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

*Markus Färkkilä, Hans-Christoph Diener, Gilles Géraud, Miguel Láinez, Jean Schoenen, Nadja Harner, Alison Pilgrim, Uwe Reuter, for the COL MIG-202 study group**

Summary

Background Lasmiditan (COL-144) is a novel, centrally acting, highly selective 5-HT$_{1F}$ receptor agonist without vasoconstrictor activity that seemed effective when given as an intravenous infusion in a proof-of-concept migraine study. We aimed to assess the efficacy and safety of oral lasmiditan for the acute treatment of migraine.

Methods In this multicentre, double-blind, parallel-group, dose-ranging study in 43 headache centres in five European countries, patients with migraine with and without aura and who were not using prophylaxis were randomly assigned (1:1:1:1:1) to treat one moderate or severe attack at home with 50 mg, 100 mg, 200 mg, or 400 mg lasmiditan, or placebo. Study drug and placebo were supplied in identical numbered tablet packs. The randomisation code was generated by an independent statistician. Patients and investigators were masked to treatment allocation. The primary endpoint was dose response for headache relief (moderate or severe becoming mild or none) at 2 h. The primary analysis was done in the modified intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00883051.

Findings Between July 8 2009, and Feb 18, 2010, 512 patients were randomly assigned to treatment, 391 of whom received treatment. 86 patients received placebo (81 included in primary analysis) and 305 received lasmiditan (50 mg n=79, 100 mg n=81, 200 mg n=69, and 400 mg n=68 included in primary analysis). There was a linear association between headache response rate at 2 h and lasmiditan dose (Cochran-Armitage test p<0·0001). Every lasmiditan treatment dose significantly improved headache response at 2 h compared with placebo (lasmiditan 50 mg: difference 17·9%, 95% CI 3·9–32·1, p=0·022; 100 mg: 38·2%, 24·1–52·4, p<0·0001; 200 mg: 28·8%, 9·6–39·9, p=0·0018; 400 mg: 38·7%, 23·9–53·6, p<0·0001). The proportion of patients with treatment-emergent adverse events increased with increasing doses (53/82 [65%], 59/82 [72%], 61/71 [86%], and 59/70 [84%] for lasmiditan 50, 100, 200, and 400 mg, respectively *vs* 19/86 [22%] for placebo). Most adverse events were mild or moderate in intensity, with 16 of 82 (20%), 23 of 82 (28%), 28 of 71 (39%), and 31 of 70 (44%) of patients on lasmiditan 50, 100, 200, and 400 mg, respectively reporting a severe adverse event compared with five of 86 (6%) on placebo. The most common adverse events were CNS related and included dizziness, fatigue, vertigo, paraesthesia, and somnolence.

Interpretation Oral lasmiditan seems to be safe and effective in the acute treatment of migraine. Further assessment in larger placebo-controlled and triptan-controlled trials are needed to assess the potential role of lasmiditan in acute migraine therapy.

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*Members listed at end of paper

University of Helsinki, Department of Neurology, Helsinki, Finland (Prof M Färkkilä MD); **University of Duisburg–Essen, Department of Neurology, Essen, Germany** (Prof H-C Diener MD); **CHU Toulouse, Pôle des Neurosciences, Service de Neurologie, Hôpital Rangueil, Toulouse, France** (Prof G Géraud MD); **Hospital Clínico Universitario University of Valencia Department of Neurology, Valencia, Spain** (Prof M Láinez MD); **University of Liège, CHR Citadelle, Department of Neurology, Liège, Belgium** (Prof J Schoenen MD); **FGK Clinical Research, Munich, Germany** (N Harner MSc); **CoLucid Pharmaceuticals, Durham, NJ, USA** (A Pilgrim BM); **and Charité Universitätsmedizin Berlin, Department of Neurology, Berlin, Germany** (U Reuter MD)

Correspondence to: Dr Uwe Reuter, Charité Universitätsmedizin Berlin, Department of Neurology, Charitéplatz 1, 10117 Berlin, Germany **uwe.reuter@charite.de**

Introduction

Migraine is one of the most common neurological disorders and is ranked by WHO as one of the 20 most debilitating disorders.[1] Although the introduction of 5-HT$_{1B/1D}$ receptor agonists (triptans) has greatly improved acute treatment of migraine, the American Migraine Prevalence and Prevention study[2] revealed that 40% of episodic migraineurs still have unmet treatment needs. Headache-related disability (19%) and dissatisfaction with present drugs (15%) were the most frequent complaints.[2] In clinical trials, over 35% of patients do not benefit from treatment with oral triptan formulations.[3,4] Because of potential vasoconstriction, patients with cardiovascular disease, uncontrolled hypertension, and certain forms of migraine (eg, hemiplegic migraine) cannot use triptans,[4,5] and side-effects such as chest tightness, throat discomfort, muscle pain, and paraesthesia lead some patients to avoid them.[6] Therefore, effective treatment options for patients who do not achieve adequate headache relief with triptans or who cannot or will not take them remains a considerable area of unmet clinical need.

5-HT$_{1F}$ receptor agonists are a potential treatment alternative to triptans.[7] The expression of 5-HT$_{1F}$ receptor mRNA in neurons of the trigeminal ganglia led to the suggestion that 5-HT$_{1F}$ receptors could be a therapeutic target for migraine.[8] Lasmiditan, a highly selective 5-HT$_{1F}$ agonist, has 470 times higher affinity for 5-HT$_{1F}$

receptors than for vasoconstrictor 5-HT_{1B} receptors.[9] Administration of lasmiditan inhibited neurogenic inflammation in the dura and decreased c-Fos expression in the trigeminal nucleus caudalis after stimulation of the trigeminal ganglion in rats; unlike triptans, lasmiditan did not cause constriction of rabbit saphenous vein—an assay predictive of human coronary artery vasoconstriction.[9]

A proof-of-concept randomised, multicentre, placebo-controlled trial with 130 patients showed that intravenous doses of lasmiditan of 20 mg and higher provided effective headache relief at 2 h of an acute migraine attack.[10] However, migraine is usually self-treated on an outpatient basis. Therefore, an oral formulation of lasmiditan was developed. In otherwise healthy patients, oral lasmiditan doses up to 400 mg were well tolerated without clinically significant effects on vital signs, electrocardiogram (ECG), or laboratory parameters.[11] We therefore undertook a dose-ranging study to assess the efficacy and safety of oral lasmiditan for the acute treatment of migraine.

