CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211280Orig1s000

SUMMARY REVIEW

Joint Supervisory Review

Date	October 11, 2019
From	Heather Fitter, MD Nick Kozauer, MD Billy Dunn, MD
Subject	Joint Supervisory Review
NDA #	211280
Applicant	Eli Lilly and Company
Date of Submission	October 11, 2018
PDUFA Goal Date	October 11, 2019
Proprietary Name	Reyvow
Established or Proper Names	Lasmiditan
Dosage Form(s)	50, 100 mg tablets
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults
Applicant Proposed Dosing Regimen(s)	50 mg, 100 mg, or 200 mg: Take one tablet at the onset of migraine. (b) (4) (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults
Recommended Dosing Regimen(s)	50 mg, 100 mg, or 200 mg: Take one tablet at the onset of migraine.

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Lasmiditan is a new molecular entity (NME) developed for the acute treatment of migraine with and without aura in adults. Unlike the triptan class of acute migraine treatments, which also target 5-hydroxytryptamine $(5\text{-HT})_{1B}$ and 5-HT_{1D} in addition to 5-HT_{1F} receptors, lasmiditan is the first selective 5-HT_{1F} receptor agonist to be reviewed in an FDA marketing application.

There are many FDA-approved drugs for the acute treatment of migraine with and without aura in adults, including triptans, dihydroergotamine (DHE), and certain non-steroidal anti-inflammatory drugs (NSAIDs); the latter of which can be used alone or in combination with a triptan. In addition, there are over-the-counter products marketed for migraine. The use of many of the marketed prescription medications for the acute treatment of migraine is restricted in patients with cardiovascular disease. The applicant asserts that lasmiditan may be an option for migraine patients that have a cardiovascular (CV) condition which may result in the avoidance of the use of acute migraine treatments including triptans, NSAIDs, and DHE.

The efficacy of lasmiditan was demonstrated in two adequate and well-controlled studies. The studies used well-validated and clinically meaningful endpoints to establish efficacy; the proportion of patients who were pain-free and most bothersome symptom (MBS)-free at 2 hours after dosing for the acute treatment of a migraine attack. One study evaluated the efficacy and safety of 100 mg and 200 mg doses of lasmiditan compared to placebo, and the other study evaluated the efficacy and safety of 50 mg, 100 mg, and 200 mg doses of lasmiditan compared to placebo. All three doses of lasmiditan tested were effective. Lasmiditan demonstrated a dose-response relationship for pain-freedom at 2 hours post-dose in both studies. Evidence of a dose-response relationship for MBS-freedom at 2 hours post-dose was evident in the study that included only the 200 mg and 100 mg doses, but was not seen in the study that included the 50 mg dose. The treatment effect size for pain freedom at 2 hours post-dose was approximately 7-18% greater than placebo over the range of the three doses tested (lasmiditan responder rate of approximately 28-39%). The treatment effect size for MBS-freedom at 2 hours was approximately 8-16% greater than placebo over the range of three doses (lasmiditan responder rate of approximately 41-49%). These studies did not establish the efficacy of a second dose of lasmiditan for rescue treatment of an incompletely treated migraine, or to treat the recurrence of the initial migraine within 24 hours of dosing. Labeling will only recommend that a single dose of lasmiditan be taken in a 24-hour period.

Lasmiditan was most commonly associated with central nervous system (CNS) effects such as dizziness and somnolence. The use of a single dose of lasmiditan resulted in an impaired ability to drive in some subjects which generally resolved by 8 hours based on the results of simulated driving safety studies. The impact of a second dose of lasmiditan on driving safety was not evaluated. Subjects with impairment did not have insight into the inability to safely operate a motor vehicle, a concerning finding for a drug intended for unanticipated use in settings where patients would typically drive (e.g., returning home from work). Labeling will recommend that patients should not drive for at least 8 hours after a dose of lasmiditan.

Lasmiditan was associated with palpitations, tachycardia, and small transient increases in blood pressure and decreases in heart rate. In combination with propranolol, lasmiditan can cause significant decreases in heart rate, in excess of what is seen when the individual drugs are given alone. Hypersensitivity reactions including angioedema were observed with lasmiditan and two patients experienced a mild serotonin syndrome. The applicant enrolled many patients with CV risk factors; however, only a small percentage of patients (1%) had ischemic heart disease, limiting the assessment of the safety in these patients. The data provided with this application, including nonclinical and human ex-vivo coronary artery vasoconstriction studies, do not support the need for CV restrictions with the use of lasmiditan; however, these data are too limited to definitively establish the CV safety of lasmiditan.

The risk/benefit profile of lasmiditan is acceptable and supports approval for the acute treatment of migraine with and without aura in adults. There is no evidence to suggest that lasmiditan is more effective than other FDA-approved drugs for the acute treatment of migraine; however, lasmiditan is the first drug to selectively target 5-HT_{1F} receptors, and may offer a needed treatment alternative to some patients. Labeling will clearly convey the known risks of treatment so that patients and prescribers can make an informed decision about the appropriateness of lasmiditan as a treatment option.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headaches are also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, and various degrees of cognitive impairment are often present. Migraine attacks typically last from 4 to 72 hours in adults. About one-third of people with migraine experience transient neurological	Migraine is a serious and frequently disabling condition that can impact the quality of patients' lives.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>symptoms before and/or during an attack, referred to as a migraine aura.
• Migraine was found to be the sixth highest cause of disability in the Global Burden of Disease Study in 2013. The prevalence of migraine is approximately 9% in males and 20% in females in the U.S., thus resulting in a major impact to public health.</td><td></td></tr>
<tr><td>Current Treatment Options</td><td>• There are many FDA-approved therapies for acute migraine such as triptans, dihydroergotamines (DHE), and certain non-steroidal anti-inflammatory drugs (NSAIDs), the latter two of which can be used alone or in combination with a triptan. Triptans and DHE are contraindicated in patients with cardiovascular disease and NSAIDS have labeling that warns patients of the risk of cardiovascular events with the use of these products. In addition, there are several over-the-counter drugs marketed for migraine.</td><td>Several classes of drugs are indicated for the acute treatment of migraine with and without aura in adults. However, many patients still do not respond adequately to these therapies.

A novel oral medication for the acute treatment of migraine could be an important treatment option for some patients.</td></tr>
<tr><td>Benefit</td><td>• The efficacy of lasmiditan was demonstrated in two adequate and well-controlled clinical studies (Studies 301 and 302). The studies used well-validated and clinically meaningful endpoints to establish efficacy, the proportion of patients that are pain-free (PF) at 2 hours post-dose, and most bothersome symptom (MBS)-free at 2 hours post-dose. Results are summarized in the table below; comparisons between the lasmiditan groups and placebo are highly statistically significant.
<table>
<tr><th></th><th>PF at 2 hours (%)</th><th>Placebo corrected PF (%)</th><th>MBS free at 2 hours (%)</th><th>Placebo corrected MBS free (%)</th></tr>
<tr><td>Study 301*</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Placebo</td><td>15.3</td><td></td><td>29.6</td><td></td></tr>
<tr><td>Lasmiditan 100 mg</td><td>28.3</td><td>13</td><td>41.2</td><td>11.6</td></tr>
<tr><td>Lasmiditan 200 mg</td><td>31.8</td><td>16.5</td><td>40.7</td><td>11.1</td></tr>
</table></td><td>Lasmiditan is effective for the acute treatment of a migraine with and without aura in adults.

