doi:10.1093/brain/awz134 BRAIN 2019: 142; 1894–1904 | 1894

BRAIN
A JOURNAL OF NEUROLOGY

CLINICAL TRIAL

Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine

Peter J. Goadsby,[1] Linda A. Wietecha,[2] Ellen B. Dennehy,[2,3] Bernice Kuca,[4] Michael G. Case,[2] Sheena K. Aurora[2] and Charly Gaul[5]

Lasmiditan, a serotonin 5-HT_{1F} receptor agonist, was effective for acute treatment of patients with migraine in a phase 3 double-blind randomized controlled study. The current study was designed to replicate these findings in a generalizable population of patients with migraine, including those with a cardiovascular medical history. This prospective, double-blind, phase 3 multicentre study randomly assigned patients with migraine with and without aura (1:1:1:1 ratio) to oral lasmiditan 200 mg, 100 mg, 50 mg, or placebo. Patients were instructed to dose at home within 4 h of onset of migraine attack of at least moderate intensity and not improving. The primary objective was to assess the proportion of patients' headache pain-free and most bothersome symptom-free at 2 h post-dose for each dose of lasmiditan versus placebo (NCT02605174). Patients ($n = 3005$) were assigned and treated ($n = 2583$, safety population): 1938 lasmiditan (200 mg $n = 528$, 100 mg $n = 532$, and 50 mg $n = 556$ included in primary analysis) and 645 placebo (540 included in primary analysis). Most patients (79.2%) had $\geqslant 1$ cardiovascular risk factor at baseline, in addition to migraine. Lasmiditan was associated with significantly more pain freedom at 2 h (lasmiditan 200 mg: 38.8%, odds ratio 2.3, 95% confidence interval 1.8–3.1, $P < 0.001$; 100 mg: 31.4%, odds ratio 1.7, 1.3–2.2, $P < 0.001$; 50 mg: 28.6%, odds ratio 1.5, 1.1–1.9, $P = 0.003$ versus placebo 21.3%) and freedom from most bothersome symptom at 2 h (lasmiditan 200 mg: 48.7%, odds ratio 1.9, 95% confidence interval 1.4–2.4, $P < 0.001$; 100 mg: 44.2%, odds ratio 1.6, 1.2–2.0, $P < 0.001$; 50 mg: 40.8%, odds ratio 1.4, 1.1–1.8, $P = 0.009$ versus placebo 33.5%). Treatment-emergent adverse events were reported in 253 of 649 (39.0%), 229 of 635 (36.1%), and 166 of 654 (25.4%) of patients on lasmiditan 200, 100, and 50 mg, respectively, versus 75 of 645 (11.6%) on placebo. Most adverse events were CNS-related and included dizziness, somnolence and paraesthesia. Lasmiditan was effective at 2 h post-dose for acute treatment of migraine at all oral doses tested. Efficacy and safety were consistent with the previous phase 3 study.

1 NIHR-Wellcome Trust King's Clinical Research Facility, King's College Hospital; SLaM Biomedical Research Centre, and King's College London, UK
2 Eli Lilly and Company, Indianapolis, Indiana, USA
3 Purdue University, Department of Psychological Sciences, West Lafayette, Indiana, USA
4 CoLucid Pharmaceuticals, Inc., a wholly owned subsidiary of Eli Lilly and Company, Cambridge, Massachusetts, USA
5 Migraine and Headache Clinic, Koenigstein im Taunus, Germany

Correspondence to: Linda A. Wietecha
Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA
E-mail: wietecha_linda_a@lilly.com

Keywords: lasmiditan; migraine; phase 3; efficacy; safety/tolerability

Abbreviations: MBS = most bothersome symptom; MIDAS = Migraine Disability Assessment Score; TEAE = treatment emergent adverse event

Received October 3, 2018. Revised February 26, 2019. Accepted March 14, 2019. Advance Access publication May 27, 2019

Introduction

Migraine is a common neurological disease that was ranked by the WHO as the second highest cause of disability worldwide as measured in years of life lost to disability (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). The American Migraine Prevalence and Prevention concluded that >40% of patients with episodic migraine have significant unmet needs including relatively high rates of moderate/severe headache-related disability (47%) and dissatisfaction with current acute medication regimen (37.4%) (Lipton *et al.*, 2013).

Triptans are considered the gold standard for acute treatment of migraine, with strong evidence in support of their efficacy (Ferrari *et al.*, 2001; Marmura *et al.*, 2015) and representing 28–36% of prescribed acute migraine medications (Mafi *et al.*, 2015; Molina *et al.*, 2018). However, triptans are not efficacious in all patients (Ferrari *et al.*, 2001; Cameron *et al.*, 2015) and are contraindicated in patients with coronary artery disease, peripheral vascular disease, or uncontrolled hypertension (Dodick *et al.*, 2004) and in patients with risk factors for undiagnosed coronary artery disease (Buse *et al.*, 2017; Lipton *et al.*, 2017).

Understanding of the pathophysiology of migraine has recently evolved away from vasodilation (vascular hypothesis) to a brain disorder involving pain and other sensory processing (Goadsby *et al.*, 2017). Migraine involves activation and sensitization, or the perception thereof, of trigeminal nociceptors in the dura mater, with neuropeptide release such as calcitonin gene-related peptide (CGRP). 5-HT_{1F} receptor agonists are a potential treatment alternative to triptans (Raffaelli *et al.*, 2017). Lasmiditan, a centrally-penetrant, highly selective and potent 5-HT_{1F} receptor agonist without vasoconstrictive activity (Rubio-Beltrán *et al.*, 2018; Vila-Pueyo, 2018), is a novel acute therapy for migraine. As current treatment approaches do not meet the needs of all patients with migraine in terms of both efficacy and tolerability (Viana *et al.*, 2013), lasmiditan may provide an alternative acute treatment option for patients with migraine.

Lasmiditan was effective in previous studies, with adverse events primarily related to its CNS activity (Ferrari *et al.*, 2010; Färkkilä *et al.*, 2012; Kuca *et al.*, 2018). We undertook a second pivotal phase 3 study to confirm the efficacy and safety of three doses of oral lasmiditan (200 mg, 100 mg and 50 mg) versus placebo for the acute treatment of a single migraine attack in patients with migraine (with and without aura).

Materials and methods

Study design

This was a prospective, randomized, double-blind, placebo-controlled, multicentre phase 3 study in patients with migraine with and without aura (Headache Classification Committee of the International Headache Society, 2013) from 125 headache centres in the USA, UK and Germany (NCT02605174). Patients were stratified for use of concomitant preventive medications that reduced frequency of their migraine attacks. The study consisted of three 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. Patients were to treat a single migraine attack of moderate-to-severe intensity with study drug within 8 weeks of enrolment on an outpatient basis. A second dose was permitted between 2 and 24 h after initial dosing, if needed, for rescue or recurrence of migraine. Patients who did not experience and/or treat a migraine attack during the study period were excluded from all safety and efficacy analyses.

