7	144	1.55 (1.20, 2.02)*	280	1.86 (1.50, 2.29)*	330	2.31 (1.88, 2.85)*
Freedom from migraine-related disability	44	4.1	21	0.96 (0.55, 1.68)	29	0.67 (0.41, 1.08)	47	1.09 (0.72, 1.66)
	118	11.1	65	1.07 (0.76, 1.50)	139	1.24 (0.96, 1.61)	172	1.58 (1.23, 2.03)*
	179	16.8	124	1.35 (1.03, 1.76)***	257	1.63 (1.32, 2.02)*	286	1.86 (1.51, 2.30)*
	247	23.2	177	1.41 (1.11, 1.79)**	343	1.64 (1.35, 1.99)*	364	1.77 (1.46, 2.14)*

\*  $P < .001$ .

\*\*  $P < .01$ .

\*\*\*  $P \leq .05$  compared with placebo.

CI = confidence interval; LTN = lasmiditan; min = minutes; n = number of patients within each specific category; N = total number of patients; OR = odds ratio.

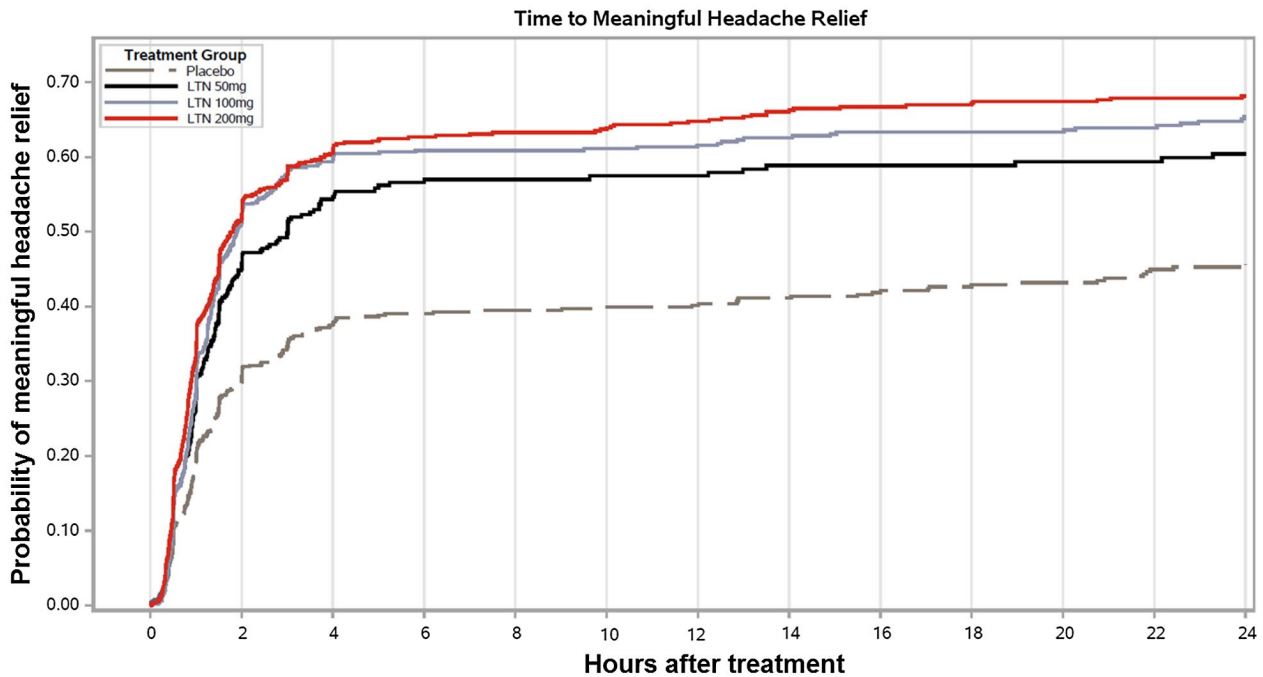


Fig. 4.—Time to meaningful headache relief: Cumulative probability of experiencing meaningful headache relief after treatment. [Color figure can be viewed at wileyonlinelibrary.com]