Methods

Patients

We undertook a randomised, double-blind, placebo-controlled, multicentre, parallel-group, dose-ranging outpatient study in patients with acute migraine from 43 headache centres in five European countries. Men or women (18–65 years) who had at least a 1-year history of migraine with or without aura (according to International Headache Society criteria 1.1 and 2.1)[12] with onset before the age of 50 years and one to eight migraine attacks per month were eligible for enrolment. Exclusion criteria included patients taking prescription or herbal migraine prophylaxis, vasoactive drugs, serotonin reuptake inhibitors, or known cytochrome P450 inhibitors. Prescription preventative migraine drugs were discontinued at least 15 days (flunarizine 30 days) before screening. By pharmacokinetic/pharmacodynamic (PK/PD) modelling, we selected doses for the study, with 50 mg predicted to have minimal efficacy and 400 mg to have both high efficacy and a rapid onset of effect.[13] The rapidly disintegrating lasmiditan tablets used in this study achieve maximum plasma concentrations at 2·0–2·5 h.

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

Randomisation and masking

Using a randomisation code generated by an independent statistician, patients were randomly assigned (1:1:1:1:1) to 50 mg, 100 mg, 200 mg, or 400 mg lasmiditan, or placebo in blocks of five. Treatment was double-blind, with all patients receiving numbered drug packs that were

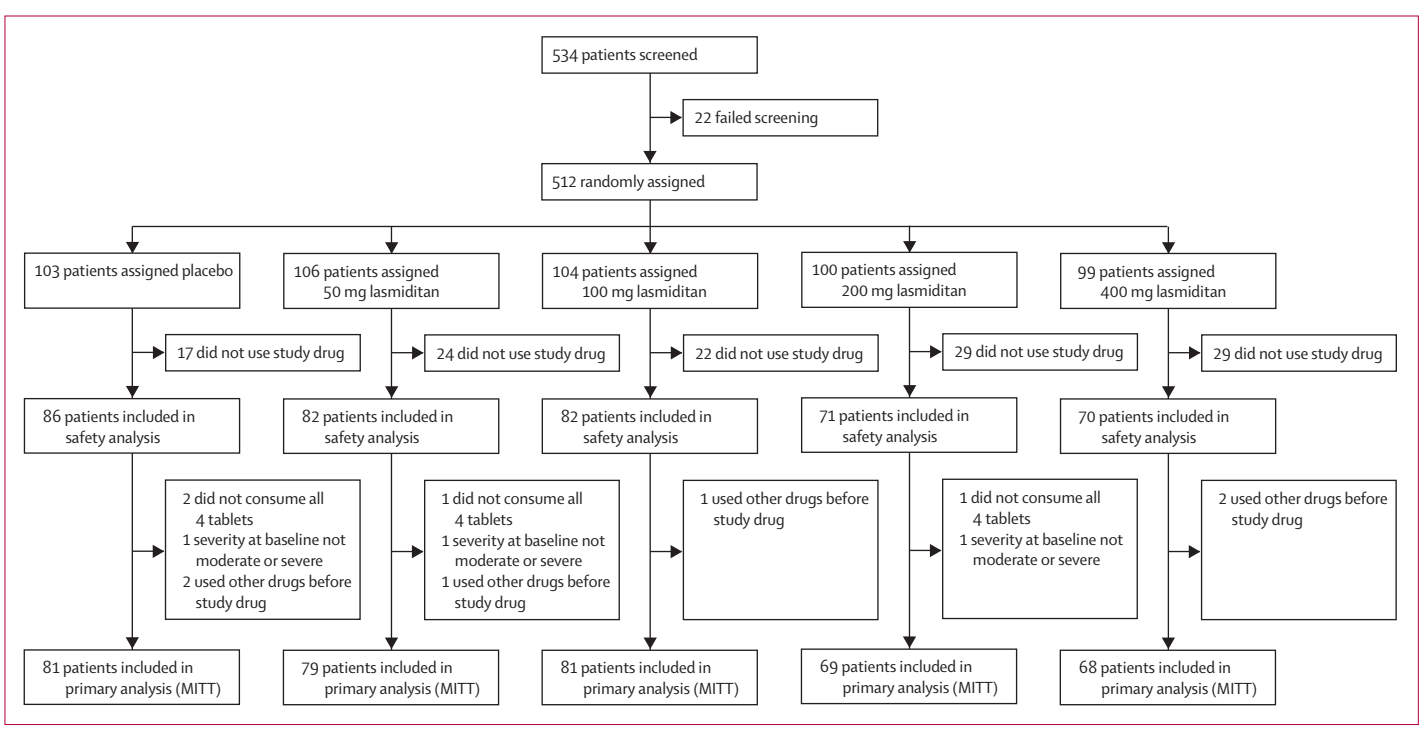


Figure 1: **Trial profile**
MITT=modified intention-to-treat population.

identical in appearance. All patients and investigators, excluding the independent statistician, were masked to treatment allocation.

Procedures

At screening, medical and migraine history were taken, and physical examination, ECG, and laboratory tests were done outside a migraine attack for all patients. Eligible patients were instructed to treat their next migraine attack within 4 h of onset, providing that any aura symptoms had resolved and their headache was moderate or severe. Rescue drugs (excluding triptans or ergotamine) could be taken after 2 h. Patients were allowed 8 weeks to treat an attack.

The primary objectives were to assess the lasmiditan dose relation for headache relief at 2 h after intake of the

	Placebo (n=86)	Lasmiditan			
		50 mg (n=82)	100 mg (n=82)	200 mg (n=71)	400 mg (n=70)
Age (years)	40·5 (10·3; 19–66)	40·4 (12·5; 18–65)	42·0 (10·6; 20–65)	39·5 (10·3; 18–57)	38·7 (10·3; 20–60)
Female sex	75 (87%)	69 (84%)	68 (83%)	65 (92%)	65 (93%)
White ethnic origin	86 (100%)	81 (99%)	81 (99%)	70 (99%)	69 (99%)
Migraine frequency (past 3 months)	3·1 (1·7)	3·3 (1·6)	3·3 (1·7)	3·3 (1·9)	3·1 (1·6)
Duration of treated attack before use of study drug (h)	2·2 (0·0–31·8)	1·8 (0·0–19·0)	2·8 (0·0–15·0)	2·3 (0·0–15·0)	2·1 (0·0–19·8)
Duration of moderate-to-severe headache before treatment (h)	0·2 (0·0–7·5)	0·1 (0·0–2·1)	0·2 (0·0–3·1)	0·3 (0·0–1·9)	0·1 (0·0–2·3)
Accompanying aura*†					
No	79 (92%)	70 (85%)	76 (93%)	68 (96%)	62 (89%)
Yes	6 (7%)	11 (13%)	5 (6%)	3 (4%)	8 (11%)
Severity*					
Moderate	51 (59%)	49 (60%)	49 (60%)	36 (51%)	39 (56%)
Severe	34 (40%)	32 (39%)	33 (40%)	34 (48%)	31 (44%)