The primary efficacy objectives were to evaluate the efficacy of each dose of lasmiditan (200 mg, 100 mg, 50 mg) at 2 h compared to placebo on the proportion of patients achieving headache pain freedom and freedom from the most bothersome symptom (MBS), as identified by the patient, from the associated symptoms of nausea, phonophobia and photophobia. Secondary efficacy objectives were to explore the effect of headache pain relief and time course of lasmiditan on pain freedom and freedom from MBS, pain relief, number of patients who experience sustained pain freedom and freedom from individual symptoms associated with migraine, pain relief, disability, and patient global impression of change. The safety objective was to assess the safety and tolerability of lasmiditan in terms of adverse events, physical examinations, vital signs, laboratory tests and ECGs.

Patients

Patients were recruited from clinical research centres in three countries.

Inclusion criteria

Males or females (≥18 years) who had at least a 1-year history of disabling migraine with or without aura (International Headache Society diagnostic criteria 1.1 and 1.2.1) (Headache Classification Committee of the International Headache Society, 2013), a Migraine Disability Assessment (MIDAS) score ≥11 (Lipton *et al.*, 2001), onset before the age of 50 years, and three to eight migraine attacks per month were eligible for enrolment.

Exclusion criteria

Included history of chronic migraine or other forms of primary or secondary headache disorder such as hemicranias continua, or medication overuse headache, where headache frequency is ≥15 headache days per month within the past 12 months; haemorrhagic stroke, epilepsy, or any other condition placing the patient at increased risk of seizures; recurrent dizziness and/or vertigo including benign paroxysmal positional vertigo, Meniere's disease, vestibular migraine, and other vestibular disorders; diabetes mellitus with complications (diabetic retinopathy, nephropathy or neuropathy); orthostatic hypotension with syncope; significant renal or hepatic impairment; current evidence of abuse of any drug, prescription or illicit, or alcohol within the previous 3 years; and patients who were at imminent risk of suicide by the Columbia Suicide Severity Rating

Scale (C-SSRS) or had a suicide attempt within 6 months prior to the screening visit. In addition, patients who used more than three doses per month of either opioids or barbiturates or had initiation of or a change in concomitant medication to reduce the frequency of migraine attacks within 3 months prior to the screening visit were considered ineligible for study entry.

Patients with cardiovascular risk factors were identified using the American College of Cardiology/American Heart Association guidelines (Goff *et al.*, 2014), which identified factors with greatest predictive potential for a first cardiovascular event. They include age, total and high-density lipoprotein cholesterol, systolic blood pressure (including treated or untreated), diabetes, and current smoking status. In contrast to the first phase 3 trial (Kuca *et al.*, 2018), this trial did not exclude individuals with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension.

The study was approved by the authorities and independent ethics committees. This study was conducted in accordance with the Declaration of Helsinki and internationally accepted standards of Good Clinical Practice. All patients gave written informed consent before enrolment.

Randomization and masking

Patients were centrally randomized via the Interactive Response Technology system to one of seven treatment sequences to receive lasmiditan (200 mg, 100 mg, 50 mg) or placebo for the first dose (in a 1:1:1:1 ratio) and the second dose of lasmiditan or placebo (in a 2:1 ratio), if needed for rescue or recurrence of migraine. All patients who were randomized to placebo for the first dose were given placebo for the second dose. Masking of treatment was achieved using a modified-dummy technique. All patients and investigators, and sponsor staff were masked to treatment allocation.

Procedures

At screening, medical and migraine history were taken, and vital signs, physical examination, ECG, clinical laboratory tests, and MIDAS and C-SSRS questionnaires were completed for all patients. Medical history and adverse events were classified based on Medical Dictionary for Drug Regulatory Activities (MedDRA) version 21.0. Patients were asked about any medication use for migraine or pain during the 90 days before enrolment and other drugs used during the 30 days before enrolment, family history of cardiovascular disease, and occurrence of any cardiovascular events in the last 6 months. Patients were provided with an electronic diary and trained to record information about their migraine, their use of study medication, and to complete post-dose assessments. Patients were randomized and provided with a dosing card (four tablets for initial and second doses). Within 7 days of the screening visit, the patients were contacted by phone to confirm eligibility.

Study conduct

Eligible patients were instructed to treat their next migraine attack within 4 h of onset, provided that their headache was moderate or severe and not improving. Triptans, ergots, opioids and barbiturates were disallowed within 24 h of study drug administration. Prior to taking their first dose of study drug, the patient identified in the electronic diary the time of onset, the severity of the pain, presence or absence of nausea, phonophobia, and photophobia and which was most bothersome, and presence or absence of vomiting. Patients recorded their response to the first dose in an electronic diary for 48 h after intake of study drug and up to 72 h if a second dose was taken.

After dosing, headache severity was assessed by the patient and recorded in the electronic diary at specified times: 0.5, 1, 1.5, 2, 3, 4, 24 and 48 h post-dose using a headache severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). Patients documented the presence or absence of any associated symptoms at the same time points. Patient disability was assessed with a 4-point item regarding the degree of interference in normal activities due to migraine (none, mild, moderate, requires bed rest). Global impression at 2 h after study drug intake was recorded by the patient on a 7-point scale (very much better, much better, a little better, no change, a little worse, much worse, and very much worse). The date and exact time when the patient became headache pain-free and experienced meaningful headache pain relief was also recorded. Patients also recorded any unusual symptom (possible adverse event) within the treatment period following initial or second doses of the study drug. Severity of adverse events (mild, moderate, severe), and causal relation to study drug, were assigned by the investigator. The 48-h evaluation period for identification of treatment emergent adverse events (TEAEs) was considered adequate in light of the 5.7-h terminal elimination half-life of lasmiditan (data on file, Eli Lilly and Company).

A second dose of the study drug was permitted up to 24 h after the first dose if the migraine did not respond at 2 h and no other rescue medication had been used or if the migraine responded within 2 h (headache becomes pain-free) but then recurred after 2 h. Patients recorded their response to the second dose in an electronic diary for 48 h after intake of the study drug.

At follow-up within 7 days after treatment, patients returned their study drug pack and compliance was assessed via the electronic diary. A physical examination, vital signs, 12-lead ECG, and laboratory assessments were done, and adverse events, concomitant drugs, and rescue drugs reported since screening were reviewed.

