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ORIGINAL RESEARCH

Rapid Onset and Sustained Efficacy of Lasmiditan Among Japanese Patients with Migraine: Prespecified Analyses of a Randomized Controlled Trial

Yasuhiko Matsumori · Mika Komori · Yuka Tanji · Akichika Ozeki · Fumihiko Sakai

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ABSTRACT

Introduction: Rapid onset and sustained efficacy are important for acute migraine treatment. Global phase 3 trials have demonstrated the early onset and sustained efficacy of the 5-HT_{1F} receptor agonist lasmiditan. In this prespecified analysis of the MONONOFU study, we assessed the onset and sustained efficacy of lasmiditan in Japanese patients with migraine.

Methods: MONONOFU was a multicenter, randomized, placebo-controlled, phase 2 study conducted in Japan (May 2019–June 2020). Eligible adults with migraine (N = 846; modified intent-to-treat population, N = 682) were randomized 7:3:7:6 to placebo, lasmiditan 50 mg, 100 mg, or 200 mg, taken orally within 4 h of moderate-to-severe migraine onset. Patients recorded headache severity and symptoms predose and 0.5–48 h postdose. Sustained and modified sustained pain freedom were defined as patients who were headache pain-free 2 h postdose and had no pain (sustained pain freedom) or had mild or no pain (modified sustained pain freedom) at 24 or 48 h without rescue/recurrence medications. Efficacy outcomes were analyzed by logistic regression. Patients also recorded the actual time of pain-free and of meaningful pain relief (Kaplan–Meier analysis).

Results: Compared with placebo, significantly more lasmiditan-treated (100 or 200 mg) patients were headache pain-free, had pain relief, were free of their most bothersome symptom, or had total migraine freedom (no headache or migraine-associated symptoms) within 30–60 min. Median time to pain-free was 9.26, 6.88, 2.75, and 2.30 h in placebo, 50-mg, 100-mg, and 200-mg lasmiditan groups, respectively. Significantly greater proportions of patients treated with 100 (19.7–29.5%) or 200 mg (21.1–35.7%) lasmiditan had sustained or modified sustained pain freedom at 24 or 48 h compared with placebo (10.4–15.8%).

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Y. Matsumori
Sendai Headache and Neurology Clinic, Sendai, Japan
e-mail: ma2mori@gmail.com

M. Komori (✉) · Y. Tanji · A. Ozeki
Japan Drug Development and Medical Affairs, Eli Lilly Japan K.K., 5-1-28, Isogamidori, Chuo-ku, Kobe 651-0086, Japan
e-mail: komori_mika@lilly.com

Y. Tanji
e-mail: Tanji_yuka@lilly.com

A. Ozeki
e-mail: ozeki_akichika@lilly.com

F. Sakai
Saitama International Headache Center, Saitama, Japan
e-mail: fsakai@mist.dti.ne.jp

Conclusion: This prespecified analysis of data from MONONOFU has confirmed that the efficacy of lasmiditan is rapid in onset and sustained in patients with moderate-to-severe migraine in Japan.
Trial Registration: ClinicalTrials.gov (NCT03962738).

Keywords: Headache; Japan; Lasmiditan; Migraine disorders; Phase 2; Onset of action; Pain freedom; Sustained efficacy

Key Summary Points

Why carry out this study?

There is an unmet need for new and effective options for the acute treatment of migraine that have rapid onset and sustained efficacy.

Global clinical trials have demonstrated that the efficacy of the 5-HT_{1F} receptor agonist lasmiditan is both rapid and sustained; however, the time course of lasmiditan efficacy in Asian patients has not been established.

This prespecified analysis of the MONONOFU randomized placebo-controlled study assessed the onset and sustained efficacy of lasmiditan in Japanese patients with migraine.

What was learned from the study?

Compared with placebo, significantly more lasmiditan-treated (100 or 200 mg) patients were headache pain-free within 30–60 min, and significantly more patients had sustained pain freedom for up to 48 h without taking rescue or recurrence medications.

These results confirm the rapid and sustained efficacy of lasmiditan for the acute treatment of moderate-to-severe migraine in Japanese patients.

INTRODUCTION

Migraine affects approximately 1 in 10 people (11.6% of people worldwide [1] and 8.4% in Japan) [2] and has substantial impacts on day-to-day functioning and quality of life [3]. Therefore, it is important to quickly resolve or improve migraine-associated symptoms when a migraine attack appears and to sustain these resolved or improved symptoms [4, 5]. Indeed, a survey of people with migraine revealed that the most important attributes of migraine medication are complete pain relief, lack of recurrence, and rapid onset [6]. There is an unmet need for acute treatments for migraine [7, 8], and new treatment options with rapid and sustained efficacy are desired [4, 5].