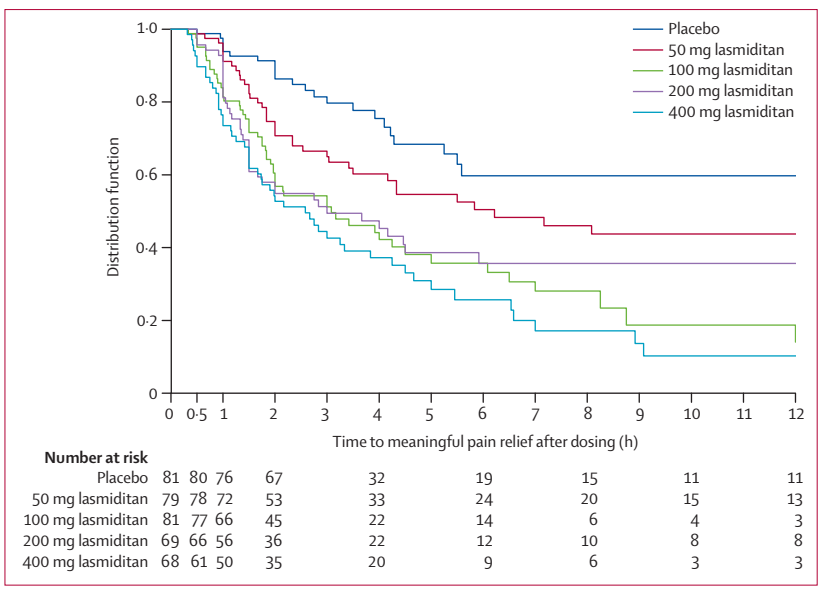
Data are mean (SD; range), number (%), mean (SD), or median (range). *Some percentages do not add up to 100% because of missing data. †If the migraine attack was accompanied by aura, the study drug was not taken until the aura had resolved.

Table 1: **Baseline demographics and clinical characteristics**

	Placebo (n=81); Response n (%; 95% CI)	Lasmiditan											
		50 mg (n=79)			100 mg (n=81)			200 mg (n=69)			400 mg (n=68)		
		Response n (%; 95% CI)	Difference (95% CI)	p value*	Response n (%; 95% CI)	Difference (95% CI)	p value*	Response n (%; 95% CI)	Difference (95% CI)	p value*	Response n (%; 95% CI)	Difference (95% CI)	p value*
Headache response at 2 h	21 (25·9%; 16·8–36·9)	34 (43%; 31·9–54·7)	17·9% (3·9–32·1)	0·022	52 (64%; 52·8–74·6)	38·2% (24·1–52·4)	<0·0001	35 (51%; 38·4–63·0)	28·8% (9·6–39·9)	0·0018	44 (65%; 52·2–75·9)	38·7% (23·9–53·6)	<0·0001
Pain free at 2 h	6 (7·4%; 2·8–15·4)	11 (14%; 7·2–23·5)	6·5% (3·0–16·0)	0·18	11 (14%; 7·1–23·3)	6·3% (3·1–15·8)	0·19	13 (19%; 10·6–30·5)	11·7% (0·1–22·6)	0·032	19 (28%; 18·0–40·7)	21·9% (8·8–33·1)	0·0007
Headache recurrence within 24 h	12 (57·1%; 34·0–78·2)	19 (56%; 37·9–78·8)	1·33% (–25·7 to 28·2)	0·93	30 (58%; 43·2–71·3)	–0·5% (–25·6 to 24·5)	0·97	22 (63%; 48·1–82·0)	9·5% (–35·8 to 16·8)	0·48	22 (50%; 34·6–65·4)	7·1% (–18·6 to 32·9)	0·59
Rescue drug 2–24 h	55 (68·8%; 57·4–78·7)	42 (55%; 42·8–65·9)	14·2% (–0·9 to 29·3)	0·067	42 (52%; 40·5–63·1)	16·9% (2·0–31·8)	0·029	41 (61%; 48·5–72·9)	7·6% (–7·9–23·0)	0·34	28 (42%; 29·8–54·5)	26·7% (11·4–42·5)	0·001
Patients' global impression (much or very much better) at 2 h	13 (16·0%; 8·8–25·9)	18 (23%; 14·1–33·6)	–6·74% (–18·9 to 5·5)	0·28	29 (36%; 25·4–47·2)	–19·7% (–32·9 to –6·6)	0·0041	19 (28%; 17·5–39·6)	–11·5% (–24·7 to 1·7)	0·087	23 (34%; 23·2–46·9)	–18·3% (–32·1 to 4·4)	0·0099
Clinical disability score at 2 h†	81 (2·0; 1·7–2·2)	79 (1·5; 1·3–1·8)	0·4 (0·1–0·7)	0·01	78 (1·4; 1·1–1·6)	0·6 (0·3–0·9)	0·0002	66 (1·5; 1·2–1·8)	0·5 (0·1–0·8)	0·0081	63 (1·5; 1·2–1·7)	0·5 (0·2–0·8)	0·0039
Headache severity at 2 h†	81 (2·1; 1·9–2·41)	79 (1·7; 1·5–1·9)	0·4 (0·1–0·7)	0·014	80 (1·3; 1·1–1·5)	0·8 (0·5–1·1)	<0·0001	68 (1·5; 1·3–1·8)	0·6 (0·3–0·9)	0·0003	67 (1·2; 0·9–1·4)	0·9 (0·6–1·2)	<0·0001

*For comparison with placebo. †For clinical disability and headache severity, data are mean (SD; 95% CI). Because the effects after 2 h were central to the primary endpoint, we only show data for this timepoint.

