Research Submission

Evaluation of 2-Hour Post-Dose Efficacy of Lasmiditan for the Acute Treatment of Difficult-to-Treat Migraine Attacks

Stewart J. Tepper, MD; Raghavendra Vasudeva, PhD; John H. Krege, MD; Suchitrita S. Rathmann, PhD; Erin Doty, MD; Bert B. Vargas, MD; Delphine Magis, MD, PhD; Mika Komori, MD, PhD

Objective.—To identify factors predicting response (2-hour headache pain freedom or most bothersome symptom freedom) to lasmiditan based on individual patient characteristics, migraine disease characteristics, and migraine attack characteristics. Further, efficacy specifically in difficult-to-treat patient/migraine disease characteristics or attack characteristics (ie, historically considered less responsive to certain acute therapies) subgroups was analyzed.

Background.—Knowledge of factors associated with a positive or negative response to acute treatment would be useful to practitioners prescribing acute treatments for migraine. Additionally, practitioners and patients would benefit from understanding the efficacy of lasmiditan specifically in subgroups of patients with migraine disease characteristics and migraine attack characteristics historically associated with decreased pain threshold, reduced efficacy of acute treatment, or increased burden of migraine.

Methods.—Pooled analyses were completed from 2 Phase 3 double-blind clinical trials, SPARTAN and SAMURAI. Data from baseline to 2 hours after taking lasmiditan (50, 100, or 200 mg) or placebo were analyzed to assess efficacy based on patient characteristics, migraine disease characteristics, and migraine attack characteristics. A total of 3981 patients comprising the intent-to-treat population were treated with placebo (N = 1130), lasmiditan 50 mg (N = 598), lasmiditan 100 mg (N = 1133), or lasmiditan 200 mg (N = 1120). Data were analyzed for the following efficacy measures at 2 hours: headache pain freedom and most bothersome symptom freedom.

Results.—None of the analyzed subgroups based on individual patient characteristics, migraine disease characteristics, or migraine attack characteristics predicted headache pain freedom or most bothersome symptom freedom response at 2 hours following lasmiditan treatment (interaction $P \geq .1$). For the difficult-to-treat patient/migraine disease characteristics subgroups (defined as those with ≥24 headache days in the past 3 months, duration of migraine history ≥20 years, severe disability [Migraine Disability Assessment score ≥21], obesity [≥30 kg/m^2], and history of psychiatric disorder), single doses of lasmiditan (100 or 200 mg) were significantly more effective than placebo ($P \leq .002$) in achieving both endpoints. Headache pain freedom response rates for higher doses of lasmiditan were numerically greater than for lower doses of lasmiditan. For the difficult-to-treat migraine attack subgroups, patients with severe headache, co-existent nausea at the time of treatment, or who delayed treatment for ≥2 hours from the time of headache onset, both endpoint response rates after lasmiditan 100 or 200 mg were significantly greater than after placebo. Among those who delayed treatment for ≥4 hours from the time of headache onset, headache pain freedom response rates for the 200 mg dose of lasmiditan met statistical significance vs placebo (32.4% vs 15.9%; odds

From the Department of Neurology, Geisel School of Medicine at Dartmouth, Hanover, NH, USA (S.J. Tepper); Eli Lilly and Company, Indianapolis, IN, USA (R. Vasudeva, J.H. Krege, S.S. Rathmann, E. Doty, and B.B. Vargas); University of Texas Southwestern Medical Center, Dallas, TX, USA (B.B. Vargas); Department of Neurology and Headache and Pain Multimodal Management Clinic, CHR East Belgium Hospital, Verviers, Belgium (D. Magis); Eli Lilly and Company, Kobe, Japan (M. Komori).

Address all correspondence to R. Vasudeva, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA, email: vasudevara@lilly.com

ratio = 2.7 [1.17, 6.07]; *P* = .018). While the predictors of response interaction test showed similar efficacy of lasmiditan vs placebo across subgroups defined by baseline functional disability (mild, moderate, or needs complete bed rest) at the time of treatment, analyses of lasmiditan efficacy within the subgroup "needs complete bed rest" appeared to show less efficacy (eg, in the 200 mg vs placebo group, 25.9% vs 18.5%; odds ratio = 1.56 [0.96, 2.53]; *P* = .070).

Conclusions.—Efficacy of lasmiditan 200 and 100 mg for headache pain freedom and most bothersome symptom freedom at 2 hours post-treatment was generally not influenced by the individual patient characteristics, migraine disease history, or migraine attack characteristics that were analyzed. In the analyses of difficult-to-treat subgroups, patients receiving lasmiditan achieved greater responses (2-hour headache pain freedom and most bothersome symptom freedom) vs placebo recipients.

Key words: lasmiditan, migraine, headache, predictors of response, difficult-to-treat

Abbreviations: BMI body mass index, CI confidence interval, ITT intent-to-treat, MBS most bothersome symptom, MIDAS Migraine Disability Assessment, OR odds ratio

INTRODUCTION

Migraine is a debilitating neurological disorder that greatly impacts the daily lives of patients and their families and is characterized by functional impairment that is most frequently secondary to intense headache pain and associated migraine symptoms, such as nausea, photophobia, and phonophobia.[1] There are many acute treatments for migraine for which evidence supports efficacy; however, acute treatment of migraine is complex, and no treatment is optimal for all patients.[2,3] Clinical features based upon the patient's general medical condition, attack-specific characteristics (eg, headache intensity and nausea), contraindications, and individualized goals of treatment may be relevant when selecting an acute medication.[3]

Knowledge of factors associated with a positive or negative response to acute treatment would be useful to practitioners prescribing acute treatment for migraine. Epidemiology and clinical trial studies have identified significant predictors of insufficient treatment efficacy (2-hour headache pain freedom) in patients with migraine based on patient- and attack-specific characteristics.[4-6] Some features of a migraine attack associated with insufficient efficacy of acute treatment (so-called "difficult-to-treat") included patients who experienced severe headache pain, nausea, or severe disability during an attack[4-6] and those who have delayed initiation of treatment (≥2 hours after migraine onset).[7-13] Migraine pain is typically more difficult to treat when it has progressed to severe pain, as would be expected clinically.[14] Further, long migraine disease history (>10 years),[15] higher number of monthly headache days,[16] greater disability based on the

Migraine Disability Assessment (MIDAS) score,[15,17] obesity,[4,18-20] and/or psychologic comorbidities such as depression, anxiety, and/or sleep disturbances[4,21,22] are also risk factors for more severe migraine attacks and reduced efficacy of acute treatment. Overall, these patient and attack characteristics associated with migraine are likely associated with central sensitization, leading to a poorer treatment outcome.[23-25]

Lasmiditan is a novel, selective, and high-affinity 5-HT_{1F} agonist, which is believed to act on both central and peripheral trigeminal pathways involved in migraine pathophysiology.[26,27] Although lasmiditan is effective in patients with migraine,[28,29] whether there are determinants of optimal response to lasmiditan has not been fully investigated. The objectives of these post hoc analyses of study data were (1) to determine the predictors of response to lasmiditan (2-hour headache pain freedom and 2-hour most bothersome symptom [MBS] freedom) in patients based on individual baseline patient characteristics, migraine disease characteristics, or migraine attack characteristics and (2) to assess the efficacy of lasmiditan specifically in subgroups of patients based on patient and/or migraine disease characteristics or migraine attack characteristics that are historically associated with reduced efficacy of acute treatment. We hypothesized that the efficacy of lasmiditan vs placebo was not different across various subgroups based on patient history, migraine disease, or attack characteristics.