The recommended doses of lasmiditan for marketing will be 50 mg, 100 mg, and 200 mg. The efficacy of a second dose for either rescue or recurrence has not been established.</td></tr>
</table>

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
<table>
<tr><th>Study 302*</th><th></th><th></th><th></th><th></th></tr>
<tr><td>Placebo</td><td>20.9</td><td></td><td>33.2</td><td></td></tr>
<tr><td>Lasmiditan 50 mg**</td><td>28.3</td><td>7.4</td><td>40.8</td><td>7.6</td></tr>
<tr><td>Lasmiditan 100 mg</td><td>31.4</td><td>10.5</td><td>44.0</td><td>10.8</td></tr>
<tr><td>Lasmiditan 200 mg</td><td>38.8</td><td>17.9</td><td>48.7</td><td>15.5</td></tr>
</table>
*all comparisons p<0.001 unless otherwise specified
**PF comparison p<0.006, MBS free comparison p<0.014

There was a dose-response relationship demonstrated for PF at 2 hours post-dose and MBS-freedom at 2 hours post-dose in Study 302. This relationship was only present for PF at 2 hours for Study 301.
Both studies planned to evaluate the efficacy of a second dose administered at least 2 hours after the initial dose for rescue or recurrence. However, due to shortcomings of the second dose analyses, these data are not informative and the efficacy of a second dose has not been established.

</td><td></td></tr>
<tr><td>Risk and Risk Management</td><td>

The most common treatment-emergent adverse events (TEAEs) in the pooled Phase 3 controlled trials (at least 2% and at least 2% greater than placebo) were related to dizziness and balance disorder (up to 18% versus 3% in placebo); sedation (up to 7% versus 2% in placebo); asthenia, fatigue, and malaise (up to 6% versus 1% in placebo); paresthesia and hypoesthesia (up to 9% versus 2% in placebo); nausea and vomiting (up to 4% versus 2% in placebo); and muscle weakness (up to 2% versus 0% in placebo).
There was no imbalance in serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation between lasmiditan and placebo in the placebo-controlled trials.
The overall rate of SAEs with a potential CV etiology was low. The most commonly reported CV TEAEs in the controlled trials were palpitations/heart rate increased/tachycardia occurring in 0.4% of patients on lasmiditan and 0.1% on placebo. The limited number of patients with ischemic heart disease in the lasmiditan safety database limit the interpretability of risk in these patients.

</td><td>There were no significant safety findings that would preclude approval of lasmiditan. Adequate labeling, including a medication guide and pharmacovigilance, will address the identified safety issues.

The WARNINGS AND PRECAUTIONS section of labeling will provide detailed descriptions and monitoring/treatment recommendations related to central nervous system effects, driving impairment (with a restriction for at least 8 hours after dosing), serotonin syndrome, and medication overuse headache.

The data submitted with this application</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Nonclinical in-vivo and ex-vivo, as well as, human ex-vivo studies do not suggest that lasmiditan exposure leads to coronary artery vasoconstriction. • In early-phase studies, increases in blood pressure and decreases in pulse were also observed within 1 hour of dosing. These findings are more informative than the results from the controlled efficacy trials where vital signs were not obtained at the time the study drug was taken. • In a drug-drug interaction study, lasmiditan 200 mg in combination with propranolol 80 mg twice daily resulted in a maximum mean decrease in pulse rate of 19.3 beats per minute 1.5 hours after dosing which was a larger decrease at the same time point than lasmiditan 200 mg or propranolol alone. • A thorough QT study showed no significant QT prolongation at supratherapeutic doses and no clinically meaningful effect on mean PR or QRS intervals. • Hypersensitivity reactions (including rash and angioedema) occurred in 0.2% of subjects who received lasmiditan compared to no subjects who received placebo in the Phase 3 placebo-controlled trials. Most of the cases were mild to moderate in severity but some led to discontinuation. • Driving impairment was observed in a double-blind, randomized, placebo-controlled simulated driving study, in which impaired subjects given a single dose of lasmiditan were affected in a manner consistent with a blood alcohol concentration of at least 0.05% at up to 90 minutes post-dose, the latest timepoint evaluated. In a second randomized, placebo-controlled, simulated driving study designed to further assess the duration of the effect of a single dose of lasmiditan on driving safety, impairment relative to placebo was not observed at 8, 12, or 24 hours post-dose. Importantly, all impaired subjects lacked insight into their inability to safely operate a motor vehicle. The effect of a second dose of lasmiditan on driving impairment has not been evaluated.	do not support the need to include CV restrictions in labeling. However, these data are also insufficient to definitely establish the CV safety of lasmiditan. The synergistic interaction with propranolol on heart rate decreases will be described in the DRUG INTERACTIONS section of the label. Because the risk of adverse outcomes in pregnancy has not been characterized, and because lasmiditan will be used in women of childbearing potential, a pregnancy registry and a pregnancy outcomes study will be postmarketing requirements. Since safety and efficacy of lasmiditan in pediatric migraine patients has not been established, studies to evaluate lasmiditan in pediatric migraine patients will be required under the Pediatric Research Equity Act (PREA). A study to evaluate whether there is a clinical drug interaction with P-gp and BCRP substrates will also be a postmarketing requirement. As the risk of malignancy has not been characterized, enhanced pharmacovigilance for malignancy should be conducted. There should also be enhanced pharmacovigilance with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• TEAEs related to abuse potential in the Phase 3 placebo-controlled trials occurred in 28.5% of subjects who received lasmiditan compared to 7.6% of subjects who received placebo. • Two cases of serotonin syndrome were observed in the controlled trials in lasmiditan-treated patients. Other uncertainties • The risk of adverse outcomes in pregnancy has not been characterized. • Given the short duration of the clinical trials the risk of malignancy has not been characterized. • Safety and efficacy in pediatric migraine patients has not been established.	periodic evaluation of cardiovascular events, hypersensitivity, and serotonin syndrome.

2. Background

This review discusses the data presented by Eli Lilly and Company (the applicant) in support of a new drug application (NDA) for lasmiditan tablets, a 5-hydroxytryptamine $(5\text{-HT})_{1F}$ receptor agonist, for the acute treatment of migraine with and without aura in adults.

Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe, accompanied by various associated symptoms. The typical headache of migraine is throbbing, unilateral, and aggravated by motion, but bilateral and/or non-throbbing headache is also commonly reported. Typical migraine-associated symptoms include nausea, vomiting, photophobia, and phonophobia, but a myriad of other neurological symptoms may occur, with various degrees of cognitive impairment often present. Migraine attacks typically last between 4 and 72 hours in adults. About one-third of individuals with migraine experience transient neurological symptoms before and/or during a migraine attack, referred to as migraine aura. Generally accepted diagnostic criteria for migraine are presented in the International Classification of Headache Disorders (ICHD).

Many products are FDA-approved for the acute treatment of migraine in adults. These products include a number of different triptans, dihydroergotamine, and nonsteroidal anti-inflammatory drugs (NSAIDs); the latter of which can be used alone or in combination with a triptan. In addition, there are many over-the-counter medications that are labeled for the acute treatment of migraine. All three classes of prescription products for the acute treatment of migraine have restrictions regarding use in patients with cardiovascular (CV) disease.

The Division had several interactions with the applicant during its development program with respect to the use of a novel co-primary endpoint approach for efficacy trials evaluating an acute treatment for migraine. Specifically, in addition to the previously accepted endpoint of the proportion of patients with pain freedom at 2 hours post-dose, the applicant also utilized a novel endpoint of the proportion of patients with most bothersome symptom (MBS) freedom at 2 hours post-dose (consisting of either nausea, photophobia, or phonophobia), an approach initially suggested by the Division. The applicant also suggests that lasmiditan may be safe for use in patients with CV contraindications because of the purported lack of any meaningful degree of agonism of the 5-HT_{1B} and 5-HT_{1D} serotonin receptors (unlike triptans which are known to target 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors). The Division stated that patients with CV disease should be included in studies to investigate the safety of lasmiditan in this population but cautioned that assay sensitivity would be expected to be low due to the infrequent number of cardiac events that would likely be observed in the clinical trials.

