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ORIGINAL RESEARCH

Efficacy of Lasmiditan Across Patient and Migraine Characteristics in Japanese Patients with Migraine: A Secondary Analysis of the MONONOFU Trial

Takao Takeshima · Mika Komori · Yuka Tanji · Akichika Ozeki · Yoshihisa Tatsuoka

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ABSTRACT

Introduction: This MONONOFU trial subgroup analysis evaluates the efficacy of lasmiditan across patient and migraine characteristics in Japanese patients with migraine.

Methods: MONONOFU trial was a multicenter, randomized, double-blind, placebo-controlled study. The patients were randomly assigned in a 3:7:6:7 ratio to receive lasmiditan 50 mg, 100 mg, 200 mg, or placebo for a single migraine attack within 4 h of pain onset. Efficacy of lasmiditan vs placebo was evaluated at 2 h post dose for proportion of patients with headache pain freedom. Efficacy was assessed across patient characteristics (age, sex, body weight, cardiovascular risk factors (CVRF), and comorbidity of tension-type headache), migraine disease characteristics (history of migraine with aura, migraine prevention therapy, triptan response, and triptan use or nonuse), and migraine attack characteristics (headache severity, aggressive headache, attack during perimenstrual period, time to dosing, time of dosing, experienced treatment-emergent adverse event (TEAE) of dizziness, and experienced TEAE of somnolence). Logistic regression was used; all subgroup analyses were not analyzed with multiplicity-adjusted statistical tests.

Results: Treatment-by-subgroup interactions (by each arm) were not significant ($p \geq 0.05$) for pain freedom at 2 h post dose across all patient subgroups and lasmiditan doses, except for CVRF (100 mg and 200 mg), migraine with aura (50 mg), triptan response (50 mg), and time to dosing (200 mg). Treatment-by-subgroup interactions (by overall) were not significant ($p \geq 0.05$) for pain freedom at 2 h post dose across all patient subgroups, except for CVRFs. Higher proportions of patients were pain free at 2 h post dose when treated with lasmiditan (50 mg, 100 mg, and 200 mg) versus placebo, irrespective of most patient characteristics, migraine disease characteristics, and migraine attack characteristics.

Conclusion: Although few interactions were observed, lasmiditan could be a promising acute treatment option in a wide range of Japanese patients with migraine, as efficacy is not generally influenced by patient and migraine characteristics.

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T. Takeshima
Tominaga Hospital, Osaka, Japan

M. Komori (✉) · Y. Tanji · A. Ozeki
Eli Lilly Japan K.K., LILLY PLAZA ONE BLDG. 8F, 5-1-28 Isogamidori, Chuo-Ku, Kobe 651-0086, Japan
e-mail: komori_mika@lilly.com

Y. Tatsuoka
Tatsuoka Neurology Clinic, Kyoto, Japan

Keywords: Efficacy; Japan; Lasmiditan; Migraine; Patient and migraine characteristics

Key Summary Points

Why carry out this study?

The knowledge of factors influencing efficacy of acute treatment is important for physicians to prescribe acute treatment for migraine.

The MONONOFU trial was a multicenter, randomized, double-blind, placebo-controlled, phase 2 study, conducted in Japanese patients with migraine.

The subgroup analysis of the MONONOFU trial was carried out to answer the clinical question of whether lasmiditan is effective across a wide range of patient and migraine characteristics.

What was learned from the study?

Although few interactions were observed, lasmiditan could be a promising acute therapeutic option in Japanese patients with migraine, as efficacy is not generally influenced by patient and migraine characteristics.

INTRODUCTION

Prevalence of migraine in Japan is 6.0–8.4%, with 5.8% of migraines without aura and 2.6% of migraines with aura [1–3]. As per the OVERCOME Japan study (cross-sectional, population-based web survey of migraine in Japan), 43% of people experiencing migraine either do not consult a physician or are never diagnosed despite consultation, even though 70% of them noticed that migraine significantly affected their daily activities [2]. Moreover, substantial disability, interictal burden, and activity impairment were reported in Japanese people with migraine [4]. This data highlights the unmet need for migraine care among people with migraine in Japan [2, 4].

Treatment of migraine can be broadly divided into two categories, acute and preventive treatments. In Japan, 87.1% of patients with migraine used acute treatment [2], and 35–40% of them have insufficient response [5]. An American Migraine Prevalence and Prevention survey was used to identify sociodemographic features and headache characteristics that could predict response to acute treatment [6]. The results indicated that male sex, higher body mass index (BMI), severe headache pain intensity, high frequency of headache days per month, and absence of use of preventative medications significantly predicted inadequate pain freedom at 2 h post dose [6]. Therefore, the knowledge of factors influencing efficacy of acute treatment could be useful to physicians for prescribing acute treatment for migraine.

Lasmiditan is a novel 5-HT receptor agonist with high affinity and selectivity for the 5-HT_{1F} serotonin receptor [7]. Lasmiditan is the first of a new class of drugs called ditans, whose chemical structure is based on a pyridinoyl-piperidine scaffold and lacks the indole core of triptans [7, 8]. The results from the randomized phase 3 trials SAMURAI (NCT02439320) and SPARTAN (NCT02605174) conducted in the USA and Europe led to the US Food and Drug Administration's approval of lasmiditan for the treatment of acute migraine with or without aura in the USA [9, 10]. According to the pooled analysis of SPARTAN and SAMURAI trials, the efficacy of lasmiditan was generally not influenced by the individual patient characteristics, migraine disease characteristics, or migraine attack characteristics [11, 12].

Similar to the SPARTAN trial [9], in Japan, the MONONOFU trial (NCT03962738), which was conducted to assess the efficacy and safety of lasmiditan, indicated that a significantly higher proportion of patients with migraine treated with lasmiditan 100 mg and 200 mg and a numerically higher proportion treated with 50 mg were headache pain free, had pain relief, and were most bothersome symptom (MBS) free vs placebo, and a significant linear dose–response relationship for pain freedom was achieved and reported in the primary

manuscript [13]. On the basis of the similarities in the primary and key secondary results from MONONOFU and SPARTAN trials, lasmiditan received regulatory approval in Japan in January 2022 [9, 10, 13].