METHODS

Study Design.—These post hoc analyses were based on pooled data from 2 prospective, double-blind, randomized, multicenter, Phase 3, single-attack studies of similar design comparing lasmiditan vs placebo in patients with episodic migraine (SAMURAI [27 April 2015-12 August 2016] and SPARTAN [19 May 2016-29 June 2017]).[28,29] Both studies consisted of 3 treatment phases: screening visit to confirm eligibility, treatment period (up to 8 weeks), and end-of-study visit (within 1 week of treating attack) for a total study duration of up to 11 weeks. Adult patients were randomized equally to oral lasmiditan 200, 100, or 50 mg (SPARTAN only) or placebo and were asked to treat a single migraine attack of moderate-to-severe intensity that was not improving. Patients used an electronic diary to record headache pain and the presence of nausea, phonophobia, and photophobia. Patients with associated symptoms selected which symptom was most bothersome at the baseline of the treated attack.

The study protocols were reviewed and approved by the institutional review board for each of the study sites. The studies were conducted according to Good Clinical Practice, the Declaration of Helsinki guidelines, and local regulatory requirements. Patients provided written informed consent before undergoing study procedures.

Patient Selection.—Male and females at least 18 years old who had at least a 1-year history of disabling migraine with or without aura (as defined by the International Headache Society diagnostic criteria 1.1 and 1.2.1),[30] a MIDAS score ≥11, onset before the age of 50 years, and 3-8 migraine attacks per month (<15 headache days/month) were eligible for enrollment. Patients on stable doses of concomitant migraine-preventive medications as well as those with cardiovascular risk factors were allowed in the studies, and there was no upper age limit. Key exclusion criteria included the history of chronic migraine within the past year or other forms of primary or secondary chronic headache disease (eg, hemicrania continua) and hemorrhagic stroke, epilepsy, or any other condition placing the patient at increased risk of seizures. In the SAMURAI study, but not in the SPARTAN study, known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension was exclusionary.

Outcome/Efficacy Measures.—The efficacy outcomes evaluated in these post hoc analyses included headache pain freedom and MBS freedom. Both outcomes were assessed at 2 hours after the first dose of study treatment in the intent-to-treat (ITT) population. Headache pain freedom was defined as a reduction in pain severity from mild, moderate, or severe at baseline to none. MBS freedom was defined as the absence of the selected MBS at 2 hours post-dose in patients who had the presence of MBS at baseline.

Predictors of Response Subgroups.—Response to study treatment was evaluated based on individual baseline patient characteristics, migraine disease characteristics, and migraine attack characteristics (Table 1). Patient characteristics included age (<65 vs ≥65 years [younger vs older population]), gender,

Table 1.—Baseline Demographics, Comorbidities, and Migraine Attacks Characteristics (ITT Population)

Characteristic	Lasmiditan 50 mg (N = 598)	Lasmiditan 100 mg (N = 1133)	Lasmiditan 200 mg (N = 1120)	Placebo (N = 1130)†
Demographic characteristics				
Age (years), n (%)				
<65 years, n (%)	565 (94.5)	1095 (96.6)	1083 (96.7)	1082 (95.8)
≥65 years, n (%)	33 (5.5)	38 (3.4)	37 (3.3)	47 (4.2)
Gender, n (%)				
Female	507 (84.8)	950 (83.8)	936 (83.6)	961 (85.1)
Male	91 (15.2)	183 (16.2)	184 (16.4)	168 (14.9)
Race, n (%)				
Caucasian	482 (80.6)	887 (78.3)	875 (78.1)	911 (80.7)
Non-Caucasian	116 (19.4)	246 (21.7)	244 (21.8)	218 (19.3)
Missing	0 (0)	0 (0)	1 (0.1)	0 (0)
BMI (kg/m^2), n (%)				
<30 kg/m^2	352 (58.9)	660 (58.3)	600 (53.6)	621 (55.0)
≥30 kg/m^2 (obese)	245 (41.0)	472 (41.7)	518 (46.3)	506 (44.8)
Missing	1 (0.2)	1 (0.1)	2 (0.2)	2 (0.2)
Body weight (kg), n (%)				
<90	420 (70.2)	770 (68.0)	732 (65.4)	756 (67.0)
≥90	177 (29.6)	362 (32.0)	386 (34.5)	371 (32.9)
Missing	1 (0.2)	1 (0.1)	2 (0.2)	2 (0.2)
Oral contraceptive use in females, n (%)				
Yes	72 (12.0)	143 (12.6)	126 (11.3)	141 (12.5)
No	526 (88.0)	990 (87.4)	994 (88.8)	988 (87.5)
Migraine disease characteristics				
MIDAS total score, n (%)				
<21	208 (34.8)	443 (39.1)	380 (33.9)	430 (38.1)
≥21	389 (65.1)	690 (60.9)	738 (65.9)	699 (61.9)
Missing	1 (0.2)	0	2 (0.2)	0
Duration of migraine history (years), n (%)				
≥20	241 (40.3)	495 (43.7)	449 (40.1)	459 (40.7)
<20	357 (59.7)	638 (56.3)	670 (59.8)	670 (59.3)
Missing	0	0	1 (0.1)	0
Average number of migraine attacks/month, n (%)				
≤5	379 (63.4)	714 (63.0)	681 (60.8)	672 (59.5)
>5	219 (36.6)	419 (37.0)	438 (39.1)	457 (40.5)
Missing	0 (0)	0 (0)	1 (0.1)	0 (0)
Headache days in past 3 months, n (%)				
<24	439 (73.4)	841 (74.2)	834 (74.5)	836 (74.0)
≥24	159 (26.6)	292 (25.8)	285 (25.4)	292 (25.9)
Missing	0 (0)	0 (0)	1 (0.1)	1 (0.1)
History of aura, n (%)				
Yes	238 (39.8)	429 (37.9)	422 (37.7)	445 (39.4)
No	356 (59.5)	699 (61.7)	687 (61.3)	675 (59.8)
Missing	4 (0.7)	5 (0.4)	11 (1.0)	9 (0.8)
Comorbidities				
History of psychiatric disorders‡, n (%)	186 (31.1)	416 (36.7)	387 (34.6)	417 (36.9)
Characteristics of migraine attacks				
Time of migraine headache onset, n (%)				
4-8 AM	99 (16.6)	164 (14.5)	194 (17.3)	199 (17.6)
8 AM-12 PM	146 (24.4)	293 (25.9)	244 (21.8)	254 (22.5)
12-4 PM	135 (22.6)	257 (22.7)	239 (21.3)	293 (26.0)
4-8 PM	134 (22.4)	260 (22.9)	287 (25.6)	254 (22.5)
8 PM-12 AM	63 (10.5)	111 (9.8)	113 (10.1)	89 (7.9)
12 AM-4 AM	21 (3.5)	48 (4.2)	43 (3.8)	40 (3.5)
Severity of headache at the time of dosing, n (%)				
Severe	165 (27.6)	324 (28.6)	327 (29.2)	331 (29.3)
Moderate	421 (70.4)	794 (70.1)	771 (68.8)	782 (69.3)
Mild	12 (2.0)	15 (1.3)	22 (2.0)	16 (1.4)