The applicant provides data from two placebo-controlled efficacy trials, Studies 301 and 302, in patients with migraine with and without aura to support the efficacy of lasmiditan for the proposed indication. Three doses of lasmiditan were evaluated between these studies: 50, 100, and 200 mg. Both studies were conducted under a special protocol assessment (SPA) agreement (April 2014 and February 2016, respectively).

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson-Lee (refer to her review for the entire OPQ list of participants in the review of this application). Lasmiditan's drug substance can be referred to as lasmiditan hemisuccinate or lasmiditan succinate and has a molecular weight of 436 g mol^{-1}. This compound is highly water-soluble and (b) (4) is stable under recommended drug substance storage conditions and stable at accelerated storage conditions for at least 6 months. OPQ has determined that the overall stability data submitted provide adequate support for a shelf-life of 24 months at USP Controlled Room Temperature. The manufacturing facilities for this application were found to be acceptable.

The drug product is a film-coated immediate release tablet supplied in 50 mg and 100 mg strengths intended for oral administration. The applicant has committed to completing and reporting stability data for its ongoing studies, as well as three production drug product batches, under recommended storage conditions up to 36 months and at accelerated conditions for 6 months.

The biopharmaceutics review consisted of an evaluation of the proposed disintegration testing in lieu of dissolution testing, quality control testing of the proposed drug product, bridging of clinical and commercial formulations, and bridging of formulations manufactured at different sites. From a biopharmaceutics perspective, the provided information is adequate and supports approval of the 50 and 100 mg tablets.

The OPQ review team has determined that lasmiditan meets all applicable standards regarding identity, strength, quality, and purity. OPQ recommends approval of this application from a quality perspective.

4. Nonclinical Pharmacology/Toxicology

The nonclinical primary reviewer for this application was Dr. Ed Nesti, with Dr. Lois Freed performing the secondary review. A standard battery of nonclinical studies was conducted. Refer to Dr. Nesti's review of this NDA for a detailed discussion of these studies. The following are among the key conclusions from these studies:

- A 39-week toxicology study in dog demonstrated CNS findings (tremor, ataxia, myoclonic jerks, and hypoactivity) and reduced weight gain, plasma lasmiditan exposures (AUC) at the No Observed Adverse Effect Level (NOAEL) approximately 7-fold above the exposures in humans at the maximum recommend human dose (MRHD) of 200 mg.

- A 26-week toxicology study in rat demonstrated death, convulsions, cardiomyopathy intracytoplasmic neuronal inclusions (possibly lipofuscin) in brain stem and spinal cord, and chronic progressive neuropathy. The NOAEL was associated with plasma lasmiditan exposures (AUC) approximately 9-fold above the exposures in humans at the MRHD.

- There were no observed adverse effects on fertility in rat. The embryofetal development study in rat revealed increases in skeletal variations in the mid- and high-dose and reduced fetal body weight at the high dose, which was associated with maternal toxicity. Plasma lasmiditan exposure (AUC) at the NOAEL for these findings was approximately 10-fold above the exposures in humans at the MRHD. In the embryofetal developmental study in rabbit, skeletal and visceral malformations, increases in skeletal variations and embryofetal mortality, and reduced fetal body weight were observed at the high dose, which was associated with maternal toxicity. Plasma lasmiditan exposure (AUC) at the NOAEL was less than observed in humans at the MRHD.

- In the pre- and post-natal development study in rat, stillbirth and neonatal mortality were increased at the high dose, which was associated with maternal toxicity. Plasma lasmiditan exposure (AUC) at the NOAEL for these findings was approximately 16-fold above the exposures in human at the MRHD.

- Lasmiditan was not genotoxic in a standard battery of genetic toxicology assays or carcinogenic based on the results of adequately designed and well-conducted studies in T.rasH2 mouse and in rat.

In addition, a series of in vitro and in vivo studies was conducted to assess the potential for lasmiditan to cause vasoconstriction. Lasmiditan demonstrated no vasoconstrictive effects in these studies. Lasmiditan inhibited hERG current in vitro, with an IC_{50} of 3.1 µM. In an acute-dose in vivo cardiovascular study in dogs, there were no drug-related findings.

Drs. Nesti and Freed conclude that the nonclinical data are adequate to support approval of this NDA.

5. Clinical Pharmacology

The primary reviewers for the Office of Clinical Pharmacology (OCP) review were Drs. Priya Brunsdon and Bilal AbuAsal. Dr. Sabarinath Sreedharan was the team leader. The following are the key conclusions from the OCP review.

Mechanism of Action
Lasmiditan is proposed to be a selective 5-HT_{1F} receptor agonist which is thought to alleviate migraine through decreasing neuropeptide release and inhibiting pain pathways in the central and peripheral trigeminal system. However, the exact mechanism by which agonism at the 5-HT_{1F} receptor might mediate the therapeutic effect of lasmiditan is not fully understood.

Absorption
Peak plasma concentrations were reached approximately 1.8 hours after oral administration. Bioavailability varies from approximately 55-66%. Lasmiditan exposure increased in a slightly greater than dose proportional manner over the dose range of 50-200 mg. Food had a minimal effect on plasma concentration of lasmiditan with median T_{max} in the fed state at 2.5 hours and

median T_{max} in the fasted state at 1.5 hours. C_{max} and AUC increased approximately 20% after a high fat meal.

Distribution
The apparent central volume of distribution of lasmiditan was 558 L, and the human plasma protein binding was in the 55-60% range and was independent of concentration over the range of 15-500 ng/mL which covers the range of exposures for dose levels of 50-200 mg.

Metabolism and Elimination
Lasmiditan is extensively metabolized by non-cytochrome P450 enzymes and excreted in the urine as a primary metabolite, M8. Eighty-seven percent of drug material is excreted in the urine with 8% excreted in feces. Based on a population pharmacokinetic (PK) analysis, the estimated apparent clearance is 114L/h. The elimination half-life is approximately 5.7 hours.

Special Populations/Intrinsic Factors
Clinical studies demonstrated that there was no significant effect on lasmiditan exposure due to age, hepatic, or renal impairment. Population PK analyses revealed that body weight, sex, race, and ethnicity did not have a clinically relevant effect on lasmiditan exposure.

Food Effect
Lasmiditan administration is not expected to be associated with clinically relevant food-drug interactions.

Dosing
Drs. Brunsdon and AbuAsal recommend approval for lasmiditan doses of 50 mg, 100 mg, and 200 mg to treat an acute migraine with the maximum dose not exceeding 200 mg in a 24-hour period. They do not recommend administering a second dose within 24 hours, primarily due to the potential for prolonged driving impairment (discussed in Section 8 of this review). They also state that the safety of treating an average of more than 4 migraines attacks in a 30-day period has not been established.

Drug-drug Interactions
Lasmiditan is not a significant substrate, inhibitor, or inducer of major CYP enzymes or transporters, with the exception of P-gp and BCRP. Dr. Brunsdon recommends avoiding the concomitant use of P-gp or BCRP substrate drugs with lasmiditan. In addition, she recommends a postmarketing requirement (PMR) to evaluate whether there is a clinical drug interaction with P-gp and BCRP substrates to verify the drug-drug interaction (DDI) potential.

Driving Impairment
The OCP review also evaluated two simulated driving safety studies conducted with lasmiditan during the development program. Section 8 of this review discusses the evaluation of these studies.

Thorough QT Study
No significant QT prolongation at supratherapeutic doses and no clinically meaningful effect on mean PR and QRS intervals were demonstrated in a thorough QT study.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Viveca Livezey was the clinical reviewer for this application. Dr. Joanne Liu was the biometrics reviewer and Dr. Kun Jin was the biometrics team leader.

