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CLINICAL TRIAL REPORT

Lasmiditan in Japanese Patients with Common Migraine Comorbidities or Concomitant Medications: A Post Hoc Safety and Efficacy Analysis from the MONONOFU Study

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Background: Migraine is often comorbid with other disorders. People with migraine may be prescribed one or more concomitant medications. This post hoc analysis assessed the safety and efficacy of lasmiditan in Japanese people with migraine comorbidities or using concomitant medications.

Patients and Methods: The MONONOFU study was a Phase 2, randomized, placebo-controlled, multicenter study of lasmiditan for acute migraine treatment in Japanese adults. Patients reported comorbidities (pre-existing or coexisting conditions) during screening. Concomitant medications (any drugs taken ±48 hours of the study drug) and treatment-emergent adverse events (TEAEs) were recorded in a paper diary. Study drug efficacy (pain freedom 2 hours after administration of study drug) was reported in an eDiary. Logistic regression models were used for subgroup analyses of safety (incidence of TEAEs) and efficacy (pain freedom at 2 hours post dose) of lasmiditan in relation to presence/absence of comorbidities, and safety in relation to concomitant medications.

Results: Common comorbidities (occurring in ≥10% of any lasmiditan dose group) were seasonal allergies, allergic rhinitis, tension-type headache, cervicobrachial syndrome, dysmenorrhea, nasopharyngitis, musculoskeletal stiffness, chronic gastritis, constipation, and insomnia. There was no significant interaction of treatment with comorbidity for safety or efficacy. There was also no significant interaction between treatment and concomitant medication groups of special interest (acetaminophen/nonsteroidal anti-inflammatory drugs, triptans, antiemetics, central nervous system depressant medications, serotonergic medications, antiepileptics, antihypertensive medications, Chinese herbal medicines, and contraceptives) for incidence of TEAEs.

Conclusion: In Japanese people with migraine, the safety of lasmiditan appeared to be independent of common comorbidities and concomitant medications; efficacy appeared to be independent of comorbid conditions.

Clinical Trials Registration: NCT03962738 (ClinicalTrials.gov).

Keywords: comorbidity, drug therapy, headache, Japan, migraine disorders, safety

Introduction

Migraine is a highly prevalent disorder globally and causes substantial disability.[1] In Japan, the prevalence of migraine is estimated at around 8.5% of the population.[2,3]

Migraine is often comorbid with other highly prevalent disorders.[4] Common comorbidities of migraine include cardiovascular conditions, gastrointestinal disorders, obesity, anxiety, depression, panic disorder, bipolar disorder, asthma, sleep disorders, arthritis and chronic pain, and fatigue.[4] People with migraine may therefore be prescribed one or more concomitant medications to treat comorbid disorders, in addition to medication(s) prescribed for their migraine. Migraine treatment itself may also involve multiple medications, whether by combination of prescription and over-the-counter treatments, or by combination of preventive and acute migraine treatments.[2,5]

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Effective acute treatment of migraine is required to quickly resolve or improve migraine symptoms in order to reduce impacts on day-to-day functioning and quality of life.

However, acute treatment options may be limited by drug contraindications for comorbidities.[6] Lasmiditan is a selective 5-HT_{1F} (serotonin) receptor agonist that acts at the trigeminal nerve system to inhibit release of neurotransmitters and at the central nervous system (CNS) to inhibit pain transmission, without causing vasoconstriction.[4,7] The efficacy and safety of lasmiditan have been confirmed in global Phase 3 studies in non-Japanese patients[8–10] and in a Phase 2 study of Japanese adults (the MONONOFU study).[11–14] Lasmiditan was approved as an oral treatment for migraine in the USA in 2019[15] and in Japan in January 2022.

In a post hoc analysis of the global Phase 3 studies of lasmiditan, the efficacy and safety of lasmiditan appeared to be independent of comorbidities[4] and concomitant medications.[5] The impact of concomitant medications other than migraine preventives and of comorbidities common in Asian populations on the efficacy and safety of lasmiditan has not previously been assessed. In this post hoc analysis, data from the MONONOFU study were used to assess the impact of comorbidities on the safety and efficacy of lasmiditan, and the impact of concomitant medications (not limited to migraine preventives) on lasmiditan safety, in Japanese people with migraine.

Materials and Methods

Study Design, Study Population, and Treatment Protocol

The MONONOFU study design has been described previously.[11] Briefly, MONONOFU was a prospective, multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of lasmiditan in Japanese people with migraine (ClinicalTrials.gov identifier: NCT03962738). The primary objective was to evaluate the efficacy of lasmiditan 200 mg for achieving freedom from pain versus placebo. Included patients were aged ≥18 years and had migraine with or without aura fulfilling the International Headache Society diagnostic criteria,[16] a history of disabling migraine for ≥1 year, a history of 3–8 migraine attacks/month and <15 headache days/month during the past 3 months, and a Migraine Disability Assessment score ≥11.[17,18] The study protocol was approved by the Institutional Review Board for each study site (Supplementary Table 1). All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and 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.

Eligible patients were randomized to oral placebo or lasmiditan 50, 100, or 200 mg (7:3:7:6); the study drug was self-administered within 4 hours of onset of a single migraine attack (moderate-to-severe).[11] Efficacy data were collected in an electronic diary. Study participants recorded the date and time of the migraine attack, the time at which the study drug was taken, and migraine severity using the 4-point International Headache Society headache severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). Migraine severity was rated prior to taking the study drug and at 0.5, 1, 1.5, 2, 3, 4, 24, and 48 hours post dose. Patients recorded adverse events (AEs) in a paper diary.

The medical history of each patient, including comorbidities and concomitant medications, was collected at the screening visit. Comorbidities were coded as System Organ Classes (SOCs) and Preferred Terms (PTs) using the international Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. During the study, patients recorded concomitant medication use (including use of rescue or recurrence medications during the migraine attack) in the paper diary. Medications prohibited from 24 hours prior to 2 hours after administration of the study drug were acetaminophen (ACE), nonsteroidal anti-inflammatory drugs (NSAIDs), caffeine, antiemetics, triptans, ergots, opioids, and barbiturates. From 2 hours post dose, ACE, NSAIDs, caffeine, and antiemetics were allowed as rescue medications. From 24 hours post dose, triptans, ergots, opioids, and barbiturates were allowed for recurrence of a migraine attack. Migraine preventive medications were allowed if treatment was stable for 3 months prior to baseline.

