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Lasmiditan for the acute treatment of migraine: Subgroup analyses by prior response to triptans

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Abstract

Background: Lasmiditan demonstrated superiority to placebo in the acute treatment of migraine in adults with moderate/severe migraine disability in two similarly designed Phase 3 trials, SAMURAI and SPARTAN. Post-hoc integrated analyses evaluated the efficacy of lasmiditan in patients who reported a good or insufficient response to triptans and in those who were triptan naïve.

Methods: Subgroups of patients reporting an overall response of "good" or "poor/none" to the most recent use of a triptan at baseline (defined as good or insufficient responders, respectively) and a triptan-naïve subpopulation were derived from combined study participants randomized to receive lasmiditan 50 mg (SPARTAN only), 100 mg or 200 mg, or placebo, as the first dose. Outcomes including headache pain-freedom, most bothersome symptom-freedom, and headache pain relief 2 hours post-first dose of lasmiditan were compared with placebo. Treatment-by-subgroup analyses additionally investigated whether therapeutic benefit varied according to prior triptan response (good or insufficient).

Results: Regardless of triptan response, lasmiditan showed higher efficacy than placebo (most comparisons were statistically significant). Treatment-by-subgroup analyses found that the benefit over placebo of lasmiditan did not vary significantly between patients with a good response and those with an insufficient response to triptans. Lasmiditan also showed higher efficacy than placebo in triptan-naïve patients.

Conclusions: Lasmiditan demonstrated comparable efficacy in patients who reported a good or insufficient response to prior triptan use. Lasmiditan also showed efficacy in those who were triptan naïve. Lasmiditan may be a useful therapeutic option for patients with migraine.

Trial Registration: SAMURAI (NCT02439320); SPARTAN (NCT02605174).

Keywords

Migraine, lasmiditan, triptans, efficacy, tolerability, ditan, acute therapy

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Introduction

In 2016, the World Health Organization Global Burden of Disease (GBD) study listed migraine as the second leading cause of years lived with disability worldwide, after low back pain (1). Despite the availability of multiple pharmacological options for treating migraine attacks, unmet medical needs remain high, with ~40% of people with episodic migraine reporting ≥1 unmet need with their current acute treatment in a population-based study (2). Of those with unmet needs, 37% were dissatisfied with their current migraine acute treatment (citing adverse events, lack of efficacy, or overall dissatisfaction with the medication as reasons) (2). Furthermore, people with ≥1 unmet need were more likely than those with no unmet needs to have used triptans in the past 3 months (2).

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The principal safety concern with triptans, the standard acute treatment for migraine, relates to rare reports of serious vascular adverse reactions due to vasoconstriction (3). Consequently, these drugs are contraindicated in people with certain cardiovascular/cerebrovascular conditions, such as myocardial infarction, peripheral vascular disease, ischemic heart disease, stroke, transient ischemic attack, and uncontrolled hypertension (4,5). Additionally, ~30–40% of people with migraine have insufficient efficacy or tolerability to triptans (6–10) or are unwilling to take triptans for reasons that include a fear of adverse events (11). Hence, there is a significant unmet need for novel migraine therapies with a mechanism of action distinct from that of triptans.

Lasmiditan is a highly selective 5-hydroxytryptamine $(5\text{-HT})_{1F}$ receptor agonist with central nervous system penetration. This molecule is among the first of a new class of treatments, termed ditans, investigated for the acute treatment of migraine (12). The chemical structure of lasmiditan differs from that of triptans in that it does not contain the indole core characteristic of triptans, but instead exhibits a pyridinoyl-piperidine scaffold not found in any other class of antimigraine agents (13). Lasmiditan is also thought to differ from triptans in its pharmacological effects. Triptans are potent $5\text{-HT}_{1B/1D}$ receptor agonists and are thought to exert vasoconstrictive effects via the activation of 5-HT_{1B} receptors in addition to having effects at the sensory nerves of the trigeminal system (12). In contrast, there is evidence that the pharmacological effects of lasmiditan do not include a vascular mechanism, but instead involve selective activation of $5HT_{1F}$ receptors. Although lasmiditan crosses the blood–brain barrier and 5-HT_{1F} receptors are located on trigeminal nerve terminals and other areas of the brain, the specific site of action has not been definitively elucidated (12,14–17). Lasmiditan did not vasoconstrict *ex-vivo* rabbit saphenous veins, *ex-vivo* human middle meningeal, coronary, or internal mammary arteries, or *in-vivo* dog coronary or carotid arteries (12,18,19).