Table 2: **Primary and secondary endpoints**



Number at risk

Placebo	81	80	76	67	32	19	15	11	11
50 mg lasmiditan	79	78	72	53	33	24	20	15	13
100 mg lasmiditan	81	77	66	45	22	14	6	4	3
200 mg lasmiditan	69	66	56	36	22	12	10	8	8
400 mg lasmiditan	68	61	50	35	20	9	6	3	3

Figure 2: **Time to meaningful pain relief**

study drug and to assess the safety of lasmiditan over 24 h. Secondary endpoints were headache response over time, proportion of patients who were pain free (ie, absence of headache) at 2 h, associated symptoms, time to meaningful pain relief, headache recurrence within 24 h, clinical disability within 24 h, use of rescue drugs between 2 and 24 h, and patients' global impression at 2 h. The safety objective was to assess the safety and tolerability of lasmiditan in terms of adverse events, physical examination, vital signs, laboratory tests, and ECGs.

Patients recorded migraine symptoms in a standardised paper diary immediately before and 0·5, 1, 1·5, 2, 3, 4, and 24 h after intake of study drug. Headache severity and clinical disability were rated on a four-point scale (none, mild, moderate, and severe). Headache response was defined as a reduction of moderate or severe pain to mild or no pain. Patients also recorded the date and time when they experienced meaningful relief of migraine.

Associated symptoms (nausea, vomiting, phonophobia, and photophobia) were each rated as present or absent. Patients recorded their global impression at 2 h after study drug intake on a seven-point scale (very much better, much better, a little better, no change, a little worse, much worse, and very much worse). Patients also recorded any unusual symptom (possible adverse event) within the treatment period (24 h). Adverse events were graded mild, moderate, or severe according to the judgment of the investigator, and a causal relation was assessed by the investigator.

At follow-up within 14 days after treatment, patients returned their completed diary card and study drug pack. A physical examination, vital signs, 12-lead ECG, and laboratory assessments were done and adverse events, concomitant drugs, and rescue drugs were recorded.

Because each patient received only one dose of lasmiditan within a range that had been well tolerated in phase 1 studies, the principal investigators and ethics committees did not deem a data safety monitoring board to be necessary. The trial was expected to recruit so rapidly that by the time a significant amount of data were available for review by a data safety monitoring board the trial would be near to completion. Instead, to safeguard patient safety all serious adverse events were submitted urgently to a medical monitor for review and action.

Statistical analysis

The sample size was estimated assuming a response rate of 40% in the placebo group and 65% in the 400 mg lasmiditan group on the basis of data from previous intravenous studies.[10,13] We assumed that the treatment groups were equally spaced (i.e. the dose response was linear) and that the response odds ratios (ORs) between pairs of adjacent dose groups were equal, and thus estimated the sample size needed to test for a linear association by the method of Nam.[14] Based on a 1:1:1:1:1 randomisation, a total sample size of 330 evaluable patients (66 per group) was needed for 90% power, on the basis of a two-sided test at the 5% level of significance.

Patients who did not take study drugs because of occurrence of no or mild headaches, did not record baseline headache severity, did not take all study drug, or took other migraine drugs first were excluded from the modified intention-to-treat population, as prespecified for the primary analysis. All patients who received any study drugs were included in the safety analysis.

For all tests, a two-sided significance level of 5% was applied. A hierarchical test procedure was done for the primary analysis: we used the Cochran-Armitage test for trend to calculate whether there was a linear association between response rate and dose and, if significant, we analysed individual between-treatment differences with Pearson's χ^2 tests starting with lasmiditan 400 mg versus placebo, then 200 mg and 100 mg versus placebo, followed by 50 mg versus 400 mg, and finally 50 mg versus placebo. Each test was done only if the previous test was statistically significant.

Patients who took rescue drugs within the first 2 h or failed to record headache severity at 2 h were assumed to have had no headache response. All secondary endpoint analyses were exploratory and were done with a two-sided test at the 5% level of significance.

Headache freedom and associated symptoms were analysed by similar methods to the primary analysis except that the comparison of 50 mg versus 400 mg lasmiditan was not done. For headache severity, clinical disability, and patients' global impression at 2 h after treatment, we used the Cochran-Mantel-Haenszel (CMH) mean score test to compare placebo and each dose of

lasmiditan. We made comparisons across multiple dose levels with the CMH correlation test. To analyse and display time to meaningful pain relief, we did a Kaplan-Meier analysis. Differences among treatment groups and differences between placebo and each dose of lasmiditan were compared with the log-rank test.

This study is registered with ClinicalTrials.gov, number NCT00883051.

Role of the funding source

The study was designed by the principal investigators together with the sponsor (CoLucid Pharmaceuticals). The sponsor participated in data collection, data analysis, data interpretation, and the writing of the report. All authors had full access to all the data in the study and reviewed the paper. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between July 8, 2009, and Dec 22, 2009, 534 patients were screened, of whom 512 were randomly assigned to treatment. The study finished on Feb 18, 2010. 121 patients did not use the study drug and one patient used the study drug but was lost to follow-up. The remaining 390 patients finished the study. 13 patients were excluded from the primary analysis for pre-specified protocol violations (figure 1). Table 1 shows patient demographics and features of the treated migraine attacks. Baseline headache characteristics were broadly similar across groups. However, the proportion of patients with severe headache was higher in the 200 mg lasmiditan group than in all other active treatment groups.

There was a significant linear association between headache response rate and lasmiditan dose (Cochran-Armitage test, p<0·0001). Every lasmiditan treatment dose significantly improved headache response at 2 h compared with placebo (table 2; appendix). Significantly more patients in the 400 mg lasmiditan group than in the 50 mg group reported a headache response at 2 h (difference 21·7%, 95% CI 5·9–37·4; p=0·0087).

A linear association was also noted between headache-free rates at 2 h and lasmiditan dose (Cochran-Armitage test, p=0·0006). Both the 200 mg (difference 11·7%) and 400 mg (21·9%) doses of lasmiditan were superior

