CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211280Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	211280
Priority or Standard	Standard
Submit Date(s)	October 11, 2018
Received Date(s)	October 11, 2018
PDUFA Goal Date	October 11, 2019
Division/Office	DNP
Reviewer Name(s)	Natalie Branagan, MD
Review Completion Date	October 10, 2019
Established/Proper Name	Lasmiditan
(Proposed) Trade Name	Reyvow
Applicant	Eli Lilly
Dosage Form(s)	50 mg, 100 mg tablet
Applicant Proposed Dosing Regimen(s)	(b) (6)
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura in adults
Recommendation on Regulatory Action	There do not appear to be safety concerns that would preclude approval. If efficacy is demonstrated and the benefits of lasmiditan outweight the risks, then I recommend that approval include appropriate labeling language addressing any adverse reactions of concerns.
Recommended Indication(s)/Population(s) (if applicable)	Adults

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	system organ class
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Lasmiditan is an agonist of $5HT_{1F}$ receptors and per the sponsor presumably decreases neuropeptide release and inhibits pain pathways including the trigeminal nerve without causing vasoconstriction in coronary arteries. The proposed proprietary name is Reyvow. The proposed indication is for the acute treatment of migraine with or without aura in adults. Lasmiditan is a new molecular entity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The reader is referred to the review of clinical efficacy by Dr. Viveca Livezey.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment *(Risks only)*

Lasmiditan is proposed to be used for the acute treatment of migraines with or without aura in adults. This review evaluates the safety of lasmiditan. I believe that there are no safety concerns that prevent approval of lasmiditan from the clinical safety point of view. If efficacy is demonstrated and the benefits of lasmiditan outweigh the risks, then I recommend that approval be accompanied by labeling language including a medication guide to mitigate the risks.

This document reviews the risk profile of lasmiditan. Lasmiditan causes central nervous system effects including dizziness/balance disorder and somnolence/fatigue/sedation. Lasmiditan causes impaired ability to drive after a single dose. Lasmiditan is associated with palpitations and tachycardia. Lasmiditan also causes increases in blood pressure and decreases in pulse rate within one hour of dosing. Lasmiditan in combination with propranolol resulted in heart rate lowering greater than either drug alone. Lasmiditan is associated with hypersensitivity reactions including angioedema and with serotonin syndrome. I will provide an assessment of the risk and recommendations for labeling in an effort to mitigate the risk if efficacy is demonstrated and it is determined that the benefits outweigh the risk.

Risks:
CNS adverse events: Lasmiditan is associated with adverse reactions related to dizziness and balance disorder (up to 18%) and somnolence, fatigue and sedation (up to 11%) that occurred with frequency of more than 2% greater than placebo.
Driving Impairment: A dose-dependent impairment was seen in a simulated driving study 90 minutes after administration of lasmiditan. In a second driving study, mean SDLP did not reach the threshold for driving impairment at 8, 12, and 24 hours after lasmiditan administration. Subjects lacked insight into when they might be impaired to drive based on a Self-Perceived Safety to Drive question.
Abuse Potential: Treatment-emergent adverse events related to abuse potential in the Phase 3 oral placebo-controlled studies occurred in 28.5% of subjects who received lasmiditan compared to 7.6% of subjects who received placebo.
Pulse Rate Lowering: Propranolol in combination with lasmiditan 200 mg 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. Coadministering lasmiditan with other heart-rate lowering drugs may increase the risk of pulse rate lowering.
Hypersensitivity reactions in the Phase 3 oral placebo-controlled studies occurred in 0.2% of subjects who received lasmiditan compared to 0% of subjects who received placebo.

Cardiovascular adverse events: Treatment emergent adverse events with potential cardiovascular etiology in the oral Phase 3 placebo-controlled studies occurred in 1.8% of subjects who received lasmiditan compared to 0.5% of subjects who received placebo. The most common events were palpitations and tachycardia.
Potential for fetal harm: There is limited information on the effect of lasmiditan during pregnancy.
Appropriate labeling and a Medication Guide for patients may mitigate potentially serious outcomes of these adverse reactions.