There is an urgent need in the clinical field to understand the efficacy of lasmiditan across various patients and migraine backgrounds in the Asian population. Therefore, the objective of this subgroup analysis of the MONONOFU trial was to evaluate the efficacy of lasmiditan vs placebo in Japanese patients across a wide range of patient and migraine characteristics, and to add information on the use of lasmiditan in medical practice.

METHODS

The MONONOFU trial was a multicenter, randomized, double-blind, placebo-controlled, phase 2 study that evaluated the efficacy and safety of lasmiditan in Japanese patients with migraine [13]. Participants aged 18 years or more with a history of migraine (with or without aura for at least 1 year as per the International Classification of Headache Disorders, ICHD) [14], with onset at less than 50 years of age, and 3–8 migraine attacks per month (less than 15 headache days/month for the past 3 months) were included in the trial. Key exclusion criteria included participants with known lasmiditan sensitivity, history of chronic migraine or other chronic headache disorders with at least 15 headache days/month within the past 12 months, based on the International Headache Society guideline for clinical trials of acute treatment of migraine [15]. Other exclusion criteria included hemorrhagic stroke, epilepsy, or any other condition placing the participant at increased risk of seizures, recurrent dizziness, and/or vertigo; diabetes mellitus with complications; orthostatic hypotension with syncope; significant renal or hepatic impairment; and participants who, in the investigator's judgment, were a significant suicide risk [13]. In the MONONFU trial, participants were randomly allocated 7:3:7:6 to receive oral placebo or lasmiditan 50 mg, 100 mg, or 200 mg; this ratio provided the highest statistical power for all primary and key secondary endpoints through statistical simulation [13]. Participants treated a single migraine attack with the study drug within 4 h, with the assurance that the migraine was not treated by another acute treatment within the previous 24 h. Furthermore, rescue medications for persistent migraine were allowed only after the 2-h postdose assessment. The efficacy outcomes evaluated the proportion of patients who were headache pain free, had pain relief, and were MBS free at 2 h post dose and at other time points including 24 h and 48 h with lasmiditan vs placebo. Details of the methodology are published in Sakai et al. [13].

Patient and migraine attack characteristics are known predictors of insufficient response to acute treatment [12]. In this subgroup analysis, efficacy (pain freedom at 2 h post dose) was analyzed in following subgroups:

Patient characteristics: sex, age ($\leq$ 46 years and $>$ 46 years; 46 years was the median age of the population), weight ($\leq$ 56 kg and $>$ 56 kg; 56 kg was the median weight of the population), cardiovascular risk factors (CVRFs; $\leq$ 1 and $\geq$ 2), and comorbidity of tension-type headache. CVRF subtypes were defined as CVRF1, current smokers at baseline; CVRF2, patients with hypertension at baseline; CVRF3, patients with diabetes at baseline or a baseline non-fasting glucose level of at least 200 mg/dL; CVRF4, patients with dyslipidemia at baseline; CVRF5, patients with chronic kidney disease at baseline; CVRF6, patients with obesity (BMI $\geq$ 25 kg/m^2) at baseline; CVRF7, age at baseline (male patients at least 45 years old, female patients at least 55 years old); CVRF8, sex (male, postmenopausal female) [16]. In addition, the investigators, who were headache specialists, diagnosed patients with migraine with co-existing tension-type headache as per the ICHD criteria [14].

Migraine disease characteristics: history of migraine with aura as defined by the ICHD diagnostic criteria [14], migraine prevention therapy use at baseline [17], triptan response (based on the most recent triptan experience), and triptan use. Patients who had at least one triptan within 3 months of informed consent were defined as triptan users. Triptan

responders were defined as patients with a prior history and sufficient response to triptan use. Triptan insufficient responders were defined as patients with a prior history of triptan use who had no or poor overall response, inconsistent response, discontinued triptan, poor score in migraine Treatment Optimization Questionnaire (mTOQ) at visit 2 (baseline), or triptan contraindicated participants.

Migraine attack characteristics (attack treated by study drug in MONONOFU study): headache severity (moderate or severe based on ICHD definition) [18], aggressive headache (reach severe headache within 1 h of headache onset), attack during perimenstrual period (± 2 days of menstruation), time to dosing (< 1 h and ≥ 1 h from migraine headache onset), time of dosing (4–8 a.m. or any other time), experienced treatment-emergent adverse event (TEAE) of dizziness, and experienced TEAE of somnolence, most commonly associated TEAEs during the MONONOFU trial [13].

The protocol was approved by the ethics review board of each site, and all patients provided written informed consent. The MONONOFU trial 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 (identifier NCT03962738).

Statistical Analysis

All efficacy analysis was performed in the modified intent-to-treat (mITT) population defined by all randomized patients who were treated for a migraine attack within 4 h of onset. Logistic regression is a common method to evaluate binary outcomes (pain free at 2 h) which can handle baseline differences and interactions [12, 13]; therefore, logistic regression was applied to each subgroup separately. The efficacy analysis based on proportion was performed using the logistic regression, wherein the model included terms such as treatment and baseline usage of preventative medications to reduce frequency of migraine (yes/no). Odds ratio, 95% confidence interval, and *p* value were calculated on the basis of this model. Alternatively, the analysis for subgroup interaction used a model with treatment, baseline usage of preventive medications to reduce the frequency of migraine (yes/no), subgroup, and treatment-by-subgroup interaction as input variables; the treatment effect and interaction were tested with a two-sided significance level of 0.05. Primary and key secondary analyses were adjusted for multiplicity [13], but no adjustment was done for the subgroup analysis in this paper.

RESULTS

Patient Disposition

A total of 836 randomly assigned patients completed the study. Of the 836 patients, 691 (81.7%) patients were administered study medication. Overall, 682 patients were included in the mITT population. The patient disposition details are published elsewhere [13].

Patient Characteristics of Total Population

The majority of patients (83.0%) were female, with a mean age of 45.2 years (median age 46 years) and a mean body weight of 58.3 kg (median body weight 56 kg). The majority (85.2%) of patients had migraine without aura and 37.4% had history of migraine prevention therapy use. Among the 655 patients that had history of triptan use, 73.7% were triptan responders and 26.3% were triptan insufficient responders (Table 1). Reasons for insufficient response in the subpopulation of triptan insufficient responders are described in Table S1 in the supplementary material. The majority (92.5%) of patients had moderate migraine baseline severity, but only 3.4% experienced aggressive headache. Overall, patient, migraine disease, and migraine attack demographic characteristics from the MONONOFU trial were similar across treatment groups and are described in Table 1.

