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

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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.

Funding CoLucid Pharmaceuticals.

Lancet Neurol 2012; 11: 405–13

Published Online March 28, 2012 DOI:10.1016/S1474-4422(12)70047-9

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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

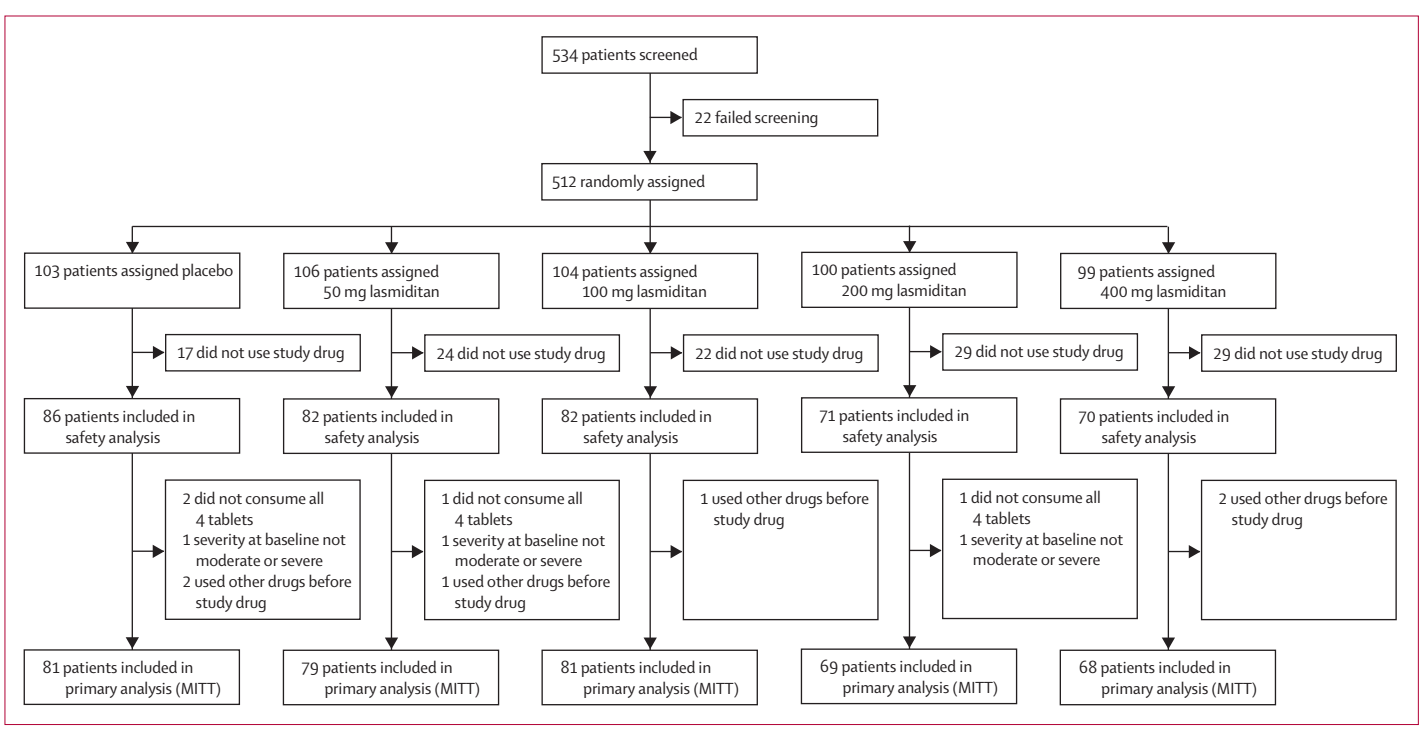

Figure 1: **Trial profile**
MITT=modified intention-to-treat population.