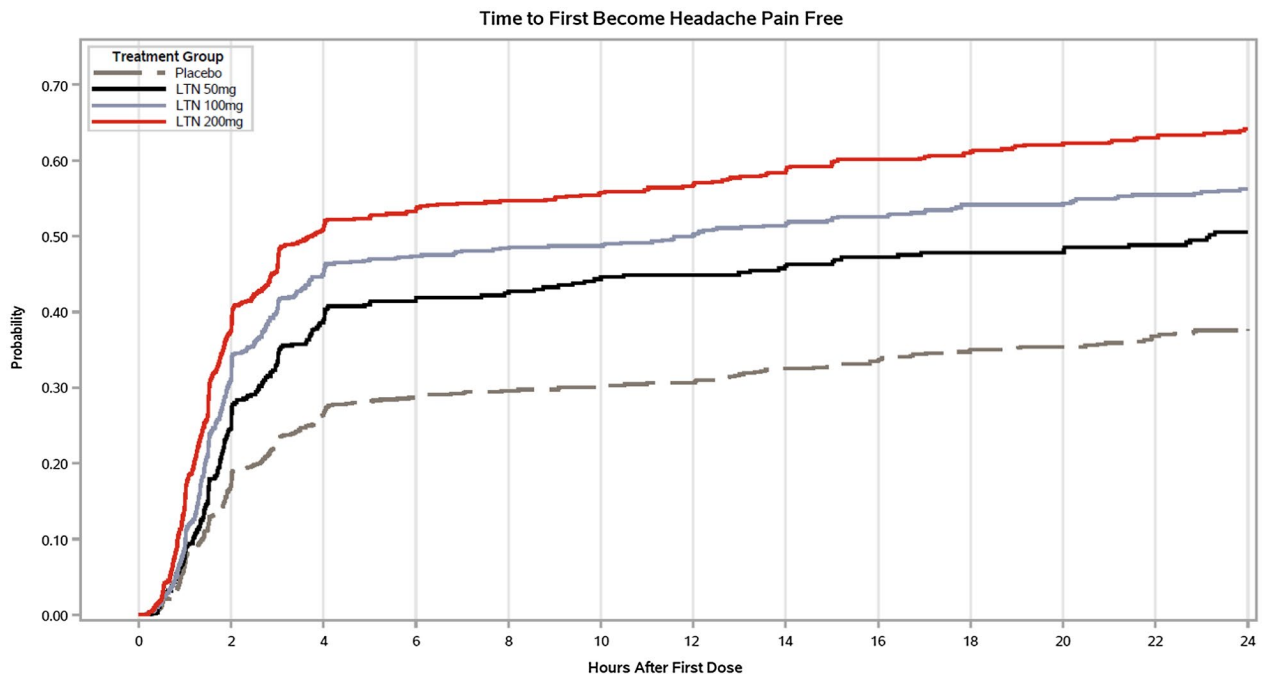


Fig. 5.—Time to first become headache pain free. [Color figure can be viewed at wileyonlinelibrary.com]

migraine-related functional disability, time to meaningful headache relief, and time to first become headache pain free.

Previously, it has been reported that SAMURAI and SPARTAN studies met primary and key secondary

efficacy endpoints for all doses (50, 100, and 200 mg) 2 hours after treatment with lasmiditan.<sup>16,17</sup> The results from the post hoc analyses presented here support and expand upon those findings. Treatment with lasmiditan achieved freedom from MBS, pain relief,

photophobia freedom, phonophobia freedom, and freedom from migraine-related functional disability as early as 30 minutes after treatment compared with placebo. Lasmiditan treatment also showed benefits over placebo at 60 minutes in terms of percentage of patients who were pain free, and experiencing TMF. The time to experiencing meaningful headache relief, and becoming headache pain free is earlier between 0 and 24 hours after treatment with lasmiditan over those treated with placebo. Overall, treatment with lasmiditan resulted in an earlier onset of efficacy compared with placebo. Lasmiditan onset of pain response is comparable to the onset of efficacy of oral triptans, which is between 30 and 120 minutes after treatment. However, direct comparison to triptans is limited by differences in study design, patient populations, and triptan formulations.<sup>22-32</sup> Moreover, there are limited data available on the onset of all outcomes measured in this report for triptans.