Table 1 Patient, migraine disease, and migraine attack demographic characteristics

Characteristic	Lasmiditan 50 mg *N* = 85	Lasmiditan 100 mg *N* = 207	Lasmiditan 200 mg *N* = 179	Placebo *N* = 211	Total *N* = 682
Patient characteristics					
Age, mean ± SD (years)	44.9 ± 9.9	45.7 ± 9.7	44.7 ± 10.4	45.2 ± 8.8	45.2 ± 9.6
Sex, female, *n* (%)	73 (85.9)	175 (84.5)	143 (79.9)	175 (82.9)	566 (83.0)
Body weight, mean ± SD (kg)	57.8 ± 10.8	58.3 ± 11.6	58.7 ± 10.8	58.2 ± 12.2	58.3 ± 11.5
Cardiovascular risk factor (CVRF)[a], *n* (%)					
CVRF ≤ 1	48 (56.5)	106 (51.2)	100 (55.9)	118 (55.9)	372 (54.5)
CVRF ≥ 2	37 (43.5)	101 (48.8)	79 (44.1)	93 (44.1)	310 (45.5)
Tension-type headache, *n* (%)					
Yes	13 (15.3)	36 (17.4)	36 (20.1)	37 (17.5)	122 (17.9)
No	72 (84.7)	171 (82.6)	143 (79.9)	174 (82.5)	560 (82.1)
Migraine disease characteristics					
History of aura, *n* (%)					
Yes	10 (11.8)	33 (15.9)	24 (13.4)	34 (16.1)	101 (14.8)
No	75 (88.2)	174 (84.1)	155 (86.6)	177 (83.9)	581 (85.2)
Use of migraine prevention therapy, *n* (%)					
Yes	33 (38.8)	75 (36.2)	66 (36.9)	81 (38.4)	255 (37.4)
No	52 (61.2)	132 (63.8)	113 (63.1)	130 (61.6)	427 (62.6)
Triptan response, *n* (%)					
Triptan responder[b]	62 (75.6)	148 (75.1)	122 (72.2)	151 (72.9)	483 (73.7)
Triptan insufficient responder[b]	20 (24.4)	49 (24.9)	47 (27.8)	56 (27.1)	172 (26.3)
History of triptan use within 3 months prior to informed consent, *n* (%)					
Triptan use	80 (94.1)	186 (89.9)	160 (89.4)	195 (92.4)	621 (91.1)
Triptan nonuse	5 (5.9)	21 (10.1)	19 (10.6)	16 (7.6)	61 (8.9)
Migraine attack characteristics					
Baseline migraine severity, *n* (%)					
Moderate	75 (88.2)	191 (92.3)	169 (94.4)	196 (92.9)	631 (92.5)
Severe	10 (11.8)	16 (7.7)	10 (5.6)	15 (7.1)	51 (7.5)
Aggressive headache[c], *n* (%)					
Yes	4 (4.7)	6 (2.9)	7 (3.9)	6 (2.8)	23 (3.4)
No	81 (95.3)	201 (97.1)	172 (96.1)	205 (97.2)	659 (96.6)

Table 1 continued

Characteristic	Lasmiditan 50 mg *N* = 85	Lasmiditan 100 mg *N* = 207	Lasmiditan 200 mg *N* = 179	Placebo *N* = 211	Total *N* = 682
Dosed during menstrual period, *n* (%)					
Yes	5 (5.9)	27 (13.0)	27 (15.1)	19 (9.0)	78 (11.4)
No	80 (94.1)	180 (87.0)	152 (84.9)	192 (91.0)	604 (88.6)
Time to dose, *n* (%)					
< 1 h	32 (37.6)	66 (31.9)	69 (38.5)	86 (40.8)	253 (37.1)
≥ 1 h	53 (62.4)	141 (68.1)	110 (61.5)	125 (59.2)	429 (62.9)
Time of dose, *n* (%)					
Dosed between 4 a.m. and 8 a.m.	9 (10.6)	29 (14.0)	20 (11.2)	29 (13.7)	87 (12.8)
Dosed other time	76 (89.4)	178 (86.0)	159 (88.8)	182 (86.3)	595 (87.2)
Experienced TEAE dizziness, *n* (%)					
Yes	18 (21.2)	78 (37.7)	91 (50.8)	7 (3.3)	194 (28.4)
No	67 (78.8)	129 (62.3)	88 (49.2)	204 (96.7)	488 (71.6)
Experienced TEAE somnolence, *n* (%)					
Yes	7 (8.2)	44 (21.3)	41 (22.9)	11 (5.2)	103 (15.1)
No	78 (91.8)	163 (78.7)	138 (77.1)	200 (94.8)	579 (84.9)

BMI, body mass index; dBP, diastolic blood pressure; *N*, total number of patients in the specified group; *n*, number of patients in the subgroup; sBP, systolic blood pressure; SD, standard deviation

[a]CVRFs include current smoker, hypertension (sBP ≥ 140 mmHg, dBP ≥ 90 mmHg), diabetes, dyslipidemia, chronic kidney disease, obesity (BMI ≥ 25 kg/m^2), age (male, ≥ 45 years; female, ≥ 55 years), sex (male or postmenopausal female), or family history of cardiovascular disease (parents, grandparents, and siblings)

[b]Proportions of patients were calculated from patients with history of triptan use (*N* = 655)

[c]Aggressive headache defined as a headache reaching severe headache ≤ 1 h of headache onset

Lasmiditan Efficacy Across Patient Characteristics (age, sex, body weight, CVRFs and comorbidity of tension-type headache) (Figure 1)

Treatment-by-subgroup interaction (by each arm) was not observed across doses (50 mg, 100 mg, and 200 mg) between headache pain freedom at 2 h post dose and patient characteristics ($p \geq 0.05$) except for CVRFs at 100 mg and 200 mg doses ($p < 0.05$). Treatment-by-subgroup interaction (overall) was not observed between patient characteristics and lasmiditan treatment vs placebo ($p \geq 0.05$), except for CVRFs ($p < 0.05$) (Fig. 1). A higher proportion of patients treated with lasmiditan 50 mg, 100 mg, and 200 mg doses were migraine pain free vs placebo, across age, sex, body weight, CVRFs, and tension-type headache, except for male patients and patients with tension-type headache treated with 50 mg dose (Fig. 1).