Paragraph #5: Analysis and Recommendation with Respect to Safety:
If lasmiditan is approved, I recommend labeling that includes Warnings for CNS effects including dizziness and somnolence, Warnings for driving impairment, hypersensitivity, and serotonin syndrome. I recommend a Medication Guide to describe these risks and symptoms of concern. I recommend enhanced pharmacovigilance postmarketing for malignancies. I suggest a consideration of whether driving impairment should be evaluated after a second dose of lasmiditan. I recommend a pregnancy registry and a pregnancy outcomes study as postmarketing requirements.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Please refer to Dr. Livezey's review of clinical efficacy.	
Current Treatment Options	Please refer to Dr. Livezey's review of clinical efficacy.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Please refer Dr. Livezey's review of clinical efficacy.	
Risk and Risk Management	Safety Database The safety database for lasmiditan includes all patients from the Phase 2 placebo-controlled trial and the two Phase 3 placebo-controlled trials allowing treatment of a single migraine attack, and the open-label extension study as well as several Phase 1 studies that including driving impairment studies and that contribute to laboratory and vital signs data. The safety database includes 4,878 subjects exposed to at least one dose of lasmiditan, including 361 subjects treating at least 2 migraines per month for at least 6 months, and 180 subjects treated over 12 months at the proposed doses. Safety Concerns • There were no deaths in the database. • The most common 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%), somnolence, fatigue and sedation (up to 11%), asthenia, fatigue, malaise, and weakness (up to 8%), paresthesia and hypoesthesia (up to 8%), and nausea and vomiting (up to 4%). • Overall, the database does not suggest cardiovascular or vascular risk. There was no imbalance in SAEs and AEs leading to discontinuation between lasmiditan vs placebo in placebo-	The safety database fulfills minimum ICH guidance and meets exposure recommendations in the Migraine: Developing Drugs for Acute Treatment Guidance. Current treatment options for acute migraine attacks have a safety profile that includes severe liver damage with acetaminophen; stomach bleeding, heart attack and stroke with non-steroidal anti-inflammatory medications; ischemic reactions such as cerebral hemorrhage, myocardial, peripheral vascular, and gastrointestinal ischemia with ergots and triptans; injection site reaction and constipation with calcitonin gene-related peptide antagonists. There were no significant safety findings that would preclude approval of lasmiditan. Adequate labeling, including a medication guide, and pharmacovigilance, will address most safety issues with lasmiditan.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	controlled trials. Treatment emergent adverse events with potential cardiovascular etiology occurred in 1.8% of lasmiditan-treated patients vs 0.5% of placebo-treated patients, with a higher percentage of lasmiditan-treated patients reporting palpitations or increased heart rate/tachycardia that each occurred in 0.4% in lasmiditan-treated patients vs 0.1% in placebo-treated patients in the Phase 2/3 controlled trials. In Phase 1 studies, increases in blood pressure and decreases in pulse were observed within 1 hour of dosing. 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. The 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 0% of 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-blinded, randomized, placebo-controlled simulated driving study, in which subjects given a single dose of lasmiditan had a SDLP difference from placebo of >4.4 centimeters, a difference previously identified to occur in subjects with a blood alcohol concentration of 0.05%. In a second randomized, placebo-	There was an imbalance between lasmiditan and placebo in AEs related to central nervous system (CNS) effects including events related to dizziness and somnolence. A Warnings and Precautions statement in the labeling could help mitigate risks in patients who have these adverse reactions. Lasmiditan results in impaired driving ability. Difference in mean SDLP did not reach the threshold for driving impairment at 8 hours or later. The impact of a second dose has not been evaluated. A Warnings and Precautions statement may help mitigate the risk. Whether to require a postmarketing trial evaluating the risk from a second dose should be considered. Potentially serious hypersensitivity reactions including angioedema have been reported. A Warnings and Precautions statement could alert patients and physicians to this risk. A Warnings and Precautions statement in the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	controlled simulated driving study designed to assess the duration of effect of a single dose lasmiditan on SDLP, difference in mean SDLP scores for lasmiditan 100 mg and 200 mg were not greater than the pre-specified inferiority margin of 4.4 centimeters at 8, 12, and 24 hours after dosing. Subjects lacked insight into when they might be impaired to drive based on a Self-Perceived Safety to Drive question. The effect of a second dose of lasmiditan on driving impairment has not been evaluated. • Treatment-emergent adverse events related to abuse potential in Phase 3 placebo-controlled trials occurred in 28.5% of subjects who received lasmiditan compared to 7.6% of subjects who received placebo. Refer to the Controlled Substance Staff review of the human abuse liability study. • Two patients met criteria for serotonin syndrome after exposure to lasmiditan. Other uncertainties • Potential for fetal harm: 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. Cardiovascular risk in patients with ischemic heart disease has not been characterized.	labeling regarding serotonin syndrome may help alert patients to the symptoms and mitigate this risk. I recommend including information about the small increases in blood pressure and decreases in pulse rate as well as events of palpitations and tachycardia in Section 6 of the labeling. I recommend describing the interaction with propranolol in section 7 of the labeling. Because the risk of adverse outcomes in pregnancy has not been characterized, and because lasmiditan will be used in women of childbearing potential, I recommend a pregnancy registry and a pregnancy outcomes study as postmarketing requirements. Because the risk of malignancy has not been characterized, I recommend enhanced pharmacovigilance for malignancy. The limited number of patients with ischemic heart disease did not allow for evaluation of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		lasmiditan safety in that population.

1.4. Patient Experience Data

The reader is referred to the review of clinical efficacy by Dr. Viveca Livezey.

2. Therapeutic Context

2.1. Analysis of Condition

Migraine is a chronic and debilitating condition. It affects 18% of women, 6% of men and 10% of children in the United States. Ninety percent of people with migraines are unable to work or function normally during a migraine. [1] Headaches are typically unilateral, throbbing, aggravated by physical activity, and are often accompanied by nausea, photophobia, and phonophobia. Attacks can last between 4 to 72 hours. Treatment is aimed at treating acute attacks as they occur and preventing recurrent attacks.

2.2. Analysis of Current Treatment Options

Current treatment options for acute attacks of migraines include analgesics such as acetaminophen and ibuprofen, ergots, calcitonin gene-related peptide (CGRP) antagonists, and triptans. Triptans act on the $5HT_{1B/1D}$ receptors of intracranial vessels, and presumably induce vasoconstriction and inhibit release of pro-inflammatory neuropeptides. Because of their presumed vasoconstrictive activity and their association with ischemic adverse events, triptans carry a class warning contraindicating their use in patients with cardiovascular disease.
The table below lists current treatment options as well as major adverse events associated with different treatment options for migraines.

Table 1. Current Treatment Options for Acute Migraines

Class of Drug	Major AEs by Drug Class
Analgesics[a]	Severe liver damage; allergic reaction; stomach bleeding; heart attack and stroke
Ergots	Cerebral hemorrhage; subarachnoid hemorrhage; stroke; other cerebrovascular events; vasospasm leading to myocardial, peripheral vascular, and colonic ischemia; elevation in blood pressure.