Efficacy outcomes/end-points

The primary efficacy objective was the comparison between each dose of lasmiditan and placebo on the proportion of patients who were headache pain-free and MBS-free at 2 h after the first dose. While patients were directed to take the study drug only when their pain was moderate to severe, a small number of patients ($n = 33$) took the study drug when their pain was mild. These patients were distributed across all four treatment groups [50 mg $n = 12$ (2.2%), 100 mg $n = 9$ (1.7%), 200 mg $n = 7$ (1.3%), and placebo $n = 5$ (0.9%)]. Thus, headache pain-free response was defined as a reduction of headache severity from mild, moderate or severe pain to none. If a second dose, or any rescue medication, was taken before 2 h, the patient was considered to be a non-responder to the first dose.

Other secondary efficacy end-points included the proportion of patients with headache pain relief [defined as a reduction in headache severity from moderate (2) or severe (3) at baseline, to mild (1) or none (0), or a reduction in headache severity from mild (1) at baseline, to none (0)]; proportions of patients who had sustained pain freedom at 24 h and 48 h after the first dose (defined as being headache pain-free at 2 h after the first dose, and at the indicated assessment time, having not used any medications after the first dose) compared to placebo; comparisons between lasmiditan 200 mg/100 mg/50 mg and placebo of the proportion of patients who were headache pain-free; MBS-free and headache pain relief at other time points; proportion of patients who were free from migraine symptoms (phonophobia, photophobia, nausea, vomiting); patient global impression of change; level of disability; and proportion of patients who used a second dose of study drug for rescue or recurrence.

Statistical analysis

The sample size was estimated based on the 2 h headache pain-free and associated symptoms (nausea, phonophobia or photophobia) free response rates observed from the previous phase 2 study (Färkkilä *et al.*, 2012). Using a one-sided, two-sample comparison at the 2.5% level of significance, a sample size of 570 patients per treatment group (as defined by the first dose) provided >90% power to detect a difference in the proportion of patients who were headache pain-free at 2 h for assumed true rates of 7.4% and 18.8% (placebo and 200 mg), 7.4% and 13.6% (placebo and 100 mg), 7.4% and 13.9% (placebo and 50 mg) and >90% power for MBS for both the 50 mg dose arm and the 100 mg dose arm and very near or >80% power for MBS in the 200 mg dose arm.

Primary efficacy analyses were performed in the full analysis set [originally referred to as the modified intent-to-treat (ITT) population], which was defined *a priori* in the protocol/statistical analysis plan as patients who used at least one dose of study drug to treat a qualifying attack within 4 h of onset and had any post-dose headache severity or symptom assessments. Secondary efficacy analyses were carried out in the intent-to-treat population, which was defined as all patients in the safety population (see below) who recorded any post-dose headache severity or symptom assessments in the electronic diary. Safety/tolerability analyses used the safety population, which was defined as all randomized patients who used at least one dose of the study drug, regardless of whether they completed any study assessments. Any event that first occurred or worsened in severity within 48 h after treatment with the study drug was considered a TEAE.

All primary and secondary efficacy analyses were made using a logistic regression model with treatment group and background use of migraine preventive medication as covariates. For treatment comparisons, an estimate of the odds ratio (OR) of achieving a response, as well as the corresponding confidence interval (CI) and *P*-value using Wald's test, were computed. Exceptions to this were global impression of change and level of disability, which used a Cochran–Mantel–Haenszel test controlling for background use of migraine preventive medication. Primary efficacy analyses on headache pain-free and MBS-free at 2 h were tested at a one-sided significance level of 0.025. A testing hierarchy was used to prevent type I error inflation for multiple comparisons: the primary efficacy end-point (pain free for the 200 mg group) was tested first and, if it was statistically significant, the MBS-free end-point was tested for the 200 mg group, followed by pain-free and MBS-free end-points for the 100 mg and then for the 50 mg groups, similarly. Continuous variables were summarized using descriptive statistics; categorical variables were summarized using counts and percentages. Other secondary efficacy end-points were tested at a two-sided significance level of 0.05.

Because each patient received up to two doses of lasmiditan within a range that had been well tolerated in prior studies, there was no data safety monitoring board for this study. This study is registered with ClinicalTrials.gov, number NCT02605174.

Data availability

Data are available to request 6 months after the indication studied has been approved in the US and EU. For details on submitting a request, please see the instructions provided at http://www.clinicalstudydatarequest.com.

Results

Between 19 May 2016 and 29 Jun 2017, 3005 patients were randomized, of whom 2869 (95.5%) had confirmed eligibility (Fig. 1). Subsequently, 2583 (86.0%) patients received at least one dose of the study medication (safety population). Of these, 2310 patients provided any post-dose headache severity or symptom assessment data (ITT), and 2156 of these patients treated the migraine within 4 h (full analysis set).

Of the 373 (12.4%) patients who discontinued (81 treated, 292 untreated), discontinuation rates were similar between treatment groups. The most common reasons for discontinuation were lost to follow-up and randomization failure (i.e. deemed ineligible at the telephone confirmation). The full analysis set included 2156 patients (71.7%) who treated a qualifying migraine within 4 h of onset.

Demographics

Table 1 shows patient demographics and clinical characteristics of previously treated migraine attacks. The majority of patients in the safety population were female (84.2%), white (80.2%), and the mean [standard deviation (SD)] age was 42.7 (12.8) years.

Baseline characteristics

At baseline, headache characteristics were similar across groups for the safety population. Patients reported having migraine for an average of 18.3 years with a mean (SD) of 5.3 (2.1) migraine attacks per month in the past 3 months. Most patients experienced moderate disability associated with their migraine attacks with a mean (SD) MIDAS total score of 32.2 (23.2). Overall, 95.3% of patients