Lasmiditan Efficacy Across Migraine Disease Characteristics (history of migraine with aura, migraine prevention therapy, triptan response, and triptan use) (Figure 2)

Treatment-by-subgroup interaction (by each arm) was not observed across doses (50 mg, 100 mg,

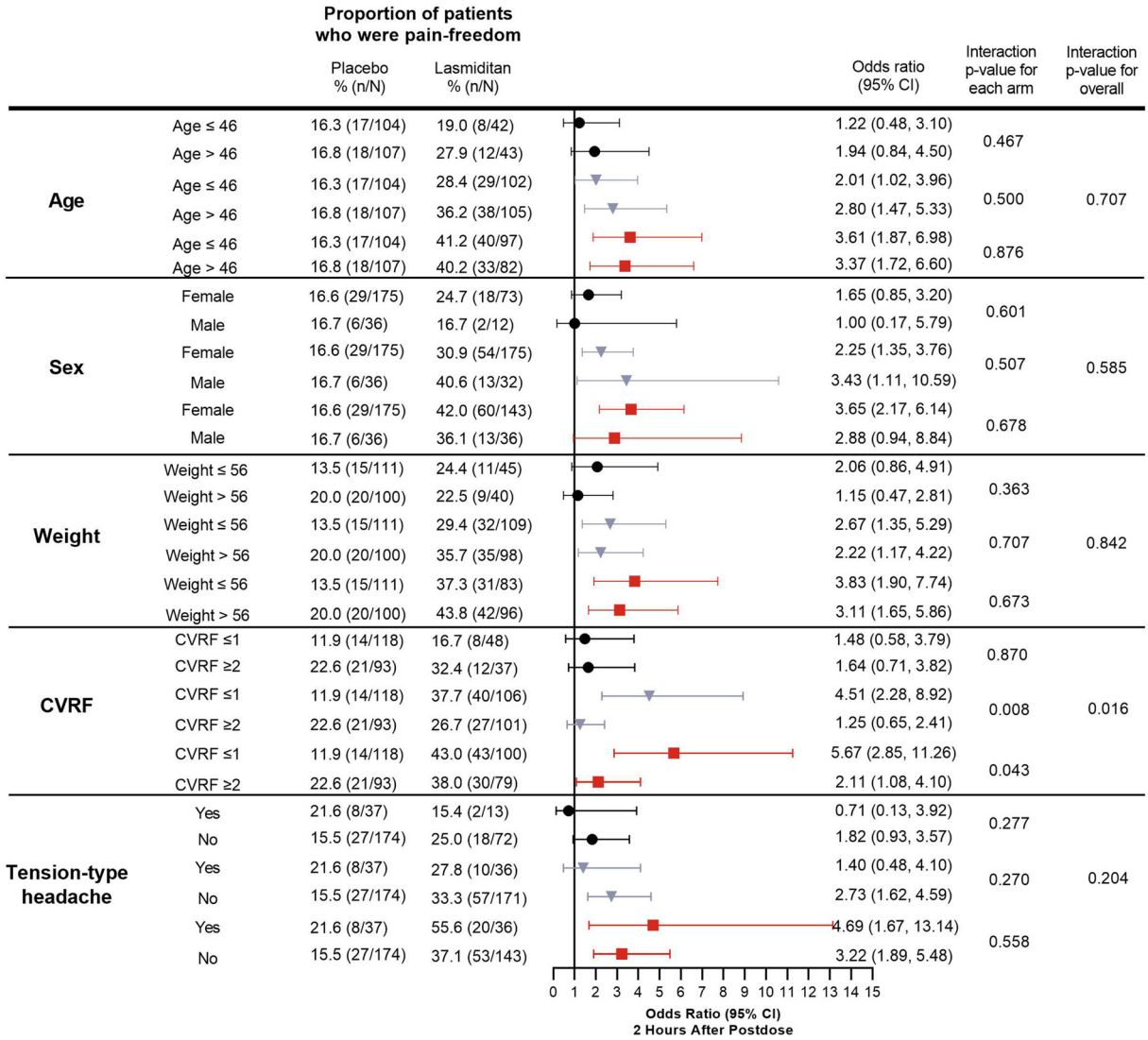


Fig. 1 Subgroup analysis for pain freedom at 2 h post dose based on patient characteristics. *CI* confidence interval, *CVRF* cardiovascular risk factor, *N* total number of patients in the specified group, *n* total number of patients in the subgroup

and 200 mg) between headache pain freedom at 2 h post dose and migraine disease baseline characteristics ($p \geq 0.05$), except for history of migraine with aura and triptan response at 50 mg dose ($p < 0.05$). Treatment-by-subgroup interaction (overall) was not observed between migraine disease baseline characteristics and lasmiditan treatment vs placebo ($p \geq 0.05$). A higher proportion of patients treated with lasmiditan 50 mg, 100 mg, and 200 mg were pain free 2 h post dose vs placebo, across history of migraine with aura, migraine prevention therapy, triptan response, and triptan use except for patients with insufficient triptan response and triptan non-users treated with 50 mg dose (Fig. 2).