Lasmiditan is a selective 5-HT_{1F} receptor agonist that has been developed for the acute treatment of migraine. Lasmiditan acts at the trigeminal nerve system to inhibit neurotransmitter release and in the central nervous system to inhibit pain transmission, without causing vasoconstriction [9, 10]. Lasmiditan has been studied in several global phase 3 placebo-controlled and long-term extension studies [11–15] and was approved as an oral treatment for migraine in the USA in 2019 and Japan in 2022. The pharmacokinetics of lasmiditan in healthy Japanese adults is similar to that in non-Japanese adults; in both groups there is a rapid absorption phase, and the half-life following a single oral dose is about 4 h [16]. Furthermore, a randomized placebo-controlled phase 2 study (MONONOFU) in adults with migraine in Japan demonstrated that the efficacy and tolerability of lasmiditan for the acute treatment of migraine were also similar to the results seen in non-Japanese adults [17].

The rapid onset and sustained efficacy of lasmiditan have been demonstrated in pooled analyses of the global phase 3 studies [18, 19]. Rates of pain relief and freedom from the most bothersome symptom (MBS) were significantly greater than placebo as early as 30 min (first assessment time) after taking lasmiditan (100 mg or 200 mg); rates of freedom from pain and total migraine freedom (i.e., pain-free and not experiencing migraine-associated

symptoms) were significantly greater than placebo starting at 1 h postdose [11, 18]. Moreover, significantly greater rates of pain-free, MBS-free, and total migraine freedom were sustained at 24 and 48 h postdose [19]. However, because the global phase 3 studies enrolled very few patients of Asian background [11–15], there is little evidence regarding the onset and sustained response to lasmiditan in Asian patients.

According to Japanese clinical practice guidelines, the ideal acute treatment for migraine headache would have rapid onset of efficacy against both pain and associated symptoms, efficacy would be sustained without recurrence or use of additional medications, side effects would be minimal, patients would be able to treat themselves easily, and the treatment would be affordable [5]. The present analysis was designed to assess the first two of these characteristics—namely, onset and sustained efficacy—for lasmiditan in the acute treatment of migraine in adults in Japan, using data from the MONONOFU study. Additionally, this analysis examines the actual time to onset of efficacy and documents the use of permitted medications after taking study drug, which were not reported in the analysis of the global studies. Unlike the global phase 3 studies, a second dose of study drug was not permitted in MONONOFU; thus, the time course reflects the efficacy of a single dose of lasmiditan.

METHODS

Study Design, Study Population, and Treatment Protocol

The design of the MONONOFU study has been described previously [17]. Briefly, MONONOFU was a multicenter, randomized, double-blind, placebo-controlled, phase 2 study conducted in Japan between May 30, 2019 and June 8, 2020. The primary objective of the MONONOFU study was to evaluate the efficacy of lasmiditan 200 mg for achieving pain freedom vs. placebo. To be included in the study, patients were aged 18 years or older, had migraine with or without aura fulfilling the International Headache Society diagnostic criteria [20], a history of disabling migraine for at least 1 year, a history of 3–8 migraine attacks/month and less than 15 headache days/month during the past 3 months, and a Migraine Disability Assessment score of at least 11 [21, 22]. Eligible patients were randomized 7:3:7:6 to oral placebo, lasmiditan 50 mg, 100 mg, or 200 mg, which was self-administered within 4 h of onset of a single moderate-to-severe migraine [17]. The protocol was approved by the ethics review board of each site (Supplementary Material Table S1), and all patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, and in compliance with the International Council for Harmonisation Guideline for Good Clinical Practice, and related laws and regulations. The study is registered at ClinicalTrials.gov (NCT03962738).

Assessments

Headache severity and symptoms were recorded in the patient's electronic diary (eDiary) at each assessment time point (predose and 0.5, 1, 1.5, 2, 3, 4, 24, and 48 h postdose). Headache severity was assessed using the International Headache Society 4-point headache severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain) [23]. Patients also recorded the actual time at which they were pain-free and the actual time at which they had what they considered meaningful pain relief.

Outcome Measures

This prespecified analysis focuses on onset and sustained efficacy of lasmiditan. Onset of efficacy was described using the time course of the proportion of patients who achieved the following endpoints: pain-free, defined as moderate or severe headache pain at baseline becoming no pain; pain relief, defined as moderate or severe headache pain at baseline becoming mild or no pain; MBS-free, defined as MBS, identified by the individual at baseline

from migraine-associated symptoms of nausea, phonophobia, or photophobia, at baseline becoming none; total migraine freedom, defined as experiencing no headache pain or any other migraine symptoms (nausea, vomiting, phonophobia, or photophobia); time to pain-free, defined as the actual time to pain-free that a patient recorded when the patient determined that moderate or severe headache pain had become "no pain"; and time to meaningful pain relief, defined as the actual time to pain relief that a patient recorded when the patient determined that headache relief had become "meaningful".