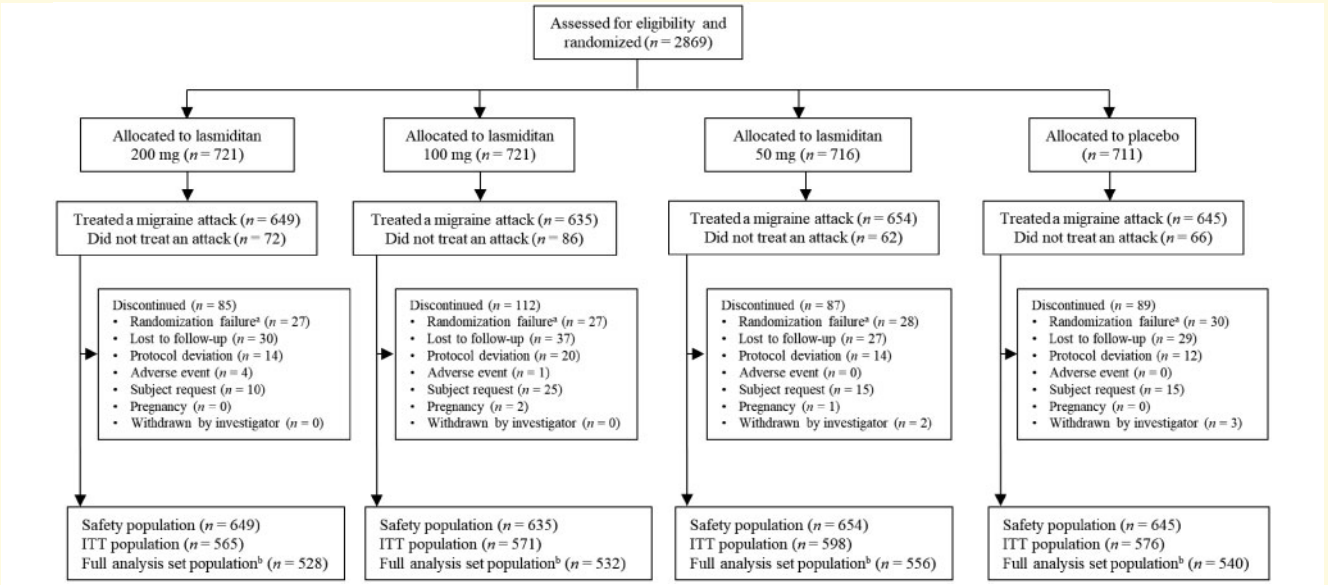

Figure 1 Study trial flow (first dose). ITT = intent-to-treat. [a]Patients who were randomized but then deemed ineligible at the telephone confirmation. [b]Originally referred to as the modified intent-to-treat population.

reported at least one prior medication for migraine, which most frequently included ibuprofen (37.6%), sumatriptan (32.2%), caffeine/paracetamol/acetylsalicylic acid (30.8%), paracetamol (18.2%), topiramate (12.1%), and rizatriptan benzoate (8.3%).

Characteristics of the treated migraine attacks in this study were similar between treatment groups (Table 1). The majority of patients reported moderate-to-severe headache, with ~90% reporting the presence of nausea, phonophobia, or photophobia; photophobia was the most commonly reported MBS across the treatment groups. The mean (SD) time to first dose from the start of the migraine attack (of any severity) was similar in the 200 mg, 100 mg, 50 mg and placebo treatment groups: 1.2 (±1.1) h, 1.2 (±1.1) h, 1.1 (±1.0) h, and 1.2 (±1.1) h, respectively.

Efficacy

The study met its primary efficacy objectives after a single dose; in each lasmiditan dose group a significantly higher proportion of patients were headache pain-free at 2 h and MBS-free at 2 h compared with placebo (Table 2). The proportion of patients who were pain-free at 2 h was significantly higher for the lasmiditan 200 mg group compared with placebo [38.8% versus 21.3%; OR = 2.3 (95% CI 1.8, 3.1); $P < 0.001$]. Significance for the proportion of patients who were pain-free at 2 h was also observed for the 100 mg and 50 mg lasmiditan dose groups compared with placebo. The proportion of patients who were MBS-free at 2 h was significantly higher for the 200 mg lasmiditan group compared with placebo [48.7% versus 33.5%; OR = 1.9 (95% CI 1.4, 2.4); $P < 0.001$]. Significance for the proportion of patients who were MBS-free at 2 h was also observed for the 100 mg and 50 mg lasmiditan dose groups compared with placebo. The time course for the proportion of patients pain-free (Fig. 2) and MBS-free (Fig. 3) show that higher doses of lasmiditan separated from placebo as early as 1 h for proportions reporting pain-free (200 mg and 100 mg; $P < 0.05$) and 0.5 h for proportions reporting MBS-free (200 mg; $P < 0.01$).

Considering the other secondary efficacy analyses, headache pain relief at 2 h post-dose was significantly higher for each lasmiditan treatment group versus placebo ($P < 0.001$) and a significant dose-related response for sustained pain freedom at 24 h was observed with lasmiditan (all doses) versus placebo (Table 2 and Fig. 4). Lasmiditan also showed benefits over placebo at 2 h in terms of the proportion of patients free from the migraine symptoms of phonophobia or photophobia ($P \leqslant 0.005$) (Table 2), and in global impression of change ratings and disability level ratings (each $P < 0.001$) (Table 3). Notably, there were significant dose-related improvements for patients who reported a global impression of 'very much better' and 'much better' across the lasmiditan treatment groups (42.5% 200 mg, 41.2% 100 mg, 36.6% 50 mg) versus placebo (28.0%).

Patients who received lasmiditan were less likely to use a second dose of study drug versus patients who received placebo: 21.2% (159/750) of the 200 mg lasmiditan group, 26.3% (198/754) of the 100 mg lasmiditan group, 34.4% (258/750) of the 50 mg lasmiditan group, and 39.5% (297/751) of the placebo group took a second dose between 2 and 24 h after the first dose. Of these second doses, 868 were taken as rescue medication, and 44 for recurrence of headache pain after initially achieving pain freedom.