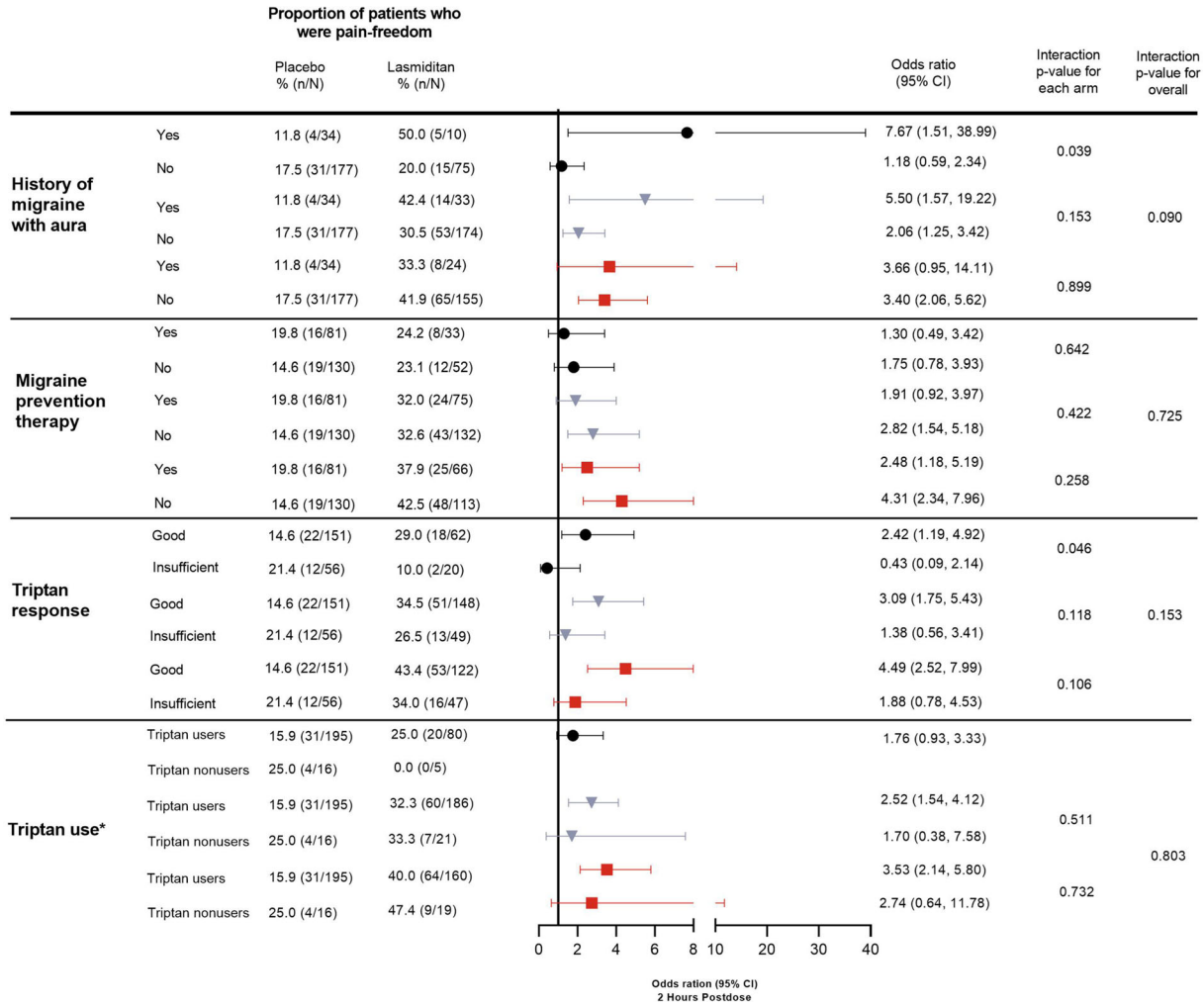
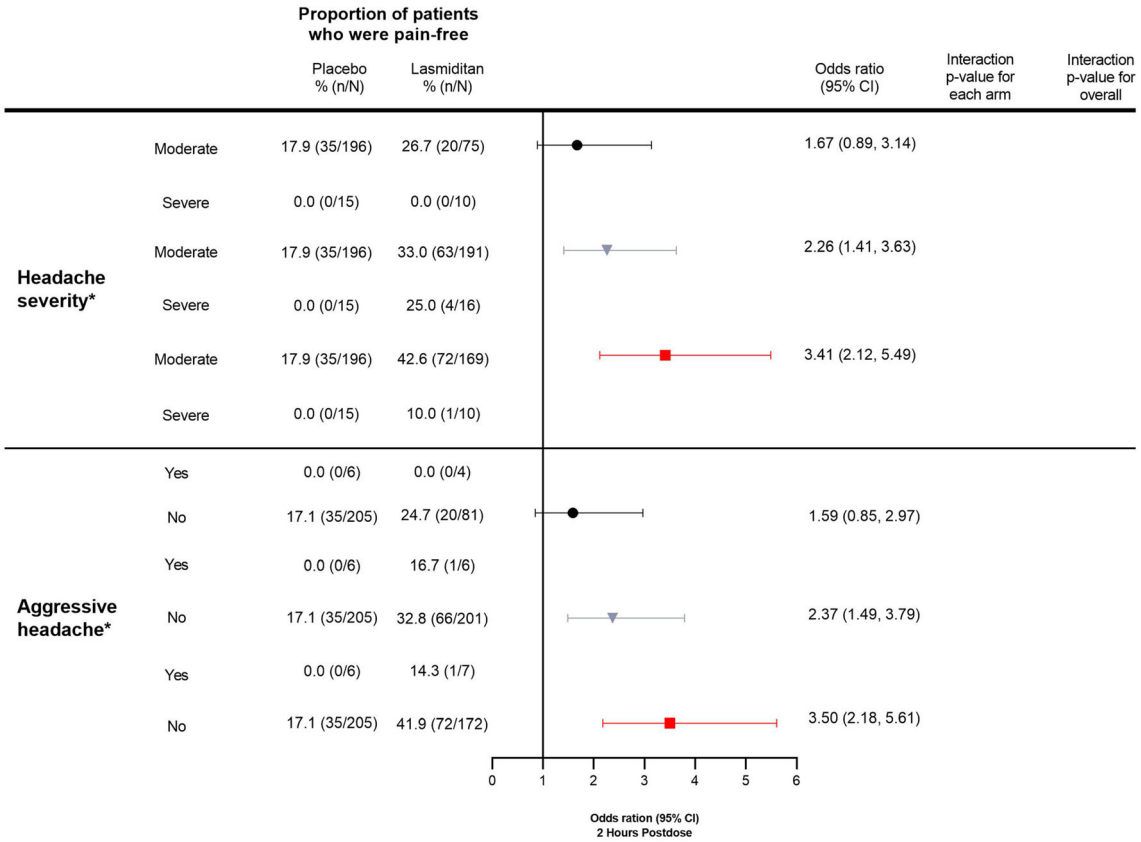
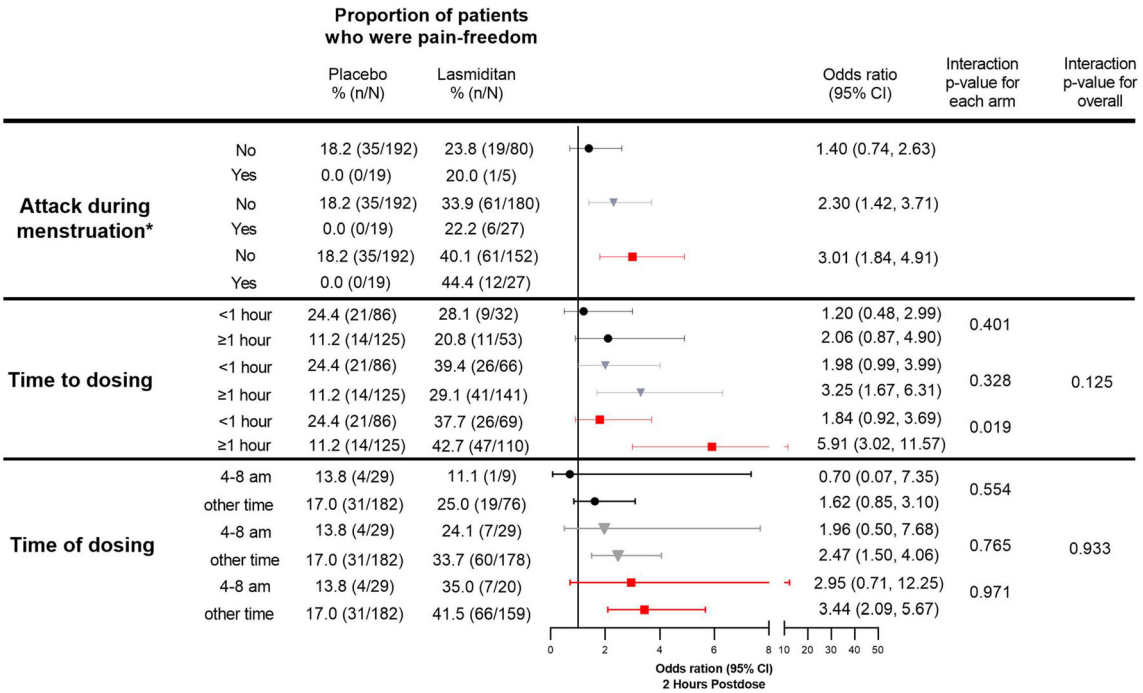