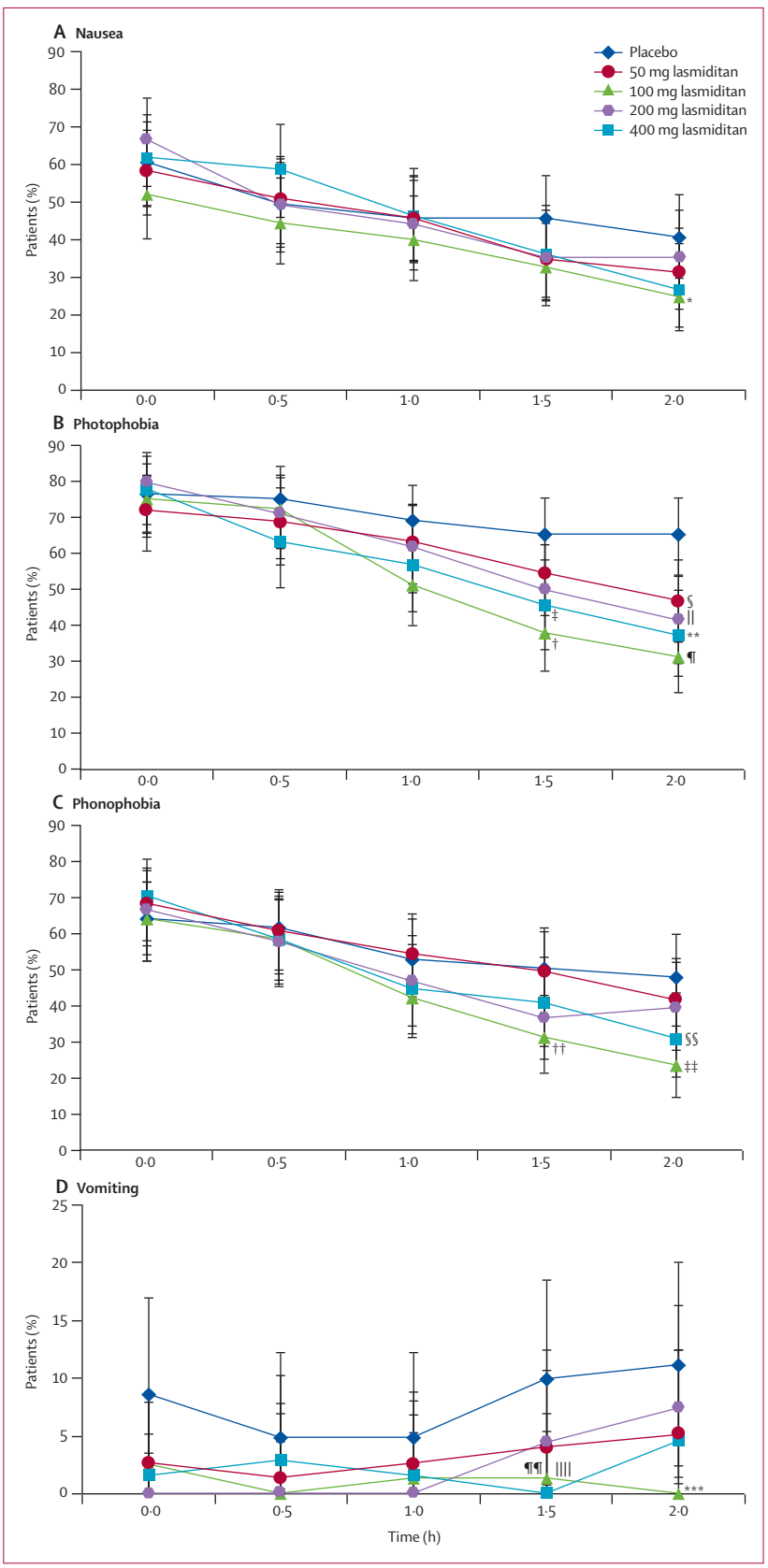


***Figure 3*: Migraine-associated symptoms**

*p=0·034 for comparison between 100 mg lasmiditan and placebo at 2 h.
†p=0·0005 for comparison between 100 mg lasmiditan and placebo at 1·5 h.
‡p=0·015 for comparison between 400 mg lasmiditan and placebo at 1·5 h.
§p=0·018 for comparison between 50 mg lasmiditan and placebo at 2 h.
¶p<0·0001 for comparison between 100 mg lasmiditan and placebo at 2 h.
||p=0·031 for comparison between 200 mg lasmiditan and placebo at 2 h.
**p=0·0006 for comparison between 400 mg lasmiditan and placebo at 2 h.
††p=0·018 for comparison between 100 mg lasmiditan and placebo at 1·5 h.
‡‡p=0·0013 for comparison between 100 mg lasmiditan and placebo at 2 h.
§§p=0·019 for comparison between 400 mg lasmiditan and placebo at 2 h.
¶¶p=0·018 for comparison between 100 mg lasmiditan and placebo at 1·5h.
||||p=0·0088 for comparison between 400 mg lasmiditan and placebo at 1·5 h.
***p=0·0027 for comparison between 100 mg lasmiditan and placebo at 2 h.

See Online for appendix

	Placebo (n=86)		Lasmiditan							
	Treatment emergent	Severe	50 mg (n=82)		100 mg (n=82)		200 mg (n=71)		400 mg (n=70)	
			Treatment emergent	Severe	Treatment emergent	Severe	Treatment emergent	Severe	Treatment emergent	Severe
Sensation of heaviness	1 (1%)	1 (1%)	4 (5%)	3 (4%)	4 (5%)	1 (1%)	7 (10%)	2 (3%)	5 (7%)	3 (4%)
Nausea	0 (0%)	0 (0%)	4 (5%)	2 (2%)	8 (10%)	0 (0%)	2 (3%)	1 (1%)	5 (7%)	0 (0%)
Paraesthesia	2 (2%)	0 (0%)	2 (2%)	1 (1%)	9 (11%)	2 (2%)	12 (17%)	4 (6%)	14 (20%)	5 (7%)
Somnolence	2 (2%)	1 (1%)	8 (10%)	3 (4%)	10 (12%)	2 (2%)	8 (11%)	2 (3%)	8 (11%)	2 (3%)
Vertigo	1 (1%)	0 (0%)	8 (10%)	1 (1%)	12 (15%)	3 (4%)	12 (17%)	3 (4%)	16 (23%)	7 (10%)
Fatigue	2 (2%)	1 (1%)	10 (12%)	5 (6%)	17 (21%)	7 (9%)	15 (21%)	11 (15%)	16 (23%)	7 (10%)
Dizziness	0 (0%)	0 (0%)	19 (23%)	1 (1%)	21 (26%)	8 (10%)	27 (38%)	11 (15%)	26 (37%)	12 (17%)

Data are number (%).

Table 3: **Most commonly reported treatment-emergent and severe adverse events**

to placebo (200 mg p=0·032; 400 mg p=0·0007; Pearson's χ^2 test).

Lasmiditan reduced headache severity starting as early as 30 min in the 400 mg group versus placebo (CMH mean score test, p=0·0137). After 1 h, all but the lowest dose of lasmiditan (50 mg) were superior to placebo, and from 1·5 to 4 h all lasmiditan groups were superior to placebo. Likewise, there were statistically significant differences between each lasmiditan dose group and placebo for time to meaningful pain relief (50 mg p=0·0294, 100 mg p<0·0001, 200 mg p=0·0003, 400 mg p<0·0001; log-rank test). Figure 2 shows data for the first 12 h after dosing, whereas the log-rank test was based on the full data up to 24 h.