Table 1 Baseline demographics and clinical characteristics

Characteristic	Lasmiditan 200 mg	Lasmiditan 100 mg	Lasmiditan 50 mg	Placebo
Safety population	*n* = 649	*n* = 635	*n* = 654	*n* = 645
Demographic characteristics				
Female, *n* (%)	536 (82.6)	539 (84.9)	554 (84.7)	545 (84.5)
Age, years, mean (SD)	41.8 (12.4)	43.4 (12.6)	42.8 (13.2)	42.6 (12.9)
Caucasian, *n* (%)	522 (80.4)	509 (80.2)	524 (80.1)	516 (80.0)
BMI (kg/m^2), mean (SD)	30.1 (8.2)	30.1 (8.3)	29.7 (7.6)	30.4 (11.1)
Clinical characteristics				
MIDAS total score, mean (SD)	32.9 (23.5)	31.3 (20.7)	33.2 (25.2)	31.5 (23.1)
Duration of migraine history, years, mean (SD)	17.6 (12.6)	19.2 (13.6)	18.6 (12.9)	17.9 (12.8)
Migraine attacks/month in past 3 months, mean (SD)	5.3 (1.9)	5.3 (1.9)	5.2 (2.0)	5.5 (2.4)
History of migraine with and without aura, *n* (%)				
With aura	229 (35.3)	238 (37.5)	226 (34.6)	244 (37.8)
Without aura	416 (64.1)	397 (62.5)	424 (64.8)	399 (61.9)
Background use of preventive migraine medication, *n* (%)	121 (18.6)	122 (19.2)	125 (19.1)	126 (19.5)
Presence of ⩾1 cardiovascular risk factor[a], *n* (%)	528 (81.4)	510 (80.3)	508 (77.7)	517 (80.2)
History of ⩾1 cardiac event	33 (5.1)	40 (6.3)	36 (5.5)	46 (7.1)
Full analysis set[b]	*n* = 528	*n* = 532	*n* = 556	*n* = 540
Characteristics of treated migraine attacks				
Severe headache pain (3), *n* (%)	147 (27.8)	159 (29.9)	152 (27.3)	165 (30.6)
Moderate headache pain (2), *n* (%)	374 (70.8)	364 (68.4)	392 (70.5)	369 (68.3)
Mild headache pain[c] (1), *n* (%)	7 (1.3)	9 (1.7)	12 (2.2)	5 (0.9)
Baseline symptoms, *n* (%)				
Phonophobia	326 (61.7)	345 (64.8)	330 (59.4)	353 (65.4)
Photophobia	397 (75.2)	406 (76.3)	427 (76.8)	419 (77.6)
Nausea	219 (41.5)	235 (44.2)	245 (44.1)	249 (46.1)
None	45 (8.5)	32 (6.0)	44 (7.9)	26 (4.8)
MBS	*n* = 483	*n* = 500	*n* = 512	*n* = 514
Phonophobia, *n* (%)	110 (20.8)	110 (20.7)	108 (19.4)	119 (22.0)
Photophobia, *n* (%)	269 (50.9)	276 (51.9)	277 (49.8)	268 (49.6)
Nausea, *n* (%)	104 (19.7)	114 (21.4)	127 (22.8)	127 (23.5)
Time to dosing from migraine attack start (h), mean (SD)	1.2 (1.1)	1.2 (1.1)	1.1 (1.0)	1.2 (1.1)
Probability of selecting symptom as MBS[d]				
Phonophobia, *n*/*N* (%)	110/326 (33.7)	110/345 (31.9)	108/330 (32.7)	119/353 (33.7)
Photophobia, *n*/*N* (%)	269/397 (67.8)	276/406 (68.0)	277/427 (64.9)	268/419 (64.0)
Nausea, *n*/*N* (%)	104/219 (47.5)	114/235 (48.5)	127/245 (51.8)	127/249 (51.0)

BMI = body mass index.

[a]Cardiovascular risk factors were defined, based on the American College of Cardiology/American Heart Association guidelines as: age, total and high-density lipoprotein cholesterol, systolic blood pressure (including treated or untreated status), diabetes, and current smoking status.

[b]Originally referred to as the modified intent-to-treat population.

[c]Patients were encouraged not to take their dose until the migraine attack headache severity was either moderate or severe as per the study protocol; however, a small number dosed at mild headache and are included in the analysis populations.

[d]Defined as the number of patients who selected the symptom as the MBS (*n*) relative to the number of patients with the particular symptom at baseline (*N*).

Tolerability and safety

The proportion of patients who reported at least one TEAE after the first dose was higher in the lasmiditan treatment groups than in the placebo group and was dose-related [253/649 (39.0%), 230/635 (36.2%), 167/654 (25.5%) for 200, 100 and 50 mg lasmiditan, respectively versus 75/645 (11.6%) for placebo]. Of the 725 TEAEs reported, the majority [676 (93.2%)] were considered to be treatment-related by the investigator. The majority of TEAEs were mild or moderate in severity. The most frequently reported TEAEs (i.e. reported by at least 2% of the lasmiditan safety population and which were also greater than reported by the placebo group) were associated with the CNS (e.g. dizziness, somnolence and paraesthesia) (Table 4). A total of five serious adverse events were reported, of which two were considered treatment-related (dystonic reaction 100 mg; presyncope 200 mg); both resolved with sequelae (positive Romberg test and fatigue, respectively). One treatment discontinuation was attributed to adverse events following 200 mg lasmiditan (fatigue and dizziness); however, the patient completed all required study assessments.

The incidence of cardiovascular-related TEAEs after the first dose was low [12 (0.5%)] (Table 4). All cardiovascular TEAEs (seven palpitations, five tachycardia) were considered reasonably or possibly related to the study drug.

Table 2 Primary and secondary efficacy end-points after single dose by treatment group

	Lasmiditan 200 mg	Lasmiditan 100 mg	Lasmiditan 50 mg	Placebo
Primary efficacy outcomes (full analysis set)[a]	*n* = 528	*n* = 532	*n* = 556	*n* = 540
Headache pain-free[b]				
% of patients pain-free[b] at 2 h	205 (38.8)	167 (31.4)	159 (28.6)	115 (21.3)
Odds ratio (95% CI)*	2.3 (1.8, 3.1)	1.7 (1.3, 2.2)	1.5 (1.1, 1.9)	
P-value*	<0.001	<0.001	0.003	
MBS-free[c]	(*n* = 483)	(*n* = 500)	(*n* = 512)	(*n* = 514)
% of patients MBS-free at 2 h	235 (48.7)	221 (44.2)	209 (40.8)	172 (33.5)
Odds ratio (95% CI)*	1.9 (1.4, 2.4)	1.6 (1.2, 2.0)	1.4 (1.1, 1.8)	
P-value*	<0.001	<0.001	0.009	
Secondary efficacy outcomes (ITT population)	*n* = 565	*n* = 571	*n* = 598	*n* = 576
Sustained pain freedom[d]				
24 h, *n* (%)	128 (22.7)	102 (17.9)	103 (17.2)	77 (13.4)
Odd ratio (95% CI)*	1.9 (1.4, 2.6)	1.4 (1.0, 1.9)	1.3 (1.0, 1.9)	
P-value*	<0.001	0.021	0.036	
48 h, *n* (%)	111 (19.6)	86 (15.1)	89 (14.9)	68 (11.8)
Odds ratio (95% CI)*	1.8 (1.3, 2.5)	1.3 (0.9, 1.9)	1.3 (0.9, 1.8)	
P-value*	<0.001	0.058	0.065	
Headache pain relief[e] at 2 h, *n* (%)	367 (65.0)	370 (64.8)	353 (59.0)	274 (47.7)
Odds ratio (95% CI)	2.4 (1.8, 3.1)	2.3 (1.7, 2.9)	1.7 (1.3, 2.2)	
P-value*	<0.001	<0.001	<0.001	
Phonophobia-free at 2 h, *n* (%)	431 (76.3)	428 (75.0)	428 (71.6)	368 (63.9)
Odds ratio (95% CI)	1.8 (1.4, 2.4)	1.7 (1.3, 2.2)	1.4 (1.1, 1.9)	
P-value*	<0.001	<0.001	0.004	
Photophobia-free at 2 h, *n* (%)	391 (69.2)	380 (66.5)	368 (61.5)	309 (53.6)
Odds ratio (95% CI)	2.0 (1.5, 2.6)	1.8 (1.4, 2.3)	1.4 (1.1, 1.8)	
P-value*	<0.001	<0.001	0.005	
Nausea-free at 2 h, *n* (%)	460 (81.4)	468 (82.0)	473 (79.1)	465 (80.7)
Odds ratio (95% CI)	1.0 (0.8, 1.4)	1.1 (0.8, 1.5)	0.9 (0.7, 1.2)	
P-value*	0.834	0.629	0.443	
Vomiting-free at 2 h, *n* (%)	557 (98.6)	567 (99.3)	588 (98.3)	571 (99.1)
Odds ratio (95% CI)	0.6 (0.2, 1.8)	1.2 (0.3, 4.6)	0.5 (0.2, 1.5)	
P-value*	0.373	0.749	0.229	