Fig. 2 Subgroup analysis for pain freedom at 2 h post dose based on migraine disease characteristics. *For pain freedom at 50 mg, odds ratio and *p* values were missing because the lasmiditan 50 mg arm had zero responders, hence calculation could not be performed. No interaction *p* values were observed for all results. *CI* confidence interval, *LTN* lasmiditan, *N* total number of patients in the specified group, *n* total number of patients in the subgroup, *PBO* placebo

Lasmiditan Efficacy Across Migraine Attack Characteristics (headache severity, aggressive headache, attack during perimenstrual period, time to dosing, time of dosing, experienced treatment-emergent adverse event (TEAE) of dizziness, and experienced TEAE of somnolence) (Figure 3)

Treatment-by-subgroup interaction (by each arm) was not observed across doses (50 mg, 100 mg, and 200 mg) between headache pain freedom at 2 h post dose and migraine attack characteristics ($p \geq 0.05$), except for the time to dosing at 200 mg dose ($p < 0.05$). Treatment-by-subgroup interaction (by overall) was not observed between migraine attack characteristics and lasmiditan treatment vs placebo ($p \geq 0.05$). Of note, treatment-by-subgroup interaction (by each arm and overall) could not be calculated for headache severity, aggressive headaches, and attack during the perimenstrual period because of the small sample size of one subgroup or the placebo arm having zero


Proportion of patients who were pain-free
Placebo % (n/N)
Lasmiditan % (n/N)
Odds ratio (95% CI)
Interaction p-value for each arm
Interaction p-value for overall
Headache severity*
Moderate 17.9 (35/196) 26.7 (20/75) 1.67 (0.89, 3.14)
Severe 0.0 (0/15) 0.0 (0/10)
Moderate 17.9 (35/196) 33.0 (63/191) 2.26 (1.41, 3.63)
Severe 0.0 (0/15) 25.0 (4/16)
Moderate 17.9 (35/196) 42.6 (72/169) 3.41 (2.12, 5.49)
Severe 0.0 (0/15) 10.0 (1/10)
Aggressive headache*
Yes 0.0 (0/6) 0.0 (0/4)
No 17.1 (35/205) 24.7 (20/81) 1.59 (0.85, 2.97)
Yes 0.0 (0/6) 16.7 (1/6)
No 17.1 (35/205) 32.8 (66/201) 2.37 (1.49, 3.79)
Yes 0.0 (0/6) 14.3 (1/7)
No 17.1 (35/205) 41.9 (72/172) 3.50 (2.18, 5.61)
0 1 2 3 4 5 6
Odds ration (95% CI)
2 Hours Postdose