Table 1.—Continued

Characteristic	Lasmiditan 50 mg (N = 598)	Lasmiditan 100 mg (N = 1133)	Lasmiditan 200 mg (N = 1120)	Placebo (N = 1130)†
Co-existent symptoms at the time of dosing, n (%)				
Nausea	260 (43.5)	483 (42.6)	485 (43.3)	503 (44.6)
Photophobia	455 (76.1)	865 (76.3)	846 (75.5)	893 (79.1)
Phonophobia	356 (59.5)	703 (62.0)	702 (62.7)	726 (64.3)
Time to dosing from migraine attack start, n (%)				
<1 hour	292 (48.8)	497 (43.9)	499 (44.6)	527 (46.7)
≤2 hours	432 (72.2)	760 (67.1)	777 (69.4)	795 (70.4)
>2 hours	166 (27.8)	373 (32.9)	343 (30.6)	334 (29.6)
>4 hours	41 (6.9)	102 (9.0)	74 (6.6)	69 (6.1)
Patient-reported migraine-related functional disability at the time of dosing, n (%)				
No disability	5 (0.8)	10 (0.9)	17 (1.5)	17 (1.5)
Mild disability	156 (26.1)	333 (29.4)	303 (27.1)	278 (24.6)
Marked disability	338 (56.5)	586 (51.7)	611 (54.6)	623 (55.2)
"Needs complete bed rest"	99 (16.6)	204 (18.0)	189 (16.9)	211 (18.7)

BMI = body mass index; ITT = intent-to-treat; MIDAS = Migraine Disability Assessment.
†n = 1129; 1 placebo-treated patient had a headache severity score of 0 and was excluded from all analyses.
‡The most common psychiatric disorders included depression, anxiety, and insomnia.

race (Caucasian vs non-Caucasian), weight (<90 vs ≥90 kg [lean vs heavier population]), body mass index (BMI) indicating obesity (<30 vs ≥30 kg/m^2), oral contraceptive use (Yes vs No), and history of psychiatric disorders (included in this subgroup are patients with depression, bipolar disorder, anxiety, sleep disorders, and/or post-traumatic stress disorder). Migraine disease characteristics included duration of migraine diagnosis (<20 vs ≥20 years), history of aura, frequency of migraine attacks (average number of migraines per month in past 3 months: ≤5 vs >5), average number of headache days in past 3 months (<24 vs ≥24), and MIDAS score (<21 vs ≥21 [severe disability]). Migraine attack characteristics included the time of migraine headache onset (4-8 AM [defined as early morning onset], 8 AM-12 PM, 12-4 PM, 4-8 PM, 8 PM-12 AM, and 12-4 AM), pain severity at the time of dosing (moderate vs severe), co-existent nausea, co-existent photophobia, co-existent phonophobia, patient-reported migraine-related functional disability during the migraine attack (no disability, mild disability, marked disability, or "needs complete bed rest"), and time to treatment from migraine headache onset (≤2 vs >2 hours).

Efficacy was evaluated for subgroups based on a specific patient, migraine disease, and attack characteristics that have been historically associated with reduced efficacy of acute treatment ("difficult-to-treat"). Analyses included the following subgroups of patients: ≥24 headache days in past 3 months, history of migraine ≥20 years, severe disability based on MIDAS score ≥21,[31] obesity[4,18] (BMI ≥30 kg/m^2), history of psychiatric disorder (depression, bipolar disorder, anxiety, sleep disorders, and/or post-traumatic stress disorder),[4,31] rapidly escalating attack (headache progressed to moderate-to-severe headache intensity within 60 minutes from pain onset),[32] severe headache at the time of treatment,[32] co-existence of nausea at the time of treatment, delayed treatment[31,32] (patients who initiated treatment at >2 and ≥4 hours post-onset of attack), and patients with patient-reported migraine-related functional disability defined as "needs complete bed rest" at the time of treatment.[5,31]

Statistical Analyses.—Efficacy analyses for headache pain freedom were performed in patients from the pooled ITT population who had headache pain severity of mild, moderate, or severe at baseline. Efficacy analyses for MBS freedom were performed in patients from the pooled ITT population who had MBS present at baseline. The pooled ITT population was defined as all randomized patients from the 2 studies who used at least 1 dose of study drug and had any

post-dose headache severity and/or symptom assessments. Approximately 13.0% (503/3981) of the patients in the pooled population (who satisfied the pain severity or the presence of MBS criteria at baseline) had missing headache pain severity or MBS data at 2-hours post-treatment and were imputed as non-responders to treatment. If a patient used rescue medication at or before 2 hours, then this patient was also counted as a non-responder.

Categorical measures were summarized with frequency and percentage and continuous measures were reported with means.

Logistic regression models with study, treatment group, subgroup, and treatment-by-subgroup interaction terms were used to identify subgroups that were associated with response to treatment. For treatment comparisons within each subgroup, Mantel-Haenszel odds ratios (ORs), 95% confidence intervals (CIs), and general association P values at the 2-hour time point, stratified by study, were calculated. For interaction tests, significance was considered at the .10 level in order to increase power. Two-tailed tests were performed. Tests for the difference in treatment effect were performed at .05 level of significance. Forest plots were used to visually present the relative therapeutic efficacy among treatments for each subgroup or characteristic of interest. SAS version 9.4 was used for conducting all statistical analyses.

Data Availability Statement.—The sponsor provides access to all individual participant data collected during the trial, after anonymization, except pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU 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.

RESULTS

Patient Baseline Characteristics.—A total of 3981 adult patients with episodic migraine were included in this post hoc analysis (N = 598 lasmiditan 50 mg; N = 1133 lasmiditan 100 mg; N = 1120 lasmiditan 200 mg; N = 1130 placebo for SAMURAI and SPARTAN studies pooled).[28,29] Baseline demographics of the pooled episodic ITT population included a mean age of 42 years, 84.3% (3354/3980) were female, 79.3% (3155/3979) were Caucasian, 43.8% (1741/3974) were obese (BMI ≥30 kg/m^2), and 12.1% (482/3980) of women were using oral contraceptives at the time study treatment was initiated (Table 1). In addition, 35.3% (1406/3980) reported having a history of psychiatric illness (such as depression, anxiety, and/or sleep disorders) at baseline. Baseline migraine disease characteristics included 41.3% (1644/3979) with migraine disease duration of ≥20 years (overall average 18.7 years), 38.8% (1534/3951) with history of aura, a mean of 5.2 migraine attacks/month, 25.8% (1028/3980) with >24 headache days in past 3 months (overall average 17.5 days with headache past 3 months), and 63.3% (2516/3977) with a MIDAS score ≥21. A complete review of patient disposition and baseline characteristics is detailed in the primary publications for these 2 studies.[28,29]