There was a dose-related reduction in use of rescue drugs in the lasmiditan groups (CMH for linear association of rescue drug intake with dose p=0·0093). A global impression rating of much or very much better was obtained from 16·0% of patients in the placebo group compared with 22·8–35·8% of patients in the lasmiditan groups (linear association with dose; CMH correlation test, p=0·0162). Similar rates of headache recurrence were reported in all groups (50–63%; table 2). In a post-hoc analysis, there was a statistically significant linear association between the decrease in severity of clinical disability and increasing dose of lasmiditan from 2 h after treatment onwards (CMH correlation test, p=0·0036).

Nausea, phonophobia, and photophobia decreased in all treatment groups within 2 h after intake of study drug, with the smallest decrease in the placebo group (figure 3). The greatest improvements after 2 h were achieved for phonophobia and photophobia with the 100 mg and 400 mg doses of lasmiditan. The proportion of patients with vomiting was low in all groups (about 0–10%) and therefore differences over time and between groups for this symptom must be interpreted with caution.

The study drug or placebo was taken by 391 patients, who were all included in the safety analysis. In general, lasmiditan was well tolerated. There were no deaths in the study and ECGs, vital signs, and laboratory assessments did not show any clinically relevant drug-related changes.

The proportion of patients who reported at least one adverse event and the proportion of patients with treatment-emergent adverse events were higher in the active treatment groups than in the placebo group. Treatment-emergent adverse events increased with increasing doses (53/82 [65%], 59/82 [72%], 61/71 [86%], 59/70 [84%] for lasmiditan 50, 100, 200, and 400 mg, respectively *vs* 19/86 [22%] for placebo). The most frequently reported treatment-emergent adverse events (table 3) were associated with the CNS (eg, dizziness, paraesthesia) or the vestibular system (eg, vertigo). The appendix lists treatment-emergent adverse events by country.

Most adverse events were mild or moderate in intensity, with 16 of 82 (20%), 23 of 82 (28%), 28 of 71 (39%), and 31 of 70 (44%) patients in the lasmiditan 50, 100, 200, and 400 mg groups, respectively, reporting a severe adverse event compared with five of 86 (6%) on placebo. Dizziness was the most frequently reported severe adverse event.

A 46-year-old woman reported moderate dizziness 30 min after taking 200 mg lasmiditan. Because this led to an overnight hospital admission, the adverse event was classified as serious. Her ECGs showed sinus bradycardia 1·5 and 4 h after study drug intake but no other abnormalities. She received a saline infusion and had recovered completely by the next day.

Discussion

This trial with oral lasmiditan confirms the results of the previous proof-of-concept trial[10] with the intravenous formulation, suggesting that 5-HT_{1F} receptor activation can dose-dependently improve acute migraine (panel). Dose-dependent efficacy was also noted in a phase 2 study with a less selective 5-HT_{1F} agonist, LY334370.[15] However, a vascular effect contributing to increased efficacy of high doses of LY334370 could not be entirely ruled out because of the affinity of LY334370 itself and of its major metabolite for the 5-HT1B receptor. The affinity

of lasmiditan for the 5-HT$_{1B}$ receptor is significantly lower than that of LY334370 and surrogate assays did not show vasoconstrictive activity, although the precise mechanism of action remains to be identified.[9] 5-HT$_{1F}$ receptors are expressed in trigeminal ganglion neurons, and activation of these neurons might contribute to the inhibition of protein leakage from venous blood vessels, probably owing to the blockade of neuropeptide release.[16] The blockade of secondary trigeminal neuron activation within the CNS might also contribute to this inhibition.[9] Further sites of action remain speculative because 5-HT$_{1F}$ receptor distribution in the brain is difficult to map owing to the absence of a specific antagonist. However, studies with ^{3}H-LY334370 show that in human beings the 5-HT$_{1F}$ receptor is present mainly in cortical areas (frontal, temporal, parietal, and occipital cortices) and in the granule cell layer of the cerebellum.[17] Some of these cortical areas have been linked to acute pain, but whether 5-HT$_{1F}$ receptor binding of lasmiditan in these regions contributes to the anti-migraine activity is unclear.

The primary endpoint of this study was met: lasmiditan improved moderate-to-severe migraine headache to mild or none at 2 h in a dose-dependent manner. Although the sample size was small, which is a shortcoming of this trial, statistically significant differences between each lasmiditan dose and placebo were noted. The beneficial effects of lasmiditan on migraine were supported by the secondary endpoints pain freedom, headache intensity, associated symptoms, and patients' global impression. The effect of 200 mg lasmiditan was lower for the primary endpoint and for some secondary endpoints than that of the 100 mg dose, which might be due to small sample sizes and random variation in migraine attack severity and response. Headache severity at baseline was higher in the 200 mg group than in all other groups. However, in a post-hoc logistic regression analysis for the primary endpoint, with treatment group and severe migraine headache just before dosing (yes/no) as covariates, there was a significant effect of severe headache (OR estimates for no headache response: 1·75 [1·13–2·70]), but adjustment for this result did not explain the lower effect of 200 mg lasmiditan (OR estimates for 50 mg, 100 mg, 200 mg, and 400 mg doses *vs* placebo 0·46 [0·23–0·90], 0·19 [0·096–0·37], 0·32 [0·16–0·64], and 0·18 [0·09–0·37], respectively).

Analyses of secondary endpoints were exploratory and we did not adjust for multiple comparisons. The results should therefore be interpreted with caution. Lasmiditan reduced migraine-associated symptoms (nausea, photophobia, and phonophobia) at 2 h, with the strongest effects with the 100 mg and 400 mg doses. Relief of these symptoms might be underestimated in this analysis because the use of rescue drugs was conservatively treated as failure, which might have contributed to the absence of statistical significance versus placebo for some parameters and timepoints, especially after 2 h.

Panel: Research in context

Systematic review

We searched Medline (1950 to December, 2011), the Cochrane Central Register of Controlled Trials (The Cochrane Library issue 12, 2011), and Embase (1988 to December, 2011) with the search terms "placebo-controlled, randomised, double-blind clinical trials", "acute migraine", "migraine treatment", "5-HT$_{1F}$ agonist"; "CGRP receptor antagonist", "triptans", "adverse events", and "triptan" alone and in several combinations. We included results from placebo-controlled, randomised, double-blind clinical trials with 5-HT$_{1F}$ receptor agonists, calcitonin gene-related peptide receptor antagonists, and triptans for the acute treatment of migraine. We also assessed meta-analyses of controlled triptan trials and articles that discussed the adverse-event profiles of triptans.