ITT = intent-to-treat.
*Versus placebo.
[a]Originally referred to as the modified intent-to-treat population.
[b]Defined as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline, to none (0).
[c]Defined as the absence of the associated symptom of migraine that was identified pre-dose as the MBS (either nausea, phonophobia or photophobia).
[d]Defined as being headache pain-free at 2 h after the first dose, and at the indicated assessment time, having not used any medications after the first dose.
[e]Defined as a reduction in headache severity from moderate (2) or severe (3) at baseline, to mild (1) or none (0), or a reduction in headache severity from mild (1) at baseline, to none (0).

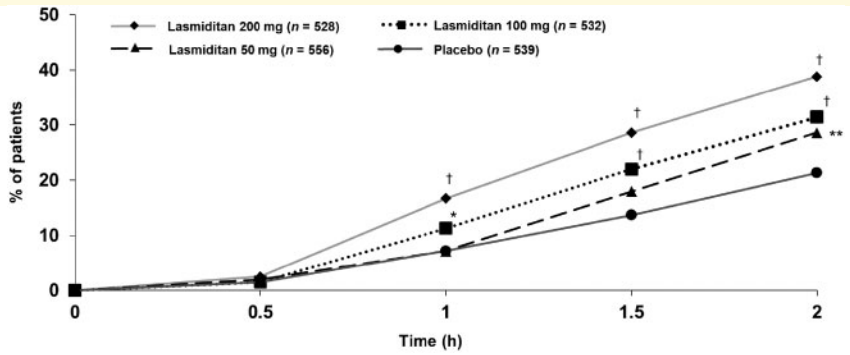

Figure 2 Headache pain-free after first dose. Full analysis set (originally referred to as the modified intent-to-treat population). $^{\dagger}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ versus placebo.

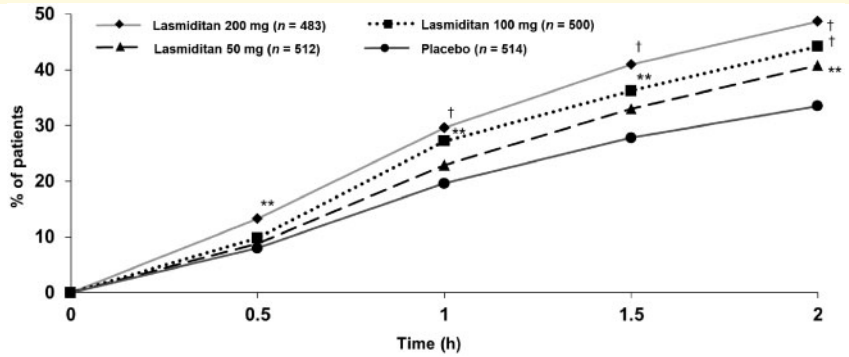

Figure 3 Most bothersome symptom-free after first dose. Full analysis set (originally referred to as the modified intent-to-treat population). $^{\dagger}P < 0.001$, $^{**}P < 0.01$ versus placebo.

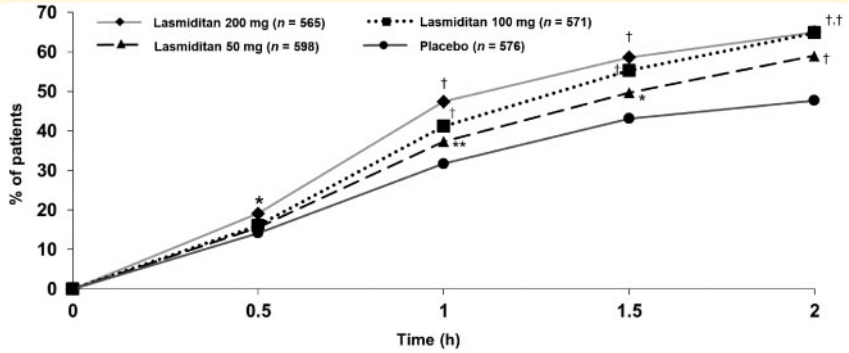

Figure 4 Headache pain-relief after first dose (intent-to-treat population). $^{\dagger}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ versus placebo.

Table 3 Global impression of change and disability level after single dose by treatment group (ITT population)

	Lasmiditan 200 mg (*n* = 565)	Lasmiditan 100 mg (*n* = 571)	Lasmiditan 50 mg (*n* = 598)	Placebo (*n* = 576)
Global impression of change at 2 h, *n* (%)				
Very much better	82 (14.5)	74 (13.0)	66 (11.0)	46 (8.0)
Much better	158 (28.0)	161 (28.2)	153 (25.6)	115 (20.0)
A little better	155 (27.4)	163 (28.5)	175 (29.3)	162 (28.1)
No change	70 (12.4)	75 (13.1)	98 (16.4)	152 (26.4)
A little worse	20 (3.5)	27 (4.7)	29 (4.8)	25 (4.3)
Much worse	13 (2.3)	10 (1.8)	11 (1.8)	15 (2.6)
Very much worse	5 (0.9)	3 (0.5)	4 (0.7)	1 (0.2)
P-value versus placebo	<0.001	<0.001	<0.001	
Disability level at 2 h, *n* (%)				
Not at all (0)	209 (37.0)	193 (33.8)	187 (31.3)	143 (24.8)
Mild interference (1)	145 (25.7)	177 (31.0)	165 (27.6)	161 (28.0)
Marked interference (2)	92 (16.3)	91 (15.9)	108 (18.1)	139 (24.1)
Completely, needs bed rest (3)	57 (10.1)	52 (9.1)	76 (12.7)	73 (12.7)
P-value versus placebo	<0.001	<0.001	0.019	

ITT = intent-to-treat.