Predictors of Response by Subgroups.—Overall, headache pain freedom at 2 hours after the first dose was achieved in 28.3% (169/598) (OR = 1.57, 95% CI 1.23, 2.00; P < .001), 29.7% (337/1133) (OR = 1.90, 95% CI 1.56, 2.32; P < .001), and 35.4% (396/1120) (OR = 2.46, 95% CI 2.03, 3.00; P < .001) of the lasmiditan 50, 100, and 200 mg treatment groups, respectively, vs 18.2% (206/1129) in the placebo group. No baseline patient characteristic (age, gender, race, weight, BMI, oral contraceptive use, or history of psychiatric disorders) predicted headache pain freedom response at 2 hours after the first dose of lasmiditan compared to placebo across dose groups (all P ≥ .10 except gender [P = .030]) (Fig. 1A). Although the interaction P value for gender was <.10 for 2-hour headache pain freedom for lasmiditan 100 and 200 mg groups, the difference in treatment effect for males vs females was primarily due to the

lower lasmiditan 50 mg response rates for males. Furthermore, none of the evaluated migraine disease characteristics (duration of migraine history,

A Patient Characteristics

B Migraine Disease Characteristics

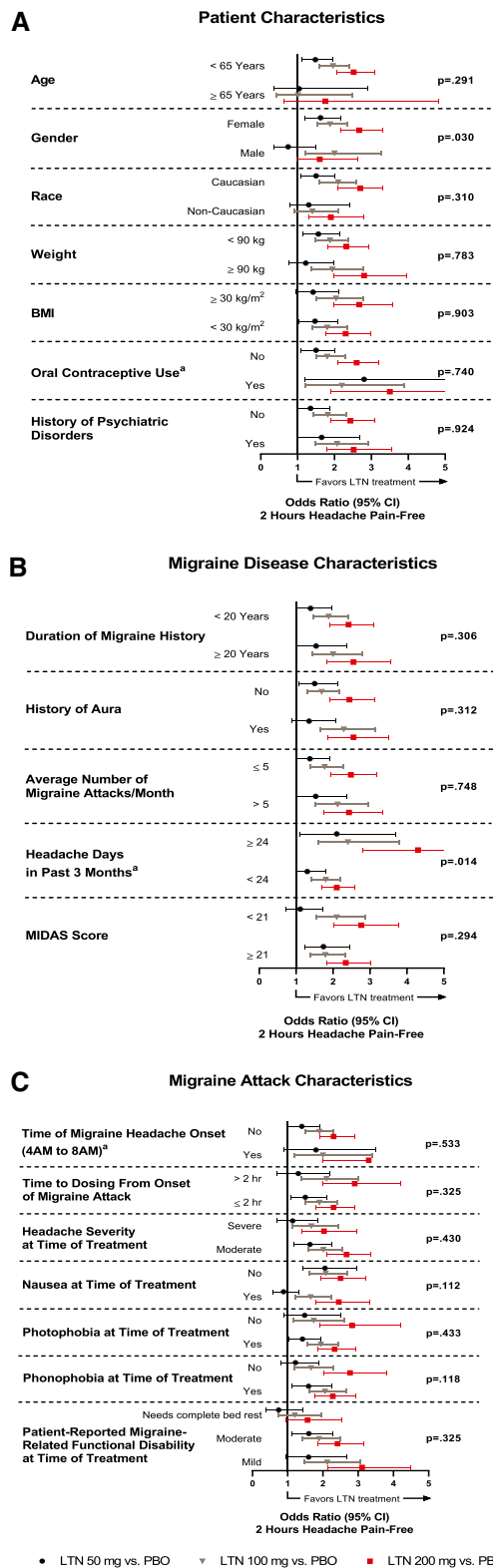**C** Migraine Attack Characteristics

Fig. 1.—Predictors of response: headache pain-free at 2 hours after the first dose of lasmiditan. (A) Patient characteristics; (B) Migraine disease characteristics; (C) Migraine attack characteristics. [a]Upper CI limit was removed when value >5. Note: interaction *P* value of *P* < .1 is considered significant. BMI, body mass index; CI, confidence interval; LTN, Lasmiditan; MIDAS, Migraine Disability Assessment; PBO, placebo.

history of aura, average number of migraine attacks/month, headache days in past 3 months, or MIDAS score) (Fig. 1B) or migraine attack characteristics (time of dosing from the onset of migraine attack, headache severity, co-existent nausea, co-existent photophobia, co-existent phonophobia, or patient-reported migraine-related functional disability) predicted 2-hour headache pain freedom response to lasmiditan (all *P* ≥ .1) (Fig. 1C). While the interaction *P* value for the average headache days in past 3 months (<24 vs ≥24) was <.10 for 2-hour headache pain freedom, the difference in treatment effect was due to the lower lasmiditan 50 mg response rate in ≥24 headache days in past 3 months subgroup (Fig. 1B). In addition, the time of migraine headache onset, including early morning migraine (4-8 AM) (Fig. 1C), did not predict lasmiditan efficacy.

Overall, MBS freedom at 2 hours after the first dose was achieved in 40.7% (224/550) (OR = 1.35, 95% CI 1.08, 1.69; *P* = .004), 43.0% (454/1057) (OR = 1.63, 95% CI 1.36, 1.94; *P* < .001), and 44.3% (458/1035) (OR = 1.72, 95% CI 1.44, 2.06; *P* < .001) of the lasmiditan 50, 100, and 200 mg treatment groups, respectively, vs 31.6% (337/1066) in the placebo group. With 1 exception (race), most evaluated baseline patient characteristics, migraine disease characteristics, or migraine attack characteristics did not predict MBS freedom at 2 hours after the first dose to lasmiditan relative to placebo across dose groups (all *P* ≥ .1) (Fig. 2a-c). However, similar to headache pain freedom, the interaction *P* value for the average headache days in past 3 months (<24 vs ≥24) was <.10 for 2-hour MBS freedom; the difference in treatment effect was due to the lower lasmiditan 50 mg response rate in ≥24 headache days in past 3 months subgroup (Fig. 2B). In addition, for the non-Caucasian subgroup, an unexpectedly high placebo response was observed (*P* = .016).

Efficacy in Difficult-to-Treat Subgroups.—Efficacy of lasmiditan within difficult-to-treat subgroups based on patient or migraine disease characteristics (Table 2) or migraine attack characteristics at the time of treatment (Table 3) is summarized.
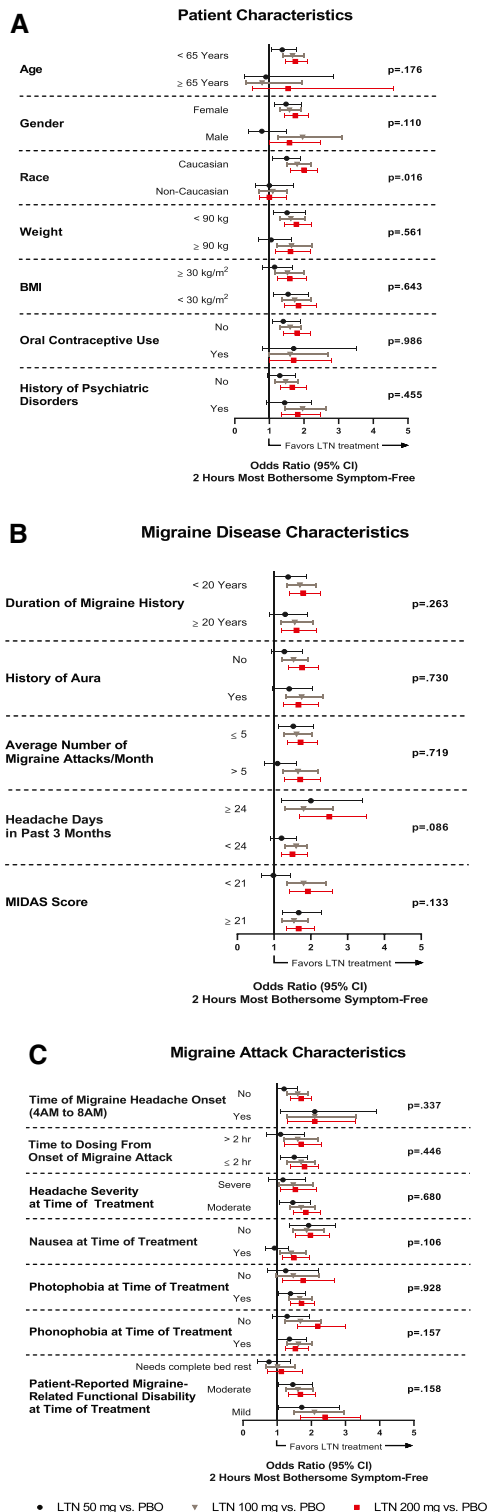