A comprehensive endpoint, TMF, was assessed in these post hoc analyses. Total migraine freedom is defined as experiencing pain freedom and freedom from other migraine-associated symptoms. These outcomes are usually measured independently, which limits the understanding of the overall effect of a therapy. Patients who are experiencing pain freedom could still be experiencing migraine-associated symptoms, which could impact their migraine-related functional disability during an attack. In these pooled analyses, we are able to show that a greater proportion of patients treated with lasmiditan (100 and 200 mg) achieved TMF as early as 60 minutes after treatment compared with patients who received placebo.

Given that migraine is associated with significant disability, it is important to have a migraine therapy that effectively mitigates the negative impact of migraine attacks on daily life. Freedom from migraine-related functional disability was achieved by patients treated with lasmiditan (200 mg) in greater proportion than by patients treated with placebo as early as 60 minutes after treatment.

Lasmiditan was associated with neurologic TEAEs, which were mostly mild or moderate in severity, self-limiting, and of short duration.<sup>18</sup> It is possible that these TEAEs could interfere with efficacy assessments. However, 2 hours posttreatment efficacy outcomes

following lasmiditan treatment such as pain freedom, freedom from MBS, patient reported migraine-related functional disability and global impression of change in patients with presence or absence of these common TEAEs' were comparable.<sup>18</sup>

A limitation of these pooled analyses include that the first post dose assessment occurred 30 minutes after treatment and it is possible that onset of efficacy for some outcomes measured may have been sooner than 30 minutes. These are post hoc analyses and the efficacy outcomes TMF, time to meaningful headache relief, time to first become headache pain free and comparisons between treatment groups were not prespecified before examining the data. In addition, multiple analyses of efficacy were conducted without correction for multiplicity. Also, the SPARTAN study was the only study evaluating a 50-mg dose of lasmiditan; thus, we had a lower number of participants in the 50-mg lasmiditan-treated group.

In conclusion, these integrated pooled analyses show that lasmiditan-treated patients experience earlier pain freedom, freedom from MBS, pain relief, freedom from migraine-associated symptoms, TMF, freedom from migraine-related functional disability, time to meaningful headache relief, and time to first become headache pain free than those treated with placebo. These results suggest that lasmiditan has demonstrated early efficacy as an acute treatment for migraine attacks.

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**REFERENCES**

- Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. *Cephalalgia*. 2019;39:687-710.
- Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55:754-762.
- Smelt AF, Louter MA, Kies DA, et al. What do patients consider to be the most important outcomes for effectiveness studies on migraine treatment? Results of a Delphi study. *PLoS ONE*. 2014;9:e98933.
- Davies GM, Santanello N, Lipton R. Determinants of patient satisfaction with migraine therapy. *Cephalalgia*. 2000;20:554-560.
- Hamelsky SW, Lipton R, Stewart WF. An assessment of the burden of migraine using the willingness to pay model. *Cephalalgia*. 2005;25:87-100.
- Lipton RB, Hamelsky SW, Dayno JM. What do patients with migraine want from acute migraine treatment? *Headache*. 2002;42:3-9.
- Mafi JN, Edwards ST, Pedersen NP, et al. Trends in the ambulatory management of headache: Analysis of NAMCS and NHAMCS data 1999-2010. *J Gen Intern Med*. 2015;30:548-555.
- Molina KC, Fairman KA, Sclar DA. Concomitant use of opioid medications with triptans or serotonergic antidepressants in US office-based physician visits. *Drug Healthc Patient Saf*. 2018;10:37-43.
- Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin, 5-HT<sub>1B/1D</sub> agonists) in migraine: Detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia*. 2002;22:633-658.
- Dodick D, Lipton RB, Martin V, et al. Consensus statement: Cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. *Headache*. 2004;44:414-425.
- Neeb L, Reuter U. Lasmiditan for acute migraine treatment. *Future Neurol*. 2013;8:631-638.
- Capi M, de Andres F, Lionetto L, et al. Lasmiditan for the treatment of migraine. *Expert Opin Investig Drugs*. 2017;26:227-234.
- Nelson DL, Phebus LA, Johnson KW, et al. Preclinical pharmacological profile of the selective 5-HT<sub>1F</sub> receptor agonist lasmiditan. *Cephalalgia*. 2010;30:1159-1169.
- Ferrari MD, Färkkilä M, Reuter U, et al. Acute treatment of migraine with the selective 5-HT<sub>1F</sub> receptor agonist lasmiditan – A randomised proof-of-concept trial. *Cephalalgia*. 2010;10:1170-1178.
- Färkkilä M, Diener HC, Géraud G, et al. Efficacy and tolerability of lasmiditan, an oral 5-HT<sub>1F</sub> receptor agonist, for the acute treatment of migraine: A phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. *Lancet Neurol*. 2012;11:405-413.
- Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: A Phase 3 randomized study. *Neurology*. 2018;91:e1-e11.
- Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*. 2019;142:1894-1904.
- Krege JH, Rizzoli PB, Liffick E, et al. Safety findings from Phase 3 lasmiditan studies for acute treatment of migraine: Results from SAMURAI and SPARTAN. *Cephalalgia*. 2019;39:957-966.
- Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24(Suppl. 1):9-160.
- Lipton RB, McGinley JS, Shulman KJ, et al. Faster improvement in migraine pain intensity and