The applicant conducted two placebo-controlled efficacy trials (Table 1) in adult migraine patients with and without aura: Study 301/LAHJ (Study 301) and Study 302/LAHK (Study 302).

Table 1: Clinical Efficacy Studies

	Population	Double-blind treatment period	Doses	Location
Study 301	Migraine with and without aura	Up to 8 weeks	100 mg, 200 mg	U.S.
Study 302	Migraine with and without aura	Up to 8 weeks	50 mg, 100 mg, and 200 mg	U.S. and Europe

Study 301

Study 301 was a multicenter (US), randomized, double-blind, placebo-controlled, parallel-arm study designed to evaluate the efficacy and safety of lasmiditan for the acute treatment of a single migraine attack. Patients were randomized in a 1:1:1 ratio to either 100 mg lasmiditan, 200 mg lasmiditan, or placebo. At randomization patients were provided one blinded dose of study drug (active drug or placebo) to use for the treatment of a qualifying migraine (defined below). A second blinded dose of study drug was also provided to optionally take for either rescue or recurrence, if necessary. Patients assigned to active drug for their first dose could be assigned to receive either active drug or placebo for their optional second dose. After participation in the double-blind portion of the trial, patients were offered enrollment into Study 305/LAHL, a 12-month open-label long-term extension trial.

Patients eligible for enrollment into Study 301 were adults 18 years of age or older with a history of migraine with or without aura with at least a 12-month history of disabling migraine. Patients had to be diagnosed with migraine before the age of 50 years and have a history of 3-8 migraines/month and less than 15 headache days per month. Patients with CV risk factors were eligible for enrollment. Patients were initially excluded if they had CV disease; however, the applicant subsequently submitted a protocol amendment to exclude only patients with known coronary artery disease (CAD), clinically significant arrhythmia, or uncontrolled hypertension.

The endpoints used to establish efficacy were the proportion of patients who were headache pain-free at 2 hours and MBS-free at 2 hours following the initial dose. Pain freedom was defined as the absence of migraine pain at 2 hours following the treatment of a qualifying

migraine attack. The MBS for a qualifying migraine attack was defined as either nausea, phonophobia, or photophobia, and was to be determined prospectively by the patient at the time of a qualifying migraine attack but before administration of study drug. The statistical analysis plan specified that both endpoints would have to be statistically significant in favor of lasmiditan in order to consider the study supportive of a treatment effect.

The applicant used a gatekeeping procedure to prevent Type I error inflation for multiple comparisons for these two efficacy analyses. The treatment effect between lasmiditan 200 mg (the highest dose) and placebo was tested first for the proportion of patients who were headache pain-free at 2 hours and then for the proportion of patents that were MBS-free at 2 hours in the modified intention-to-treat (mITT) population (defined below).

If the analysis of the 200 mg dose was statistically significant in favor of lasmiditan on both efficacy endpoints (one sided $p < 0.025$), the 100 mg dose could then be tested using a similar sequential approach. Dr. Liu has determined that the applicant's method for Type I error control in the analyses of the trial's efficacy endpoints was prospectively defined and adequate.

The mITT population was defined by the applicant as all patients who treated a qualifying migraine attack and had any post-dose efficacy assessment. Patients that took rescue medication within the first 2 hours or who did not record headache severity at 2 hours would be assumed to have no response. Importantly, in the applicant's analysis, a qualifying migraine was defined as a migraine of <u>any</u> pain severity (including none) treated with study drug within 4 hours of onset. Patients that treated either a headache with only mild or no pain would be considered to have no headache response for the mITT analysis.

Notably, the definition of a qualifying migraine used in the applicant's prespecified efficacy analyses is not consistent with FDA guidance that states that efficacy of migraine drugs should be evaluated in patients with moderate or severe intensity pain prior to receiving study medication because many patients reach that level of pain. Therefore, the efficacy analyses were subsequently conducted during this review using a mITT population defined as all patients that treated a qualifying migraine (defined as pain of <u>moderate to severe</u> intensity) within 4 hours of onset and had any post-dose efficacy assessment. The results of the efficacy analyses that are presented in this review are based on this mITT as per FDA guidance.

All other secondary and exploratory efficacy analyses were conducted using the ITT population (defined as all randomized patients who used at least 1 dose of study drug and had any post-dose pain or MBS efficacy assessment). There was no prespecified plan in place to control for Type 1 error in the analysis of all the other efficacy endpoints. Several prespecified exploratory endpoints were evaluated, including pain-relief at 2 hours, sustained pain-freedom at 24 and 48 hours, and incidence of medication use for either rescue or recurrence.

<u>Study 302</u>

Study 302 was largely similar in design to Study 301. Study 302 was a multicenter (US and Europe), randomized, double-blind, placebo-controlled, parallel-arm study. Patients were

randomized in a 1:1:1:1 ratio to either lasmiditan doses of either 50 mg, 100 mg, or 200 mg, or placebo. Randomization to the blinded initial and optional second doses of study drug was similar to Study 301. Patients with CAD, clinically significant arrhythmia, or uncontrolled hypertension were eligible for enrollment from the onset of the trial.

Outside of the conduct of the trial in both US and European sites, the inclusion of a 50 mg dose-arm, and the inclusion of patients with CV disease from the onset of the trial, the design and analysis of Study 302 was essentially the same as that of Study 301.

Results

Studies 301 and 302

The median age of the patients in both trials was 41 to 44 years. Eighty-one to 86% of subjects were female, and 77 to 83% were White. Demographic characteristics were generally balanced between treatment groups in each study with no clinically significant differences.

Baseline disease characteristics were balanced between treatment groups in both trials. The median duration of migraine history was 15-17 years, the median of the average number of migraine/month over the past 3 months was 5, and approximately 30-39% of patients experienced migraine both with and without aura.

Table 2 presents the results of the primary efficacy analyses for Studies 301 and 302.

Table 2: Studies 301 and 302- Primary Efficacy Analyses (source: modified from Dr. Livezey's review Table 41 and Dr. Liu's review Tables 6 and 18)

	Study 301			Study 302			
	Placebo N=515	100 mg N=498	200 mg N=503	Placebo N=534	50 mg N=544	100 mg N=523	200 mg N=521
Pain freedom at 2 hours post-dose				**Pain freedom at 2 hours post-dose**			
N	79/515	141/498	160/503	112/534	154/544	164/523	202/521
Percent	15.3%	28.3%	31.8%	21.0%	28.3%	31.4%	38.8%
p-value		<.001	<.001		.006	<.001	<.001
MBS freedom at 2 hours post-dose				**MBS freedom at 2 hours post-dose**			
	Placebo N=480	100 mg N=464	200 mg N=467	Placebo N=509	50 mg N=502	100 mg N=491	200 mg N=478
N	142/480	191/464	190/467	169/510	205/502	216/491	233/478
Percent	29.6%	41.2%	40.7%	33.2%	40.8%	44.0%	48.7%
p-value		<.001	<.001		<.014	<.001	<.001

Drs. Livezey and Liu both conclude that treatment with lasmiditan resulted in statistically significant increases in the proportion of patients reporting pain freedom at 2 hours post-dose and MBS freedom at 2 hours post-dose as compared to placebo for all doses tested. There was a dose-response relationship in all comparisons to placebo for the co-primary endpoint results except in Study 301 for the proportion of patients with MBS freedom at 2 hours. In that analysis, the 100 mg and 200 mg doses performed similarly.

An analysis of pain-relief at 2 hours post-dose, defined as a reduction in migraine pain from a rating of moderate-severe to a rating of none or mild, was also supportive of the results of the primary efficacy analyses; however, as noted, the analysis of the pain-relief endpoint was not controlled for Type 1 error.