Proportion of patients who were pain-freedom
Placebo % (n/N)
Lasmiditan % (n/N)
Odds ratio (95% CI)
Interaction p-value for each arm
Interaction p-value for overall
Attack during menstruation*
No 18.2 (35/192) 23.8 (19/80) 1.40 (0.74, 2.63)
Yes 0.0 (0/19) 20.0 (1/5)
No 18.2 (35/192) 33.9 (61/180) 2.30 (1.42, 3.71)
Yes 0.0 (0/19) 22.2 (6/27)
No 18.2 (35/192) 40.1 (61/152) 3.01 (1.84, 4.91)
Yes 0.0 (0/19) 44.4 (12/27)
Time to dosing
<1 hour 24.4 (21/86) 28.1 (9/32) 1.20 (0.48, 2.99) 0.401
≥1 hour 11.2 (14/125) 20.8 (11/53) 2.06 (0.87, 4.90)
<1 hour 24.4 (21/86) 39.4 (26/66) 1.98 (0.99, 3.99) 0.328 0.125
≥1 hour 11.2 (14/125) 29.1 (41/141) 3.25 (1.67, 6.31)
<1 hour 24.4 (21/86) 37.7 (26/69) 1.84 (0.92, 3.69) 0.019
≥1 hour 11.2 (14/125) 42.7 (47/110) 5.91 (3.02, 11.57)
Time of dosing
4-8 am 13.8 (4/29) 11.1 (1/9) 0.70 (0.07, 7.35) 0.554
other time 17.0 (31/182) 25.0 (19/76) 1.62 (0.85, 3.10)
4-8 am 13.8 (4/29) 24.1 (7/29) 1.96 (0.50, 7.68) 0.765 0.933
other time 17.0 (31/182) 33.7 (60/178) 2.47 (1.50, 4.06)
4-8 am 13.8 (4/29) 35.0 (7/20) 2.95 (0.71, 12.25) 0.971
other time 17.0 (31/182) 41.5 (66/159) 3.44 (2.09, 5.67)
0 2 4 6 8 10 20 30 40 50
Odds ration (95% CI)
2 Hours Postdose

◀**Fig. 3** Subgroup analysis for pain freedom at 2 h post dose based on migraine attack characteristics. *For headache severity and aggressive headache, "severe" severity and "Yes" for aggressive headaches, odds ratio and *p* values were missing because the placebo arm had zero responders, hence calculation could not be performed. *For the menstruation analysis, male patients were included as the "No" subgroup. Under the "no attacks during menstruation" subgroup, odds ratio and *p* values were missing because the placebo arm had zero responders, hence calculation could not be performed. *CI* confidence interval, *LTN* lasmiditan, *N* total number of patients in the specified group, *n* total number of patients in the subgroup, *PBO* placebo, *TEAE* treatment emergent adverse events

responders (Fig. 3). Therefore, frequency in each subgroup was considered for comparison. For headache severity (moderate vs severe), the severe subgroup had lower response rate (%) than the moderate subgroup across 50 mg (0 vs 27), 100 mg (25 vs 33), 200 mg (10 vs 43) arms; for the aggressive headache (yes vs no), the "yes" subgroup had a lower response rate (%) than the "no" subgroup across 50 mg (0 vs 25), 100 mg (17 vs 33), and 200 mg (14 vs 42) arms. A higher proportion of patients treated with lasmiditan 50 mg, 100 mg, and 200 mg were pain free 2 h post dose vs placebo, across headache severity, aggressive headache, attack during perimenstrual period, time to dosing, time of dosing, and who experienced TEAE of

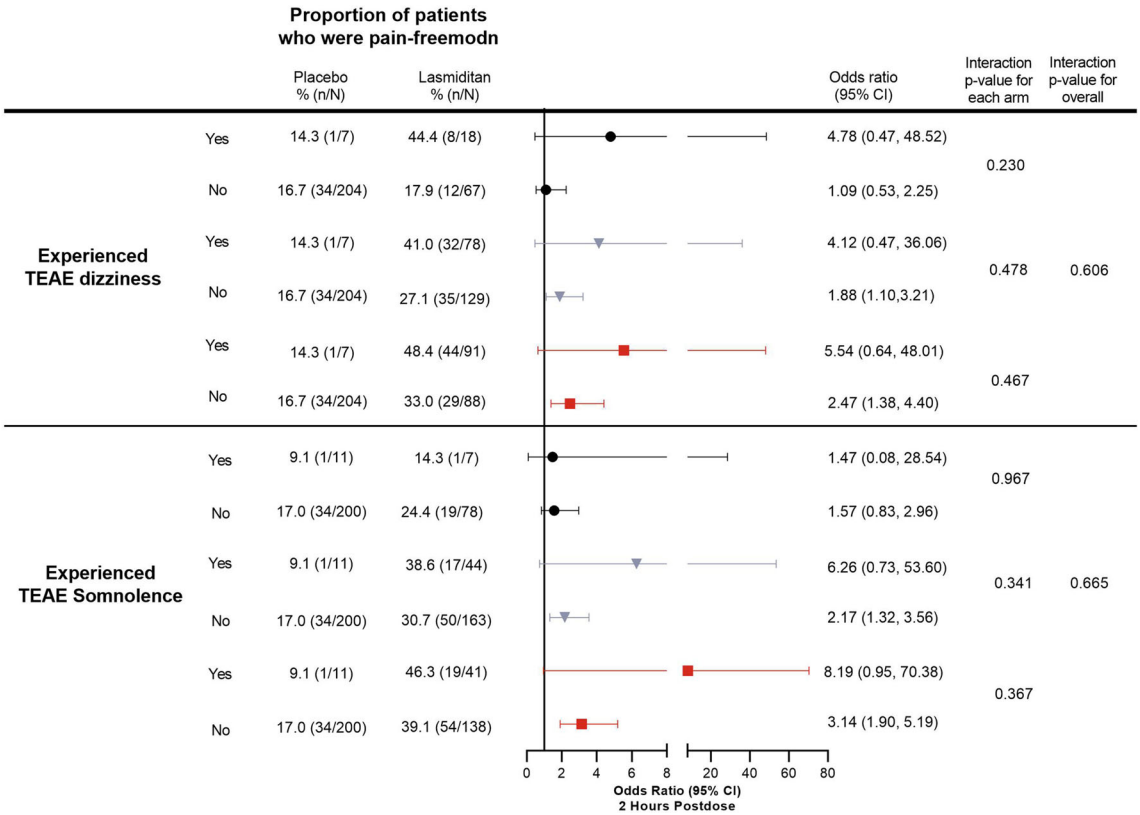


Fig. 3 continued

dizziness, and TEAE of somnolence, except for patients with severe headache severity, aggressive headache, and time of dosing 4 a.m. to 8 a.m. treated with 50 mg (Fig. 3).