- migraine-related disability at early time points with AVP-825 (sumatriptan nasal powder delivery system) versus oral sumatriptan: A comparative randomized clinical trial across multiple attacks from the COMPASS study. *Headache*. 2017;57:1570-1582.
21. Rodgers AJ, Hustad CM, Cady RK, et al. Total migraine freedom, a potential primary endpoint to assess acute treatment in migraine: Comparison to the current FDA requirement using the complete rizatriptan study database. *Headache*. 2011;51:356-368.
  22. Pascual J, Falk RM, Piessens F, et al. Consistent efficacy and tolerability of almotriptan in the acute treatment of multiple migraine attacks: Results of a large, randomized, double-blind, placebo-controlled study. *Cephalalgia*. 2000;20:588-596.
  23. Pascual J, Cabarrocas X. Within-patient early versus delayed treatment of migraine attacks with almotriptan: The sooner the better. *Headache*. 2002;42:28-31.
  24. Chen LC, Ashcroft DM. Meta-analysis examining the efficacy and safety of almotriptan in the acute treatment of migraine. *Headache*. 2007;47:1169-1177.
  25. Sheftell F, Ryan R, Pitman V, et al. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: A multicenter, double-blind, placebo-controlled study conducted in the United States. *Headache*. 2003;43:202-213.
  26. Stark R, Dahlöf C, Haughie S, et al. Efficacy, safety and tolerability of oral eletriptan in the acute treatment of migraine: results of a phase III, multicenter, placebo-controlled study across three attacks. *Cephalalgia*. 2002;22:23-32.
  27. Ryan R, Géraud G, Goldstein J, et al. Clinical efficacy of frovatriptan: Placebo-controlled studies. *Headache*. 2002;42(Suppl. 2):S84-S92.
  28. Havanka H, Dahliif C, Pop PHM, et al. Efficacy of naratriptan tablets in the acute treatment of migraine: A dose-ranging study. *Clin Ther*. 2000;22:970-980.
  29. Klassen A, Elkind A, Asgharnejad M, et al. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled, parallel-group study. *Headache*. 1997;37:640-645.
  30. Ferrari E, Loder E, McCarroll KA, et al. Meta-analysis of rizatriptan efficacy in randomized controlled clinical trials. *Cephalalgia*. 2001;21:129-136.
  31. Pfaffenrath V, Cunin G, Sjonell G, et al. Efficacy and safety of sumatriptan tablets (25, 50, and 100 mg) in the acute treatment of migraine: Defining the optimum doses of oral sumatriptan. *Headache*. 1998;38:184-190.
  32. Dowson AJ, MacGregor EA, Purdy RA, et al. Zolmitriptan orally disintegrating tablet is effective in the acute treatment of migraine. *Cephalalgia*. 2002;22:101-106.