Table 3: Study 301 and 302-Pain Relief at 2 hours (source: Dr. Liu's review Table 12a and 24a)

	Study 301			Study 302			
	Placebo	**100 mg**	**200 mg**	**Placebo**	**50 mg**	**100 mg**	**200 mg**
Pain Relief at 2 hours[a]							
N	515	498	503	534	544	523	521
% Responders	40.0	54.0	55.3	45.1	55.9	61.4	61.0
Difference from placebo (%)		14.0	5.3		10.8	16.3	15.9

[a] The analysis of pain relief was descriptive and was not controlled for Type 1 error.

During the review, the applicant submitted an amendment explaining that approximately 50% of patients failed to enter their MBS prospectively prior to taking study drug, as instructed in the protocols. Therefore, a sensitivity analysis of MBS freedom at 2 hours post-dose was conducted including only patients that prospectively recorded their MBS. An additional sensitivity analysis of patients that either prospectively recorded their MBS or recorded their MBS within 5 minutes of dosing was also performed. The results of both analyses were highly nominally significant for all doses tested in both Studies 301 and 302, confirming the strength of the mITT analyses.

Sustained Pain Freedom at 24- and 48-Hours Post-Dose (ITT)

The proportion of patients who achieve sustained pain freedom at 24- and 48-hours post-dose is a commonly evaluated endpoint in acute migraine trials. The tables below present the results of the analysis of sustained pain freedom from Studies 301 and 302 (Table 4 and Table 5). A greater proportion of patients treated with lasmiditan achieved sustained pain freedom at 24 hours as compared to those on placebo in both trials with evidence of a dose-response relationship. Additionally, a greater proportion of patients treated with lasmiditan achieved sustained pain freedom at 48 hours compared to placebo in Study 301; however, only the analysis of the 200 mg lasmiditan dose reached nominal significance for this endpoint in Study 302.

Table 4: Study 301- Sustained Pain Freedom at 24 and 48 Hours (ITT) (source: Dr. Livezey's review Table 16)

Endpoint	**Study 301**		
	Placebo N=554	100 mg N=562	200 mg N=555
Sustained pain free, 24 h, n	42	83	103
At 24 hours, % responders	7.6%	14.8%	18.6%
P value versus placebo		<.001	<.001
Sustained pain free, 48 h, n	42	84	91
At 48 hours, % responders	7.6%	14.9%	16.4%
P-value		<.001	<.001

Table 5: Study 302- Sustained Pain Freedom at 24 and 48 Hours (ITT) (source: Dr. Livezey's review Table 36)

Exploratory endpoint	**Study 302**			
	Placebo N=576	50 mg N=598	100 mg N=571	200 mg N=565
Sustained pain free, 24 h, n	77	103	102	128
At 24 hours, % responders	13.4%	17.2%	17.9%	22.7%
P value versus placebo	-	.036	.021	<.001
Sustained pain free, 48 h, n	68	89	86	111
At 48 hours, % responders	11.8%	14.9%	15.1%	19.6%
P-value versus placebo		.065	.058	<.001

Although these findings are consistent with the effect of lasmiditan on efficacy endpoints used to establish efficacy, these results can only be considered exploratory given the lack of control for Type I error in the analyses of any of the trials' secondary endpoints.

Second Dose Efficacy

As previously mentioned, patients were offered the option of taking a second dose of study drug for either rescue or recurrence. At randomization, patients were given a sequence of drugs to use for the first and optional second dose. If patients took a second dose because they were not pain-free at 2 hours, it was considered a rescue dose. If patients took a second dose because they were pain-free at 2 hours and the pain later recurred, this would be considered a second dose for recurrence. Patients that took a second dose were instructed to treat a migraine attack with a pain severity at onset of either mild, moderate, or severe.

The applicant's interpretation of the results of the second dose efficacy analyses is that there was no benefit of a second dose for rescue, but there was a trend towards a benefit for recurrence. However, in addition to the fact that these analyses lacked even nominal significance and were not controlled for Type I error, there were several additional factors that limit the interpretability of any observed trends in these endpoints, including:

- Many patients who took a second dose of study drug for rescue or recurrence also took another medication for the acute treatment of their migraine either prior to the second dose, or within 2 hours of the second dose.

- Not all patients who took a second dose of migraine medication decided to take study drug. Therefore, selection bias likely affected the results of the analysis since patients in the second dose group were more likely to have had a good response from the first dose and therefore were more likely to be responders with the use of second dose.

- There is the potential of unblinding if there were unblinding adverse effects associated with the use of this drug following the first dose (e.g., sedation).

- The number of patients in these groups were small and therefore the analysis was underpowered to identify a treatment difference between groups.

Based on these shortcomings, the second dose analyses are not adequate (b) (4) (b) (4).

Efficacy by Subgroups

Dr. Liu performed analyses of the treatment effect across subgroups for both Studies 301 and 302, and concludes that the efficacy trends observed in the primary efficacy analyses appeared to be similar across all subgroups (age, gender, and race).

Efficacy Conclusions

The applicant has provided substantial evidence of effectiveness of lasmiditan based on the results from two adequate and well-controlled investigations. Both studies were conducted in patients with migraine with and without aura and both demonstrated significant increases in

the proportion of patients who were pain-free at 2 hours post-dose and MBS-free at 2 hours post-dose in the active treatment groups as compared to placebo. There was a dose-response relationship in the analysis of both efficacy endpoints in Study 302. In Study 301 there was a dose-response relationship for pain freedom at 2 hours post-dose only, although all active doses were superior to placebo for both efficacy endpoints. The analyses of the trials' secondary endpoints are also supportive of the primary efficacy analyses, although they can only be considered exploratory because of the lack of control for Type I error. The 50 mg, 100 mg, and 200 mg doses are effective and should be described in labeling.

8. Safety

Dr. Natalie Branagan conducted the clinical safety review of this application, with Dr. Sally Jo Yasuda as the safety team leader.

As discussed by Dr. Branagan, the overall exposure to lasmiditan exceeds the minimum numbers of patients recommended by the International Council for Harmonization (ICH) E1 Guideline for chronically administered medications. She reports that 4,831 patients were exposed to at least one dose of lasmiditan, of which 3,570 were exposed in the controlled clinical trials. Three hundred and fifty patients treated at least 2 migraines per month for at least 6 months and 156 treated at least 2 migraine per month for 12 months.

Dr. Branagan also reports that the applicant studied lasmiditan in a population of patients with CV risk factors (defined as age greater than 40 years, elevated total cholesterol, low HDL cholesterol, elevated systolic blood pressure or baseline hypertension, diabetes mellitus, and/or current smoker status) and with CV disease. Dr. Branagan notes that in Studies 301 and 302, 79% of patients had 1 CV risk factor, 41% had at least 2 CV risk factors, and 15% had at least 3 CV risk factors, which she observes is a similar distribution to the prevalence of CV risk factors in the general US population with episodic migraine. She also notes the prevalence of CV disease overall was 20%, with a 17% prevalence of hypertension (HTN). The prevalence of other CV disease was less than 2%. Only 1% had ischemic heart disease, which Dr. Branagan suggests limits the ability to interpret the safety of lasmiditan in these patients.

Deaths

There were no deaths in the lasmiditan safety database.

Serious Adverse Events (SAEs)

Dr. Branagan notes that there were few overall SAEs. There was no imbalance in the frequency of SAEs in the controlled trials between the lasmiditan and placebo arms, although the frequency of SAEs was greater in the 200 mg dose than in the lower doses (see Table 9 below). Most SAEs occurred in just 1 patient. The nervous system disorder system organ class (SOC) had more than 1 SAE, which were dizziness and presyncope, occurring in the 200 mg dose in 2 different patients (and in no placebo patients). There was no imbalance in SAEs between dose-arms in Study 305 (the long-term open-label safety study).