Class of Drug	Major AEs by Drug Class
Calcitonin gene-related peptide antagonists	Injection site reaction; constipation
Triptans	Myocardial ischemia/infarction; Prinzmetal's angina; arrhythmias; chest/throat/neck/jaw pain; tightness; pressure or heaviness; cerebral hemorrhage; subarachnoid hemorrhage; stroke; gastrointestinal ischemic reactions and peripheral vasospastic reactions; serotonin syndrome

[a]Acetaminophen, ibuprofen

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lasmiditan is a new molecular entity. It is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Ownership changed from Eli Lilly and Co to Colucid Pharmaceutics, Inc. in 2005.
Ownership changed from Colucid Pharmaceutics, Inc. to Eli Lilly and Co in 2017.

3.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing experience.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The reader is referred to the OSI review.

4.2. Product Quality

The reader is referred to the Product Quality review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Nonclinical Pharmacology and Toxicology reviews. The following was information submitted by the sponsor in the Nonclinical Overview. In ex-vivo studies, lasmiditan did not constrict the rabbit saphenous vein, human mammary artery or the human proximal or distal coronary artery. In vivo, lasmiditan did not change coronary or carotid artery diameter in anesthetized beagle dogs. Rats were noted in a 26-week study to have increased heart weights which the sponsor attributed to species-specific background risk.

4.5. Clinical Pharmacology

The reader is referred to the Clinical Pharmacology review. The following information is from the clinical pharmacology section of the Clinical Overview submitted by the sponsor. Lasmiditan has a median t_{max} of absorption of 1.8 hours and a terminal half-life of 5.7 hours. No accumulation of lasmiditan was noted with repeated once daily dosing. Lasmiditan undergoes hepatic and extrahepatic metabolism primarily by non-cytochrome P450 enzymes. Hepatic impairment (Child Pugh A and B) and renal impairment (eGFR < 30 mL/minute/1.73 m^2) did not have a clinically relevant effect on PK and no dose adjustment is recommended for patients with mild or moderate hepatic impairment or patients with renal impairment. Coadministration of lasmiditan with sumatriptan, propranolol, and topiramate did not result in any clinically meaningful changes in exposure to lasmiditan. Lasmiditan when administered with propranolol decreased the heart rate by 5 beats per minute compared to propranolol alone.

The sponsor's proposed dose for lasmiditan is 50 mg, 100 mg, or 200 mg, with a maximum daily recommended dose of 200 mg.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The reader is referred to the review of clinical efficacy by Dr. Viveca Livezey for a table of clinical studies. For a table of key clinical studies for the safety review, see section 8.1.

5.2. Review Strategy

The clinical review of NDA 211280 is divided into a review of clinical efficacy (by Dr. Viveca Livezey) and this review of clinical safety. Information submitted as part of NDA 211280 and published literature are discussed in this review. I will primarily present analysis conducted by myself. An evaluation of abuse potential will be performed by the Controlled Substance Staff.

6. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable to the review of clinical safety. The reader is referred to the review of clinical efficacy by Dr. Viveca Livezey.

7. Integrated Review of Effectiveness

Not applicable to the review of clinical safety. The reader is referred to the review of clinical efficacy by Dr. Viveca Livezey.

8. Review of Safety

8.1. Safety Review Approach

The table below contains the key phase 2 and 3 studies that were analyzed for the clinical review of safety. I refer to these studies by their numerical names for the remainder of this review.

Table 2. Phase 2 and Phase 3 Studies Supporting Safety[a]

Study and Location	Objective	Type of Study	Dose (Safety population)
202/LAHO Belgium, Finland, France, Germany, Spain	Evaluate the efficacy of a range of oral doses of lasmiditan on migraine	Double-blinded, randomized, placebo-controlled, dose-ranging study in subjects with	Placebo (86) Lasmiditan 50 mg (82) Lasmiditan 100 mg (82) Lasmiditan 200 mg (71)

Study and Location	Objective	Type of Study	Dose (Safety population)
		migraines.	Lasmiditan 400 mg (70)
301/LAHJ U.S.	Evaluate the efficacy of a 100 mg and of a 200 mg dose of lasmiditan compared to placebo on migraine	Double-blinded, randomized, placebo-controlled trial in subjects with migraines.	Placebo (617) Lasmiditan 100 mg (630) Lasmiditan 200 mg (609)
302/LAHK U.S., United Kingdom, Germany	Evaluate the efficacy of a 50 mg, and of a 100 mg, and of a 200 mg dose of lasmiditan compared to placebo on migraine	Double-blinded, randomized, placebo-controlled trial in subjects with migraines.	Placebo (645) Lasmiditan 50 mg (654) Lasmiditan 100 mg (635) Lasmiditan 200 mg (649)
305/LAHL U.S., United Kingdom, Germany (Safety cut-off date of Mar 6, 2018)	Evaluate the safety and tolerability of long-term, intermittent use of 100 mg and of 200 mg of lasmiditan as a first and second dose on migraine.	Randomized, open-label, long-term extension safety study in subjects with migraines.	Lasmiditan 100 mg (963) Lasmiditan 200 mg (1015)

[a]Study 201 evaluated an intravenous formulation of lasmiditan and safety information is included where relevant.

As part of this safety review, I analyzed vital signs from Phase I clinical studies as vitals were obtained at the time of dosing with lasmiditan which was not the case in studies 202, 301, 302 and 305. The following table identifies key Phase 1 studies that I reviewed.