A Patient Characteristics

B Migraine Disease Characteristics

C Migraine Attack Characteristics

• LTN 50 mg vs. PBO   ▼ LTN 100 mg vs. PBO   ■ LTN 200 mg vs. PBO

Fig. 2.—Predictors of response: most bothersome symptom-free at 2 hours after the first dose of lasmiditan. (A) Patient characteristics; (B) Migraine disease characteristics; (C) Migraine attack characteristics. Note: interaction *P* value of *P* < .1 is considered significant BMI, body mass index; CI, confidence interval; LTN, Lasmiditan; MIDAS, Migraine Disability Assessment; PBO, placebo.

In the overall population, all doses (50, 100, or 200 mg) of lasmiditan were statistically significant vs placebo in achieving headache pain freedom and MBS freedom at 2 hours post-treatment. In difficult-to-treat subgroups based on patient or migraine disease characteristics (Table 2), headache pain freedom, and MBS freedom response rates at 2 hours following single doses of lasmiditan (100 or 200 mg) were significantly greater compared to placebo. Headache pain freedom response rates with higher doses of lasmiditan were numerically greater than those with lower doses of lasmiditan. Efficacy of the lowest dose of lasmiditan (50 mg) was also significant in these subgroups, except obese patients, where headache pain freedom was 28.2% (69/245) with lasmiditan 50 mg vs 17.6% (89/506) with placebo (*P* = .090) and MBS freedom was 38.8% (90/232) with lasmiditan 50 mg vs 33.3% (161/484) with placebo (*P* = .469).

Lasmiditan efficacy in difficult-to-treat subgroups based on migraine attack characteristics including rapidly escalating migraine, those with treatment delayed >2 or ≥4 hours after onset of headache, severe headache pain, co-existent nausea, or patient-reported migraine-related functional disability ("needs complete bed rest") at the time of taking treatment is summarized in Table 3. For patients with severe headache or with associated nausea at the time of treatment, headache pain freedom and MBS freedom response rates at 2 hours following single doses of lasmiditan (100 or 200 mg) were significantly greater compared to placebo. In patients who waited for 2 or more hours to treat their migraine, headache pain freedom and MBS freedom response rates in the lasmiditan 100 or 200 mg treatment groups were significantly greater than those in the placebo group. Among those who waited for 4 or more hours to treat their migraine, only headache pain freedom response

Table 2.—Efficacy Endpoints 2 Hours After Single Dose by Treatment Group for Difficult-to-Treat Patient and Migraine Characteristics (ITT Population)

	Lasmiditan 50 mg	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo
Headache pain-freedom†, %				
≥24 headache days in the past 3 months	n = 38 23.9 OR = 2.06 (1.15, 3.71) P = .014*	n = 72 24.7 OR = 2.43 (1.56, 3.79) P < .001	n = 105 36.8 OR = 4.26 (2.77, 6.55) P < .001	n = 35 12.0
History of migraine ≥20 years	n = 69 28.6 OR = 1.54 (1.00, 2.37) P = .048	n = 128 25.9 OR = 2.00 (1.44, 2.78) P < .001	n = 137 30.5 OR = 2.55 (1.84, 3.55) P < .001	n = 68 14.8
Severe disability (MIDAS score ≥21)	n = 112 28.8 OR = 1.74 (1.23, 2.46) P = .002	n = 187 27.1 OR = 1.79 (1.38, 2.32) P < .001	n = 241 32.7 OR = 2.34 (1.83, 3.01) P < .001	n = 120 17.2
Obese (≥30 kg/m^2)	n = 69 28.2 OR = 1.42 (0.95, 2.13) P = .09	n = 142 30.1 OR = 2.04 (1.51, 2.77) P < .001	n = 186 35.9 OR = 2.67 (1.99, 3.58) P < .001	n = 89 17.6
History of psychiatric disorder	n = 49 26.3 OR = 1.65 (1.01, 2.68) P = .043	n = 116 27.9 OR = 2.07 (1.48, 2.91) P < .001	n = 124 32.0 OR = 2.52 (1.80, 3.54) P < .001	n = 66 15.8
MBS-freedom‡, %				
≥24 headache days in past 3 months	n = 58 39.7 OR = 2.05 (1.25, 3.37) P = .004*	n = 104 38.4 OR = 1.81 (1.26, 2.61) P = .001	n = 123 45.9 OR = 2.46 (1.71, 3.54) P < .001	n = 71 25.5
History of migraine ≥20 years	n = 94 42.5 OR = 1.30 (0.88, 1.92) P = .188	n = 181 39.3 OR = 1.56 (1.18, 2.06) P = .002	n = 166 40.0 OR = 1.61 (1.21, 2.15) P = .001	n = 126 29.3
Severe disability (MIDAS score ≥21)	n = 149 41.7 OR = 1.67 (1.21, 2.29) P = .001	n = 253 39.4 OR = 1.54 (1.22, 1.93) P < .001	n = 283 41.3 OR = 1.67 (1.33, 2.09) P < .001	n = 198 29.7
Obese (≥30 kg/m^2)	n = 90 38.8 OR = 1.15 (0.79, 1.66) P = .469	n = 191 43.0 OR = 1.52 (1.17, 1.99) P = .002	n = 210 44.0 OR = 1.59 (1.22, 2.07) P < .001	n = 161 33.3
History of psychiatric disorder	n = 66 37.7 OR = 1.44 (0.93, 2.22) P = .098	n = 170 42.8 OR = 1.96 (1.46 2.63) P < .001	n = 149 41.1 OR = 1.82 (1.35, 2.47) P < .001	n = 111 27.7

CI = confidence interval; ITT = intent-to-treat; MBS = most bothersome symptom; MIDAS = Migraine Disability Assessment; OR = odds ratio (95% CI).
*All OR and P values vs placebo.
†Defined as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0).
‡Defined as the absence of the associated symptom of migraine that was identified pre-dose as the MBS (either nausea, phonophobia, or photophobia).

rates for the 200 mg dose of lasmiditan met statistical significance compared to placebo (32.4% [24/74] vs 15.9% [11/69]; P = .018). None of the lasmiditan doses significantly differed from placebo in achieving MBS freedom if patients waited for 4 or more hours to treat their migraine attack. However, the sample

Table 3.—Efficacy Endpoints 2 Hours After Single Dose by Treatment Group for Difficult-to-Treat Migraine Attacks (ITT Population)