Post Hoc Analysis

This post hoc analysis examined the safety and efficacy of lasmiditan in patient groups defined by comorbidities and concomitant medications. The safety endpoint for this analysis was any treatment-emergent adverse event (TEAE).

TEAEs were defined as AEs that occurred or worsened in severity within 48 hours after administration of the study drug, regardless of a causal relationship to the study drug. SOCs and PTs of TEAEs were coded using MedDRA Version 23.0.

The efficacy endpoint for this analysis was pain freedom 2 hours after administration of the study drug. Pain freedom was defined as moderate or severe headache pain (severity rating ≥2) becoming none (severity rating = 0).

The statistical procedure and analysis software used for the post hoc analysis is described in the Statistical Analysis section.

Comorbidities

Comorbidities were defined as pre-existing or coexisting conditions at baseline. Common comorbidities were defined as those that occurred in ≥10% of any treatment group.

Concomitant Medications

For this analysis, concomitant medications were defined as any drugs taken within 48 hours of the study drug (before or after), including rescue or recurrence medications. Concomitant medications were categorized into nine groups of special interest: ACE/NSAIDs (subgroups: ACE only, NSAIDs only), triptans, antiemetics, CNS depressant medications (subgroups: CNS depressants except antihistamines, antihistamines only), serotonergic medications, antiepileptics, antihypertensive medications, Chinese herbal medicines, and contraceptives. These medication groups were selected because they are common medications that are frequently used for migraine and/or headache treatment (eg, ACE, NSAIDs, triptans, antiemetics, Chinese herbal medicines); are specifically listed within the "precautions for co-administration" section of the package insert for lasmiditan (CNS depressants, serotonergic medications, and specific antihypertensive medications);[19] and/or are used to treat conditions that may be comorbid with migraine (eg, serotonergic medications, contraceptives [for menstruation-linked migraine], CNS depressants, antihypertensive medications).

For five of the concomitant medication groups, a set of special interest TEAEs were defined per the descriptions in the package insert for lasmiditan.[19] In the triptan and serotonergic medication groups, special interest TEAEs were those that could potentially be symptoms of serotonin syndrome (according to either the Hunter[20] or Sternbach[21] criteria). These included the PTs agitation, anxiety, chills, clonus, confused state, diarrhea, hyperhidrosis, hyperreflexia, hypomania, myoclonus, muscle rigidity, pyrexia, oculoclonus myoclonus, and tremor. In the CNS depressant group, special interest TEAEs were any TEAEs in the SOCs nervous system disorder, psychiatric disorder, or general disorder that occurred in ≥2% of the patients in any treatment group. In the antiemetic group, special interest TEAEs were nausea and vomiting. In the antihypertensive medication group, special interest TEAEs were any TEAEs in the cardiac disorder SOC that occurred in ≥2% of the patients in any treatment group. Special interest TEAEs were not defined for the ACE/NSAIDs, antiepileptics, Chinese herbal medicines, or contraceptives subgroups.

Statistical Analysis

All safety analyses were conducted using the safety analysis set (all randomized patients who received the study drug). TEAE incidence was calculated according to the presence or absence of comorbidities (or use of concomitant medications), and odds ratios (ORs) were calculated for the all-lasmiditan group (All LTN, which consisted of the lasmiditan 50-, 100-, and 200-mg arms combined) versus the placebo group. Logistic regression models were used for subgroup analyses of comorbidities (presence/absence) and concomitant drugs (presence/absence). The objective variable was the incidence of TEAEs. Covariates in the logistic regression models were treatment group (All LTN vs placebo), subgroup, and treatment-by-subgroup interaction. Results are presented as ORs with 95% confidence intervals (CIs). OR and treatment-by-subgroup interaction p-values were calculated with a significance level of 0.05 (2-sided test).

Efficacy analyses were conducted on data from the modified intent-to-treat (mITT) population (all randomized patients who took ≥1 dose of study drug within 4 hours of onset of the migraine attack and had any post-dose efficacy assessments). A logistic regression model was used for a subgroup analysis of efficacy in relation to comorbidities (presence/absence). The objective variable was pain freedom at 2 hours post dose. Because many concomitant drugs may have been taken >2 hours after the lasmiditan dose (eg, ACE/NSAIDs, caffeine, and antiemetics were allowed as rescue drugs 2–24 hours post dose), we did not model the influence of concomitant medication on the efficacy endpoint of pain

freedom at 2 hours. Covariates in the logistic regression model were treatment group (All LTN vs placebo), baseline usage of preventive migraine medications (Yes/No), subgroup, and treatment-by-subgroup interaction. OR and treatment-by-subgroup interaction p-values were calculated with a significance level of 0.05 (2-sided test). All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Disposition and Characteristics

The patient disposition and baseline characteristics for the MONONOFU study have been described previously.[11] Briefly, 846 patients were randomized and 691 took the study drug (safety population); the mITT population was 682 patients.[11] Most patients were female (83.1%) and the mean age was 45.2 years.[11] Baseline migraine characteristics of the study population included a mean migraine history duration of 24.2 years and a mean baseline Migraine Disability Assessment total score of 22.3.[11] Overall, 37.5% of the patients reported taking preventive migraine medication.[11]

Safety and Efficacy of Lasmiditan in Relation to Common Comorbidities

Comorbidities were very common in the safety population (Table 1; Supplementary Table 2). Among the patients who received any dose of lasmiditan (All LTN group, N=477), 444 (93.1%) had ≥1 comorbidity. The most common comorbidities (occurring in >15% of the patients) in the All LTN group were seasonal allergies, allergic rhinitis, tension-type headache, and cervicobrachial syndrome (26.6%, 23.1%,19.1%, and 16.8% of the All LTN group, respectively).

Safety

Overall, TEAEs were common in patients treated with lasmiditan (Table 2). In the All LTN group, the overall incidence of patients with ≥1 TEAE was 70.9%. Among the common comorbidity groups, the nasopharyngitis group reported the highest incidence of TEAEs, with 82.8% (53/64) of patients with nasopharyngitis in the All LTN group reporting ≥1 TEAE. The ORs for the incidence of TEAEs in the All LTN group with and without each comorbidity (vs placebo) were generally similar (Figure 1). There was no statistically significant treatment-by-subgroup interaction for any comorbidity.