Dr. Branagan identified five CV SAEs in the controlled trials that she considers potentially related to lasmiditan. These cases are discussed in detail in her review and include dizziness in

a 46-year-old female with bradycardia (heart rate of 40), uncontrolled HTN in a 43-year-old female that had a history of HTN and had been compliant with her HTN medications, hypotension/dystonic reaction in a 67-year-old female that experienced orthostatic hypotension and dystonic reaction 20 minutes after taking lasmiditan, and presyncope reported in a 53-year-old female that occurred immediately after taking lasmiditan 200 mg. Dr. Branagan comments that the overall rate of SAEs with a potential CV etiology is low in Studies 202, 301, 302, and 305. Please also refer to the integrated discussion of CV safety below.

Discontinuations

The only discontinuation in the controlled trials occurred in a lasmiditan-treated patient (related to dizziness and fatigue). As Dr. Branagan comments, the fact that there was only a single discontinuation in these trials is likely a result of their design as patients could take a minimum of only 1 dose of study drug. In Study 305, discontinuations due to adverse events (AEs) occurred in approximately 13% of patients and demonstrated a dose-response relationship. The most frequent AEs resulting in discontinuation in Study 305 that occurred more frequently in the 200-mg dose arm include dizziness and lightheadedness; asthenia, fatigue, malaise, and weakness; paresthesia and hypoesthesia; and nausea and vomiting.

Table 6 summarizes the occurrence of SAEs and discontinuations due to AEs in Studies 301, 302, and 305.

Table 6: Studies 301, 302, 305- SAEs and Discontinuations due to Adverse Events (source: adapted from Dr. Yasuda's review page 11)

	Studies 301 and 302			
	Placebo (N=1262) n (%)	Lasmiditan 50 mg (N=654) n (%)	Lasmiditan 100 mg (N=1265) n (%)	Lasmiditan 200 mg (N=1258) n (%)
SAEs	3 (0.2)	1 (0.2)	1 (0.08)	4 (0.3)
Discontinuations[a]	0	0	0	1 (0.08)
	Study 305[b]			
			Lasmiditan 100 mg (N=991) n (%)	Lasmiditan 200 mg (N=1039) n (%)
SAEs			30 (3.0)	32 (3.1)
Discontinuations[a]			112 (11.3)	148 (14.2)

[a]Withdrawal from treatment because of AEs
[b] Reflects the results as of the 120 Day Safety Update

Treatment Emergent Adverse Events (TEAEs)

Table 7, reproduced from Dr. Branagan's review, summarizes the most common TEAEs from the controlled trials. This analysis grouped related terms.

Table 7: Studies 301 and 302, grouped-TEAEs after First Dose with an Incidence of At Least 2% and At Least 2% Greater than Placebo

MedDRA AEs (preferred term), grouped	50 mg N=654	100 mg N=1265	200 mg N=1258	Placebo N=1262
Dizziness, balance disorder	9%	15%	17%	3%
Sedation	6%	6%	7%	2%
Fatigue (includes asthenia and malaise)	4%	5%	6%	1%
Paresthesia, hypoesthesia	3%	7%	9%	2%
Nausea, vomiting	3%	4%	4%	2%
Muscle Weakness	1%	1%	2%	0%

As Table 7 indicates, dizziness/balance disorder, fatigue, and paresthesia events demonstrated a dose-response relationship. For sedation and muscle weakness, where the incidence in the 50 and 100 mg arms were the same, the higher dose of 200 mg was associated with a higher incidence. For nausea and vomiting events, where the incidence in the 100 mg and 200 mg lasmiditan dose-arms were the same, the incidence was higher than that reported for the 50 mg lasmiditan dose-arm. The TEAE profile of lasmiditan from Study 305 was consistent with the findings from the controlled trials.

Laboratory Findings

Dr. Branagan does not find clinically meaningful differences or consistent trends between lasmiditan and placebo in changes from baseline or in high or low abnormal laboratory test results in the controlled trials. However, Dr. Branagan believes that the Phase 1 laboratory data are more representative of any potential laboratory changes related to lasmiditan as the laboratory assessments in the controlled trials were not obtained at the time when the study drug was taken.

Dr. Branagan identified one patient in the Phase 1 trials with an unconfounded elevation of transaminases greater than 5X upper limit of normal (ULN). Dr. Branagan also identified one patient from the controlled trials with a bilirubin elevation greater than 2X ULN. No patients met Hy's law criteria. Dr. Branagan reviewed the narratives of patients with hepatic injury or abnormal hepatic enzymes and found confounding factors in most cases.

Drs. Branagan and Yasuda conclude that overall there were no clinically meaningful changes in chemistry or hematology findings after lasmiditan dosing and that there is no apparent signal for hepatic injury identified in this database.

Vital Signs

Similar to the laboratory data, Dr. Branagan also believes that the Phase 1 laboratory data are more representative of any potential vital sign changes related to lasmiditan as the vital sign

assessments in the controlled trials were not obtained at the time when the study drug was taken.

Dr. Branagan notes that lasmiditan appears to be associated with small increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and decreases in heart rate when compared to placebo. There did not seem to be significant changes in orthostatic blood pressure with the use of lasmiditan.

Dr. Branagan notes that mean increases in SBP and DBP occurred at 1 hour post-dose but without evidence of a dose-response relationship. The maximum mean change from baseline in SBP was an increase of 7.1 mm Hg for lasmiditan 200 mg (3.7 mm Hg for 400 mg and 1.1 mm Hg for placebo), and the maximum mean change for DBP was 4.3 mm Hg for lasmiditan 200 mg (1.9 mm Hg for 400 mg and -0.2 mm Hg for placebo). She found a mean decrease in heart rate of approximately 10 beats per minute (bpm) for both doses of lasmiditan, with maximum decreases at 2 to 3 hours post-dose (compared to a mean decrease of approximately 5-6 bpm for placebo).

A pharmacodynamic drug-drug interaction with propranolol found that co-administration with lasmiditan resulted in a decrease in pulse rate of 19.3 bpm when given together, which was a greater change than when either drug given alone.

Electrocardiogram (ECG)
Similar to laboratory and vital sign measurements, ECGs were also not obtained at the time when the study drug was taken in the controlled and uncontrolled trials; therefore, the findings from these studies do not meaningfully characterize the effect of lasmiditan on ECG findings. However, as previously mentioned, a thorough QT study was conducted and did not reveal any clinically meaningful effects on mean PR or QRS intervals, nor was there significant QT prolongation.

Human Carcinogenicity or Tumor Development
Dr. Branagan notes that 2 events in the neoplasm SOC occurred in lasmiditan-treated patients in the controlled trials, and none in placebo. Twenty AEs in the neoplasm SOC occurred in the open-label safety study. The types of events were disparate and Dr. Branagan notes that the onset of these events occurred within 8 months of exposure, suggesting that these events are not drug related. Enhanced postmarketing pharmacovigilance for malignancy will be requested.

Submission Specific Safety Issues

Cardiovascular Risk
The applicant asserts that as lasmiditan is a selective 5-HT_{1F} receptor agonist, it does not cause coronary artery vasoconstriction (unlike triptans). The applicant intended to support the CV safety of lasmiditan by including patients with CV risk factors and CV disease into the clinical studies. Dr. Branagan notes that approximately 80%, 41%, 15%, and 4% of patients had 1, 2, 3, and 4 CV risk factors, respectively, but only 1% of patients in the controlled trials had ischemic heart disease, which limits the interpretability of safety in this population, as

previously noted. Vital signs from Phase 1 studies showed evidence of small increases in SBP and DBP (7.1 mm Hg and 4.3 mm Hg, respectively) and decreases in heart rate (maximum mean decrease of 10 bpm). There was no evidence of QTc prolongation in a thorough QT study with lasmiditan doses up to 400 mg.