Table 3. Phase 1 Studies Supporting Safety

Study and Location	Objective	Patient Population
COL MIG-113/H8H-CD-LAHN Canada	Evaluate PK profile of lasmiditan following single oral 200 mg dose in subjects with impaired renal function	Normal renal function and renal impairment

Study and Location	Objective	Patient Population
COL MIG-114/H8H-CD-LAHF Canada, U.S.	Evaluate PK profile of lasmiditan following single oral 200 mg dose in subjects with mild and moderate impaired hepatic function relative to matched controls with normal hepatic function	Normal hepatic function and hepatic impairment
COL MIG-105/H8H-CD-LAHP	To determine the effects of lasmiditan 100 mg and 400 mg on cardiac de- and re-polarization duration as measured by the QT interval	Healthy subjects 18 to 60 years of age.
COL MIG-106/H8H-CD-LAHG Canada	Determine the effects of acute doses of lasmiditan 50 mg, 100 mg and 200 mg compared to placebo and positive control (alprazolam 1.0 mg) on simulated driving performance in health subjects as measured by standard of deviation of lateral position (SDLP)	Healthy subjects 21 to 50 years of age.
H8H-MC-LAIF U.S.	Determine the duration of effects of acute doses of lasmiditan 100 mg and 200 mg compared to placebo on simulated driving performance in health subjects	Healthy subjects 21 to 50 years of age.

Safety Pools for Studies 202, 301, 302, and 305

The safety population was defined as all patients who were randomized and received at least 1 dose of lasmiditan. Study 305 was put on an administrative hold after initiation until the protocol was submitted to the IND. Patients randomized prior to the administrative hold were considered the "pre-administrative hold population" and included 297 subjects. Of these subjects, 196 were re-randomized to the post-administrative hold population and received at least one dose of study drug. The sponsor noted in an update to a Protocol Summary of Changes that subjects in the pre-administrative hold population of study 305 were not included in the analysis. The sponsor proposed 3 safety pools to analyze safety outcomes. The safety pools are outlined in the below table.

Table 4. Safety Pools by Study

Name of Pool	Description	Studies	Lasmiditan	Placebo
Phase 3 pool	Oral-placebo controlled Phase 3 studies	301 302	3177	1262
Phase 2/3 pool[a]	Oral-placebo controlled Phase 2 and 3 studies	301 302 202	3412	1347

Name of Pool	Description	Studies	Lasmiditan	Placebo
All Lasmiditan pool[b]	All lasmiditan-treated patients from oral Phase 2 and 3 studies	301 302 305 202	4081	Not applicable

[a]The Phase 2/3 pool excludes patients who received a 400 mg dose in study 202.
[b]The All Lasmiditan pool includes patients from studies 301, 302 and 202 including those who received a 400 mg dose and patients from study 305 who had initially received placebo in study 301 and 302.
This table was created by the reviewer using the IDB dataset, ADSL, using JMP where ASETBFL=Y for Phase 3 Pool, ASETAFL = Y for Phase 2/3 Pool, SAFLTNFL = Y for All Lasmiditan Pool and treatment indicated by TRT01A.

Reviewer comments: The Phase 3 pool allows for a comparison of adverse events between placebo and lasmiditan in the two key pivotal trials of efficacy. The Phase 2/3 pool includes study 202, a placebo-controlled trial that is similar in design to studies 301 and 302 and provides additional data for comparing adverse events in lasmiditan-exposed patients compared to placebo. The All Lasmiditan pool includes all patients treated with lasmiditan from studies 202, 301, 302 and 305 and allows for detection of safety events occurring in patients treated with lasmiditan for up to 12 months. The sponsor's pooling strategy was discussed at a guidance meeting and agreed upon with the FDA.

Anticipated Areas of Interest for the Safety Review
The sponsor has proposed that the label for lasmiditan not include ischemia-related class labeling seen with triptans as lasmiditan does not bind to $5HT_{1B/1D}$ receptors. The sponsor studied a population of patients with cardiovascular risk factors and cardiovascular disease to support omitting the class warning.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The total number of subjects in Phase 1, 2, and 3 studies exposed to at least 1 dose of lasmiditan was 4,831. The table below indicates number of subjects enrolled across Phase 1, 2 and 3 studies by population type.

Table 5. Safety Population, Size, and Denominators

Safety database for the study drug Individuals exposed to any treatment in this development program for the indication under review N=6654 (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	Lasmiditan (n=4831)	Placebo (n=1823)
Healthy volunteers	653	379
Other populations: (recreational drug users, renal-impaired, hepatic-impaired, migraine patients)	97	55
Controlled trials	3570	1389
Uncontrolled trials	511	N/A

The above data is calculated from data presented in the Clinical Overview Table 2.5.1.1 submitted by the sponsor.

Trial Design in Studies 202, 301, 302, and 305

In study 301, subjects were randomized to receive as a first dose placebo, lasmiditan 100 mg or lasmiditan 200 mg for the acute treatment of migraine. Patients were randomized to take as a second dose placebo, lasmiditan 100 mg or lasmiditan 200 mg for rescue or reoccurrence of migraine within 2 to 24 hours of the first dose. Study 302 was similar in design to study 301 except that patients could be randomized to placebo, lasmiditan 50 mg, lasmiditan 100 mg, or lasmiditan 200 mg for first and second doses. Study 202 was a randomized, double-blinded, dose-ranging study were patients were assigned to a single dose of lasmiditan 50 mg, 100 mg, 200 mg, 400 mg or placebo for treatment of a single migraine. Study 305 was a prospective, randomized, open-label study extension study in patients who had completed study 301 or 302. Patients were randomized to either lasmiditan 100 mg or 200 mg dosing and could treat all migraine attacks with study drug for up to 12 months. A second dose was permitted between 2 and 24 hours after the first dose for rescue or reoccurrence of migraine.