Efficacy

Regardless of comorbidity status, the proportion of patients who achieved pain freedom at 2 hours was higher for All LTN than placebo (Figure 2; Supplementary Table 3). However, the OR of All LTN versus placebo was significant among patients with a comorbidity only for the seasonal allergy group (OR [95% CI]: 3.29 [1.43–7.57], p=0.005; Figure 2; Supplementary Table 3). Among the common comorbidity groups, the insomnia group reported the highest proportion of

Table 1 Most Common Comorbidities (Occurring in ≥10% of Any Lasmiditan Dose Group) by MedDRA Preferred Term (Safety Population)

PT[a], n (%)	PBO (n=214)	LTN 50 mg (n=87)	LTN 100 mg (n=208)	LTN 200 mg (n=182)	All LTN (n=477)	All Patients (N=691)
Patients with any comorbidity	199 (93.0)	81 (93.1)	194 (93.3)	169 (92.9)	444 (93.1)	643 (93.1)
Seasonal allergies	56 (26.2)	22 (25.3)	57 (27.4)	48 (26.4)	127 (26.6)	183 (26.5)
Allergic rhinitis	36 (16.8)	19 (21.8)	51 (24.5)	40 (22.0)	110 (23.1)	146 (21.1)
Tension-type headache	37 (17.3)	14 (16.1)	37 (17.8)	40 (22.0)	91 (19.1)	128 (18.5)
Cervicobrachial syndrome	39 (18.2)	11 (12.6)	38 (18.3)	31 (17.0)	80 (16.8)	119 (17.2)
Dysmenorrhea[b]	19 (10.7)	11 (14.7)	24 (13.6)	22 (15.2)	57 (14.4)	76 (13.2)
Nasopharyngitis	27 (12.6)	9 (10.3)	31 (14.9)	24 (13.2)	64 (13.4)	91 (13.2)
Musculoskeletal stiffness	21 (9.8)	13 (14.9)	17 (8.2)	21 (11.5)	51 (10.7)	72 (10.4)
Chronic gastritis	18 (8.4)	8 (9.2)	23 (11.1)	16 (8.8)	47 (9.9)	65 (9.4)
Constipation	19 (8.9)	9 (10.3)	20 (9.6)	16 (8.8)	45 (9.4)	64 (9.3)
Insomnia	26 (12.1)	6 (6.9)	23 (11.1)	15 (8.2)	44 (9.2)	70 (10.1)

Notes: [a]Preferred Terms from MedDRA Version 23.0. [b]Denominator adjusted because this was a sex-specific event for females: n=178 (placebo), n=75 (LTN 50 mg), n=176 (LTN 100 mg), n=145 (LTN 200 mg), n=396 (All LTN).
Abbreviations: LTN, lasmiditan; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PT, Preferred Term.

Table 2 Incidence of TEAEs in Patients Who Reported Comorbidities[a] (Safety Population)

	PBO (n=214)	LTN 50 mg (n=87)	LTN 100 mg (n=208)	LTN 200 mg (n=182)	All LTN (n=477)
Overall population (≥1 TEAE), n (%)	50 (23.4)	44 (50.6)	147 (70.7)	147 (80.8)	338 (70.9)
TEAE incidence by comorbidity (PT)[b], n1/n2[c] (%)					
Seasonal allergies	12/56 (21.4)	11/22 (50.0)	44/57 (77.2)	33/48 (68.8)	88/127 (69.3)
Allergic rhinitis	9/36 (25.0)	12/19 (63.2)	37/51 (72.5)	33/40 (82.5)	82/110 (74.5)
Tension-type headache	11/37 (29.7)	7/14 (50.0)	28/37 (75.7)	32/40 (80.0)	67/91 (73.6)
Cervicobrachial syndrome	10/39 (25.6)	5/11 (45.5)	31/38 (81.6)	27/31 (87.1)	63/80 (78.8)
Dysmenorrhea	4/19 (21.1)	6/11 (54.5)	19/24 (79.2)	19/22 (86.4)	44/57 (77.2)
Nasopharyngitis	6/27 (22.2)	5/9 (55.6)	26/31 (83.9)	22/24 (91.7)	53/64 (82.8)
Musculoskeletal stiffness	6/21 (28.6)	3/13 (23.1)	11/17 (64.7)	17/21 (81.0)	31/51 (60.8)
Chronic gastritis	7/18 (38.9)	5/8 (62.5)	15/23 (65.2)	13/16 (81.3)	33/47 (70.2)
Constipation	4/19 (21.1)	3/9 (33.3)	15/20 (75.0)	12/16 (75.0)	30/45 (66.7)
Insomnia	10/26 (38.5)	2/6 (33.3)	18/23 (78.3)	11/15 (73.3)	31/44 (70.5)

Notes: [a]Comorbidities in this table are presented in the same order as in Table 1. [b]PTs from MedDRA Version 23.0. [c]Where n1 = number of patients with ≥1 TEAE in the comorbidity–treatment group and n2 = total number of patients in the comorbidity–treatment group.
Abbreviations: LTN, lasmiditan; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PT, Preferred Term; TEAE, treatment-emergent adverse event.

patients who achieved pain freedom at 2 hours (18/43; 41.9%). The lowest proportion of patients who achieved pain freedom at 2 hours was in the dysmenorrhea comorbidity group (15/56; 26.8%). There was no statistically significant treatment-by-subgroup interaction for any comorbidity.

Safety of Lasmiditan in Relation to Concomitant Medications

The most commonly reported concomitant medications (taken by >40% of the patients in the All LTN group) were within the groups ACE/NSAIDs and triptans (53.0% and 42.3% of the All LTN group, respectively; Table 3). Antihypertensive medications (19.7%), CNS depressants (18.4%), and antiemetics (17.6%) were the next most common groups of concomitant medications.