Lasmiditan has demonstrated superiority to placebo in the acute treatment of migraine in two similarly designed Phase 3, prospective, randomized, double-blind, placebo-controlled, single migraine attack trials, SAMURAI and SPARTAN (20,21). In both studies, the percentage of patients who were migraine pain-free 2 hours post-dose was significantly greater with all doses of lasmiditan than with placebo (primary endpoint) (20,21).

Given that lasmiditan and triptans exhibit structural and pharmacological differences, this post-hoc integrated analysis of data from the SAMURAI and SPARTAN studies was conducted to investigate the response to lasmiditan for the acute treatment of migraine in patients who reported a good or insufficient response to prior triptan use, and in those who were triptan naïve.

Methods

SAMURAI and SPARTAN were similarly designed studies (see the Supplemental Material) (20,21). Brief descriptions of the patient populations and designs of the two studies are given below; full details have been published (20,21).

Study populations

SAMURAI (NCT02439320) and SPARTAN (NCT02605174) were conducted in adults diagnosed with migraine with or without aura (International Classification of Headache Disorders 2nd edition, subtypes 1.1 and 1.2.1) (22); a history of 3–8 migraine attacks (<15 headache days) per month and moderate/severe migraine disability (Migraine Disability Assessment [MIDAS] score ≥11). SAMURAI, but not SPARTAN, excluded patients with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension. Inclusion and exclusion criteria common to both studies are provided in the Supplemental Material.

Study designs

Participants were randomized evenly to receive lasmiditan 50 mg (SPARTAN only), 100 mg, 200 mg, or placebo. Randomization was stratified for the use of migraine preventives. Information on medication history and concomitant medications was collected at baseline. For each previous migraine medication, patients were asked to rate whether their overall response to treatment had been "good," "poor," or "none." Participants were asked to treat their next migraine attack within 4 hours of pain onset provided that the headache was of at least moderate severity and not improving. Participants were instructed to record pain, associated symptoms, and interference with normal activities at the start of a migraine attack and at prespecified intervals (0.5, 1, 1.5, 2, 3, 4, 24, and 48 hours) post-dose using an electronic diary (eDiary).

At each time point, patients recorded the following: Severity of pain using the International Headache Society (IHS) 4-point pain severity rating scale (none, mild, moderate, or severe); presence/absence of self-identified most bothersome migraine-associated symptom (e.g. nausea, phonophobia, or photophobia); and level of migraine-associated disability (degree of interference with normal activities) using a 4-point scale ("not at all," "mild interference,"

"marked interference," and "need complete bed rest"). Two hours post-dose, patients completed the Patient Global Impression of Change (PGIC) choosing from one of seven responses, ranging from "very much better" to "very much worse."

The eDiary was also used daily to record how patients were feeling (possible answers: "fine/normal" or "not well") and if they felt "anything unusual" since taking the study medication not experienced previously with a migraine attack (possible answers: "yes" or "no"). "Not well" or "yes" answers to these questions prompted investigation by the site to determine if an adverse event (AE) had occurred.

Outcomes investigated

The primary efficacy endpoint for both studies was the difference between lasmiditan and placebo in the proportion of patients who were headache pain-free at 2 hours post-dose (defined as a reduction in pain severity from mild, moderate, or severe at baseline to no pain). This outcome was assessed in the modified intent-to-treat (mITT) population, defined as all randomized participants who used at least one dose of the study drug and underwent any post-dose headache severity or symptom assessments (intent-to-treat [ITT] group) and who treated a migraine attack within 4 hours of pain onset. The key secondary efficacy endpoint was the comparison between lasmiditan and placebo in the proportion of patients who were most bothersome symptom (MBS)-free at 2 hours post-dose (mITT population).

