Lasmiditan (200 mg and 100 mg) Compared to Placebo for Acute Treatment of Migraine

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Migraine is a disabling neurological disease\(^1\)

Approximately 36 million migraineurs in the United States (U.S.); 18% of women and 6% of men in the U.S.\(^1\)

Although treatment options are available, a large percentage of patients still have unmet treatment needs\(^1\)

Complicating the clinical picture is the association between migraine and cardiovascular (CV) events\(^2\)

Lasmiditan is a novel serotonin (5HT-1F) agonist under development for the acute treatment of migraine with or without aura

- penetrates the central nervous system
- selectively targets 5HT-1F receptors expressed in the trigeminal pathway (does not have vasoconstrictive activity unlike 5-HT [1B/1D] triptan agents\(^3\))
**Figure 1. Study Design**

**Migraine Attack**
- Migraine Disability Assessment (MIDAS) score ≥11
- Headache severity at least moderate and not improving
- History of migraine ≥1 year and 3-8 migraine attacks/month
- Migraine onset <50 years of age

**First Dose**
≤4 hours of migraine onset
1:1:1 randomization

**Rescue**¹ or **Recurrence**²
≥2 to 24 hours after 1ˢᵗ dose

- **Lasmiditan 200 mg PO**
- **Lasmiditan 100 mg PO**
- **Placebo**

- **Lasmiditan 200 mg PO**
- **Placebo**
- **Lasmiditan 100 mg PO**
- **Placebo**
- **Placebo**

2:1 randomization lasmiditan:placebo if first dose was lasmiditan
If first dose was placebo, then second dose was placebo

**Abbreviations:** PO=orally

¹ Rescue: did not achieve headache pain-free status at 2 hours, completed the 2-hour assessments, and took a second dose of study drug between 2 and 24 hours post-first dose

² Recurrence: achieved headache pain-free status at 2 hours, but then experienced recurrence of mild, moderate, or severe migraine pain and took a second dose of study drug up to 24 hours from the first dose
**Methods**

**Primary Objectives:** Efficacy of lasmiditan 200 mg compared to placebo at 2 hours on:
- Migraine headache pain
- Most bothersome symptom (MBS; nausea, phonophobia, or photophobia)

**Additional Objectives:**
- Lasmiditan 100 mg compared to placebo at 2 hours on migraine headache pain and MBS
- Time course and effect of lasmiditan 200 mg and 100 mg on headache pain relief and MBS
- Effect of a second dose of lasmiditan 200 mg and 100 mg compared to placebo on headache pain relief and MBS when used for rescue and for recurrence of migraine
- Safety and tolerability of lasmiditan 200 mg and 100 mg, as the first dose and as a second dose

**Efficacy Measures:** Captured by electronic diary:
- International Headache Society 4-point headache severity rating scale: 0=none; 1=mild pain; 2=moderate; and 3=severe pain
- MBS (patient-centric): assessed as yes/no for presence of nausea, phonophobia, and photophobia
- Vomiting: assessed as yes/no
- Headache severity and MBS captured at timepoints: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 24, and 48 hours post-dose

**Safety Parameters:** Adverse events (AEs), vital signs, clinical laboratory evaluations, and electrocardiograms
- Treatment-emergent AEs (TEAEs) were those reported as "different" from what was typically experienced with migraine; the subject was contacted in a follow-up phone call
Methods

Statistical Analysis:

- Study populations:
  - Safety Population: All randomized subjects who used ≥1 dose of study drug, regardless of whether or not they underwent any study assessments. Subjects were evaluated by the drug they used, not by the drug to which they were randomized
  - Endpoints: adverse events and safety variables
  - Intent-to-Treat (ITT) Population: All randomized subjects who used ≥1 dose of study drug and had any post-dose headache severity or symptom assessments. Subjects were evaluated by the drug to which they were randomized
  - Endpoints: second dose for rescue or recurrence; headache pain relief
  - Modified ITT (mITT) Population: All ITT subjects who treated a migraine attack within 4 hours of onset. Subjects were evaluated by the drug to which they were randomized
  - Endpoints: Primary objectives: migraine headache pain and MBS freedom