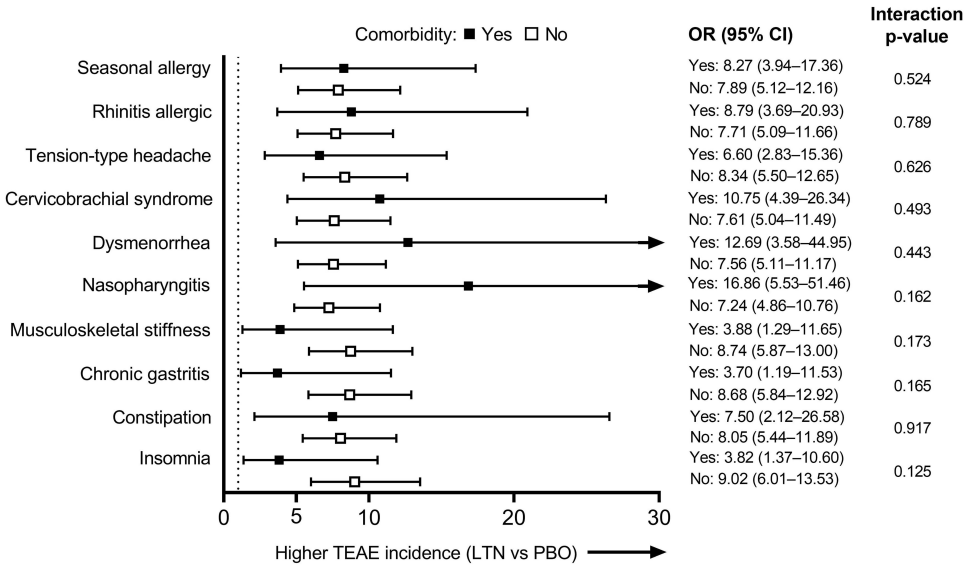

Figure 1 TEAE incidence: Forest plot of ORs (All LTN group vs PBO) for each of the most common comorbidity groups (safety population). Larger ORs indicate a higher incidence of TEAEs in the All LTN group compared with PBO. Dotted line indicates OR = 1. The interaction p-values shown are for the treatment-by-comorbidity interaction.
Abbreviations: CI, confidence interval; LTN, lasmiditan; OR, odds ratio; PBO, placebo; TEAE, treatment-emergent adverse event.

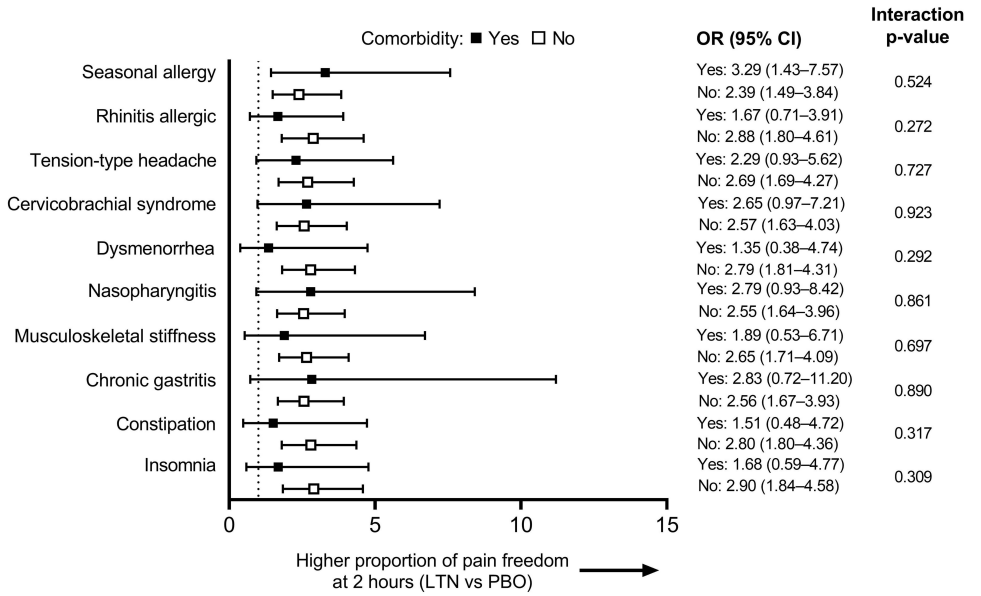

Figure 2 Efficacy: Forest plot of ORs (All LTN group vs PBO) for each of the most common comorbidity groups (mITT population). Larger ORs indicate a higher proportion of patients with pain freedom at 2 hours in the All LTN group compared with PBO. Dotted line indicates OR = 1.
Abbreviations: CI, confidence interval; LTN, lasmiditan; mITT, modified intent-to-treat; OR, odds ratio; PBO, placebo.

Safety

At least 1 TEAE was reported by approximately two-thirds to three-quarters of patients who received lasmiditan in the concomitant medication groups (Figure 3). TEAE incidence was higher in the groups taking antiepileptics, Chinese herbal medicines, and contraceptives (incidence of ≥1 TEAE: 73.2%, 72.7%, and 77.8%, respectively) versus the overall All LTN group.

Table 3 Concomitant Medication[a] Groups of Special Interest (Safety Population)

Concomitant Medication Group[b] Subgroup	Drug Class(es) Included in Group	PBO (n=214)	All LTN (n=477)
ACE/NSAIDs		131 (61.2)	253 (53.0)
ACE	Analgesics[c]	33 (15.4)	50 (10.5)
NSAIDs	Nonsteroidal anti-inflammatory drugs	118 (55.1)	226 (47.4)
Triptans	Triptans	85 (39.7)	202 (42.3)
Antiemetics	Dopamine receptor agonists	50 (23.4)	84 (17.6)
CNS depressants		41 (19.2)	88 (18.4)
CNS depressants other than antihistamines	Opioids, benzodiazepines, non-benzodiazepine anxiolytics/hypnotics, and antipsychotics	20 (9.3)	45 (9.4)
Antihistamines	Antihistamines	21 (9.8)	47 (9.9)
Serotonergic medications	Tricyclic/tetracyclic antidepressants, SSRIs, SNRIs, NaSSAs or other antidepressants, and MAO inhibitors	32 (15.0)	60 (12.6)
Antiepileptic drugs	Anticonvulsants and benzodiazepines	38 (17.8)	82 (17.2)
Antihypertensive drugs	Calcium blockers and beta blockers	42 (19.6)	94 (19.7)
Chinese herbal medicines	Unspecified traditional and herbal medicines[d]	10 (4.7)	22 (4.6)
Contraceptives	Progestins, estrogens, and combination progestins/estrogens	18 (8.4)	27 (5.7)