Sustained efficacy was described via the outcome measures of "sustained pain freedom" and "modified sustained pain freedom". Sustained pain freedom was assessed by the proportion of patients who experienced no headache pain at 2 h postdose and no pain at 24 h or 48 h postdose, having not used any rescue/recurrence medications. Modified sustained pain freedom was assessed by the proportion of patients who experienced no headache pain at 2 h postdose and had no or mild pain at 24 h or 48 h postdose, having not used any rescue/recurrence medications; this definition is based on a meta-analysis of triptan trials by Ferrari et al., who suggested that recurrence of mild headache that did not require rescue medication was unlikely to be clinically significant [24]. For the analysis of modified sustained pain freedom, patients with a missing evaluation at 24 h were excluded from the 24-h analysis, instead of being treated as a nonresponder; similarly, patients with a missing evaluation at 48 h were excluded from the 48-h analysis. Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, caffeine, and/or antiemetic drugs were permitted as rescue/recurrence medications after completion of assessment at 2 h postdose, and triptans, ergots, opioids, and barbiturates were permitted after completion of assessment at 24 h postdose (Fig. 1). Taking a prohibited rescue/recurrence medication or taking a permitted medication outside the allowed times was considered a protocol deviation. A second dose of study drug was not permitted at any time.

Statistical Analyses

All analyses in this article were prespecified. Analyses were conducted in the intent-to-treat (ITT) population, defined as all randomized patients with a moderate or severe migraine headache who received at least one dose of study drug and had any postdose headache assessment data, or the modified ITT (mITT) population, defined as all patients in the ITT population who treated a moderate or severe migraine headache within 4 h of onset. Time to pain-free and time to meaningful pain relief were estimated using the Kaplan–Meier method, and 95% confidence intervals were derived. Patients were censored at the first time they took rescue or recurrence medication or at 48 h if they did not become pain-free or achieve meaningful pain relief. Other endpoints were analyzed using logistic regression with p values based on Wald's test. Treatment dose and baseline use of preventive migraine medications (Yes/No) were used as factors. Patients who took rescue or recurrence medications were treated as nonresponders at all subsequent time points. At 2 h postdose, a multiplicity adjustment was conducted by comparing placebo and the lasmiditan 200-mg group for pain-free, and placebo and the lasmiditan 100-mg group for pain relief (gate-keeping method). The other analyses reported herein were not adjusted for multiplicity. Hypothesis tests were based on a two-sided $\alpha = 0.05$. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Disposition and Characteristics

As described previously [17], 846 patients were randomized, 691 took the study drug (safety population), 687 were in the ITT population, and 682 were in the mITT population. Most patients were female (83.1%), mean age was 45.2 years, mean duration of migraine history was 24.2 years, and mean baseline Migraine Disability Assessment total score was 22.3 [17]. Most patients (92.5%) reported that the treated

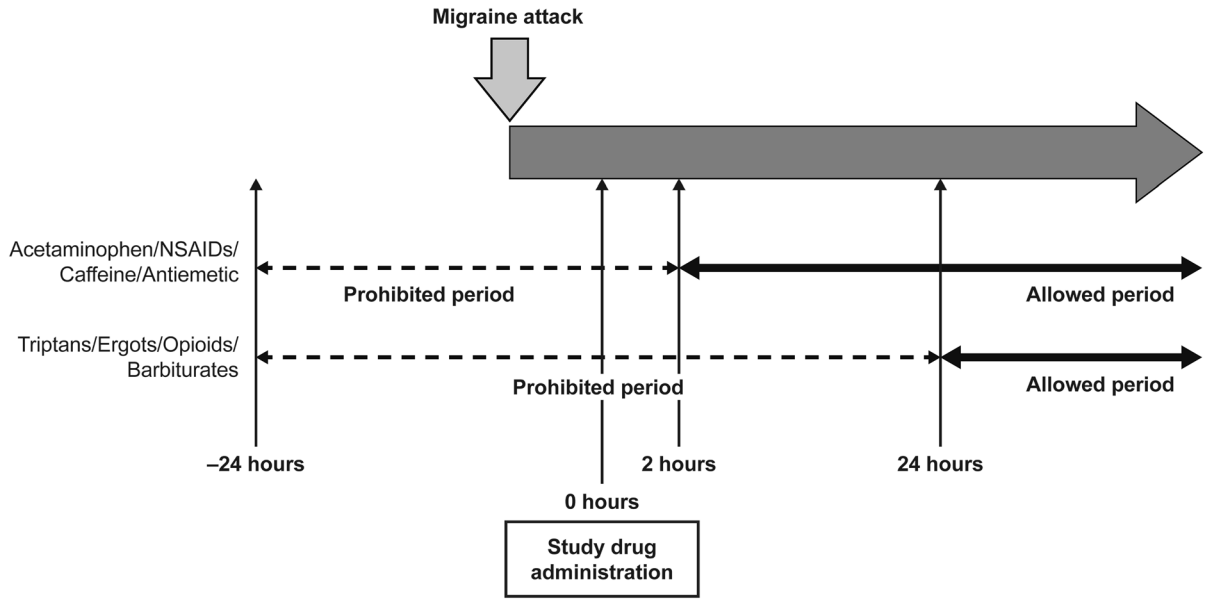

Fig. 1 Allowance periods for restricted and recurrence medications. *NSAID* nonsteroidal anti-inflammatory drug

migraines were moderate in severity and most (71.4%) reported experiencing associated symptoms of nausea, phonophobia, and/or photophobia [17].