- Comparisons were made via logistic regression with terms for treatment group and background migraine preventative use
- Odds ratio, with 95% confidence interval, for achieving response and p-value from Wald's test reported for each treatment group compared with placebo
- Tests of the primary and key secondary endpoints were conducted at a 1-sided significance level of 0.025; tests of all other endpoints were conducted at a 2-sided significance level of 0.05
RESULTS
Table 1. Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lasmiditan 200 mg n=609</th>
<th>Lasmiditan 100 mg n=630</th>
<th>Placebo n=617</th>
<th>ALL Subjects N=1856</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>41.4 (12.0)</td>
<td>42.2 (11.7)</td>
<td>42.4 (12.3)</td>
<td>42.0 (12.0)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>515 (84.6%)</td>
<td>512 (81.3%)</td>
<td>525 (85.1%)</td>
<td>1552 (83.6%)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>450 (73.9%)</td>
<td>471 (74.8%)</td>
<td>479 (77.6%)</td>
<td>1400 (75.4%)</td>
</tr>
<tr>
<td>History of migraine (years), mean (SD)</td>
<td>18.9 (13.1)</td>
<td>19.7 (13.0)</td>
<td>19.3 (12.7)</td>
<td>19.3 (12.9)</td>
</tr>
<tr>
<td>Migraines/month, mean (SD)†</td>
<td>5.3 (2.3)</td>
<td>5.1 (1.8)</td>
<td>5.1 (1.8)</td>
<td>5.1 (1.9)</td>
</tr>
<tr>
<td>Migraines with aura, n (%)</td>
<td>195 (32.0%)</td>
<td>205 (32.5%)</td>
<td>194 (31.4%)</td>
<td>594 (32.0%)</td>
</tr>
<tr>
<td>Migraine preventative medication use, n (%)</td>
<td>167 (27.4%)</td>
<td>158 (25.1%)</td>
<td>154 (25.0%)</td>
<td>479 (25.8%)</td>
</tr>
</tbody>
</table>

Abbreviations: SD=standard deviation

† Past 3 months

Overall mITT population (N=1545) averages:
- MIDAS Total score = 31.3
- Days with headache in past 3 months = 17.5
- Severity of headache pain = 7.5
  (0 = no pain and 10 = pain as bad as it can be)
Overall, 82.0% of subjects had migraine and ≥1 CV risk factors (in addition to migraine)

Migraine headaches are a known risk factor for coronary artery disease (CAD) events and stroke

<table>
<thead>
<tr>
<th>Variable, n (%)</th>
<th>Lasmiditan 200 mg n=609</th>
<th>Lasmiditan 100 mg n=630</th>
<th>Placebo n=617</th>
<th>ALL Subjects N=1856</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant family history of CAD</td>
<td>202 (33.2%)</td>
<td>221 (35.1%)</td>
<td>201 (32.6%)</td>
<td>624 (33.6%)</td>
</tr>
<tr>
<td>Postmenopausal women, n/N (%) †</td>
<td>43/515 (8.3%)</td>
<td>54/512 (10.5%)</td>
<td>57/525 (10.9%)</td>
<td>154/1552 (9.9%)</td>
</tr>
<tr>
<td>Former smoker, n/N (%)</td>
<td>107/575 (17.6%)</td>
<td>100/602 (15.9%)</td>
<td>98/591 (15.9%)</td>
<td>305/1768 (16.4%)</td>
</tr>
<tr>
<td>Current smoker, n/N (%)</td>
<td>79/575 (13.0%)</td>
<td>90/602 (14.3%)</td>
<td>81/591 (13.1%)</td>
<td>250/1768 (13.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>100 (16.4%)</td>
<td>100 (15.9%)</td>
<td>104 (16.9%)</td>
<td>304 (16.4%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>46 (7.6%)</td>
<td>32 (5.1%)</td>
<td>36 (5.8%)</td>
<td>114 (6.1%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>21 (3.4%)</td>
<td>28 (4.4%)</td>
<td>28 (4.5%)</td>
<td>77 (4.1%)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>21 (3.4%)</td>
<td>19 (3.0%)</td>
<td>17 (2.8%)</td>
<td>57 (3.1%)</td>
</tr>
</tbody>
</table>

Abbreviations: CAD=coronary artery disease
† Percentage reflects percentage of females only – not full population
**Table 3. Freedom From Headache Pain and Most Bothersome Symptom (mITT Population)**

**First Dose:** Primary endpoints were met

- Significantly more subjects treated with lasmiditan 200 mg were **headache pain free**† and **MBS free**‡ at 2 hours compared with placebo (p<.001)
- Lasmiditan 100 mg also provided more freedom from headache pain and freedom from MBS at 2 hours compared with placebo (p<.001)
- Significantly more subjects experienced **headache pain relief**§ at 2 hours with lasmiditan 200 mg and 100 mg compared with placebo (p<.001)