Notes: [a]Concomitant medications were defined as any drugs taken within 48 hours of the study drug (before or after), including rescue or recurrence medications. [b]Patients could belong to multiple concomitant medication groups. [c]ACE/paracetamol only. [d]The top three types of Chinese herbal medicines reported were kakkonto, goreisan, and goshuyuto, all of which are common herbal medicines in Japan.
Abbreviations: ACE, acetaminophen; CNS, central nervous system; LTN, lasmiditan; MAO, monoamine oxidase; NaSSA, noradrenergic and specific serotonergic antidepressant; NSAID, nonsteroidal anti-inflammatory drug; PBO, placebo; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

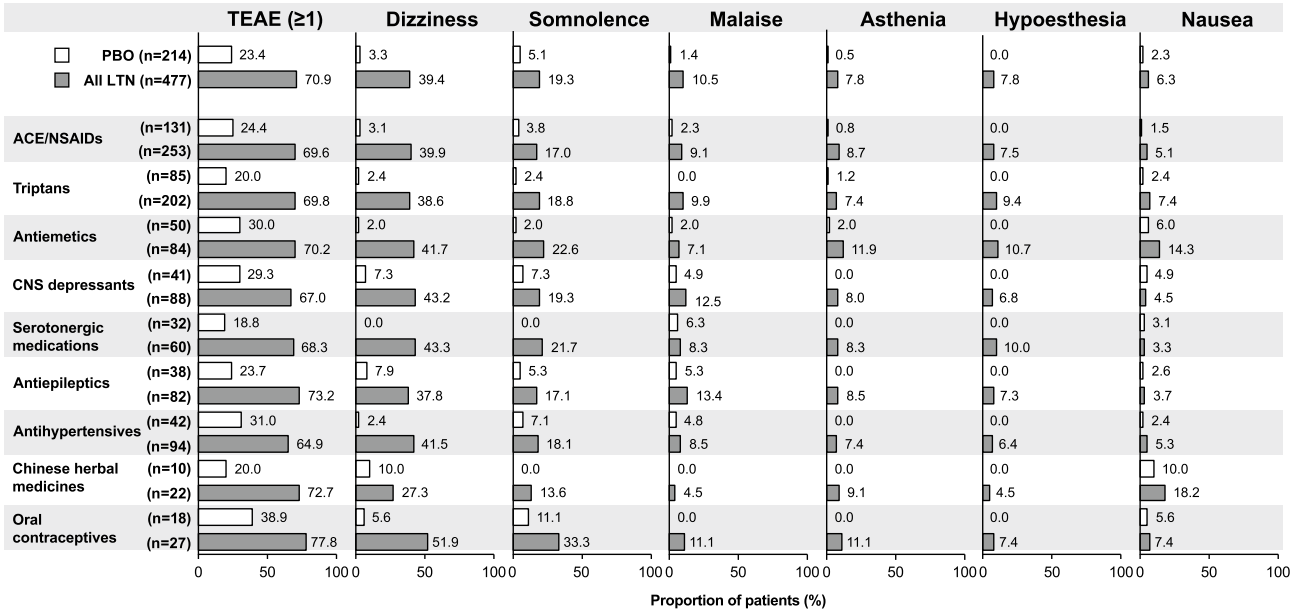

Figure 3 Most common TEAEs (≥5% in the All LTN group) in the MONONOFU study[11] and their incidence in the concomitant medication groups (safety population).
Abbreviations: ACE, acetaminophen; CNS, central nervous system; LTN, lasmiditan; NSAID, nonsteroidal anti-inflammatory drug; PBO, placebo; TEAE, treatment-emergent adverse event.

As previously reported, the six most common TEAEs (≥5% in the All LTN group) in the MONONOFU study were dizziness, somnolence, malaise, asthenia, hypoesthesia, and nausea.[11] The incidence of these TEAEs varied between the concomitant medication groups (Figure 3). The contraceptives group reported the highest incidences of dizziness (51.9%, 14/27 patients) and somnolence (33.3%, 9/27 patients) in All LTN patients. Malaise was highest in the antiepileptic–All LTN group (13.4%, 11/82 patients), while asthenia and hypoesthesia were highest in the antiemetic–All LTN group (11.9%, 10/84 patients and 10.7%, 9/84 patients, respectively). The Chinese herbal medicines group reported the highest incidence of nausea in All LTN patients (18.2%, 4/22 patients).

Within each of the concomitant medication groups, the ORs for the incidence of ≥1 TEAE in the All LTN group with and without each medication (vs placebo) were generally similar (Figure 4). The highest ORs were seen for patients who took Chinese herbal medicines (OR for All LTN vs placebo [95% CI]: 10.67 [1.74–65.27]), serotonergic medications (9.35 [3.30–26.48]), and triptans (9.25 [5.02–17.02]). The treatment-by-subgroup interaction was not significant for any of the concomitant medication groups.

In patients who took CNS depressant medications and received lasmiditan as the study drug, around two-thirds reported ≥1 TEAE (59/88 patients, 67.0%; Table 4). The most common special interest TEAE in this group was dizziness (43.2% of the All LTN group with CNS depressants; 38/88 patients). There was no statistically significant interaction between lasmiditan treatment and CNS depressants for the incidence of CNS TEAEs.

There was no evidence of increased risk of serotonin syndrome symptoms in patients who received lasmiditan and either triptans or serotonergic medications (Table 5). Symptoms of confused state, hypomania, agitation, myoclonus, hyperreflexia, clonus, muscle rigidity, or oculoclonus myoclonus were not observed. Diarrhea, chills, tremor, pyrexia, and anxiety were reported at low incidence (0.5–2.5%) in triptan users; hyperhidrosis was not present in this group. In users of serotonergic medications, diarrhea, pyrexia, tremor, and hyperhidrosis were reported at low incidence (1.7% for each), while chills and anxiety were not reported. There was no statistically significant interaction between lasmiditan treatment and triptans or serotonergic medications for the incidence of these TEAEs.