Onset of Efficacy

Compared with placebo, a significantly higher proportion of patients reported that they were pain-free after receiving lasmiditan 100 mg or 200 mg (Fig. 2a; Supplementary Material Table S2). As reported previously [17], significant differences from placebo were observed starting at 0.5 h for the lasmiditan 200-mg group and at 1 h for the lasmiditan 100-mg group. These differences were maintained through the time point of 4 h in both the 200-mg and 100-mg dose groups. A significant difference from placebo was also seen for the 50-mg lasmiditan group at 4 h. A similar pattern was seen for pain relief, although a significant difference was seen in the lasmiditan 50-mg group starting at 2 h postdose (Fig. 2b; Supplementary Material Table S2). Compared with placebo, the proportion of patients who were MBS-free was significantly higher in the lasmiditan 50-mg, 100-mg, and 200-mg groups starting at 3, 1, and 2 h postdose, respectively (Fig. 2c; Supplementary Material Table S2). The proportion of patients with total migraine freedom in the lasmiditan 200-mg and 100-mg treatment groups was significantly higher than in the placebo group starting from 1 h postdose, and in the lasmiditan 50-mg group at 4 h postdose (Fig. 2d; Supplementary Material Table S3).

Median time to pain-free and median time to meaningful pain relief were numerically shorter in all lasmiditan treatment groups than in the placebo group (Table 1). Median time to pain-free was 2.30, 2.75, and 6.88 h in the lasmiditan 200-mg, 100-mg, and 50-mg groups, respectively, vs. 9.26 h in the placebo group. Median time to meaningful pain relief was 1.14, 1.31, and 1.80 h in the lasmiditan 200-mg, 100-mg, and 50-mg groups, respectively, vs. 2.99 h in the placebo group.

The time to first becoming headache pain-free and the time to having meaningful pain relief were assessed by Kaplan–Meier analysis of eDiary data recorded at the time of each event. There was a rapid increase in the proportion of patients who were pain-free or who had meaningful pain relief from lasmiditan, which reached a maximum level at about 3–4 h postdose (Fig. 3; Supplementary Material Tables S4 and S5). The proportion of patients who were pain-free or who had meaningful pain relief was