DISCUSSION

This is the first subgroup analysis performed in Asian patients with migraine across patient and migraine characteristics. The results of the study across the four enrolled groups (lasmiditan 50 mg, 100 mg, 200 mg, and placebo) indicated that the efficacy of lasmiditan is generally not influenced by patient characteristics, migraine disease characteristics, and migraine attack characteristics. Lasmiditan 200 mg demonstrated the most effective dose in patients across most subgroups compared with placebo. The results from this subgroup analysis were in concordance with the MONONOFU trial and other phase 3 trials [9, 10, 12, 13, 19]. These findings suggest that lasmiditan could be a promising and effective acute treatment option for a wide group of Japanese patients with migraine.

Some patient characteristics such as age, sex, body weight, BMI, and tension-type headache are known to influence acute treatment response [6, 20–22]. Triptans are widely used as an acute treatment, but are contraindicated for patients with a history of cardiovascular disease or with CVRFs [23, 24]. The results of the treatment-by-subgroup interaction (by each arm and by overall) indicated that efficacy of lasmiditan was not generally influenced by patient characteristics in Japanese patients. Of note, treatment-by-subgroup interaction (by each arm; at 100 mg and 200 mg [both $p < 0.05$]) and treatment-by-subgroup interaction (by overall; [$p < 0.05$]) was observed only for CVRF subgroup. These results could be attributed to the dose-dependent difference in the odds ratio between treatment and placebo groups. Notably, point estimates difference between placebo CVRF ≤ 1 and CVRF ≥ 2 subgroups were about 10% (11.9% vs 22.6%). Given that, this placebo result may have influenced the odds ratios and interactions. Moreover, a post hoc analysis of the pooled results of the randomized phase 3 trials SAMURAI and SPARTAN demonstrated no significant difference in the proportion of patients achieving headache pain freedom at 2 h post lasmiditan dose in patients with CVRF ≤ 1 and with CVRF ≥ 2, indicating that lasmiditan efficacy is not influenced by the presence of CVRFs [25]. Thus, these observed treatment-by-subgroup interactions (by each arm and overall) for CVRFs in our study may not be considered as clinically meaningful and additional data is warranted.

Previous studies indicated that insufficient response to triptans, the commonly prescribed acute treatment in migraine, could affect the quality of life of patients [2, 26–28]. Furthermore, only 12.1% were currently using preventive medication within the patients who were eligible for the preventive medication [2]. Notable proportions of patients (more than 20%) experienced at least one problem with their preventive therapy, and lack of efficacy was the mostly frequently identified problem with preventive medication in Japan [29, 30]. Therefore, it was essential to evaluate the efficacy of lasmiditan across migraine disease characteristics. Treatment-by-subgroup interactions (by each arm) was observed at 50 mg dose for history of migraine with aura and triptan response. The proportion of pain freedom in the patients with aura (50.0%) was relatively higher than the proportion of the overall population in the 50 mg group (23.5%), explaining the significant interaction in the history of migraine with aura subgroup at 50 mg dose [13]. Similarly, the proportion of pain-free patients with insufficient response to triptans in the placebo group (21.4%) was relatively higher than the proportion of the overall population in the placebo (16.6%) group, explaining the significant interaction in the triptan response subgroup at 50 mg dose [13]. These variabilities could be derived from the small number of patients in the 50 mg groups. Previously reported results with a higher sample size demonstrated that efficacy of lasmiditan was independent of history of migraine with aura and prior response to triptans [11, 12, 31]. In summary, although treatment-by-subgroup interactions (by each arm) were observed with respect to the 50 mg dose as a result of the small

sample size, our findings suggested that the efficacy of lasmiditan in Japanese patients with migraine is not influenced by migraine disease characteristics.

Menstrual migraines are clinically more severe and difficult to treat compared with non-menstrual migraines [28, 29]. Furthermore, migraine attack characteristics including aggressive headache (headache that progresses rapidly and peaks to moderate-to-severe headache intensity in less than 1 h), delayed access to treatment (more than 2 h), and severe headache pain are known as predictors for poorer response to acute treatment [6, 32–36]. In addition, on the basis of the MONONOFU study results, a certain number of patients experienced dizziness and somnolence as the most commonly reported TEAEs. Treatment-by-subgroup interaction (by each arm) was observed for the time to dosing subgroup at 200 mg dose. This interaction might be derived from the variability in the proportion of placebo groups for the less than 1 h after the attack subgroup (24.4%) and at least 1 h after attack subgroup (11.2%). However, there is no clinical meaningful difference in the proportion of pain freedom between the patients who took lasmiditan 200 mg less than 1 h after the attack (37.7%) and at least 1 h after the attack subgroups (42.7%). In concordance with our results, another subgroup study indicated that efficacy of lasmiditan was not impacted by time to dosing, time of dosing, and headache severity [12]. Furthermore, presence of common TEAEs, such as dizziness, paresthesia, somnolence, or fatigue did not appear to have a negative influence on pain freedom [37]. Together, our findings suggested that the efficacy of lasmiditan in Japanese patients with migraine is not influenced by migraine attack characteristics.

This subgroup analysis evaluated the response of lasmiditan in Japanese patients across several patient and migraine characteristics including patients with insufficient response to acute treatment; however, the study had a few limitations, including the small sample size compared with global studies including SAMURAI and SPARTAN [9, 10, 19] and the lack of statistical power to signify a difference between lasmiditan and placebo in some subgroups. In addition, this study was not designed to show statistical significance in lasmiditan 50 mg dose compared to placebo for any efficacy analysis because of the anticipated smaller effect size compared to the higher doses. One multiplicity-adjusted endpoint showed a linear dose–response trend for lasmiditan efficacy [13]. Therefore, the subgroup analysis result would, at best, show a dose–response trend for lasmiditan efficacy. Additional studies in subgroups with larger sample size could alleviate the limitations.

CONCLUSION

In the MONONOFU study, a single dose of lasmiditan was effective in eliminating moderate to severe migraine pain at 2 h post dose, and a significant linear dose–response relationship for pain freedom was achieved [13]. In this secondary analysis, lasmiditan demonstrated consistent efficacy irrespective of patient characteristics, migraine disease characteristics, and migraine attack characteristics, indicating that lasmiditan could be used as an effective acute treatment option for a wide range of Japanese patients with migraine.

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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 https://vivli.org/.

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