Exposure in studies 202, 301, 302 and 305

The overall number of patients who received at least 1 dose of lasmiditan in studies 202, 301, 302 and 305 was 4,081 patients. In patients treating an average of 2 or more migraines per month, the maximum length of time of exposure to lasmiditan was 12 months and occurred in study 305. In study 305, a median of 6 migraine attacks were treated (range 1-71) and each migraine attack was treated with an average of 1.4 doses of study drug. The table below summarizes exposure in patients with 2 or more migraines in study 305 over 12 months.

Table 6. Patients Who Treated on Average 2 or More Migraines per Month in Study 305.

	Number of patients exposed to the study drug.		
Dosage	**≥3** months	**≥6** months	12 months
100 mg	372	177	84
200 mg	338	173	72
Total	710	350	156

This table was created by the reviewer joining IDB ADSL dataset with HLSAFFL=Y and Study 305 ADSL dataset with SAFFL=Y. The table was grouped by USUBJID, TROL01A, SAF203FL, SAF206FL and SAF212FL.

The sponsor also evaluated lasmiditan for the treatment of recurrent migraine. The table below shows exposure to lasmiditan in studies 301 and 302 who took 1 versus 2 doses of study drug.

Table 7. Exposure to One Versus Two Doses of Study Drug in Studies 301 and 302.

Dose	1 Dose n (%)	2 Doses n (%)
Placebo/placebo (1262)	500 (39.6)	762 (60.3)
Lasmiditan 50 mg/ placebo (225)	129 (57.3)	96 (42.7)
Lasmiditan 50 mg/ lasmiditan 50 mg (429)	223 (52.0)	206 (48.0)
Lasmiditan 100 mg/ placebo (409)	240 (58.7)	169 (41.3)
Lasmiditan 100 mg/lasmiditan 100 mg (856)	476 (55.6)	380 (44.4)
Lasmiditan 200 mg/placebo (418)	265 (63.4)	153 (36.6)
Lasmiditan 200 mg/lasmiditan 200 mg (840)	537 (63.9)	303 (36.1)
All Lasmiditan (3177)	1870 (58.9)	1307 (41.1)

This table was created by the reviewer using the IDB dataset, ADSL, using JMP subset to ASETBFL=Y where SAFFL=Y for all exposed patients and SAF2FL=Y for patients exposed to 2 doses. Treatment=ACTARM.

Exposure in Phase I trials

The below table outlines exposure in Phase 1 studies in nonelderly healthy subjects by dose.

Table 8. Exposure in Nonelderly Health Volunteers in Phase 1 Studies.

Trial design	50 mg	100 mg	200 mg	Placebo
Nonelderly, single dose	115	206	422	315
Nonelderly, multiple dose	n/a	n/a	168	166

Data is taken from the ISS submitted by the sponsor, Table ISS.19.2.

Reviewer comment: Overall, a smaller number of patients were exposed to lasmiditan in Phase 1 studies compared to Phase 3 studies.

At the time of the 120 Day Safety Update report, the total number of subjects exposed to at least one dose of lasmiditan was 4,878. The safety population of study 305 contained an additional 52 subjects. One of the 52 subjects had been previously enrolled in study 305; however, had not taken lasmiditan prior to the cut-off date. Five of the 52 subjects were enrolled in study 305 under Addendum 1 of Study 305 Protocol which allowed for enrollment of subjects from studies 301 or 302 with completion dates in those studies > 12 weeks from the time of enrollment into study 305. Forty-six of the 51 subjects were enrolled under Addendum 2 of the Study 305 Protocol which allowed for enrollment of subjects who had not been enrolled in either study 301 or 302. The following table shows the number of subjects in the safety population at the time of the 120 Day Safety Update for study 305 and for the All-Lasmiditan Pool.

Table 9. Exposure at the time of 120 Day Safety Update for Study 305 and All-Lasmiditan Pool.

Name of Pool	Description	Studies	Lasmiditan	Placebo
Study 305	Open-label extension study	305	2030	Not applicable
All Lasmiditan pool[a]	All lasmiditan-treated from oral Phase 2 and 3 studies	202 301 302 305	4128	Not applicable

Data from this table was taken from data submitted by the sponsor with 120 Day Safety Update ISS Table 5.1.
[a]The All Lasmiditan pool includes patients from studies 301, 302 and 202 including those who received a 400 mg dose and patients from study 305 who had initially received placebo in study 301 and 302.

At the time of the safety update, 728 subjects had been exposed to lasmiditan for 3 months, 361 subjects had been exposed for 6 months, and 180 subjects had been exposed for 12 months.

8.2.2. Relevant Characteristics of the Safety Population:

The below table shows demographics for studies 301 and 302 by treatment group for the safety population.