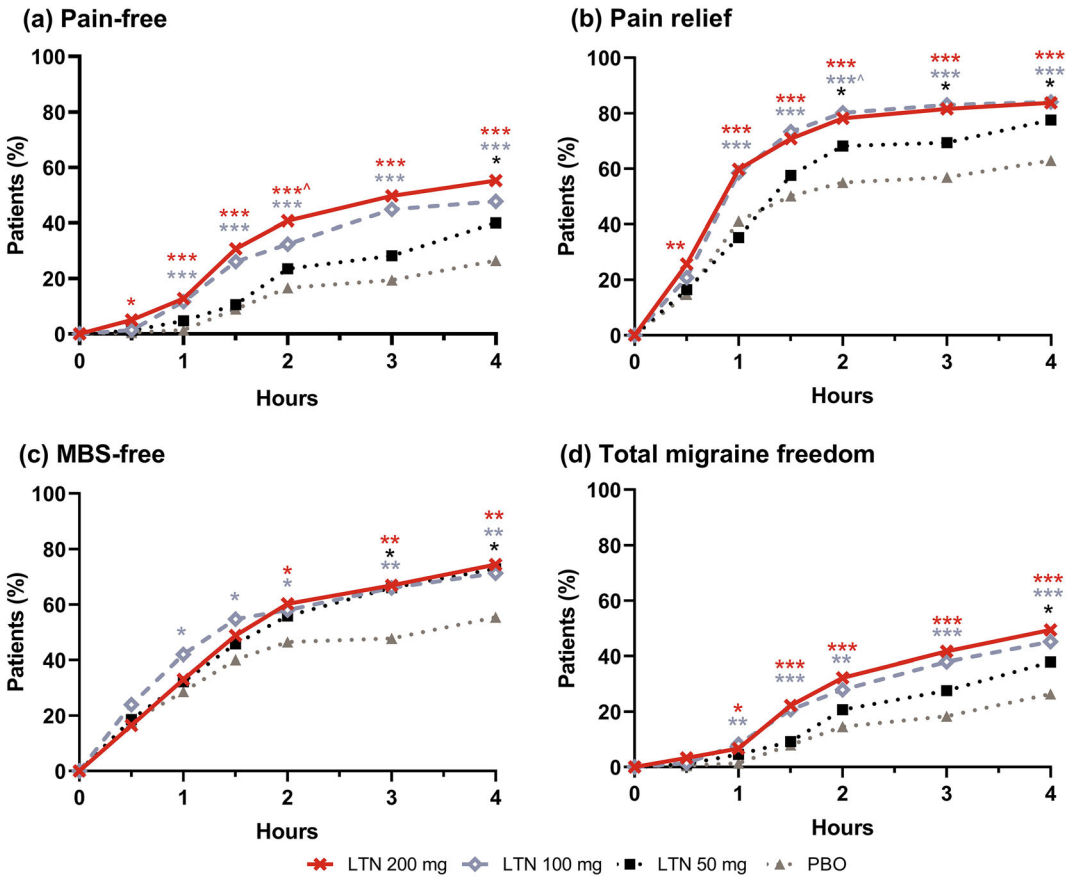

Fig. 2 Onset of efficacy of lasmiditan. Proportion of patients over time who **a** were pain-free (mITT population); **b** achieved relief from pain (mITT population); **c** were free of their MBS (mITT population); and **d** experienced total migraine freedom (no pain or any other migraine-associated symptoms [nausea, vomiting, phonophobia, or photophobia]) (ITT population). At 2 h postdose, a multiplicity adjustment was conducted by comparing placebo and the LTN 200-mg group for pain-free, and placebo and the LTN 100-mg group for pain relief (denoted by ^). Patients who took rescue or recurrence medications were treated as nonresponders at all subsequent time points. Lasmiditan treatment groups were compared with placebo using logistic regression analysis with treatment and baseline use of preventive medications as factors. Data for pain-free, pain relief, and MBS-free up to 2 h were reported previously [17]. Asterisks indicate significant differences compared with placebo: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. *ITT* intent-to-treat, *LTN* lasmiditan, *MBS* most bothersome symptom, *mITT* modified intent-to-treat, *PBO* placebo

numerically higher in the lasmiditan 200-mg and 100-mg groups than in the placebo group starting at 1 h postdose and continuing for at least 8 h. The proportion of patients in the lasmiditan 50-mg group who were pain-free or who had meaningful pain relief was intermediate between placebo and the higher lasmiditan dose groups.

Sustained Efficacy

In the ITT population, no patients in any treatment group took a rescue or recurrence medication between 0 and 2 h postdose, or between 24 and 48 h postdose (Table 2). The proportion of patients who took a rescue or recurrence medication between 2 and 24 h postdose was generally low (0.6%, 1.9%, and 2.3% in the lasmiditan 200-mg, 100-mg, and

Table 1 Onset of efficacy (ITT population)

	Placebo (N = 212)	LTN 50 mg (N = 87)	LTN 100 mg (N = 208)	LTN 200 mg (N = 180)
Time to pain-free[a], h	9.26 (6.26–13.44)	6.88 (3.46–15.19)	2.75 (2.40–3.78)	2.30 (1.54–3.02)
Time to meaningful pain relief[a], h	2.99 (2.61–3.88)	1.80 (1.45–3.05)	1.31 (1.15–1.54)	1.14 (0.99–1.42)

CI confidence interval, *eDiary* electronic diary, *ITT* intent-to-treat, *LTN* lasmiditan
Values are median (95% CI)
[a]Times to pain-free and meaningful pain relief were based on the patient's eDiary record of the actual times they achieved each outcome and was estimated using the Kaplan–Meier method

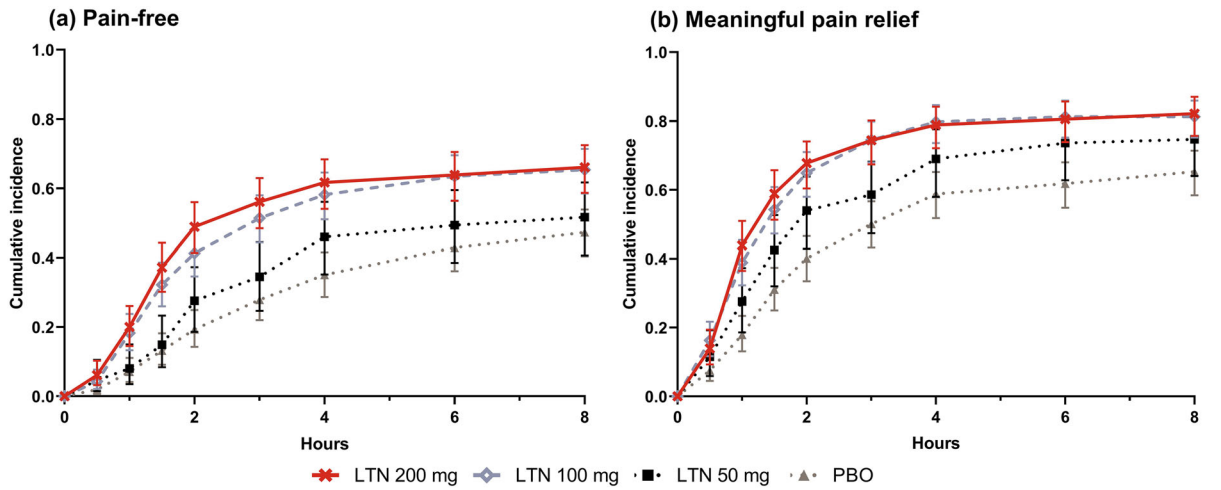

Fig. 3 Time to pain-free and time to meaningful pain relief. Proportion (95% CI) of patients (ITT population) over time who **a** were pain-free and **b** had meaningful pain relief. When deriving point estimators using the Kaplan–Meier method, the 95% CIs were derived by the Greenwood formula at the specific time points (0.5, 1, 1.5, 2, 3, 4, 6, and 8 h). The figure shows the estimates at these specific time points connected by lines. Patients who took rescue or recurrence medications were censored at that time point. *CI* confidence interval, *ITT* intent-to-treat, *LTN* lasmiditan, *PBO* placebo

50-mg groups, respectively, and 3.8% in the placebo group; Tables 2 and 3). Among the ITT population, the proportion of patients who were pain-free at 2 h, who did not take rescue or recurrence medications, and who experienced sustained pain freedom (Fig. 4a) or modified sustained pain freedom (Fig. 4b) at 24 and 48 h postdose was significantly higher in the lasmiditan 100-mg and 200-mg treatment groups, and numerically higher in the lasmiditan 50-mg group, than in the placebo group. The proportion of patients who had mild pain at 24 or 48 h was relatively small (Table 3).