Laboratory tests

Patients completed laboratory assessments at the end of study visit, usually conducted within 7 days of dosing. There were no clinically meaningful differences in haematology, blood chemistry, urinalysis, vital signs, physical examination, or ECGs across the treatment groups, or with regards to changes from baseline.

Table 4 Most commonly reported treatment-emergent adverse events after single dose by treatment group (safety population)

Preferred term	Lasmiditan 200 mg (*n* = 649)	Lasmiditan 100 mg (*n* = 635)	Lasmiditan 50 mg (*n* = 654)	Placebo (*n* = 645)
Subjects with at least one first-dose TEAE, *n* (%)	253 (39.0)	229 (36.1)	166 (25.4)	75 (11.6)
Dizziness	117 (18.0)	115 (18.1)	56 (8.6)	16 (2.5)
Somnolence	42 (6.5)	29 (4.6)	35 (5.4)	13 (2.0)
Paresthesia	43 (6.6)	37 (5.8)	16 (2.4)	6 (0.9)
Fatigue	31 (4.8)	26 (4.1)	18 (2.8)	6 (0.9)
Nausea	17 (2.6)	21 (3.3)	18 (2.8)	8 (1.2)
Lethargy	14 (2.2)	8 (1.3)	8 (1.2)	1 (0.2)
Incidence of cardiac disorder TEAEs, *n* (%)				
Palpitations	2 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)
Tachycardia	2 (0.3)	2 (0.3)	1 (0.2)	0

TEAEs were events that occurred or worsened 0–48 h after taking study drug. TEAEs listed here are those that occurred ⩾2% in any treatment group and occurred more often than in the placebo group, except for cardiac disorder events. During this phase 3 study, patients were asked if they felt anything unusual since taking the study medication that they had not felt with a migraine attack before, and if so, a follow-up phone call from the site was made. If the symptom was new or different, or was a usual symptom but worsened in severity, it was recorded as a TEAE.

Discussion

This phase 3 randomized, double-blind, placebo-controlled study demonstrated that at all doses, a significantly greater proportion of patients receiving a single dose of lasmiditan were headache pain-free at 2 h compared with placebo. The data confirm the efficacy, tolerability and safety findings of the recently reported first phase 3 trial (Kuca *et al.*, 2018). In addition, lasmiditan was more effective in achieving freedom from the MBS at all doses. Patients were primarily white, middle-aged females with an established history of migraine and most had at least one cardiovascular risk factor at baseline in addition to migraine. Approximately 20% of patients reported currently prescribed preventive migraine medications. These findings support the efficacy of lasmiditan for acute treatment of migraine, and the hypothesis that 5-HT_{1F} receptor activation can relieve the pain and symptoms associated with a migraine attack (Raffaelli *et al.*, 2017), although from these data the relative contribution of central versus peripheral action cannot be determined. Across the 2583 patients in the safety population, two treatment-related serious adverse events were reported and resolved with sequelae. The most common TEAEs were associated with the CNS; rates of cardiovascular-related TEAEs were low.

This study evaluated three doses of lasmiditan (50, 100, 200 mg) for the acute treatment of patients with migraine attacks. The randomization ratio (1:3) for placebo versus active was chosen to inform dosing choice, but may have contributed to a relatively elevated placebo response (Pfaffenrath *et al.*, 1998). Randomization ratios are always a balance between a design that answers the experimental question and takes into account the number of patients receiving placebo versus active treatment. This study was positive, and a dose effect response was shown. The randomization ratio, while potentially affecting the drug placebo difference, did not mask the effect of lasmiditan as all single doses of lasmiditan resulted in significantly higher proportions of patients who were headache pain-free at 2 h and MBS-free at 2 h. Of clinical importance, higher doses of lasmiditan (100, 200 mg) were associated with time to headache pain-free as early as 1 h, and time to MBS-free as early as 0.5 h after the single dose. Patients value complete resolution of migraine pain and early onset of effect (Lipton and Stewart, 1999). Furthermore, 17–24% of lasmiditan-treated patients had sustained pain freedom at 24 h after the single dose. A dose-related response was observed from 0.5–2 h after the first dose of lasmiditan in the percentage of patients who had headache pain-relief. The beneficial effects of lasmiditan on migraine were also supported by significant reductions in the individual associated symptoms of phonophobia and photophobia, but not nausea. Global impression of change ('very much better/much better'), as well as having no disability (score of 0), appeared to be dose-related with 200 mg lasmiditan-treated patients reporting the most benefit after a single dose.

Safety and tolerability of lasmiditan following a single dose was consistent with the previous phase 3 study (Kuca *et al.*, 2018). In this study, the most frequent TEAEs after a single lasmiditan dose (those reported by ⩾2% in any lasmiditan group and greater than reported by placebo group) were nervous system related. The most notable difference between the lasmiditan treatment groups and placebo was the observed increased incidence of dizziness (8.6–18.1% versus 2.5%, respectively). Dizziness is also reported with triptans (Goadsby *et al.*, 2002), and CNS adverse events are somewhat more common with more centrally penetrant triptans (Goadsby *et al.*, 2007). In addition, fatigue, nausea and lethargy were more commonly reported after lasmiditan compared with placebo. Further information on efficacy and safety/tolerability of a second dose will be described in a future publication.

The majority of the study population (~80%) reported at least one cardiovascular risk factor at baseline in addition to migraine (Hippisley-Cox *et al.*, 2017; Mahmoud *et al.*, 2018) and a small proportion reported related medical history ($n = 155$, 6.0%). Notably, the first phase 3 study (Kuca *et al.*, 2018) permitted enrolment of patients with cardiovascular risk factors but not patients with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension. Accordingly, the current study suggests that lasmiditan is effective and well-tolerated in a broad population of patients. However, future publications will detail efficacy and safety/tolerability of lasmiditan in the subpopulation of patients with cardiovascular risk factors and/or disease.

Limitations

Because enrolled patients were primarily middle-aged white females, these findings may not extrapolate to other patient populations. Because this study enrolled low numbers of patients with pre-existing cardiovascular disease, additional data are needed to confirm the efficacy and safety/tolerability of lasmiditan in this more seriously ill patient population. Another limitation is that study findings were limited to primarily a single dose; safety/tolerability and efficacy of lasmiditan will need to be validated following continued dosing. Finally, with the exception of adverse events, safety/tolerability parameters were not collected near the time of dosing and may have limited clinical relevance.