	Lasmiditan 50 mg	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo
Headache pain-freedom†, %				
Time to dosing from migraine headache onset				
<1 hour (rapidly escalating attacks)	n = 96	n = 165	n = 185	n = 117
	32.9	33.2	37.1	22.2
	OR = 1.48 (1.03, 2.14)	OR = 1.74 (1.32, 2.30)	OR = 2.07 (1.57, 2.73)	
	P = .035	P < .001	P < .001	
≥2 hours	n = 36	n = 103	n = 120	n = 52
	21.7	27.6	35.0	15.6
	OR = 1.26 (0.73, 2.18)	OR = 2.06 (1.42, 2.99)	OR = 2.92 (2.02, 4.24)	
	P = .406	P < .001	P < .001	
≥4 hours	n = 10	n = 28	n = 24	n = 11
	24.4	27.5	32.4	15.9
	OR = 1.13 (0.39, 3.26)	OR = 1.92 (0.88, 4.19)	OR = 2.67 (1.17, 6.07)	
	P = .824	P = .097	P = .018	
Severe headache	n = 45	n = 85	n = 96	n = 58
	27.3	26.2	29.4	17.5
	OR = 1.14 (0.70, 1.86)	OR = 1.67 (1.14, 2.43)	OR = 2.03 (1.39, 2.96)	
	P = .592	P = .008	P < .001	
Co-existence of nausea	n = 54	n = 122	n = 159	n = 86
	20.8	25.3	32.8	17.1
	OR = .88 (0.58, 1.33)	OR = 1.65 (1.21, 2.25)	OR = 2.45 (1.81, 3.32)	
	P = .534	P = .001	P < .001	
Migraine-related functional disability ("needs complete bed rest")	n = 20	n = 46	n = 49	n = 39
	20.2	22.6	25.9	18.5
	OR = .74 (0.38, 1.44)	OR = 1.20 (0.74, 1.94)	OR = 1.56 (0.96, 2.53)	
	P = .376	P = .467	P = .070	
MBS-freedom‡, %				
Time to dosing from migraine headache onset				
<1 hour (rapidly escalating attacks)	n = 117	n = 212	n = 193	n = 161
	44.2	45.2	43.1	32.9
	OR = 1.40 (0.99, 1.99)	OR = 1.69 (1.30, 2.20)	OR = 1.55 (1.19, 2.03)	
	P = .059	P < .001	P = .001	
≥2 hours	n = 54	n = 146	n = 143	n = 102
	34.8	42.7	43.9	31.9
	OR = 1.11 (0.69, 1.78)	OR = 1.59 (1.16, 2.19)	OR = 1.67 (1.21, 2.30)	
	P = .660	P = .004	P = .002	
≥4 hours	n = 14	n = 41	n = 27	n = 22
	37.8	44.6	38.0	32.8
	OR = 1.17 (0.45, 3.06)	OR = 1.60 (0.83, 3.10)	OR = 1.26 (0.62, 2.53)	
	P = .755	P = .162	P = .526	
Severe headache	n = 62	n = 118	n = 122	n = 94
	39.2	38.7	39.0	29.8
	OR = 1.17 (0.74, 1.84)	OR = 1.47 (1.05, 2.06)	OR = 1.53 (1.10, 2.15)	
	P = .499	P = .024	P = .012	
Co-existence of nausea	n = 93	n = 198	n = 204	n = 167
	35.8	41.0	42.1	33.1
	OR = .92 (0.65, 1.32)	OR = 1.41 (1.09, 1.83)	OR = 1.49 (1.15, 1.93)	
	P = .664	P = .010	P = .003	
Migraine-related functional disability ("needs complete bed rest")	n = 32	n = 68	n = 64	n = 67
	34.0	34.2	35.2	32.7
	OR = .76 (0.42, 1.38)	OR = 1.01 (0.66, 1.53)	OR = 1.12 (0.73, 1.73)	
	P = .367	P = .978	P = .595	

CI = confidence interval; ITT = intent-to-treat; MBS = most bothersome symptom; OR = odds ratio (95% CI).
*All OR and P values vs placebo.
†Defined as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0).
‡Defined as the absence of the associated symptom of migraine that was identified pre-dose as the MBS (either nausea, phonophobia, or photophobia).

size for the ≥4 hours subgroup was small (<10% in the overall study population). All tested doses of lasmiditan were significantly effective in achieving headache pain freedom in the rapidly escalating attack subgroup. Lasmiditan 100 or 200 mg doses were also effective compared to placebo treatment in achieving MBS freedom in this subgroup.

In the patient subgroups who rated migraine-related functional disability as "mild" or "moderate" at the time of treatment, response rates of 2-hour headache pain freedom were higher in all treated doses of lasmiditan compared to the placebo group (in the mild disability subgroup 31.4% (49/156) [P = .080], 35.1% (117/333) [P < .001], and 44.6% (135/303) [P < .001] vs 20.5% (57/278) and in the moderate disability subgroup 28.7% (97/338) [P = .010], 28.5% (167/586) [P < .001], and 33.6% (205/611) [P < .001] vs 17.5% (109/623), for lasmiditan 50, 100 and 200 mg vs placebo-treated group, respectively). While the predictors of response interaction test showed similar efficacy of lasmiditan vs placebo across subgroups defined by various levels of functional disability at the time of treatment, analyses of lasmiditan efficacy within the subgroup "needs complete bed rest" appeared to show less efficacy. In this subgroup, the response rate for headache pain freedom 2 hours post-treatment for lasmiditan 200 mg was numerically higher compared to placebo (25.9% [49/189] vs 18.5% [39/211]; P = .070) (Table 3). A similar pattern of response was observed for the 2-hour MBS freedom in these subgroups.

DISCUSSION

The demographic characteristics in the lasmiditan Phase 3 clinical development program represent the intended treatment population. These studies enrolled older patients (including some greater than 65 years), and selection criteria did not exclude patients with a history of cardiovascular or psychiatric disorders. This post hoc analysis of subgroups from 2 clinical studies, SAMURAI and SPARTAN,[28,29] shows that patient characteristics, migraine disease characteristics, or migraine attack characteristics at the time of dosing were not predictive of the efficacy of single-dose lasmiditan as determined by headache pain freedom and MBS freedom at 2 hours post-dose. These findings suggest that the efficacy of lasmiditan is generally consistent across many patient subgroups, indicating that lasmiditan may be beneficial in treating migraine headaches in a wide range of patients or attack characteristics. These data extend previous findings that the efficacy of lasmiditan was not compromised in patients who had an insufficient response to triptans, were currently using migraine preventive medications, or had the presence of cardiovascular risk factors/comorbidities.[33-35]

Certain patient characteristics are known to negatively impact migraine and/or response to acute treatment of migraine. These include, but are not limited to, obesity,[4,18,19] a long history of migraine,[15] higher number of monthly headache days,[16] greater disability based on the MIDAS score,[15,17] or presence of psychiatric comorbidities such as depression, anxiety, and/or sleep disturbances.[4,21,22] Obesity as reflected by a high BMI has been associated with severe and progressive forms of migraine in previous studies and with less favorable treatment outcomes;[4,18,19,20] however, in our post hoc analyses, obesity did not appear to influence the efficacy of lasmiditan at higher doses (100 or 200 mg). Obese patients treated with a lower dose (50 mg) of lasmiditan did not show statistical significance vs placebo for headache pain freedom or MBS freedom, possibly as a result of insufficient drug exposure and the small sample size (50 mg dose was only included in 1 study).