DISCUSSION

This prespecified analysis of the MONONOFU study confirmed the rapid and sustained efficacy of lasmiditan for the acute treatment of migraine in Asian patients. Compared with placebo, significantly more patients treated with lasmiditan 100 mg or 200 mg were free of

Table 2 Incidence of rescue or recurrence medication use (ITT population)

Time since dosing	Placebo (N = 212)	LTN 50 mg (N = 87)	LTN 100 mg (N = 208)	LTN 200 mg (N = 180)
≥ 0 to < 2 h				
n (%)[a]	0 (0)	0 (0)	0 (0)	0 (0)
OR (95% CI)[b]	–	NA	NA	NA
≥ 2 to < 24 h				
n (%)[a]	8 (3.8)	2 (2.3)	4 (1.9)	1 (0.6)
OR (95% CI)[b]	–	0.6 (0.12–2.88)	0.51 (0.15–1.72)	0.14 (0.02–1.16)
p value vs. placebo[b]	–	0.52	0.28	0.07
≥ 24 to ≤ 48 h				
n (%)[a]	0 (0)	0 (0)	0 (0)	0 (0)
OR (95% CI)[b]	–	NA	NA	NA

CI confidence interval, *ITT* intent-to-treat, *LTN* lasmiditan, *NA* not applicable, *OR* odds ratio

[a]The number of patients who received rescue or recurrence medication at least once during the specified time frame

[b]ORs vs. placebo were estimated by logistic regression model with treatment group and baseline usage of preventive medications as factors

pain within 30–60 min, with similar results for other measures of efficacy, including total migraine freedom. In addition, lasmiditan treatment reduced the median time to being free of pain and the median time to meaningful pain relief. Moreover, the proportion of patients who were pain-free at 2 h, did not take subsequent medications, and had no pain at 24 or 48 h was higher with lasmiditan than with placebo. These results indicate that lasmiditan may be a new acute treatment option for migraine in Asian patients that is both fast-acting and long-lasting.

Lasmiditan treatment, especially the 100-mg and 200-mg doses, was associated with a rapid onset of efficacy. Significantly more patients treated with lasmiditan than with placebo reported being pain-free, having pain relief, being MBS-free, and having total migraine freedom within 2 h. These results are consistent with the analysis of global lasmiditan trials [18] and are similar to reports of triptan onset [25]. Previous studies have shown that acute treatments that result in complete freedom from pain are likely to improve other clinically important measures of efficacy (e.g., MBS-free) [26] and reduce the risk of developing chronic migraine [27]. Importantly, in the current study, significantly higher rates of total migraine freedom, which includes not only freedom from pain but also freedom from migraine-related symptoms such as nausea, vomiting, phonophobia, and photophobia, were also achieved as early as 1 h after treatment in the higher lasmiditan dose groups. Total migraine freedom may be a more accurate reflection of a patient's ability to function in daily life than pain alone [28]. In addition, the median time to being free of pain was reduced from more than 9 h in the placebo group to as short as 2.3 h in the lasmiditan 200-mg group; median time to meaningful pain relief was also shortened from approximately 3 h with placebo to just over 1 h with lasmiditan 200 mg. In addition, using Kaplan–Meier analysis of the time to pain freedom, we could also observe higher rates of freedom from pain in the ITT population between 4 and 8 h postdose when headache severity assessments were not scheduled. Overall, these results support the rapid alleviation of both pain and migraine-associated symptoms by lasmiditan.

Table 3 Pain freedom and use of rescue/recurrence medication at 24 and 48 h postdose (ITT population)