Other secondary efficacy endpoints assessed 2 hours post-first dose in the ITT population were: headache pain relief, a migraine-related disability score of "not at all," and a PGIC rating of "very much better" or "much better." Disability shift from baseline was also assessed.

Proportions of patients with any treatment-emergent AE (safety population, defined as all randomized participants who used at least one dose of the study drug, regardless of whether or not they underwent any post-dose study assessments) were investigated. A treatment-emergent AE was defined as an event that started or worsened after the first dose of study medication and occurred within 48 hours of the last dose (a duration well over five times the half-life of lasmiditan (data on file, Eli Lilly and Company).

The main subpopulations studied (based on patient-reported prior use of triptans at baseline) were:

- Triptan experienced: Patients who had at least one triptan recorded as a current or prior migraine treatment, regardless of time elapsed since last triptan. Subgroups of patients reporting an overall response of "good" or "poor/none" to the most recent use of a triptan at baseline were defined as good or insufficient responders, respectively.
- Triptan naïve: Patients who did not have a triptan recorded as a current or prior migraine treatment.

The results of analyses conducted in triptan-experienced (good or insufficient responders) and triptan-naïve subpopulations, and for the outcomes headache pain-freedom (primary efficacy endpoint), MBS-freedom, and headache pain relief at 2 hours post-dose are reported here. Results of analyses conducted in additional triptan user subpopulations and for the other secondary outcomes (all subpopulations) are presented in the Supplemental Material.

For all subpopulations, response to lasmiditan was assessed versus placebo.

Statistical analyses

These post-hoc analyses evaluated combined SAMURAI and SPARTAN data. For each subpopulation, outcomes were compared between treatment groups using a two-sided test from a logistic regression model with study, treatment group, and background use of medication to reduce the frequency of migraine attacks as covariates. Comparisons versus placebo were considered statistically significant at the $p < 0.05$ level. For comparisons between the triptan good responder and insufficient responder subgroups, Mantel–Haenszel odds ratios, 95% confidence intervals, and general association p-values at each measured time point, stratified by study, are displayed.

Patients with missing data for any outcome at any particular time point were assumed not to have achieved that outcome at that time point.

Additional treatment-by-subgroup analyses of outcomes were carried out to determine whether therapeutic benefit varied according to prior triptan response versus placebo. For each outcome, the p-value for treatment-by-subgroup interaction was based on a logistic regression model with treatment-by-subgroup interaction term and study, treatment group, and subgroup as covariates. Significance for interaction was defined as $p < 0.1$.

Results

A total of 3981 patients were included in these analyses; patient demographics and disease characteristics for the triptan-experienced and -naïve subpopulations are described in Table 1.

Of the combined SAMURAI and SPARTAN populations, 45% overall had used at least one triptan (triptan-experienced subpopulation) previously at some point.

Table 1. Baseline patient demographics and disease characteristics of triptan-experienced and triptan-naïve subpopulations.

	Triptan experienced* (n = 1786)	Triptan naïve (n = 2195)
Age, years	44.1 (11.9)	40.6 (12.6)
Female, n (%)	1581 (88.5)	1774 (80.8)
Years since migraine diagnosis	21.5 (13.3)	16.4 (12.0)
Migraine attacks/month**	5.3 (1.9)	5.2 (1.9)

*Includes patients with a good or insufficient response to prior triptan use.

**Based on response to the question in migraine history section of the case report form: "Frequency of migraine attacks (average) during the last three months."

Note: Data are means (standard deviations) unless otherwise stated.

Efficacy response to lasmiditan versus placebo in patients with good or insufficient response to triptans

Patients who described themselves as insufficient responders to their last triptan comprised 31% of the triptan-experienced subpopulation.