<table>
<thead>
<tr>
<th></th>
<th>Lasmiditan 200 mg (n=518)</th>
<th>Lasmiditan 100 mg (n=503)</th>
<th>Placebo (n=524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of subjects pain free† at 2 hours, odds ratio (95% CI)</td>
<td>32.2% 2.6 (2.0 – 3.6)*</td>
<td>28.2% 2.2 (1.6 – 3.0)*</td>
<td>15.3%</td>
</tr>
<tr>
<td>MBS recorded at time of dosing</td>
<td>n=481</td>
<td>n=469</td>
<td>n=488</td>
</tr>
<tr>
<td>% of subjects MBS free‡ at 2 hours, odds ratio (95% CI)</td>
<td>40.7% 1.6 (1.3 – 2.1)*</td>
<td>40.9% 1.7 (1.3– 2.2)*</td>
<td>29.5%</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; MBS=most bothersome symptom; mITT=modified intent-to-treat

† Defined as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0) at the indicated assessment time

‡ MBS of nausea, phonophobia, or photophobia

§ 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), at the indicated assessment time

* p<.001
Figure 2. Headache Pain Freedom – First Dose (mITT Population)

* p-value < .001 versus placebo

% Subjects Headache Pain Free

0.5 hr 1.0 hr 1.5 hrs 2 hrs 3 hrs 4 hrs

Lasmiditan 200 mg (n=518) Lasmiditan 100 mg (n=503) Placebo (n=524)
Figure 3. Headache Pain Relief – First Dose (ITT Population)

* p-value <.005 versus placebo

% Subjects With Headache Pain Relief

0.5 hr  1.0 hr  1.5 hrs  2 hrs  3 hrs  4 hrs

- Lasmiditan 200 mg (n=555)
- Lasmiditan 100 mg (n=562)
- Placebo (n=554)
Table 4. Rescue - Second Dose Freedom From Headache Pain and Most Bothersome Symptom and Headache Pain Relief (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Lasmiditan 200 mg/200 mg (n=109)</th>
<th>Lasmiditan 200 mg/Placebo (n=52)</th>
<th>Lasmiditan 100 mg/100 mg (n=139)</th>
<th>Lasmiditan 100 mg/Placebo (n=62)</th>
<th>Placebo (n=319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache pain free†</td>
<td>29 (26.6%)</td>
<td>12 (23.1%)</td>
<td>40 (29.0%)</td>
<td>8 (12.9%)</td>
<td>54 (16.9%)</td>
</tr>
<tr>
<td>MBS free‡</td>
<td>32 (33.7%)</td>
<td>16 (36.4%)</td>
<td>48 (40.3%)</td>
<td>10 (19.6%)</td>
<td>78 (28.0%)</td>
</tr>
<tr>
<td>Headache pain relief§</td>
<td>51 (46.8%)</td>
<td>25 (48.1%)</td>
<td>73 (52.9%)</td>
<td>26 (41.9%)</td>
<td>129 (40.4%)</td>
</tr>
</tbody>
</table>

Abbreviations: MBS=most bothersome symptom
† Headache pain free is defined as a reduction in headache severity from mild (1), moderate (2), or severe (3) at baseline to none (0) at the indicated assessment time
‡ MBS of self-described nausea, phonophobia, or photophobia
§ Headache pain relief after second dose is defined as a reduction in headache severity from moderate (2) or severe (3) at second dose baseline to mild (1) or none (0), or a reduction in headache severity from mild (1) at baseline to none (0), at the indicated assessment time

♦ Rescue: The proportion of subjects who took a second dose for rescue were:
  Lasmiditan 200 mg = 28.6%
  Lasmiditan 100 mg = 35.0%
  Placebo = 57.8%

♦ Recurrence: The proportions of subjects who took a second dose of study drug for recurrence of headache pain was low (3.1%) with no significant difference across the treatment groups
**Table 5. Treatment-Emergent Adverse Events† - First Dose (Safety Population)**

- Incidence of ≥1 TEAEs and most frequently reported TEAEs were similar in subjects with ≥1 CV risk factors (in addition to migraine) following first dose of treatment