	Placebo	LTN 50 mg	LTN 100 mg	LTN 200 mg
Pain-free at 2 h	35/212 (16.5)	20/87 (23.0)	67/208 (32.2)	73/180 (40.6)
Sustained freedom from pain				
24 h				
Pain-free at 24 h without taking rescue/recurrence medication	22/212 (10.4)	13/87 (14.9)	42/208 (20.2)	42/180 (23.3)
Did not take rescue/recurrence medications and missing data	20/212 (9.4)	11/87 (12.6)	25/208 (12.0)	26/180 (14.4)
Took rescue/recurrence medication and not missing data	6/212 (2.8)	1/87 (1.1)	2/208 (1.0)	1/180 (0.6)
Took rescue/recurrence medication and missing data	2/212 (0.9)	1/87 (1.1)	2/208 (1.0)	0/180 (0)
48 h				
Pain-free at 48 h without taking rescue/recurrence medication	26/212 (12.3)	13/87 (14.9)	41/208 (19.7)	38/180 (21.1)
Did not take rescue/recurrence medications and missing data	32/212 (15.1)	25/87 (28.7)	50/208 (24.0)	40/180 (22.2)
Took rescue/recurrence medication and not missing data	5/212 (2.4)	2/87 (2.3)	2/208 (1.0)	0/180 (0)
Took rescue/recurrence medication and missing data	3/212 (1.4)	0/87 (0)	2/208 (1.0)	1/180 (0.6)
Modified sustained freedom from pain[a]				
24 h				
Mild or no pain at 24 h without taking rescue/recurrence medication	27/190 (14.2)	16/75 (21.3)	48/181 (26.5)	55/154 (35.7)
Mild pain at 24 h without taking rescue/recurrence medication	5/190 (2.6)	3/75 (4.0)	6/181 (3.3)	13/154 (8.4)
Did not take rescue/recurrence medications and missing data[a]	NA	NA	NA	NA
Took rescue/recurrence medication and not missing data	6/190 (3.2)	1/75 (1.3)	2/181 (1.1)	1/154 (0.6)
Took rescue/recurrence medication and missing data[a]	NA	NA	NA	NA
48 h				
Mild or no pain at 48 h without taking rescue/recurrence medication	28/177 (15.8)	14/62 (22.6)	46/156 (29.5)	49/139 (34.5)
Mild pain at 48 h without taking rescue/recurrence medication	2/177 (1.1)	1/62 (1.6)	5/156 (3.2)	10/139 (7.2)

Table 3 continued

	Placebo	LTN 50 mg	LTN 100 mg	LTN 200 mg
Did not take rescue/recurrence medications and missing data[a]	NA	NA	NA	NA
Took rescue/recurrence medication and not missing data	5/177 (2.8)	2/62 (3.2)	2/156 (1.3)	0/139 (0)
Took rescue/recurrence medication and missing data[a]	NA	NA	NA	NA

Data are shown as *n*/*N* (%)

ITT intent-to-treat, *LTN* lasmiditan, *NA* not applicable

[a]For the modified sustained freedom from pain analysis, patients with missing evaluation at 24 or 48 h were excluded from the analysis at that time point instead of being treated as a nonresponder

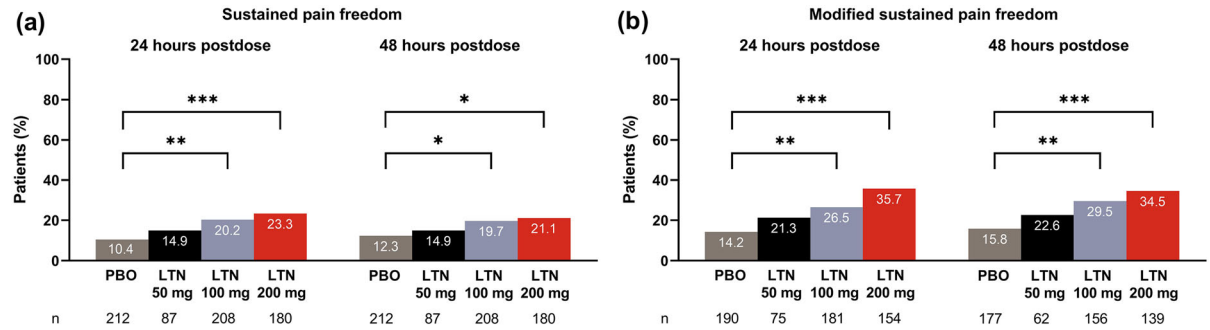

Fig. 4 Sustained efficacy. Proportion of patients (ITT population) who **a** were pain-free at 2 h postdose and had no pain at 24 h and 48 h postdose, having not used any rescue or recurrence medications (sustained pain freedom) (previously reported in Sakai et al. 2021 [17]) or **b** were pain-free at 2 h postdose and experienced mild or no pain at 24 h and 48 h postdose, having not used any rescue or recurrence medications (modified sustained pain freedom). The proportion of patients was calculated using the number of patients in the analysis population at given time points as the denominator. Asterisks indicate significant differences compared with placebo: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. *ITT* intent-to-treat, *LTN* lasmiditan, *PBO* placebo

Most previous studies of lasmiditan and other acute treatments for migraine have allowed the use of rescue/recurrence medications (in some instances, including a second dose of study drug) after the standard efficacy time point of 2 h. However, inclusion of patients taking additional medications in analyses may obscure the effect of the primary dose of study drug [29]. In our study, rescue or recurrence medications were prohibited during the first 2 h and restricted thereafter (NSAIDs/acetaminophen/caffeine/antiemetics allowed after 2 h, triptans/ergots/opioids/barbiturates allowed after 24 h); a second dose of study drug was not permitted. Only a small proportion of patients took permitted rescue or recurrence medications, all between 2 and 24 h postdose, and the proportion was smaller in the lasmiditan groups (0.6–2.3%) than in the placebo group (3.8%). These rates of additional medication were much lower than the rates of taking a second dose of study drug in the global phase 3 studies (21.2–39.0% in lasmiditan groups vs. 39.5–59.9% in placebo groups) [13, 14]. This difference may be related to the difference in study design in which permitting a second dose of study drug in the global studies—compared with the medication restrictions

in this study—might have encouraged more patients to supplement the initial lasmiditan dose.