In subgroup analyses, lasmiditan showed efficacy in both triptan good responders and triptan insufficient responders for the outcomes of headache pain-freedom, MBS-freedom, and headache pain relief, with all comparisons being statistically significant versus placebo for the 100 mg and 200 mg doses (Figure 1).

Treatment-by-subgroup analyses found that the benefit over placebo of lasmiditan 50 mg, 100 mg, or 200 mg did not vary significantly between prior triptan good and insufficient responders based on the same three efficacy measures at 2 hours post-first dose (Figure 2).

Efficacy response to lasmiditan versus placebo in triptan-naïve patients

Lasmiditan demonstrated efficacy in the triptan-naïve subpopulation, with all responses to lasmiditan 100 mg and 200 mg across all outcomes (headache pain-freedom, MBS-freedom, and headache pain relief) being significantly higher ($p < 0.05$) than with placebo (Figure 3).

Adverse events

Across subpopulations, treatment-emergent AE profiles in patients receiving lasmiditan were generally similar regardless of prior experience with, or response to, triptan use (data not shown).

Discussion

In this integrated analysis of two similarly designed Phase 3, prospective, randomized, double-blind, placebo-controlled trials (SAMURAI and SPARTAN), response to lasmiditan for the acute treatment of migraine was found to be effective versus placebo in both good and insufficient responders to prior triptans, and in patients who were triptan naïve.

About 45% of the combined SAMURAI and SPARTAN study populations had previously used a triptan. As would be expected, prior triptan use was higher in SAMURAI and SPARTAN (both studies were conducted in patients with moderate-to-severe migraine disability [MIDAS score ≥11]) (20,21) than in longitudinal and cross-sectional population-based and real-world studies (18–37%) (23–26).

Evidence from controlled trials and observational studies suggests that ~30–40% of people with migraine have insufficient efficacy or tolerability to triptan therapy (6–9), a finding reflected in the results of this combined analysis: 31% of patients in the triptan-experienced subpopulation reported an insufficient response to prior triptans. Patients may consider themselves insufficient responders to triptans for a variety of reasons, including a lack of efficacy and intolerable adverse events (2,27).

In this integrated analysis, lasmiditan demonstrated higher efficacy versus placebo for all outcomes in patients who reported an insufficient response to prior triptan therapy. Additionally, response to lasmiditan versus placebo in patients who self-reported an insufficient response to prior triptan use was similar to that in those who reported a good response to triptans, again across all outcomes.

Unmet needs with acute therapy for migraine remain high, with some patients unable to achieve optimal outcomes with current therapies (2,28). Lasmiditan might offer an effective acute treatment option for these patients and would expand the therapeutic choices available both for people with migraine and their treating physicians.

Triptan-naïve patients may have contraindications to triptans (e.g. cardiovascular/cerebrovascular conditions) (4,5). Additionally, such patients may be unwilling to take a triptan, or physicians may be reluctant to prescribe a triptan, for reasons that include a fear of AEs (11,29). Responses to lasmiditan were generally superior to placebo for headache pain-freedom, MBS-freedom, and headache pain relief 2 hours post-first dose in the triptan-naïve subpopulation in this integrated analysis. These findings suggest a possible role for lasmiditan as an option for the acute treatment of migraine in triptan-naïve patients.