Patients with more frequent migraine attacks or presence of greater headache days/month have been reported to be less likely to experience a positive response with acute treatments;[4,16] however, the efficacy of lasmiditan in our analyses was retained in the patient subgroup who reported higher headache days (≥24 days in the past 3 months). These data need to be cautiously interpreted, as our studies included only patients with <15 headache days/month and patients with chronic migraine were excluded.

Similar to the subgroup of patients with higher headache days in the past 3 months, patients with a greater MIDAS score, and/or with psychiatric comorbidities are at higher risk to experience more severe migraine attacks and are likely to develop central sensitization, which may lead to a poorer treatment outcome, previously reported in these populations.[23-25,36] In patient subgroups with MIDAS score of ≥21 or presence of psychiatric comorbidities (such as anxiety, depression, and/or sleep disturbance), headache pain

freedom, and MBS freedom response rates at 2 hours following single doses of lasmiditan were significantly greater compared to placebo.

Rapidly escalating migraine attacks (headache progresses rapidly and peaks to moderate-to-severe headache intensity in <60 minutes), delayed access to treatment (>2 hours), severe headache pain, co-existent nausea, and migraine-related functional disability defined as "needs complete bed rest" at the time of treatment are also migraine attack characteristics known to predict a poorer response to acute treatment.[4-13] In our analyses of these subgroups of difficult-to-treat migraine attacks, patients receiving lasmiditan (100 and 200 mg) generally had greater 2-hour headache pain freedom responses compared with those who received placebo. The exception was in patients with migraine-related functional disability that "needs complete bed rest" at the time of treatment. In this subgroup, lasmiditan 200 mg appeared to increase headache pain freedom response numerically at 2 hours albeit not significantly (lasmiditan 200 mg 25.9% vs placebo 18.5%; $P = .070$).

Migraine headaches peak in intensity within 60 minutes of onset 60%-80% of the time.[37] Faster bioavailability and greater systemic exposure are necessary for treating rapidly escalating attacks.[38] Not all oral drugs meet this pharmacokinetic requirement and hence are not suitable for treating rapidly escalating migraine attacks.[39] Oral treatment with lasmiditan achieves therapeutic concentrations in systemic circulation within 30-60 minutes.[40]

There are a number of reports in the scientific literature describing clinical trials in patients with migraine that purport to demonstrate the benefits of "early" treatment, taken when the pain is mild, over "late" treatment, when pain is moderate or severe.[41] According to the American Migraine Prevalence and Prevention (AMPP) Study, higher headache pain intensity is one of the significant predictors of inadequate 2-hour headache pain freedom response to acute treatment,[4] including triptans.[6,32,42] Unfortunately, it is not always logistically possible for patients to treat their migraine attacks before the pain becomes severe or within 2 hours of headache onset. Our analysis indicates that lasmiditan (100 or 200 mg) is effective in treating attacks with severe

headache intensity or in those patients who waited >2 hours to treat their migraine attack from its onset. Burstein et al. have shown in animal models that early application of triptans blocks the development of central sensitization, whereas late application of triptans is insufficient to counteract established central sensitization.[23] These data suggest that lasmiditan, a centrally penetrant drug, may be effective in the setting of the central sensitization process, as suggested by the efficacy data for severe pain intensity or dosing late during a migraine attack. Clinically, patients often describe the necessity of treating migraine late in the day or after a migraine has peaked, suggesting there may be a role for lasmiditan in these clinical circumstances.

Migraine attacks with associated nausea may sometimes not be optimally treated by oral medications, and the presence of nausea predicts poor response to oral triptans.[43] However, treatment with lasmiditan 100 or 200 mg provided significantly better 2-hour headache pain freedom and MBS freedom response rates compared with placebo among patients who reported nausea at baseline.

Clinicians and patients must continue to consider medication efficacy, potential medication-related adverse events, migraine characteristics, and patient-specific contraindications, needs, and goals of treatment when prescribing or taking acute medications for migraine. The selection of the optimal treatment to abort a migraine attack is nuanced and necessitates careful strategizing. Lasmiditan, a first-in-class "ditan" molecule, provides a novel treatment option for migraine attacks and appears to be effective at doses of 100 and 200 mg in treating migraine attacks that are historically considered to be difficult to treat with oral medications.

Certain limitations may preclude the generalizability of these post hoc analyses. Lack of predictors in these analyses may be due to insufficient sample size (<20% of the overall study population) in certain subgroups (eg, geriatric patients [>65 years], male sex, or the patient-reported migraine-related functional disability "needs complete bed rest"). Statistical power for the interaction tests was not assessed in the designing of the studies because it was not among the primary or key secondary objectives

(ie, the studies were not powered to detect a significant interaction between treatment effect and baseline disease and demographic factors). Therefore, some subgroup analyses may not be sufficiently powered to draw conclusions. Because we were not expecting to see any particular subgroup effects a priori, we did not control for type I error (false-positive findings). Finally, the SPARTAN study[29] was the only study evaluating a 50-mg dose of lasmiditan; thus, there was a lower number of participants in the 50-mg lasmiditan-treated group.

CONCLUSIONS

In these post hoc analyses, the efficacy of lasmiditan at 2 hours following a single dose was similar for subgroups of patients defined by baseline demographics, migraine disease characteristics, and migraine attack characteristics. Furthermore, treatment effects of lasmiditan 100 or 200 mg were seen for the primary endpoints in most subgroup analyses, suggesting that lasmiditan may be an effective alternative for the types of migraine headache that are historically referred to as "difficult-to-treat."

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Raghavendra Vasudeva, John H. Krege, Suchitrita S. Rathmann, Erin Doty
(b) Acquisition of Data
Suchitrita S. Rathmann
(c) Analysis and Interpretation of Data
Raghavendra Vasudeva, John H. Krege, Suchitrita S. Rathmann, Erin Doty

Category 2

(a) Drafting the Manuscript
Raghavendra Vasudeva, John H. Krege, Suchitrita S. Rathmann, Erin Doty

(b) Revising It for Intellectual Content
Stewart J. Tepper, Raghavendra Vasudeva, John H. Krege, Suchitrita S. Rathmann, Erin Doty, Bert B. Vargas, Delphine Magis, Mika Komori

Category 3

(a) Final Approval of the Completed Manuscript
Stewart J. Tepper, Raghavendra Vasudeva, John H. Krege, Suchitrita S. Rathmann, Erin Doty, Bert B. Vargas, Delphine Magis, Mika Komori

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2018;38:1-211.
2. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55:3-20.
3. Becker WJ. Acute migraine treatment in adults. *Headache*. 2015;55:778-793.
4. Lipton RB, Munjal S, Buse DC, Fanning KM, Bennett A, Reed ML. Predicting inadequate response to acute migraine medication: Results from the American Migraine Prevalence and Prevention (AMPP) study. *Headache*. 2016;56:1635-1648.
5. Diener HC, Ferrari M, Mansbach H. Predicting the response to sumatriptan: The sumatriptan naratriptan aggregate patient database. *Neurology*. 2004;63:520-524.
6. Diener HC, Dodick DW, Goadsby PJ, Lipton RB, Almas M, Parsons B. Identification of negative predictors of pain-free response to triptans: Analysis of the eletriptan database. *Cephalalgia*. 2008;28:35-40.
7. Brandes JL, Kudrow D, Cady R, Tiseo PJ, Sun W, Sikes CR. Eletriptan in the early treatment of acute migraine: Influence of pain intensity and time of dosing. *Cephalalgia*. 2005;25:735-742.
8. Cady RK, Sheftell F, Lipton RB, et al. Effect of early intervention with sumatriptan on migraine pain: Retrospective analyses of data from three clinical trials. *Clin Ther*. 2000;22:1035-1048.
9. Freitag FG, Finlayson G, Rapoport AM, et al. Effect of pain intensity and time to administration on responsiveness to almotriptan: Results from AXERT

12.5 mg time versus Intensity Migraine Study (AIMS). *Headache*. 2007;47:519-530.