For patients who took antiemetics, the OR (All LTN vs placebo) for nausea was lower than for those who did not take antiemetics (2.61 vs 3.89, respectively; Table 6). However, the interaction between lasmiditan treatment and antiemetic use was not significant.

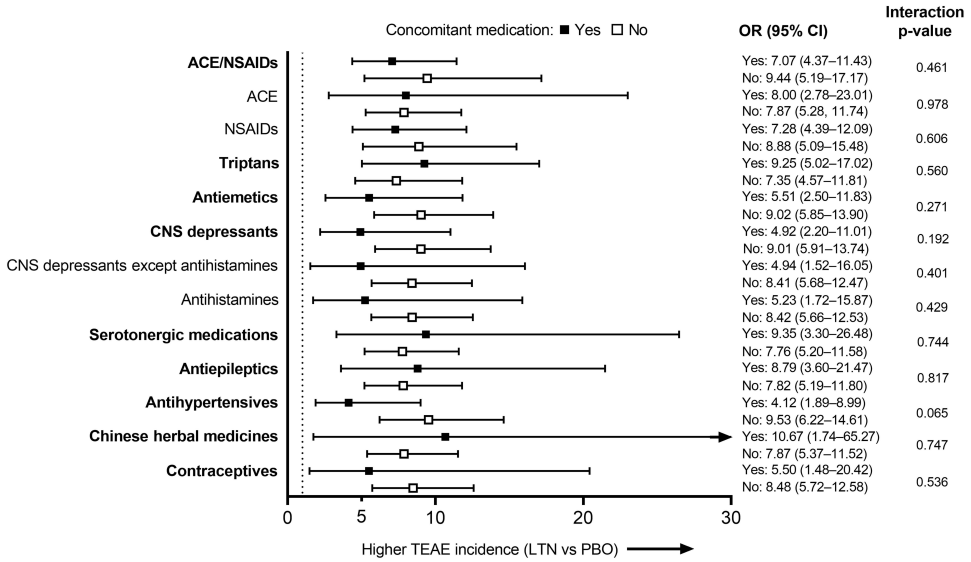

Figure 4 TEAE incidence: Forest plot of ORs (All LTN group vs PBO) for each of the concomitant medication groups (safety population). Larger ORs indicate a higher incidence of TEAEs in the All LTN group compared with PBO. Dotted line indicates OR = 1. The interaction p-values shown are for the treatment-by-concomitant medication interaction. Bold indicates concomitant medication groups and plain type indicates subgroups.

Abbreviations: ACE, acetaminophen; CI, confidence interval; CNS, central nervous system; LTN, lasmiditan; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PBO, placebo; TEAE, treatment-emergent adverse event.

In patients who took antihypertensive medications, the OR for palpitations was lower than in patients who did not take antihypertensive medications (0.89 vs 3.46, respectively; Table 7), but the interaction between lasmiditan and antihypertensive medications was not significant.

Discussion

This post hoc analysis of data from the MONONOFU study evaluated the safety and efficacy of lasmiditan for treatment of a single migraine attack among patients with and without common comorbidities, and safety of lasmiditan with and without concomitant medications. This is the first such analysis in an Asian patient population. In Japanese patients with migraine, comorbidities and concomitant medications did not affect the safety of lasmiditan. In general, the efficacy of lasmiditan was not affected by comorbidities. These results confirm the safety and efficacy of lasmiditan for migraine in patients with common comorbidities and/or using common concomitant medications.

In the current analysis, we evaluated safety and efficacy in relation to the most common comorbidities (defined as comorbidities that occurred in ≥10% of any lasmiditan dose group). The incidence of TEAEs was similar across all the common comorbidity groups, and the treatment-by-subgroup interaction was not significant for any comorbidity. Similarly, the proportion of patients who achieved pain freedom at 2 hours did not show any significant treatment-by-subgroup interaction for any comorbidity. These results are consistent with the results of a similar post hoc analysis of global Phase 3 trial data for lasmiditan.[4] In the global post hoc analysis, the comorbidity groups were 13 categorical groups based on common migraine comorbidities. Despite this difference in approach, both our analysis and the global analysis found no evidence of a differential treatment effect (lasmiditan vs placebo) dependent on subgroup (ie, comorbidity "yes" vs comorbidity "no") on the safety or efficacy of lasmiditan.

We examined a broader range of concomitant medications in our analysis than in the post hoc analysis of 2 global Phase 3 trials, which examined only medications often prescribed as migraine preventive treatments (even if taken for other reasons).[5] Overall incidence of TEAEs was similar across all the concomitant medication groups in our analysis, and the treatment-by-subgroup interaction was not significant for any concomitant medication. This was similar to the pattern seen in the global study population.[5] However, our results suggest this may be a broader pattern across a larger range of medications. This is important given that migraine is comorbid with multiple diseases, many of which require regular medication.

Table 4 Occurrence of Special Interest TEAEs[a] with and without CNS Depressant Use (Safety Population)

PT, n (%)	PBO (n=214)		All LTN (n=477)		OR (95% CI), All LTN vs PBO		p-value[b]
	Without CNS Depressants (n=173)	With CNS Depressants (n=41)	Without CNS Depressants (n=389)	With CNS Depressants (n=88)	Without CNS Depressants	With CNS Depressants	
Patients with ≥1 TEAE[c]	38 (22.0)	12 (29.3)	279 (71.7)	59 (67.0)	9.01 (5.91–13.74)	4.92 (2.20–11.01)	0.192
Dizziness	4 (2.3)	3 (7.3)	150 (38.6)	38 (43.2)	26.52 (9.64–72.97)	9.63 (2.76–33.56)	0.217
Somnolence	8 (4.6)	3 (7.3)	75 (19.3)	17 (19.3)	4.93 (2.32–10.46)	3.03 (0.84–11.01)	0.524
Malaise	1 (0.6)	2 (4.9)	39 (10.0)	11 (12.5)	19.17 (2.61–>99.99)	2.79 (0.59–13.19)	0.135
Asthenia	1 (0.6)	0	30 (7.7)	7 (8.0)	14.37 (1.94–>99.99)	NA	NA
Hypoesthesia	0	0	31 (8.0)	6 (6.8)	NA	NA	NA
Fatigue	1 (0.6)	0	12 (3.1)	1 (1.1)	5.47 (0.71–42.44)	NA	NA
Feeling abnormal	0	0	10 (2.6)	1 (1.1)	NA	NA	NA
Chills	0	1 (2.4)	5 (1.3)	2 (2.3)	NA	0.93 (0.08–10.56)	NA
Dizziness postural	0	0	5 (1.3)	0	NA	NA	NA
Tremor	0	0	5 (1.3)	0	NA	NA	NA
Nightmares	0	0	4 (1.0)	1 (1.1)	NA	NA	NA
Discomfort	0	0	4 (1.0)	0	NA	NA	NA
Insomnia	0	0	3 (0.8)	0	NA	NA	NA
Feeling hot	0	0	3 (0.8)	0	NA	NA	NA
Pyrexia	1 (0.6)	0	0	1 (1.1)	0.00 (NA–NA)	NA	NA