<table>
<thead>
<tr>
<th>TEAE‡, n (%)</th>
<th>Lasmiditan 200 mg (n=609)</th>
<th>Lasmiditan 100 mg (n=630)</th>
<th>Placebo (n=617)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ≥1 TEAEs</td>
<td>257 (42.2%)</td>
<td>229 (36.3%)</td>
<td>99 (16.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>99 (16.3%)</td>
<td>79 (12.5%)</td>
<td>21 (3.4%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>48 (7.9%)</td>
<td>36 (5.7%)</td>
<td>13 (2.1%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>33 (5.4%)</td>
<td>36 (5.7%)</td>
<td>14 (2.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (3.1%)</td>
<td>26 (4.1%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (5.3%)</td>
<td>19 (3.0%)</td>
<td>12 (1.9%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>15 (2.5%)</td>
<td>12 (1.9%)</td>
<td>2 (0.3%)</td>
</tr>
</tbody>
</table>

Abbreviations: TEAE=treatment-emergent adverse event

† TEAEs are events that occurred or worsened 0-48 hours after taking study drug, or an event that worsened or was different relative to the subject's usual symptoms of a migraine attack

‡ TEAEs that occurred ≥2% in any treatment group and occurred more often than in the placebo group
### Table 6. Treatment-Emergent Adverse Events† - Second Dose (Safety Population)

<table>
<thead>
<tr>
<th>TEAE‡, n (%)</th>
<th>L200 / L200 (n=159)</th>
<th>L200 / PBO (n=79)</th>
<th>L100 / L100 (n=203)</th>
<th>L100 / PBO (n=86)</th>
<th>PBO / PBO (n=401)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ≥1 TEAEs</td>
<td>26 (16.4%)</td>
<td>22 (27.8%)</td>
<td>38 (18.7%)</td>
<td>16 (18.6%)</td>
<td>44 (11.0%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (7.5%)</td>
<td>9 (11.4%)</td>
<td>5 (2.5%)</td>
<td>7 (8.1%)</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (0.6%)</td>
<td>1 (1.3%)</td>
<td>7 (3.4%)</td>
<td>2 (2.3%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0 (0%)</td>
<td>1 (1.3%)</td>
<td>3 (1.5%)</td>
<td>2 (2.3%)</td>
<td>6 (1.5%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (1.3%)</td>
<td>1 (1.3%)</td>
<td>5 (2.5%)</td>
<td>1 (1.2%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (0.6%)</td>
<td>2 (2.5%)</td>
<td>3 (1.5%)</td>
<td>1 (1.2%)</td>
<td>3 (0.7%)</td>
</tr>
</tbody>
</table>

Abbreviations: L100=lasmiditan 100 mg; L200=lasmiditan 200 mg; PBO=placebo; TEAE=treatment-emergent adverse event

† TEAEs are events that occurred or worsened 0–48 hours after taking study drug, or an event that worsened or was different relative to the subject’s usual symptoms of a migraine attack

‡ TEAEs that occurred ≥2% in any treatment group and occurred more often than in the placebo group.
Table 7. Treatment-Emergent Cardiovascular Adverse Events – First Dose (Safety Population)

- Incidences of CV TEAEs were similar in subjects with ≥1 CV risk factors (in addition to migraine) following first dose of treatment

<table>
<thead>
<tr>
<th>Cardiovascular TEAE†</th>
<th>Lasmiditan 200 mg (n=609)</th>
<th>Lasmiditan 100 mg (n=630)</th>
<th>Placebo (n=617)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders, n (%)</td>
<td>5 (0.8%)</td>
<td>4 (0.6%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>4 (0.7%)‡</td>
<td>2 (0.3%)§</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>1 (0.2%)§</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>0</td>
<td>0</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: LV=left ventricular; TEAE=treatment-emergent adverse event
† All cardiovascular TEAEs were coded as mild or moderate
‡ 3 (0.5%) reasonably or possibly related
§ All reasonably or possibly related

- Following second dose of treatment, only palpitations (n=1) and tachycardia (n=1) were reported in the lasmiditan 100 mg/100 mg and 100 mg/placebo groups, respectively
Conclusions

- Significantly more subjects dosed with lasmiditan experienced freedom from headache pain and experienced headache pain relief at 2 hours than those dosed with placebo
  - significant differences between lasmiditan and placebo emerged as early as 1 hour
- Significantly more subjects dosed with lasmiditan reported relief from their self-described most bothersome migraine attack symptom at 2 hours than those receiving placebo
- Subject population was reflective of severe disability associated with migraine and many had at least one CV risk factor (in addition to migraine)
- Lasmiditan was well tolerated both on the first and second dose in overall population
Disclosures

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