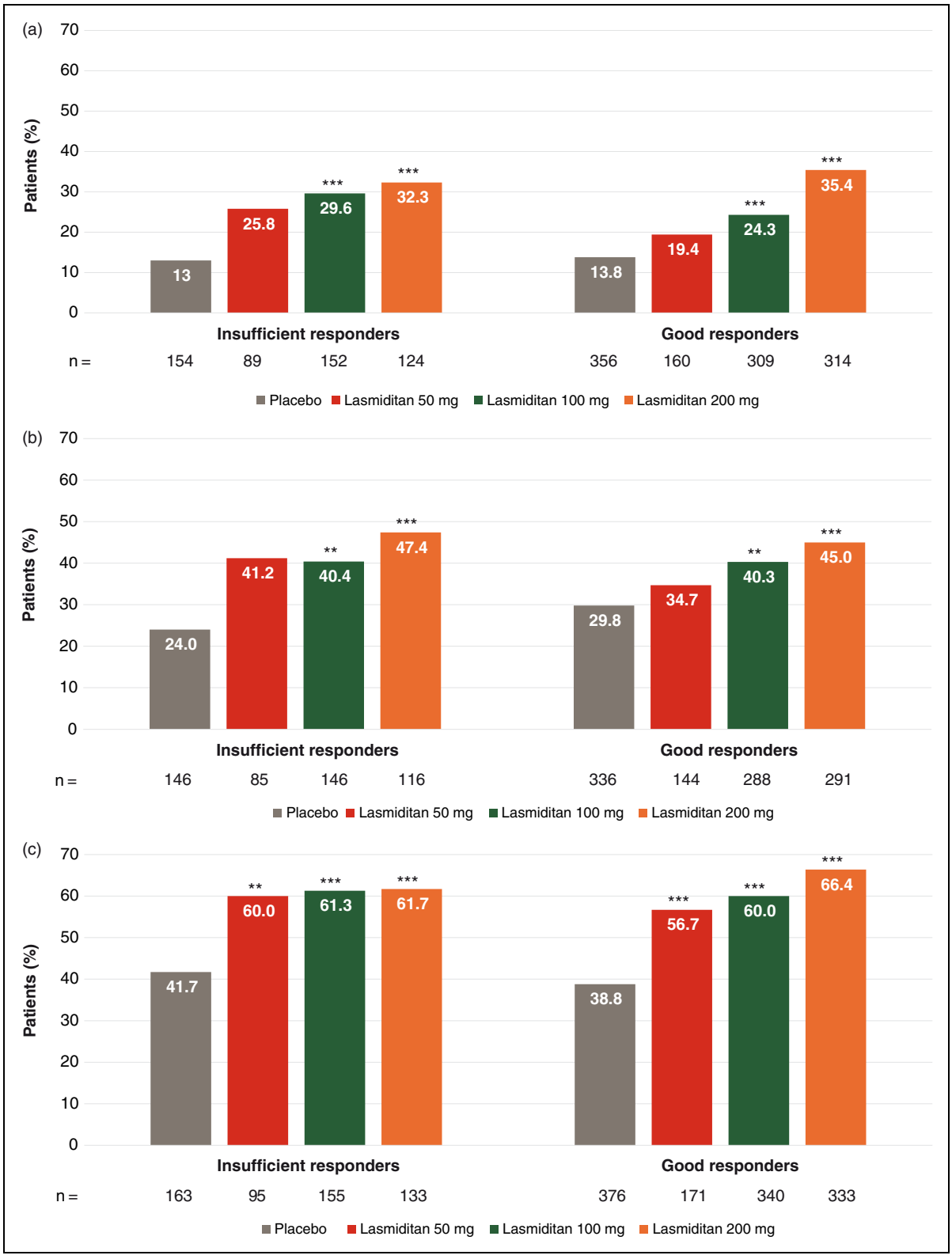

Figure 1. Subgroup analyses by response to prior triptan therapy (good or insufficient) for (a) headache pain freedom, (b) MBS freedom, and (c) headache pain relief 2 hours post-first dose with lasmiditan 50 mg, 100 mg, and 200 mg versus placebo.
**$p < 0.01$ vs. placebo.
***$p < 0.001$ vs. placebo.
†Assessed in the modified intention-to-treat (ITT) population.
††Assessed in the ITT population.
MBS, most bothersome symptom.