Interpretation

Our study confirms that selective activation of 5-HT$_{1F}$ receptors with oral or intravenously administered agonists without vasoconstrictive activity reduces headache severity in migraine attacks compared with placebo. Both efficacy and nervous system-related adverse effects showed a clear dose response. The adverse-event profile of lasmiditan in this trial is similar to those of a previous study with an intravenous formulation and a study with a less selective 5-HT$_{1F}$ agonist (LY334370), and is distinctly different from that of triptans.[10,15] However, long-term safety needs to be established.

In a study of the 5-HT$_{1F}$ receptor agonist LY334370,[15] CNS side-effects were dose-dependent and seemed to be more frequent with lasmiditan than with triptans.[18] However, chest, neck, and jaw heaviness, tightness, or pain, reported by up to a quarter of patients taking an oral triptan,[19] were uncommon and no more frequent after lasmiditan than placebo. Dizziness was the main treatment-emergent complaint attributed to the CNS, followed by vertigo and fatigue. Vertigo and dizziness might be related to the activation of 5-HT$_{1F}$ receptors in the lateral vestibular nucleus, temporoparietal cortex, and cerebellum, because 5-HT$_{1F}$ receptor expression has been detected in these areas in rodents.[20,21] In the human brain, radioactive ligands bind significantly to 5-HT$_{1F}$ receptors in the cerebellum, a structure that is strongly linked to the vestibular system.[17] However, the differences between countries in the rates of vertigo and dizziness suggest that cultural and linguistic factors might have led patients to confuse the two events, with possible over-reporting of vertigo. Modification of the adverse event data collection procedure in future studies should resolve this issue. The CNS side-effects are unlikely to have been mediated by 5-HT$_{1A}$ receptor activation, as has been suggested for LY334370,[15] because the 5-HT$_{1A}$ affinity of lasmiditan is extremely low.[9]

This study provides important information for dose selection for phase 3 clinical trials. The lowest dose of lasmiditan in this trial was 50 mg and was expected to be ineffective or only marginally effective. Based on PK/PD modelling of the intravenous data described by Ferrari and colleagues,[10] the peak plasma concentration with this oral dose is about 30 ng/mL and higher plasma concentrations were expected to be necessary to achieve efficacy.[10,13] However, 50 mg lasmiditan seems superior to placebo in this study, suggesting that lower oral doses might be

sufficient for pain relief in some patients. The significant headache response at 2 h and the favourable adverse-event profile compared with higher doses supports the use of a lasmiditan dose of 100 mg for future clinical trials.

We have shown that in migraineurs selective 5-HT_{1F} agonism with lasmiditan results in a greater reduction in headache response than placebo. All oral lasmiditan doses seemed more effective than placebo and the 100 mg dose produced headache response rates comparable with established treatment options. The placebo-subtracted headache response rate of lasmiditan is comparable to that reported with oral triptans.[3] Also, pain relief after 2 h seems to be similar to results from trials with oral calcitonin gene-related peptide receptor antagonists.[22,23]

The neural site of action and absence of vasoconstrictor activity might be of benefit in clinical practice, where a substantial proportion of patients are unable to take triptans or are poorly or inconsistently responsive to them. Adverse events with lasmiditan were qualitatively different from those reported with triptans. The typical triptan sensations such as chest or neck pain, tightness, or heaviness were rare and occurred with similar frequency after placebo and lasmiditan. The extent to which the CNS adverse events might limit use, and the place of lasmiditan in treatment relative to triptans, need to be studied in larger comparator trials that more closely resemble clinical practice. Our results suggest that non-vascular mechanisms are sufficient for the treatment of acute migraine and thereby support the notion of migraine as a neuronal rather than a vascular disease.

Contributors

All authors contributed to the study design, the study analysis, and the interpretation of the results. MF, H-CD, GG, ML, JS, and UR treated patients. UR wrote the first draft of the manuscript. UR and AP wrote most of the manuscript. NH was responsible for the statistical analysis plan and analysis.

COL MIG-202 study group

Belgium N de Klippel (Hospital Hasselt, Hasselt), L Herroelen (University Leuven, Leuven), B Vandersmissen, M Pandolfo (Hospital Erasme, Brussels), J Schoenen (University Liege, Liege), M Van Zandijcke (Sint Jan AV, Bruges). *France* G Géraud (principal investigator [PI]) M Barege (University of Toulouse, Toulouse), P Giraud (Hospital Region Anneciennce, Pringy Cedex), E Guegan-Massadier (Hospital Charles Nicolle, Rouen), M Lanteri-Minet (PI), H Alchaar (University of Nice, Nice), C Lucas (Hospital Salengro, CHRU Lille), D Valade (Hospital Lariboisiere, Paris). *Finland* M Färkkila (PI), M Kallela (Meilahti Hospital, Helsinki), M Ilmavirta (Central Hospital, Jyväskylö), T Jolma (Suomen Erikoisneurologiakeskus, Pori), E Kinnunen (Lääkärikeskus Pipetti, Hyvinkää), J Liukkonen (Mikkelin Neurologipalvelu, Mikkeli), E Säko (PI), M Nissila (Suomen Terveystalo Clinical Research Oy, Turku), M L Sumelahti (Suomen Terveystalo Operon, Tampere). *Germany* A Beckmann-Reinholdt (private practice, Hamburg), R Brandt (Migraine Clinic, Königstein), H-C Diener (PI), C Gaul (University of Duisburg-Essen, Essen), S Evers (University of Münster, Münster), H Kaube (University of Freiburg, Freiburg), K Längler (private practice, Erkelenz), A May (University of Hamburg, Hamburg), T Nolte, R Brosius (private practice, Wiesbaden), A Peikert (private practice, Bremen), V Pfaffenrath (private practice, Munich), M Ribbat (private practice, Itzehoe), C Riemasch-Becker (private practice, Wiesbaden), U Reuter (PI), J Hoffmann, (Charité Universitätsmedizin Berlin, Berlin), H Staudenmayer (private practice, Göttingen), A Straube (University of Munich, Munich), T M Wallasch (private practice, Berlin). *Spain* S Diaz-Insa (PI), G Belandria (Hospital Francesc de Borja, Valencia), T Temprano Fernandez (Hospital Central de Asturias, Oviedo), J G Menacho (University Hospital Sant Joan, Reus), P Irimia (University of Navarra, Pamplona), D Jimenez (Virgen del Rocío Hospital, Sevilla), M Láinez (University of Valencia), R Leira (Hospital Clínico Universitario, Santiago de Compostella), J Pareja (Hospital Universitario Fundación Alcorcón, Alcorcón), P Pozo-Rosich (Hospital Universitario Vall d'Hebron, Barcelona).