Notes: [a]Any TEAE in the SOCs nervous system disorder, psychiatric disorder, or general disorder that occurred in ≥2% of the patients in any treatment group. [b]For the treatment-by-subgroup (with/without CNS depressants) interaction. [c]Patients with any TEAE, not limited to special interest TEAEs.

Abbreviations: CI, confidence interval; CNS, central nervous system; LTN, lasmiditan; NA, not applicable; OR, odds ratio; PBO, placebo; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

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Table 5 Occurrence of Special Interest TEAEs[a] with or without Triptan or Serotonergic Medication Use (Safety Population)

PT, n (%)	**PBO (n=214)**		**All LTN (n=477)**		**OR (95% CI), All LTN vs PBO**		
Triptan Group	Without Triptans (n=129)	With Triptans (n=85)	Without Triptans (n=275)	With Triptans (n=202)	Without Triptans	With Triptans	p-value[b]
Patients with ≥1 TEAE[c]	33 (25.6)	17 (20.0)	197 (71.6)	141 (69.8)	7.35 (4.57–11.81)	9.25 (5.02–17.02)	0.560
Diarrhea	2 (1.6)	3 (3.5)	8 (2.9)	5 (2.5)	1.90 (0.40–9.09)	0.69 (0.16–2.97)	0.354
Chills	1 (0.8)	0	5 (1.8)	2 (1.0)	2.37 (0.27–20.50)	NA	NA
Tremor	0	0	2 (0.7)	3 (1.5)	NA	NA	NA
Anxiety	1 (0.8)	0	0	2 (1.0)	0.00 (NA–NA)	NA	NA
Pyrexia	1 (0.8)	0	0	1 (0.5)	0.00 (NA–NA)	NA	NA
Hyperhidrosis	0	0	1 (0.4)	0	NA	NA	NA
Serotonergic Medication Group	Without Serotonergic Medications (n=182)	With Serotonergic Medications (n=32)	Without Serotonergic Medications (n=417)	With Serotonergic Medications (n=60)	Without Serotonergic Medications	With Serotonergic Medications	p-value[d]
Patients with ≥1 TEAE[c]	44 (24.2)	6 (18.8)	297 (71.2)	41 (68.3)	7.76 (5.20–11.58)	9.35 (3.30–26.48)	0.744
Diarrhea	4 (2.2)	1 (3.1)	12 (2.9)	1 (1.7)	1.32 (0.42–4.14)	0.53 (0.03–8.69)	0.552
Chills	1 (0.5)	0	7 (1.7)	0	3.09 (0.38–25.30)	NA	NA
Anxiety	1 (0.5)	0	2 (0.5)	0	0.87 (0.08–9.68)	NA	NA
Pyrexia	1 (0.5)	0	0	1 (1.7)	0.00 (NA–NA)	NA	NA
Tremor	0	0	4 (1.0)	1 (1.7)	NA	NA	NA
Hyperhidrosis	0	0	0	1 (1.7)	NA	NA	NA

Notes: [a]Any TEAE that could potentially be symptoms of serotonin syndrome (according to either Sternbach's diagnostic criteria[21] or Hunter Serotonin Toxicity Criteria[20]). Symptoms of confused state, hypomania, agitation, myoclonus, hyperreflexia, clonus, muscle rigidity, or oculoclonus myoclonus were not observed in the MONONOFU population. [b]For the treatment-by-subgroup (with/without triptans) interaction. [c]Patients with any TEAE, not limited to special interest TEAEs. [d]For the treatment-by-subgroup (with/without serotonergic medications) interaction.

Abbreviations: CI, confidence interval; LTN, lasmiditan; NA, not applicable; OR, odds ratio; PBO, placebo; PT, Preferred Term; TEAE, treatment-emergent adverse event.

Table 6 Occurrence of Special Interest TEAEs[a] with and without Antiemetic Medication Use (Safety Population)

PT, n (%)	PBO (n=214)		All LTN (n=477)		OR (95% CI), All LTN vs PBO		p-value[b]
	Without Antiemetics (n=164)	With Antiemetics (n=50)	Without Antiemetics (n=393)	With Antiemetics (n=84)	Without Antiemetics	With Antiemetics	
Patients with ≥1 TEAE[c]	35 (21.3)	15 (30.0)	279 (71.0)	59 (70.2)	9.02 (5.85–13.90)	5.51 (2.56–11.83)	0.271
Nausea	2 (1.2)	3 (6.0)	18 (4.6)	12 (14.3)	3.89 (0.89–16.95)	2.61 (0.70–9.75)	0.693
Vomiting	2 (1.2)	0	7 (1.8)	1 (1.2)	1.47 (0.30–7.15)	NA	NA

Notes: [a]Nausea and vomiting only. [b]For the treatment-by-subgroup (with/without antiemetic medication) interaction. [c]Patients with any TEAE, not limited to special interest TEAEs.
Abbreviations: CI, confidence interval; LTN, lasmiditan; NA, not applicable; OR, odds ratio; PBO, placebo; PT, Preferred Term; TEAE, treatment-emergent adverse event.