Table 10. Baseline Demographics by Treatment Group in Studies 301 and 302

Demographic Parameters	Placebo	Treatment Group			Total[a]
	N=1262 n (%)	50 mg N=654 n (%)	100 mg N=1265 n (%)	200 mg N=1258 n (%)	N=4439 n (%)
Sex					
Male	192 (15.2)	100 (15.3)	214 (16.9)	207 (16.5)	713 (16.1)
Female	1070 (84.8)	554 (84.7)	1051 (83.1)	1051 (83.6)	3726 (83.9)
Age					
Mean years (SD)	42.5 (12.6)	42.8 (13.2)	42.8 (12.2)	41.6 (12.2)	42.4 (12.5)
Median (years)	43	42	43	41	42
Min, max (years)	18, 79	18, 77	18, 78	18, 81	18, 81
Age Group					
18-29	234 (18.5)	119 (18.2)	206 (16.3)	235 (18.7)	794 (17.9)
30-49	639 (50.6)	315 (48.2)	669 (52.9)	682 (54.2)	2305 (51.9)
50-64	335 (26.6)	182 (27.8)	343 (27.1)	294 (23.4)	1154 (26.0)
≥65	54 (4.3)	38 (5.8)	47 (3.7)	47 (3.7)	186 (4.2)
Race					
White	995 (78.8)	524 (80.1)	980 (77.5)	972 (77.3)	3471 (78.2)
Black or African American	229 (18.1)	106 (16.2)	226 (17.9)	231 (18.4)	792 (17.8)
Asian	5 (0.4)	5 (0.8)	10 (0.8)	11 (0.9)	31 (0.7)
American Indian or Alaska Native	6 (0.5)	3 (0.5)	9 (0.7)	9 (0.7)	27 (0.6)
Native Hawaiian or other Pacific Islander	4 (0.3)	2 (0.3)	2 (0.2)	5 (0.4)	13 (0.3)
Multiple	11 (0.9)	8 (1.2)	16 (1.3)	11 (0.9)	46 (1.0)
Other	12 (1.0)	6 (0.9)	22 (1.7)	18 (1.4)	58 (1.3)
Ethnicity					
Hispanic or Latino	208 (16.5)	135 (20.6)	219 (17.3)	213 (16.9)	775 (17.5)
Not Hispanic or Latino	1047 (83.0)	515 (78.7)	1037 (82.0)	1038 (82.5)	3637 (81.9)
BMI (kg/m^2)					
Mean (SD)	30.2 (7.5)[b]	29.7 (7.6)	30.0 (8.1)	30.5 (8.2)	30.2 (8.5)
Median	29.1	28.3	28.4	29.1	28.8
Min, Max	16.1, 62.6[b]	16, 71.1	15.5, 68.9	13.4, 90.5	13.4, 90.5[b]
Region					
United States	1156 (91.6)	542 (82.9)	1161 (91.8)	1151 (91.5)	4010 (90.3)

Demographic Parameters	Placebo	Treatment Group			Total[a]
	N=1262 n (%)	50 mg N=654 n (%)	100 mg N=1265 n (%)	200 mg N=1258 n (%)	N=4439 n (%)
Europe (Germany, UK)	106 (8.4)	112 (17.1)	104 (8.2)	107 (8.5)	429 (9.7)

This table was created by the reviewer using the IDB dataset, ADSL, using JMP subset to ASETBFL=Y. The columns were defined as Actual Treatment period for 01 (TRT01A). [a]Total refers to the combined lasmiditan and placebo arms.) [b]Analysis performed after changing units for height from cm to inches for subject (b) (6) as sponsor noted that original unit was likely in error.

Reviewer comment: Migraine affects females to males in a 3:1 ratio in the U.S. population.[2] The ratio of females to males enrolled in studies 301 and 302 was approximately 5:1 which is higher then what is seen in the background population. Migraine most commonly affects people between the ages of 25 to 55 and the mean age of patients in studies 301 and 302 was 42 years which is similar to the affected age in the U.S. population. In terms of race, the trials had 78.2% of patients that were white, 17.8% black, 17.5% Hispanic or Latino ethnicity which is similar to percentages seen in the U.S. population.[3] In terms of location of the studies, study 301 was conducted in the U.S. and study 302 was conducted in the U.S. and Europe. Age > 65 years is represented by less than 5% of the population which potentially limits the ability to predict safety of lasmiditan in this age group.

I reviewed the baseline demographics of the safety population in study 305 randomized to lasmiditan 100 mg and 200 mg and note that the demographics of the dosing groups were similar with respect to sex, age, race, ethnicity, geography, cardiovascular risk factors and cardiovascular disease. The baseline demographics of the safety population was also similar to the safety population in studies 301 and 302.

Demographics in Phase 1 Studies

The below table shows demographics of Phase 1 studies by number of doses of study drug.

Table 11. Baseline Demographics for Nonelderly, Healthy Subjects Enrolled in Phase 1 Studies

Demographic Parameter	Single dose, N=587 (%)	Multiple dose, N=70 (%)
Sex		
Male	372 (63.4)	40 (57.1)

Demographic Parameter	Single dose, N=587 (%)	Multiple dose, N=70 (%)
Female	215 (36.6)	30 (42.9)
Age		
Mean years (SD)	37.8 (10.9)	40.9 (11.5)
Median (years)	37.0	42.0
Min, max (years)	18, 65	20, 63
Race		
White	464 (79.0)	38 (54.3)
Black or African American	99 (16.9)	31 (44.3)
Asian	10 (1.7)	0
American Indian or Alaska Native	2 (0.3)	0
Native Hawaiian or other Pacific Islander	0	0
Multiple	4 (0.7)	1 (1.4)
Other	6 (1.0)	0
BMI (kg/m^2)		
Mean (SD)	25.2 (3.4)	27.3 (3.5)
Median	24.9	27.5
Min, Max	18.2, 35.6	20.4, 34.5

Data was summarized from the ISS submitted by the sponsor, from Table ISS.19.3

Reviewer comment: The population enrolled in Phase 1 studies differed from the Phase 3 studies primarily in that subjects did not have a diagnosis of migraine, were more likely to be male, and were more likely to have lower BMI values. Although the baseline demographics were different in Phase 1 studies compared to Phase 3 studies, analyses of vital sign from Phase 1 studies should be informative in understanding the effects of lasmiditan on blood pressure and heart rate.

Population of patients with cardiovascular risk factors and cardiovascular disease

The sponsor has proposed that the class-warnings for ischemia found on triptan labeling be omitted from the label for lasmiditan. To support the exclusion of the class labeling, the sponsor studied lasmiditan in a population of patients with cardiovascular risk factors and with cardiovascular disease.