When the durability of efficacy of acute treatments is assessed, the International Headache Society has recommended sustained freedom from pain as a more robust outcome than recurrence rate because it combines initial response, use of rescue medication, and relapse [23]. Consistent with the pooled analysis of global data [19], more lasmiditan-treated patients experienced sustained freedom from pain without taking rescue/recurrence medications at 24 and 48 h than placebo-treated patients. Between 21% and 36% of lasmiditan-treated patients had modified sustained pain freedom at 24 and 48 h compared with 14–16% of placebo-treated patients. These rates, particularly for lasmiditan 200 mg, are higher than those seen for sumatriptan (20% at 24 h) and most other triptans [24]. Another indirect comparison with the pooled analysis of global lasmiditan data suggested that lasmiditan 200 mg is similar in sustained effect to sumatriptan 100 mg [19].

Although triptans are the accepted first-line prescription medication for acute treatment of moderate or severe migraine, some patients respond poorly, experience recurrences within 24–48 h, or have contraindications to triptan use, such as cardiovascular disease [30, 31]. These unmet needs have prompted the development of several new classes of migraine therapies, including lasmiditan and the calcitonin gene-related peptide receptor antagonists (gepants), two of which (rimegepant and ubrogepant) have been approved in the USA as oral acute treatments for migraine [32, 33]. Tfelt-Hansen and Diener have recommended that a therapeutic gain (i.e., the difference in pain-free rate between treatment and placebo groups) of greater than 5% is a clinically relevant threshold for marking the onset of efficacy [34]. In the global lasmiditan trials, this threshold was reached for pain-free at 60 min for the 200-mg dose and 90 min for the 100-mg dose [18], earlier than seen with the oral gepants [34, 35]. In this analysis of the MONONOFU study, the therapeutic gain for pain freedom exceeded the 5% threshold at 60 min for both the 200-mg (therapeutic gain 11.4%) and 100-mg (therapeutic gain 10.2%) doses, confirming the early onset of clinically meaningful efficacy with lasmiditan. Although efficacy measures between 2 and 24 h were not reported in the primary global lasmiditan trials [13, 14], a subsequent Kaplan–Meier analysis confirmed that the therapeutic gains at 6 and 8 h were 25% for lasmiditan 200 mg and 18% for lasmiditan 100 mg [29]. Moreover, the therapeutic gain at 2 h (21% and 15% for 200 mg and 100 mg, respectively) appeared to be greater than with the gepants (7–9.5%) [29], although head-to-head trials are needed to determine if any true difference exists. The Kaplan–Meier analysis presented in this report confirms that the therapeutic gain of lasmiditan over placebo is maintained between 2 and 8 h postdose (200 mg: 29.6% at 2 h, 18.8% at 8 h; 100 mg: 22.0% at 2 h, 18.1% at 8 h).

Three lasmiditan dose groups were included in the MONONOFU study and in these prespecified analyses. Although lasmiditan 200 mg may be preferred over 50 mg and 100 mg with respect to rapid onset of action and long-lasting effect, the proportion of patients reporting at least one treatment-emergent adverse event increases with higher lasmiditan dose [17]. Therefore, considering the risk-to-benefit balance, we believe the optimal dose of lasmiditan is 100 mg. However, given that the severity of migraine attacks and patient backgrounds vary, having several dose options would be beneficial for patients.

This report presents the results of prespecified analyses of the randomized placebo-controlled MONONOFU study that included multiple measures of efficacy related to pain and migraine-associated symptoms every 30 min for the first 2 h to capture early onset of lasmiditan efficacy. In addition, we analyzed the actual time to freedom from pain and time to meaningful pain relief using data reported by patients in the eDiary. These are the first prespecified analyses performed to describe the onset and sustained efficacy of lasmiditan in a clinical trial; the previous global results were from a pooled post hoc integrated analysis [19]. This report also provides the first analyses of sustained efficacy of lasmiditan in an Asian

population. However, because efficacy assessments did not start until 30 min after dosing, earlier effects occurring before 30 min could not be detected. Unlike the global studies, rescue and recurrence medications were restricted in MONONOFU and did not include a second dose of study drug. Moreover, few patients in this study took rescue medications through 48 h. As a limitation, the small sample size in the lasmiditan 50-mg arm restricts interpretation of the statistical analysis results. In addition, the number of patients with missing evaluations at 24 or 48 h was relatively high, which will have affected the analysis of sustained and modified sustained pain freedom. Finally, although these results are in a Japanese population, they are consistent with observations in trial populations from the USA, UK, and Germany [18, 19].

CONCLUSION

This prespecified analysis of data from the MONONOFU study has confirmed that the efficacy of lasmiditan is rapid in onset and sustained in patients with moderate-to-severe migraine in Japan.

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Compliance with Ethics Guidelines. The protocol and protocol amendments were approved by the institutional review boards at each study site (Supplementary Material Table S1). All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, and in compliance with the International Council for Harmonisation Guideline for Good Clinical Practice, and related laws and regulations.

Data Availability. Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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