Table 7 Occurrence of Special Interest TEAEs[a] with and without Antihypertensive Medication Use (Safety Population)

SOC PT, n (%)	PBO (n=214)		All LTN (n=477)		OR (95% CI), All LTN vs PBO		p-value[b]
	Without Anti-Hypertensives (n=172)	With Anti-Hypertensives (n=42)	Without Anti-Hypertensives (n=383)	With Anti-Hypertensives (n=94)	Without Anti-Hypertensives	With Anti-Hypertensives	
Patients with ≥1 TEAE[c]	37 (21.5)	13 (31.0)	277 (72.3)	61 (64.9)	9.53 (6.22–14.61)	4.12 (1.89–8.99)	0.065
Cardiac disorder	2 (1.2)	1 (2.4)	15 (3.9)	2 (2.1)	3.46 (0.78–15.32)	0.89 (0.08–10.11)	0.350
Palpitations	2 (1.2)	1 (2.4)	15 (3.9)	2 (2.1)	3.46 (0.78–15.32)	0.89 (0.08–10.11)	0.350

Notes: [a]Any TEAE in the cardiac disorder SOC that occurred in ≥2% of the patients in any treatment group. [b]For the treatment-by-subgroup (with/without antihypertensive medication) interaction. [c]Patients with any TEAE, not limited to special interest TEAEs.
Abbreviations: CI, confidence interval; LTN, lasmiditan; OR, odds ratio; PBO, placebo; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

Several of the concomitant medication groups may be associated with specific TEAEs or groups of TEAEs. Because lasmiditan is a centrally penetrant drug,[7,22] we hypothesized that lasmiditan may interact with CNS depressants to make CNS-specific TEAEs more common. However, in this study in Japanese patients, we found that this was not the case, and there was no significant interaction between lasmiditan and CNS depressants for any CNS-specific TEAE. As lasmiditan can be associated with nausea,[11] we expected that there might be lower rates of nausea in patients who received lasmiditan plus antiemetics than in those receiving lasmiditan without antiemetics. However, we also found no interaction between lasmiditan and antiemetics in the incidence of nausea or vomiting. Our results suggest that patients took antiemetics because they experienced nausea, resulting in a relatively high proportion of patients with nausea among antiemetic users regardless of treatment group. Finally, we also checked for an interaction between antihypertensive medications and lasmiditan, as both can be associated with bradycardia.[19,23,24] We found no interaction between lasmiditan and antihypertensive drugs in the incidence of cardiac TEAEs generally. The only cardiac disorder TEAE that occurred in ≥2% of the patients receiving lasmiditan was palpitations, which was more common in patients who were not using antihypertensive medications.

Because lasmiditan is a serotonin receptor agonist, we also assessed whether TEAEs potentially indicative of serotonin syndrome were impacted by the interaction of lasmiditan with triptans (also serotonergic) or general serotonergic medications. The serotonin syndrome symptoms of confused state, hypomania, agitation, myoclonus, hyperreflexia, clonus, muscle rigidity, or oculoclonus myoclonus were not observed in the MONONOFU study. Other TEAEs that may be related to serotonin syndrome (anxiety, chills, diarrhea, hyperhidrosis, tremor, and pyrexia) were observed only at low incidence. We found no significant interactions between lasmiditan treatment and triptans or serotonergic medications for the incidence of these TEAEs. These results are consistent with an earlier safety analysis of the whole MONONOFU population, in which none of the participants met the Hunter or Sternbach criteria for serotonin syndrome (based on medical review).[13]

Because of the study design, some concomitant medications may have been taken >2 hours after the lasmiditan dose as rescue medication (eg, ACE/NSAIDs, caffeine, and antiemetics). As a result, we were unable to model the influence of concomitant medication on the efficacy endpoint of pain freedom at 2 hours. Headache treatment guidelines in several

countries advise the addition of an NSAID if a single dose of a triptan provides insufficient pain relief.[25–29] The effectiveness of combining lasmiditan with other acute medications, particularly those that also target 5-HT receptors such as triptans and ergots, is an area that warrants further investigation.

The strengths of this post hoc analysis included the use of data from a randomized, placebo-controlled, multicenter clinical trial. In addition, these are the first assessments of the efficacy and safety of lasmiditan in relation to comorbidities or concomitant medications in an Asian population. Our analysis of concomitant medications was broad, including not only medications commonly used as migraine preventives but also other concomitant medications in frequent use. We also considered comorbidities within the framework of disease type rather than the SOC affected.

Limitations of our analysis include that our findings are based on post hoc analyses from a study that was limited to a single dose of lasmiditan and was not designed to investigate relationships between lasmiditan and comorbidities or concomitant medications. Because concomitant medications were taken at any time within 48 hours of the study drug, it is possible that the onset of some TEAEs was prior to the use of concomitant medications. In addition, we cannot rule out the effects of polypharmacy; in cases where a patient used lasmiditan and >1 category of concomitant medication, there was the potential for TEAEs to be associated with an interaction between lasmiditan and multiple categories of concomitant medications. In general, the small sample sizes in the comorbidity "yes" versus "no" and concomitant medication "yes" versus "no" subgroups meant that interaction hypothesis tests were unlikely to be rejected due to wider CIs (eg, as seen for the Chinese medication subgroup). In addition, our post hoc analyses were performed without multiplicity adjustment, which potentially inflated the overall Type 1 error rate.

Conclusion

In Japanese patients with migraine, comorbidities and concomitant medications did not affect the safety of lasmiditan. The efficacy of lasmiditan appeared to be independent of comorbid conditions.

Abbreviations

ACE, acetaminophen; AE, adverse event; CI, confidence interval; CNS, central nervous system; LTN, lasmiditan; MedDRA, Medical Dictionary for Regulatory Activities; mITT, modified intent-to-treat; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; PT, Preferred Term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

Data Sharing Statement

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 United States 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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Author Contributions

All authors made a significant contribution to the work reported, either in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising, or

critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

SK reports lecture fees from Daiichi Sankyo Company, Limited and Otsuka Pharmaceutical Co., Ltd., outside the submitted work. NI reports payments or honoraria for lectures and presentations from Eli Lilly Japan K.K. and Daiichi Sankyo Company, Limited, during the conduct of the study; personal fees from Otsuka Pharmaceutical, Amgen, and Sawai Pharmaceutica, outside the submitted work. YT, AO, and MK are employees of Eli Lilly Japan K.K. and have minor shareholdings in Eli Lilly and Company. The authors report no other conflicts of interest in this work.

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