Cardiovascular risk factors were defined as age >40 years, elevated total cholesterol, low high-density lipoprotein (HDL) cholesterol, elevated systolic blood pressure or baseline hypertension, diabetes mellitus, and current smoker status.

In studies 301 and 302, 79% percent of patients had ≥ 1 cardiovascular risk factor, 41% had ≥ 2 cardiovascular risk factors, 15% had ≥ 3 cardiovascular risk factors and 4% had ≥ 4 risk factors. The mean number of risk factors across treatment groups was 1.

Reviewer comment: A study published by Lipton et al. evaluated the presence of cardiovascular risk factors in patients with episodic migraine in the U.S. population aged ≥ 22 years. Cardiovascular risk factors were defined as hyperlipidemia, hypertension, diabetes mellitus, BMI ≥30, and current smoking status. The frequency of patients with ≥ 1, ≥ 2, and ≥ 3 cardiovascular risk factors was 70%, 39%, and 19%, respectively.[4] I conclude that the population in studies 301 and 302 had a similar prevalence of cardiovascular risk factors as the general U.S. population with episodic migraine.

The sponsor used the following list of SMQs to define cardiovascular disease.

> Hypertension; Cardiac arrhythmias; Embolic and thrombotic events; Ischemic heart disease; Embolic and Thrombotic events, arterial; Tachyarrhythmias; Other ischemic heart disease; Bradyarrhythmias; Central nervous system vascular disorders; CNS hemorrhages and cerebrovascular conditions; Embolic and thrombotic events, venous; Conduction defects; Supraventricular tachyarrhythmias; Ischemic CNS vascular conditions; Cardiomyopathy; Myocardial infarction; Cardiac arrhythmia terms, nonspecific; Disorders of sinus node function; Ventricular tachyarrhythmias; Embolic and thrombotic events, vessel type; Pulmonary hypertension; Tachyarrhythmia terms, nonspecific; Torsade's de pointes/QT prolongation; Cardiac failure; Hemorrhagic CNS vascular conditions.

The following table shows cardiovascular disease at baseline by SMQ term as identified by the sponsor in descending order of frequency for studies 301 and 302 with prevalence ≥1%.

Table 12. Cardiovascular Disease by SMQ term with Prevalence **≥1%** for Studies 301 and 302.

SMQ Term	Studies 301 and 302 (N=4439)	% of Total Population Enrolled in Studies 301 and 302
Hypertension	758	17.1
Cardiac arrhythmias	104	2.3
Embolic and thrombotic events	84	1.9
Ischemic heart disease	51	1.1

SMQ Term	Studies 301 and 302 (N=4439)	% of Total Population Enrolled in Studies 301 and 302
Embolic and thrombotic events, arterial	47	1.1
Tachyarrhythmias	46	1.0
Other ischemic heart disease	45	1.0
Bradyarrhythmias	44	1.0
Total number of patients with baseline cardiovascular disease[a]	904	20.4

This table was created by the reviewer using from the sponsor's submission ISS Appendix Table ISS.APP.18.2. and IDB ADSL dataset, study ID=301 and 302, SAFFL=Y, CVBSGPFL=Y. [a]Patient could be represented by more than 1 cardiovascular disease SMQ.

Reviewer comment: The low number of patients enrolled with ischemic heart (n=51) potentially limits the ability to interpret the safety of lasmiditan in patients with ischemic heart disease.

8.2.3. Adequacy of the safety database:

The exposure of the safety database overall appears adequate in terms of size and dosing. The Phase 3 studies meet ICH E1A guidelines for exposure of at least 300 patients at 6 months, 100 patients at 12 months and over 1500 patients overall at the proposed doses. The database includes 683 patients who received 2 doses at 100 mg or 200 mg. The population appears representative of the U.S. population in terms of geography and race. The low number of patients with ischemic heart disease and patients age > 65 years in studies 301 and 302 potentially limits the ability to predict safety in these populations.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of the datasets was evaluated by the Office of Computational Science Jumpstart team and they identified missing data. An information request was sent to the sponsor and the sponsor submitted a response. The following key issues affected the quality of this submission.

There were 5 subjects where the date the drug was recorded as being administered occurred after the end date of the study. The sponsor noted that the date discrepancies were due to a failure to collect the electronic diary and study drug from the patient prior to being discharged from the study.

There were cases where 2 dates were listed for when a study drug was taken. The sponsor attributed this discrepancy to different dates being recorded in the electronic diary and on the case report form. The sponsor noted that in each case, the case report form was assumed to be more accurate as the electronic diary could not be edited.

The Clinical Inspection Summary noted underreporting of non-serious AEs occurring in 2 out of 50 subjects (4%) at one clinical site in study 301 (#120). In both subjects, the AE was documented on paper forms but not transferred to the electronic case report form. One subject (b) (6) experienced a tingling sensation that was mild, lasted for 20 minutes, and occurred 45 minutes after taking a lasmiditan 100 mg dose. A second subject (b) (6) experienced lethargy that was mild in severity and occurred after taking lasmiditan 200 mg administration.

Reviewer comment: Overall, underreporting of these AEs did not affect percentages calculated for the common AEs table.

8.3.2. Categorization of Adverse Events

The sponsor's definition of Adverse Events, Serious Adverse Events, Treatment Emergent Adverse Events.

Adverse events were classified by the sponsor based on version 21.0 of the Medical Dictionary for Drug Regulatory Activities (MedDRA). An adverse event was defined as an untoward medical occurrence in a patient that did not necessarily have a causal relationship with the treatment.