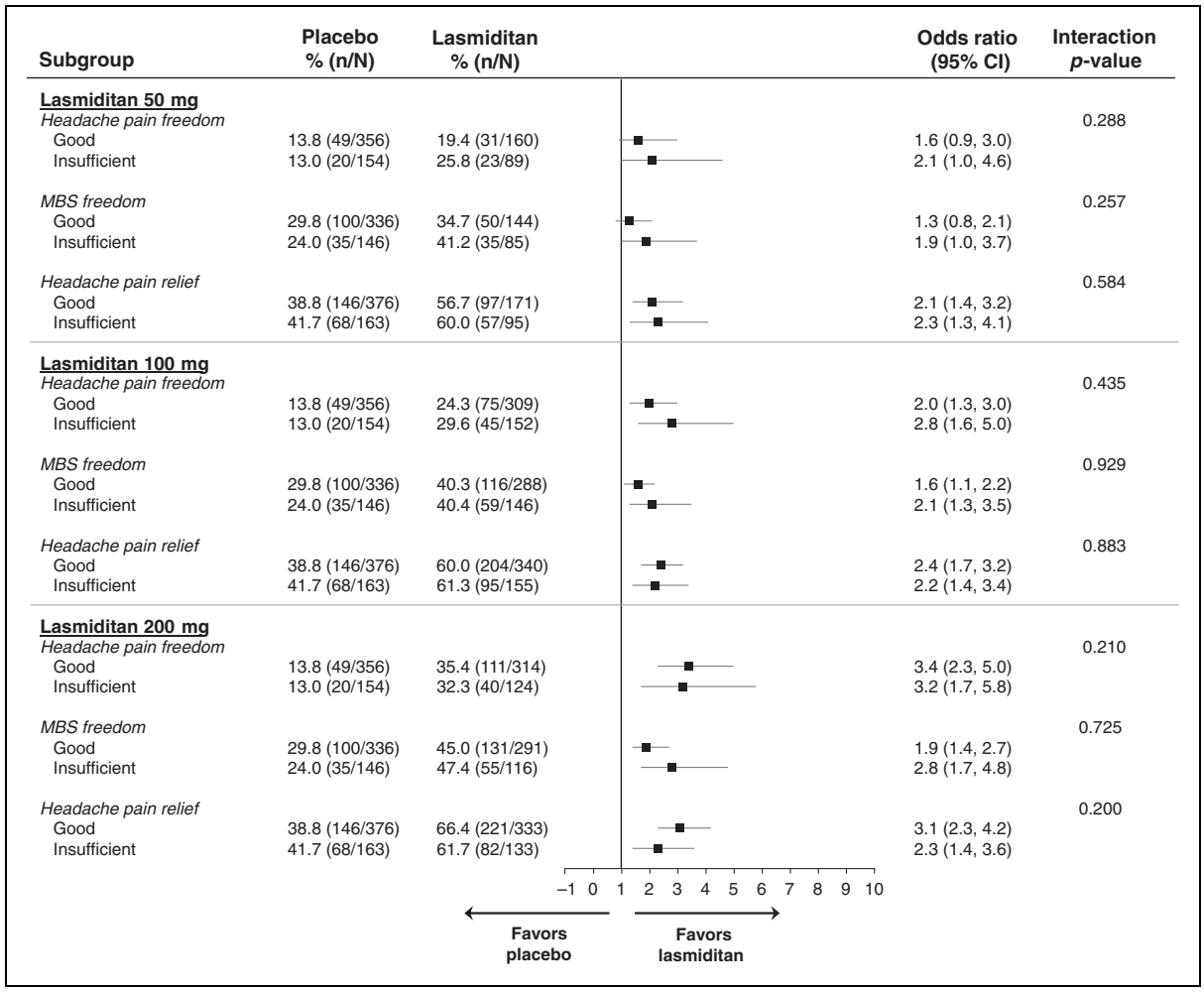

Figure 2. Treatment-by-subgroup analyses by response to prior triptan therapy (good or insufficient) for headache pain freedom, MBS freedom, and headache pain relief 2 hours post-first dose with lasmiditan 50 mg, 100 mg, and 200 mg versus placebo.
CI: confidence interval; MBS: most bothersome symptom.