In conclusion, lasmiditan, dosed at 200 mg, 100 mg and 50 mg, was efficacious and relatively well tolerated in the acute treatment of a single migraine attack. The study met its primary objective by demonstrating that a statistically significantly higher percentage of patients in each of the lasmiditan treatment groups versus placebo were headache pain-free at 2 h post-dose and MBS-free at 2 h post-first dose. Safety of lasmiditan will be further assessed in the ongoing long-term, open-label, multi-dose safety study (NCT02565186).

Acknowledgements

The authors thank Joel Raskin, MD, Director Medical Affairs Migraine at Eli Lilly and Company, for his critical review of these data. Writing support was provided by Teresa Tartaglione, PharmD (Synchrogenix, a Certara Company, Wilmington, Delaware) who received funding from Eli Lilly and Company.

Funding

The study was designed by the principal investigators together with the sponsor (CoLucid Pharmaceuticals) and consultation with the Food and Drug Administration. The sponsor participated in data collection, data analysis, data interpretation, and the writing of the report. Eli Lilly and Company provided additional statistical and writing support following the acquisition of CoLucid Pharmaceuticals.

Competing interests

P.J.G. reports grants and personal fees from Amgen and Eli Lilly and Company, and personal fees from Alder Biopharmaceuticals, Allergan, Autonomic Technologies Inc., Dr Reddy's Laboratories, Electrocore LLC, eNeura, Novartis, Scion, Teva Pharmaceuticals, and Trigemina Inc., and personal fees from MedicoLegal work, Up-to-Date, Oxford University Press, Massachusetts Medical Society, and Wolters Kluwer; and a patent Magnetic stimulation for headache assigned to eNeura without fee. A.W., E.D., M.G.C., and S.K.A. are full time employees and minor stockholders for Eli Lilly and Company. B.K. was a full-time employee and minor stockholder for CoLucid Pharmaceuticals when the study was designed and conducted. C.G. has received honoraria for consulting and lectures within the past three years from Allergan Pharma, Ratiopharm, Boehringer Ingelheim Pharma, Lilly Germany, Novartis Pharma, Desitin Arzneimittel, Cerbotec, Bayer vital, Hormosan Pharma, electroCore, Grünenthal, Reckitt Benckiser, and TEVA. He does not hold any stocks of pharmaceutical companies or medical device companies.

References

Buse DC, Reed ML, Fanning KM, Kurth T, Lipton RB. Cardiovascular events, conditions, and procedures among people with episodic migraine in the US Population: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache 2017; 57: 31–44.

Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, et al. Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. Headache 2015; 55 (Suppl 4): 221–35.

Dodick DW, Lipton RB, Martin V, Papademetriou V, Rosamond W, MaassenVanDenBrink A, et al.; Triptan Cardiovascular Safety Expert Panel. Consensus statement: cardiovascular safety profile of triptans (5-$HT_{1B/1D}$ agonists) in the acute treatment of migraine. Headache 2004; 44: 414–25.

Färkkilä M, Diener HC, Géraud G, Láinez M, Schoenen J, Harner N, et al. Efficacy and tolerability of lasmiditan, an oral 5-HT_{1F} receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. Lancet Neurol 2012; 11: 405–13.

Ferrari MD, Färkkilä M, Reuter U, Pilgrim A, Davis C, Krauss M, et al. Acute treatment of migraine with the selective 5-HT_{1F} receptor agonist lasmiditan—a randomised proof-of-concept trial. Cephalalgia 2010; 30: 1170–78.

Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin, 5-$HT_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials. Lancet 2001; 358: 1668–75.

GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1260–1344.

Goadsby PJ, Dodick DW, Almas M, Diener HC, Tfelt-Hansen P, Lipton RB, et al. Treatment-emergent CNS symptoms following triptan therapy are part of the attack. Cephalalgia 2007; 27: 254–62.

Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev 2017; 97: 553–622.

Goadsby PJ, Lipton RB, Ferrari MD. Migraine—current understanding and treatment. N Engl J Med 2002; 346: 257–70.

Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. JACC 2014; 63: 2935–59.

Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders: 3rd edition. Cephalalgia 2013; 33: 629–808.

Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ 2017; 357: j2099.

Kuca B, Silberstein SD, Wietecha L, Berg PH, Dozier G, Lipton RB; COL MIG-301 Study Group. Lasmiditan is an effective acute treatment for migraine: a phase 3 randomized study. Neurology 2018;91: e2222–32.

Lipton RB, Buse DC, Serrano D, Holland S, Reed ML. Examination of unmet treatment needs among persons with episodic migraine: results of the American migraine prevalence and prevention (AMPP) study. Headache 2013; 53: 1300–11.

Lipton RB, Reed ML, Kurth T, Fanning KM, Buse DC. Framingham-based cardiovascular risk estimates among people with episodic migraine in the US population: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache 2017; 57: 1507–21.

Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? Headache 1999; 39 (Suppl 2): S20–26.

Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: the migraine disability assessment (MIDAS) questionnaire. Headache 2001; 41: 854–61.

Mafi JN, Edwards ST, Pedersen NP, Davis RB, McCarthy EP, Landon BE. Trends in the ambulatory management of headache: analysis of NAMCS and NHAMCS data 1999–2010. J Gen Intern Med 2015; 30: 548–55.

Mahmoud AN, Mentias A, Elgendy AY, Qazi A, Barakat AF, Saad M, et al. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1,152,407 subjects. BMJ Open 2018; 8: e020498.

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.

Molina KC, Fairman KA, Sclar DA. Concomitant use of opioid medications with triptans or serotonergic antidepressants in US office-based physician visits. Drug Healthc Patient Saf 2018; 10: 37–43.

Pfaffenrath V, Cunin G, Sjonell G, Prendergast S. Efficacy and safety of sumatriptan tablets (25 mg, 50 mg, and 100 mg) in the acute treatment of migraine; defining the optimum doses of oral sumatriptan. Headache 1998; 38: 184–90.

Raffaelli B, Israel H, Neeb L, Reuter U. The safety and efficacy of the 5-HT 1F receptor agonist lasmiditan in the acute treatment of migraine. Expert Opin Pharmacother 2017; 18: 1409–15.

Rubio-Beltrán E, Labastida-Ramírez A, Villalón CM, MaassenVanDenBrink A. Is selective 5-HT_{1F} receptor agonism an entity apart from that of the triptans in antimigraine therapy? Pharmacol Ther 2018; 186: 88–97.

Vila-Pueyo M. Targeted 5-HT_{1F} therapies for migraine. Neurotherapeutics 2018; 15: 291–303.

Viana M, Genazzani AA, Terrazzino S, Nappi G, Goadsby PJ. Triptan nonresponders: do they exist and who are they? Cephalalgia 2013; 33: 891–6.