As previously noted, the overall rate of SAEs with a potential CV etiology was low. The most commonly reported CV TEAEs in the controlled trials were palpitations/heart rate increased/tachycardia occurring in 0.4% of patients on lasmiditan and 0.1% on placebo.

Please also refer to the nonclinical discussion in this review, which discusses the lack of nonclinical evidence of vasoconstrictive effects of lasmiditan.

Drs. Yasuda and Branagan conclude that the current database does not support an increased CV risk with lasmiditan and that labeling should not include CV restrictions. However, these data are also insufficient to definitively establish the CV safety of lasmiditan, and enhanced pharmacovigilance in the postmarket setting will be recommended

Driving Impairment

Lasmiditan has been shown to cause CNS depression. Therefore, two studies (Study 106 and Study LAIF) were conducted with lasmiditan in healthy volunteer subjects to assess its impact on the ability to safely operate a motor vehicle. Dr. Branagan notes that in both studies the primary endpoint was the standard deviation of lateral position (SDLP) in which the prespecified inferiority margin was 4.4 centimeters (consistent with a blood alcohol concentration of 0.05%).

Study 106 evaluated lasmiditan doses of 50 mg, 100 mg, and 200 mg at 90 minutes after dosing compared with placebo and alprazolam 1 mg, as a positive control, in a 5-period randomized, crossover study. Dr. Branagan notes that the difference in the least square means for all doses tested compared to placebo was greater than 4.4 cm, indicating that lasmiditan was inferior to placebo. Despite objective evidence of driving impairment in some subjects, no subjects receiving lasmiditan 100 mg or 200 mg felt unsafe to drive at any time point. Refer to **Error! Reference source not found.**for these results. APPEARS THIS WAY ON ORIGINAL

Table 8: Study 106- Difference in LS Means in SDLP (cm) Compared to Placebo (source: applicant Table 11-3 of CSR)

Parameter	Lasmiditan 50 mg N=87	Lasmiditan 100 mg N=86	Lasmiditan 200 mg N=89	Alprazolam 1 mg N=85
Difference in LS Means compared to placebo	9.86	15.35	21.06	22.71
95% CI	(7.39, 12.33)	(12.87, 17.82)	(18.60, 23.52)	(20.23, 25.18)

Study LAIF was a 4-period randomized, crossover study evaluating the effect of a single dose of lasmiditan 100 mg or 200 mg on SDLP at 8, 12, and 24 hours after dosing compared with placebo and diphenhydramine 50 mg, as a positive control. The results, described by Dr.

Branagan, are consistent with noninferiority of lasmiditan with placebo as demonstrated in **Error! Reference source not found.**.

Table 9: Study LAIF- Difference in LS Means in SDLP (cm) Compared to Placebo (source: applicant's table LAIF 7.10 in CSR)

Drug	8 hour (CI)	12 hour (CI)	24 hour (CI)
Diphenhydramine 50 mg	5.0 (3.6, 6.4)	4.31 (3.2, 5.5)	4.05 (2.7, 5.4)
Lasmiditan 100 mg	1.0 (-0.4, 2.4)	-0.12 (-1.3, 1.0)	-1.0 (-2.3, 0.3)
Lasmiditan 200 mg	1.8 (0.3, 3.2)	-0.32 (-1.5, 0.8)	-1.0 (-2.4, 0.3)

Dr. Priya Brunsdon, from OCP, evaluated the exposure-response relationship in lasmiditan-treated subjects from these studies and did not find differences in exposure that would explain impaired driving. In addition, gender differences in lasmiditan exposure are not observed. Dr. Brunsdon also concludes that prolonged driving impairment cannot be explained by sleepiness as measured by the Karolinska Sleepiness Scale. The effect of a second dose on driving has not been evaluated.

Drs. Branagan and Yasuda suggest that a warning be added to the prescribing information (PI) with respect to the risk of driving impairment with lasmiditan. Such a warning will need to clearly convey the finding that subjects should not drive for at least 8 hours after taking lasmiditan and that subjects lacked the ability to accurately self-evaluate their driving impairment.

Combined with the lack of demonstration of the efficacy of a second dose of lasmiditan, the absence of any data regarding the impact of a second dose on driving makes any description of repeat dosing inappropriate. The PI will limit patients to only one dose in a 24-hour period.

Suicidality and Depression

Dr. Branagan has evaluated the risks of suicidality and depression using AE terms and using results of the Columbia Suicide Severity Rating Scale (C-SSRS) and concludes that there does not appear to be an increased risk of depression or suicidality among patients treated with lasmiditan.

Serotonin Syndrome

Dr. Branagan notes that because lasmiditan acts on serotonin receptors and could potentially cause effects seen with serotonin excess, serotonin syndrome was an area of special interest during the review. Triptans have warnings in labeling regarding serotonin syndrome. Drs. Yasuda and Branagan comment that although the 5-HT_{1A} and 5-HT_2 receptors are most commonly implicated, the role of other serotonin receptors in serotonin syndrome is not well-understood.

Dr. Branagan and the applicant have identified 2 patients in the lasmiditan safety database that developed serotonin syndrome based on the Sternbach criteria, one of three published sets of criteria for the diagnosis of serotonin syndrome. One case occurred 25 minutes after a single dose of lasmiditan 400 mg (mental status changes, tremor, incoordination, muscle weakness, and dizziness) and the other 1.5 hours after a single dose of lasmiditan 100 mg (muscle

twitching, tremor, and agitation). Additional details of these cases are provided in Dr. Branagan's review. Although both cases were relatively mild, given the mechanistic plausibility, the potential seriousness of serotonin syndrome, and the potential for drug interactions with other products that may cause serotonin syndrome, Drs. Yasuda and Branagan suggest including information labeling regarding the risk of serotonin syndrome. Such information would be appropriate as a warning in the PI.

Hypersensitivity
Dr. Branagan reports that there was a small imbalance in hypersensitivity reactions observed for lasmiditan compared to placebo in the controlled trials (0.2% vs 0%). Reactions included rash, pruritus, swollen tongue, facial swelling, and photosensitivity. In some cases, these events occurred after administration of the first dose. Dr. Branagan concludes that a role for lasmiditan in these cases cannot be ruled out.

Injuries, Accidents, and Impaired Mental Ability Caused by CNS Effects
Dr. Branagan notes that there was not an increase in injuries and accidents in patients with CNS-related TEAEs.

Dr. Branagan notes that 21.2% of lasmiditan-treated patients versus 5.1% of placebo-treated patients had at least 1 TEAE in the nervous system and psychiatric disorder categories in the Phase 3 controlled studies with similar findings when the safety results from the controlled Phase 2 and Phase 3 studies are combined.

In addition to dizziness, lethargy, and sedation that occurred more frequently in lasmiditan than placebo, reports of cognitive disorder and mental impairment each occurred in 0.1% (n=3) of lasmiditan patients with none in placebo. Confusional state and disorientation occurred in 0.2% of lasmiditan and 0.1% of placebo patients in the controlled studies.

Labeling will convey the risk of CNS effects with lasmiditan.

Special Populations
Dr. Branagan evaluated the incidence of common TEAEs of dizziness, fatigue, nausea, paresthesia, somnolence, and vomiting by demographics of sex, age, ethnicity, and race. She did not identify clinically meaningful differences, except with regard to the incidence of common TEAEs of dizziness, which occurred more frequently in patients at least 65 years of age, and the incidence of paresthesia, which increased by increasing age groups.