The efficacy and tolerability of lasmiditan in patients with cardiovascular contraindications to triptans is of interest. Known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension were exclusion criteria for the SAMURAI, but not the SPARTAN, study. However, the limited number of patients with pre-existing cardiovascular conditions included in this integrated analysis of the two studies precluded meaningful investigations into outcomes with lasmiditan in this patient subpopulation.

When conducting multiple subgroup analyses, there is a substantial probability of false-positive findings (30). A strength of this study is that any multiplicity issues arising from treatment-by-subgroup analyses were addressed by comparing the actual number of significant findings with those expected by chance alone (30). The results reported here are supported by the additional analyses provided in the Supplemental Material. Based on a total of 35 independent tests for interaction at the 0.1 significance level conducted in total, the number found to be significant (2; both in the additional analyses reported in the Supplemental Material) was in line with that expected (3), suggesting that there was no heterogeneity in the response of any subgroup versus its complementary subgroup. Limitations include that neither SAMURAI nor SPARTAN had an active triptan comparator; hence, it was not possible to compare the efficacy of lasmiditan directly with that of a triptan in patients with an inadequate prior response to triptans. Additionally, analyses were post-hoc and low patient numbers in some subpopulations limited the conclusions that could be drawn. Results for the 50 mg dose of lasmiditan were based solely on data from the SPARTAN study. Although patient responses to this dose were all numerically higher than those to placebo for all