10. Goadsby PJ, Zanchin G, Geraud G, et al. Early vs. non-early intervention in acute migraine – 'Act when Mild (AwM)'. A double-blind, placebo-controlled trial of almotriptan. *Cephalalgia*. 2008;28:383-391.

11. Hu XH, Raskin NH, Cowan R, Markson LE, Berger ML, United States Migraine Study Protocol (USMAP) Group. Treatment of migraine with rizatriptan: When to take the medication. *Headache*. 2002;42:16-20.

12. Lanteri-Minet M, Mick G, Allaf B. Early dosing and efficacy of triptans in acute migraine treatment: The TEMPO study. *Cephalalgia*. 2012;32:226-235.

13. Mathew NT, Finlayson G, Smith TR, et al; AEGIS Investigator Study Group. Early intervention with almotriptan: Results of the AEGIS trial (AXERT® Early Migraine Intervention Study). *Headache*. 2007;47:189-198.

14. Cady RK, Lipton RB, Hall C, Stewart WF, O'Quinn S, Gutterman D. Treatment of mild headache in disabled migraine sufferers: Results of the Spectrum Study. *Headache*. 2000;40:792-797.

15. Lipton RB, Bigal ME, Ashina S, et al; American Migraine Prevalence Prevention Advisory Group. Cutaneous allodynia in the migraine population. *Ann Neurol*. 2008;63:148-158.

16. Dodick DW, Reed ML, Fanning KM, et al. Predictors of allodynia in persons with migraine: Results from the migraine in America symptoms and treatment (MAST) study. *Cephalalgia*. 2019;39:873-882.

17. Baykan B, Ekizoglu E, Karli N, et al. Characterization of migraineurs having allodynia: Results of a large population-based study. *Clin J Pain*. 2016;32:631-635.

18. Saracco MG, Allais G, Tullo V, et al. Efficacy of frovatriptan and other triptans in the treatment of acute migraine of normal weight and obese subjects: A review of randomized studies. *Neurol Sci*. 2014;35(Suppl. 1):S115-S119.

19. Center for Drug Evaluation and Research. *Application Number: 211765Orig1s000 Clinical Review*. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211765Orig1s000MedR.pdf. Accessed January 31, 2020.

20. Munjal S, Gautam A, Rapoport AM, Fisher DM. The effect of weight, body mass index, age, sex, and race on plasma concentrations of subcutaneous sumatriptan: A pooled analysis. *Clin Pharmacol*. 2016;8:109-116.

21. Grassini S, Nordin S. Comorbidity in migraine with functional somatic syndromes, psychiatric disorders and inflammatory diseases: A matter of central sensitization? *Behav Med*. 2017;43:91-99.

22. Buse DC, Reed ML, Fanning KM, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: Results of the migraine in America symptoms and treatment (MAST) study. *J Headache Pain*. 2020;21:23.

23. Burstein R, Collins B, Jakubowski M. Defeating migraine pain with triptans: A race against development of cutaneous allodynia. *Ann Neurol*. 2004;55:19-26.

24. Dodick D, Silberstein S. Central sensitization theory of migraine: Clinical implications. *Headache*. 2006;46(Suppl. 4):S182-S191.

25. Harte SE, Harris RE, Clauw DJ. The neurobiology of central sensitization. *J Appl Behav Res*. 2018;23:e12137.

26. Neeb L, Meents J, Reuter U. 5-HT$_{1F}$ receptor agonists: A new treatment option for migraine attacks? *Neurotherapeutics*. 2010;7:176-182.

27. Capi M, de Andrés F, Lionetto L, et al. Lasmiditan for the treatment of migraine. *Expert Opin Investig Drugs*. 2017;26:227-234.

28. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. *Neurology*. 2018;91:e2222-e2232.

29. Goadsby P, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*. 2019;142:1894-1904.

30. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.

31. Lipton RB, Munjal S, Buse DC, et al. Unmet acute treatment needs from the 2017 migraine in America symptoms and treatment study. *Headache*. 2019;59:1310-1323.

32. Tepper SJ, Dodick DW, Schmidt PC, Kellerman DJ. Efficacy of ADAM zolmitriptan for the acute treatment of difficult-to-treat migraine headaches. *Headache*. 2019;59:509-517.

33. Knievel K, Buchanan AS, Lombard L, et al. Lasmiditan for the acute treatment of migraine: Subgroup analyses by prior response to triptans. *Cephalalgia*. 2020;40:19-27.

34. Loo LS, Ailani J, Schim J, et al. Efficacy and safety of lasmiditan in patients using concomitant migraine preventive medications: Findings from SAMURAI and SPARTAN, two randomized phase 3 trials. *J Headache Pain*. 2019;20:84.

35. Shapiro RE, Hochstetler HM, Dennehy EB, et al. Lasmiditan for acute treatment of migraine in patients with cardiovascular risk factors: Post hoc analysis of pooled results from 2 randomized, double-blind, placebo-controlled, phase 3 trials. *J Headache Pain*. 2019;20:90.

36. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine progression: A systematic review. *Headache*. 2019;59:306-338.

37. Pryse-Phillips W, Aubé M, Bailey P, et al. A clinical study of migraine evolution. *Headache*. 2006;46:1480-1486.

38. Cady RK, Munjal S, Cady RJ, Manley HR, Brand-Schieber E. Randomized, double-blind, crossover study comparing DFN-11 injection (3 mg subcutaneous sumatriptan) with 6 mg subcutaneous sumatriptan for the treatment of rapidly-escalating attacks of episodic migraine. *J Headache Pain*. 2017;18:17.

39. Tfelt-Hansen P. Parenteral vs. oral sumatriptan and naratriptan: Plasma levels and efficacy in migraine. A comment. *J Headache Pain*. 2007;8:273-276.

40. Ashina M, Vasudeva R, Jin L, et al. Onset of efficacy following oral treatment with lasmiditan for the acute treatment of migraine: Integrated results from 2 randomized double-blind placebo-controlled phase 3 clinical studies. *Headache*. 2019;59:1788-1801.

41. Ferrari MD. Should we advise patients to treat migraine attacks early: Methodologic issues. *Eur Neurol*. 2005;53(Suppl. 1):17-21.

42. Cortelli P, Allais G, Benedetto C. Overview of triptans in the treatment of acute migraine. *Eur Neurol Rev*. 2017;12:71-77.

43. Newman LC. Why triptan treatment can fail: Focus on gastrointestinal manifestations of migraine. *Headache*. 2013;53(Suppl. 1):11-16.