Drug Interaction Studies
Dr. Branagan reviewed pharmacodynamic drug interaction studies with sumatriptan, topiramate, and propranolol, since these are drugs that could commonly be administered with lasmiditan. The most notable result was the synergistic effect of lasmiditan and propranolol on heart rate, as discussed previously.

Safety Conclusions
The safety profile of lasmiditan is acceptable for the acute treatment of migraine with and without aura in adults. There are no safety issues that preclude approval.

Perhaps the most notable safety finding with lasmiditan is the prolonged impact of a single dose on the ability of patients to safely operate a motor vehicle for up to 8 hours. Concerningly, subjects in the simulated driving safety studies lacked any insight into their impairment. These findings are highly significant in the context of a drug that will be taken acutely and unexpectedly, often in situations where patients would generally need to drive (e.g., returning home from work). Therefore, it is critical that the labeling convey this risk clearly so that patients and prescribers can determine the appropriateness of lasmiditan as a treatment option in the context of an individual patient's specific circumstances.

Lasmiditan was also found to cause CNS AEs such as dizziness and somnolence and CV AEs such as palpitations, tachycardia, and transient increases in blood pressure and decreases in heart rate (exacerbated in combination with propranolol). However, the currently available data do not suggest that lasmiditan labeling should include the CV restrictions that are present in the approved labels for triptans, NSAIDs, and DHE. Hypersensitivity reactions, including angioedema, were also observed. Additionally, there appears to be a mechanistically plausible risk of serotonin syndrome both in the presence and absence of other concomitant serotonergic drugs. Two cases of mild serotonin syndrome were observed in lasmiditan-treated patients during development.

The risks of lasmiditan can be accurately conveyed with labeling. Labeling will include WARNINGS AND PRECAUTIONS sections regarding driving impairment, CNS depression, and serotonin syndrome. Additionally, there are no data to suggest that frequent treatment with lasmiditan would not increase the risk of medication overuse headache, known to occur with other acute migraine treatments. Therefore, the PI should include class language regarding MOH risk.

A pregnancy registry and pregnancy outcome studies will be required. There should be routine pharmacovigilance with periodic evaluation of cardiovascular events, hepatotoxicity, hypersensitivity and serotonin syndrome, and enhanced pharmacovigilance for malignancy.

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because it was clear that the applicant had provided substantial evidence of effectiveness from two adequate and well-controlled studies, using clinical trial designs similar to those of trials for previously approved drugs for the acute treatment of migraine. Moreover, the safety profile was deemed acceptable for the treatment of migraine, without controversial issues.

10. Pediatrics

Lasmiditan was discussed at a Pediatric Review Committee (PeRC) meeting on September 17, 2019. Agreement was reached with the applicant's plan for requesting a partial waiver of clinical trials in patients 0 to less than 6 years of age (on the basis that such studies are highly impracticable) and a post-approval deferral of such trials in patients 6 to 17 years of age. Please refer to Section 14 of this memo for the required pediatric postmarketing studies.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI)
Dr. Cara Alfaro was the primary OSI reviewer for this application and Dr. Phillip Kronstein was the team leader. Dr. Alfaro states that four clinical sites were inspected in support of this NDA, specifically for protocols 301 and 302. She reports that although inspectional observations were noted at some clinical sites inspected, she concludes that the studies appear to have been conducted adequately and the data generated by the sites appear acceptable in support of the proposed indication. She notes that there was under-reporting of adverse events for two out of 50 patients randomized to lasmiditan at one site, and she recommended that the safety analysis be updated to include these two patients. Following incorporation of these additional cases into the safety analysis, the incidence of paresthesia and lethargy in the overall safety database was unchanged.

Controlled Substance Staff (CSS)
Drs. Shalini Bansil and Dr. Edward Hawkins were the primary CSS reviewers for this application and Dr. Silvia Calderon was the team leader. Drs. Bansil and Hawkins evaluated the abuse-related nonclinical and clinical data submitted in this application. They note that lasmiditan is a 5-HT_{1F} receptor agonist and a $GABA_A$ channel positive allosteric modulator that penetrates the CNS. Based on the proposed mechanism of action, lasmiditan was evaluated for its abuse potential.

Drs. Bansil and Hawkins report that the half-life of lasmiditan is approximately 5 hours and that levels in the brain are nearly 2-fold higher than those in plasma one hour after oral administration in rats indicating that this drug can effectively cross the blood brain barrier. Lasmiditan is metabolized into three major metabolites in humans, and one of the metabolites binds to $GABA_A$ channels although it does not seem to have relevant physiological activity. In a self-administration study in rats, lasmiditan produced some self-administration that was greater than saline, similar to diazepam, but not as high as heroin.

In the human abuse potential study (HAPS), all doses of lasmiditan showed significantly higher drug liking scores than placebo, consistent with the conclusion that lasmiditan has abuse potential. Results from the Phase 1-3 studies indicate that lasmiditan is associated with more abuse-related adverse events than placebo, although these AEs with lasmiditan occur at a low frequency (1%). The applicant proposes that lasmiditan be placed under Schedule V of the Controlled Substances Act, and Drs. Bansil, Hawkins, and Calderon agree.

Division of Medication Error Prevention and Analysis (DMEPA)
Dr. Chad Morris was the primary reviewer and Dr. Briana Rider was the secondary reviewer for the DMEPA review. DMEPA indicates that the final agreed-upon PI, medication guide (MG), and carton and container labeling are acceptable.

Dr. Morris reviewed the proposed proprietary name, Reyvow, and concluded that this name is acceptable.

12. Labeling

See the final negotiated product label. Agreement was reached with the applicant on labeling.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
The Division of Risk Management (DRISK) has determined that a REMS is not necessary for lasmiditan.

Pharmacovigilance
There should be enhanced pharmacovigilance postmarketing with periodic evaluation of malignancy, hypersensitivity, serotonin syndrome, and cardiovascular events.

Postmarketing Requirements (PMRs)

PMR-1 An open-label pharmacokinetics, safety, and tolerability study in pediatric migraine patients with body weight less than or equal to 40 kg. This study should identify doses to be used in the efficacy and long-term extension study for patients less than or equal to 40 kg.

PMR-2 A randomized, double-blind, placebo-controlled efficacy and safety study under PREA to evaluate the two doses of Reyvow (high dose and low dose) compared to placebo during a single migraine attack in pediatric patients ages 6 to less than 18 years. This study must be designed to show superiority of lasmiditan over placebo and is to be submitted as a special protocol assessment (SPA).

PMR-3 An open-label, long-term safety study under PREA in pediatric patients ages 6 to 18 years, for up to one year.

PMR-4 Submit the final study report for your completed juvenile animal toxicology study of lasmiditan in rat.

PMR-5 Conduct a prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Reyvow during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Reyvow before or during pregnancy, and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR-6 Conduct a pregnancy outcomes study using a different study design than provided for in PMR-5 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to Reyvow during pregnancy compared to an unexposed control population.

PMR-7 Conduct a clinical drug interaction trial to evaluate the effect of lasmiditan at its highest approved dose level on the pharmacokinetics of a sensitive P-gp substrate (e.g., digoxin) to address the potential for increased exposure and excessive drug toxicity. Design and conduct the study in accordance with the FDA Guidance for Industry entitled, "Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications".

PMR-8 Conduct a clinical drug interaction trial to evaluate the effect of lasmiditan at its highest approved dose level on the pharmacokinetics of a sensitive BCRP substrate (e.g., rosuvastatin) to address the potential for increased exposure and excessive drug toxicity. Design and conduct the study in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications".

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/s/

HEATHER D FITTER
10/11/2019 12:41:39 PM

NICHOLAS A KOZAUER
10/11/2019 12:49:28 PM

WILLIAM H Dunn
10/11/2019 12:58:09 PM