Conflicts of interest

MF has received consultation fees and travel grants from CoLucid. H-CD has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Coherix, CoLucid, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Lilly, Roche, 3M Medica, Medtronic, Menarini, Minster, MSD, Neuroscore, Novartis, Johnson and Johnson, Pierre Fabre, Pfizer, Schaper and Brümmer, Sanofi, St Jude, and Weber and Weber. H-CD has received financial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag, MSD, Pfizer, German Research Council (DFG), BMBF, and the EU. GG has received consulting honoraria and travel grants from AstraZeneca, Allergan SA, Pfizer, MSD, and Ménarini. ML has received compensation or research support for activities with Allergan, Almirall, ATI, Boston Scientific, CoLucid, GlaxoSmithKline, Ferrer International, Janssen-Cilag, Merck and Co, Medtronic, Pfizer, and Servier SA. JS is a consultant for Autonomic Technologies and STX-Med. JS has contributed to advisory boards for CoLucid, Allergan, Bristol-Myers Squibb, St Jude, and ATI. NH is employed by FGK Clinical Research. AP is a consultant for CoLucid Pharmaceuticals. UR has received honoraria for participation in clinical trials, contribution of advisory boards, and oral presentations from Addex Pharma, Allergan, Almirall, Boehringer Ingelheim, CoLucid, and Jansen-Cilag. Headache research in the Department of Neurology at Charité Universitätsmedizin Berlin is supported by the BMBF, Johnson and Johnson, and Vasopharm.

References

1 WHO. World Health Report 2001. Geneva: World Health Organization, 2001.

2 Lipton RB, Buse DC, Serrano D, Ng-Mak DS, Pearlman SH, Reed M. Examination of unmet treatment needs among persons with episodic migraine: results of the American Migraine Prevalence and Prevention study (P1342). *Eur J Neurol* 2011; **18** (suppl 2)**:** 66–343.

3 Ferrari MD, Goadsby PJ, Roon KI, Lipton RB. Triptans (serotonin 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia* 2002; **22:** 633–58.

4 Tepper SJ, Millson D. Safety profile of the triptans. *Expert Opin Drug Saf* 2003; **2:** 123–32.

5 MaasenVanDenBrink A, Reekers M, Bax WA, Ferrari MD, Saxena PR. Coronary side-effect potential of current and prospective antimigraine drugs. *Circulation* 1998; **98:** 25–30.

6 Gallagher RM, Kunkel R. Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. *Headache* 2003; **43:** 36–43.

7 Neeb L, Meents J, Reuter U. 5-HT1F receptor agonists: a new treatment option for migraine attacks? *Neurotherapeutics* 2010; **7:** 176–82.

8 Adham N, Bard JA, Zgombick JM, et al. Cloning and characterization of the guinea pig 5-HT1F receptor subtype: a comparison of the pharmacological profile to the human species homolog. *Neuropharmacology* 1997; **36:** 569–76.

9 Nelson DL, Phebus LA, Johnson KW, et al. Preclinical pharmacological profile of the selective 5-HT1F receptor agonist lasmiditan. *Cephalalgia* 2010; **30:** 1159–69.

10 Ferrari MD, Färkkilä M, Reuter U, et al. Acute treatment of migraine with the selective 5-HT1F receptor agonist lasmiditan—a randomised proof-of-concept trial. *Cephalalgia* 2010; **30:** 1170–78.

11 Pilgrim AJ, Dussault B, Rupniak N, et al. COL-144, an orally bioavailable selective 5-HT1F receptor agonist for acute migraine therapy. *Cephalalgia* 2009; **29** (suppl 1)**:** 24–25.

12 International Classification of Headache Disorders: 2nd Edition. *Cephalalgia* 2004; **24** (suppl 1)**:** 1–160.

13 Liefaard L, Drenth H-J, Pilgrim AJ, et al. Prediction of therapeutically effective dose of COL-144 based on relationship between plasma concentrations and headache response (poster). *Cephalalgia* 2009; **29** (suppl 1)**:** 24.

14 Nam JM. A simple approximation for calculating sample sizes for detecting linear trend in proportions. *Biometrics* 1987; **43:** 701–05.

15 Goldstein DJ, Roon KI, Offen WW, et al. Selective serotonin 1F (5-HT1F) receptor agonist LY334370 for acute migraine: a randomized controlled trial. *Lancet* 2001; **358:** 1230–34.

16 Bouchelet I, Cohen Z, Case B, Seguela P, Hamel E. Differential expression of sumatriptan-sensitive 5-hydroxytryptamine receptors in human trigeminal ganglia and cerebral blood vessels. *Mol Pharmacol* 1996; **50:** 219–223.

17 Lucaites VL, Krushinski JH, Schaus JM, Audia JE, Nelson DL. [3H]LY334370, a novel radioligand for the 5-HT1F receptor. II. Autoradiographic localization in rat, guinea pig, monkey and human brain. *Arch Pharmacol* 2005; **371:** 178–84.

18 Dodick DW, Martin V. Triptans and CNS side-effects: pharmacokinetic and metabolic mechanisms. *Cephalalgia* 2004; **24:** 417–24.

19 Loder L. Triptan therapy in migraine. *N Engl J Med* 2010; **363:** 63–70.

20 Bruinvels AT, Landwehrmeyer B, Gustafson EL et al. Localization of 5-HT1B, 5-HT1D alpha, 5-HT1E and 5-HT1F receptor messenger RNA in rodent and primate brain. *Neuropharmacology* 1994; **33:** 367–86.

21 Ahn S-K, Khalmuratova R, Jeon S-Y, et al. Colocalization of 5-HT1F receptor and calcitonin gene-related peptide in rat vestibular nuclei. *Neurosci Lett* 2009; **465:** 151–56.

22 Ho TW, Ferrari MD, Dodick DW, et al. Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. *Lancet* 2008; **372:** 2115–23.

23 Diener HC, Barbanti P, Dahlöf C, et al. BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. *Cephalalgia* 2011; **31:** 573–84.