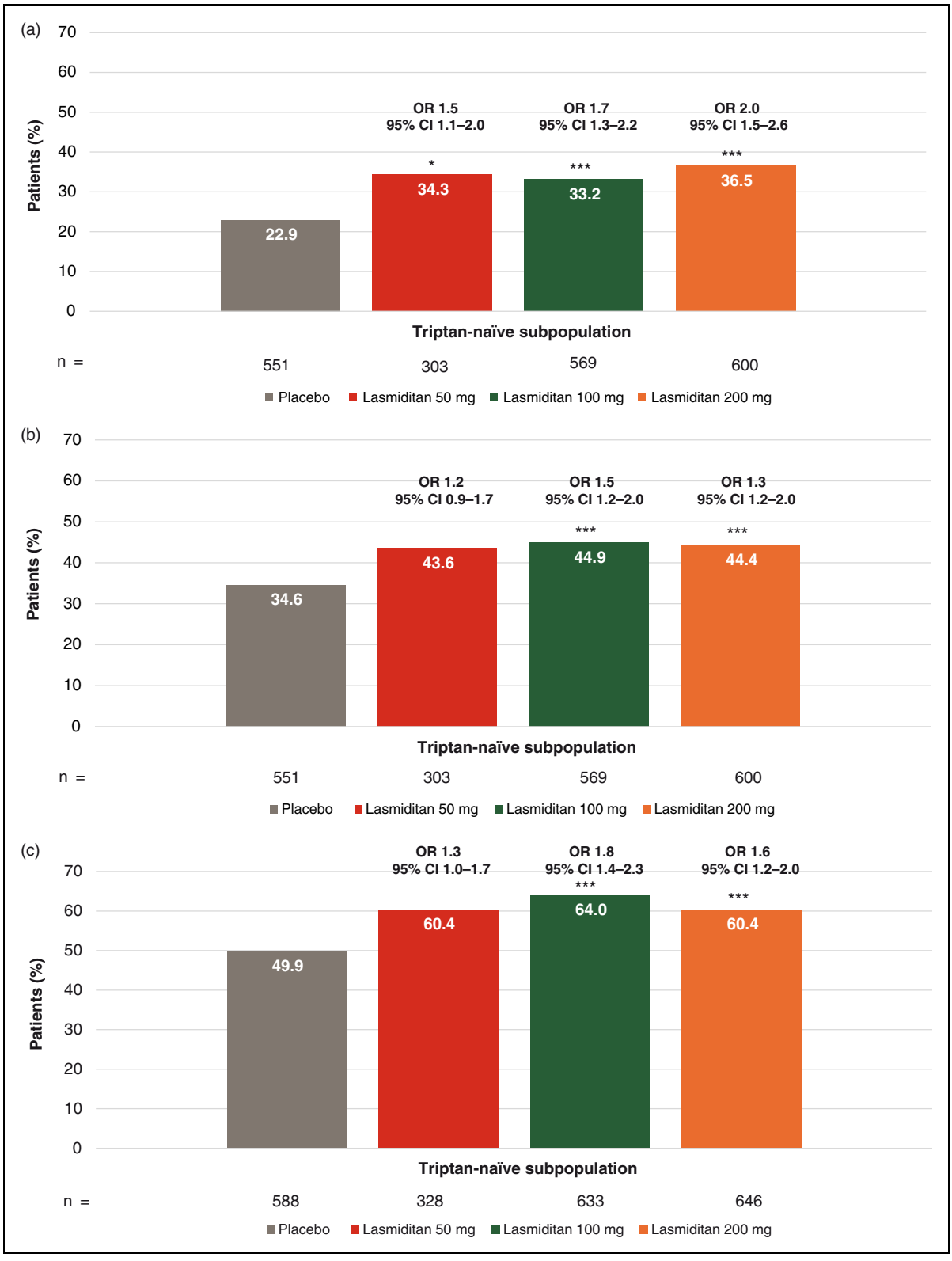

Figure 3. Proportions of patients (a) headache pain-free, (b) MBS-free, and (c) with headache pain relief at 2 hours post-first dose with lasmiditan 50 mg, 100 mg, and 200 mg versus placebo in the triptan-naïve subpopulation.
*$p < 0.05$ vs. placebo.
***$p < 0.001$ vs. placebo.
†Assessed in the modified intention-to-treat (ITT) population.
††Assessed in the ITT population.
CI: confidence interval; MBS: most bothersome symptom; OR: odds ratio.

subpopulations and outcomes assessed, in some instances there was not enough evidence to declare statistical significance. In both the SAMURAI and SPARTAN studies, response to previous triptan therapy (good or insufficient) was a subjective assessment by the patient, and reasons for each patient's assessment were not explored (20,21).

Details, such as the timing of triptan dosing relative to migraine onset (current recommendations are to treat early) (31), and information on dosing (including up titration) or route of administration, were not collected.

Conclusion

Lasmiditan demonstrated efficacy in both patients with a good response and those with an insufficient response to prior triptan therapy, as well as in those who were triptan naïve.

Clinical implications

- Lasmiditan demonstrated efficacy in patients who reported a good or insufficient response to prior triptan therapy, as well as in those who were triptan naïve.
- Lasmiditan efficacy was also generally similar between those who reported a good response and those who reported an insufficient response to prior triptan therapy.
- Lasmiditan may be a useful treatment option for the acute treatment of migraine regardless of prior triptan response and for patients naïve to triptans.

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Authorship

KK, LL, JR, LSL, and MK were involved with the interpretation of the data for the work. SB was involved with the analysis and interpretation of the data. AB and JHK was involved with the design of the work and interpretation of the data. JT was involved with the acquisition and interpretation of the data. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, have provided critical revision of the manuscript for important intellectual content, and have given their approval for this version to be published. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Data accessibility

The datasets generated and/or analyzed during these studies are not publicly available. All of the relevant data are included in this published article and its Supplemental information files.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: KK has received compensation for speaking and/or consulting from Allergan, Amgen, and Eli Lilly and Company. AB, LL, SB, JHK, LSL, and MK are full-time employees and minor stockholders of Eli Lilly and Company. JR is a retired employee of Eli Lilly and Company and was a full-time employee with minor stockholdings at the inception of the work. JT has received compensation from Eli Lilly and Company for speaking and advisory board service, and indirect compensation for work related to clinical trials.

Ethics or Institutional Review Board approval

Asa post-hoc analysis of data from the SAMURAI and SPARTAN studies, approval by independent ethics committees or institutional review boards was not required for this study. The SAMURAI and SPARTAN studies were individually approved by independent ethics committees (or institutional review boards) at each study site, and all participants provided informed consent before taking part.

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