For studies 301 and 302, a treatment emergent adverse event (TEAE) was defined as an adverse event that first occurred or worsened in severity compared to baseline within 48 hours of the first dose. A serious adverse event (SAE) was defined as any adverse event that resulted in death, life-threatening experience, required or prolonged hospitalization, resulted in persistent or significant disability or incapacity, resulted in a congenital anomaly or a medical event that may have jeopardized the patient and required intervention to prevent it from meeting the above criteria for an SAE.

Adverse events were recorded from the time that the subject signed the informed consent until the completion of the end of study visit which occurred 7 days after the first dose. Adverse events were sought by non-directive questioning of the subject at each study visit. In addition, adverse events were elicited from visit 1 to visit 2 with the prompt "Do you feel anything unusual since you took the Study Medication that you have not felt with a migraine before?" Additionally, an electronic diary prompted patients to record associated symptoms at 0.5, 1, 1.5, 2, 3, 4, 24, and 48 hours following dosing of study drug. Patients were prompted to complete a daily check-in using the electronic diary that included a question as to how the patient was feeling and could trigger a phone call from the study site.

Severity of the adverse event was assessed using the WHO Toxicity Criteria with grade 1 through 4 to indicate severity. If an event was not listed under WHO Toxicity Criteria, the investigator judged the severity of event as mild, moderate, severe or life threatening. Adverse events were followed until they resolved or returned to baseline or were determined to be chronic or stable.

The investigator assessed whether an adverse event was reasonably or possibly related to study drug or not reasonably or not possibly related to the study drug based upon a review of information from the Investigator's Brochure, the subjects' pre-existent medical condition and concomitant medication list and chronology of event in light of when a dose was taken. An AE was recorded regardless of whether it was assessed as related to the study drug.

Reviewer comment: The 48-hour time limit for TEAEs appears adequate given that it represents greater than 5 times the terminal half-life of lasmiditan of 5.8 hours reported by the sponsor. In my review of adverse events, I searched for adverse events occurring outside of 48 hours and did not find any events that I considered to be treatment emergent. The adverse event assessment strategy appears to be adequate.

Study 202 differed from studies 301 and 302 mainly by the following. Treatment emergent adverse events were recorded if they were defined as adverse events with a possible, probable, or definite relationship to the study medication. Adverse events were graded as mild, moderate, and severe and investigators were advised to assess an event as unrelated, possibly related, probably related, or definitely related.

Reviewer comment: Given that TEAEs in study 202 were defined by the likelihood of the event being related to the study drug they are likely an underestimate of adverse events occurring within 48 hours of study drug administration.

In study 305, the study visit intervals occurred at 1, 3, 6, 9 and 12 months.

I evaluated the sponsor's translation of adverse events from verbatim terms to preferred terms for studies 202, 301, 302 and 305 and the translations appeared adequate.

8.3.3. Routine Clinical Tests

Vital signs

For studies 301 and 302, vital signs were collected at the screening/baseline visit and then again within 7 days after treatment or after 8 weeks if no attack was treated. For study 202, vital signs were collected at the screening/baseline visit and the end of study visit.

In study 305, vital signs were obtained at the screening visit, then month 1, 3, 6, 9 and the end

of study visit. If the screening visit for study 305 occurred on the same day as the end of study visit for 301 and 302, then the vitals were also used for 305.

Reviewer comment: The vital signs obtained in studies 202, 301, 302 and 305 did not occur at the time of when the study drug was taken and do not reflect the effects of the drug on blood pressure and heart rate.

In Phase 1 studies, periods for when vital signs were collected included the following times: 30 minutes, 1, 2, 3, 4, 6, 8, 12, and 24 hours.

Reviewer comment: The vital signs from Phase 1 studies are more likely to reflect changes in blood pressure and heart rate due to the study drug as compared to vital signs obtained in Phase 2 or 3 studies.

Laboratory Tests

In studies 301 and 302, clinical laboratory tests were collected at the screening/baseline visit and then again within 7 days after treatment or after 8 weeks if no attack was treated. Laboratory testing included hematology, biochemistry, lipid profile, urine analysis and pregnancy test for women of childbearing potential. The investigator categorized the results of all laboratory testing as clinically significant or not clinically significant using the WHO Toxicity Criteria as a guide.

Reviewer comment: *The laboratory assessments obtained in studies 202, 301, 302 and 305 did not occur at the time of study drug administration; therefore, I reviewed laboratory assessments performed in clinical pharmacology studies.*

In study 305, laboratory testing occurred at the first visit as long as there were no laboratory results from an end of study visit from studies 301 and 302 within 2 weeks. Laboratory testing was performed at the baseline/screening visit, months 1 and 6, and the end of study visit.

ECGs

For studies 301 and 302, a 12-lead ECG was collected at the screening/baseline visit and at the end of study visit. For study 305, ECG testing occurred at the screening/baseline visit as long as there were no ECGs from an end of study visit from studies 301 or 302 within 2 weeks. A 12-lead ECG was obtained at month 6 and at the end of study visit.

Reviewer comment: The ECGs obtained in studies 202, 301, 302 and 305 did not occur at the time of when the study drug was taken and therefore I reviewed the thorough QT study for ECG changes and clinical pharmacology studies for adverse events related to ECG changes.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in patients taking the study drug in Phase 1, 2 or 3 trials.

One death occurred prior to study drug administration in study 301 (b) (6). A 48-year-old male with history of hypertension, low back pain and osteoarthritis died from an accidental overdose of methadone and oxycodone.

Of note, a death was recorded in study 302 due to a data entry error (b) (6).

120 Day Safety Update Report for Deaths
No deaths were recorded through the 120-day Safety Update for study 305.

8.4.2. Serious Adverse Events

The data sources I used for this summary of SAEs included the narrative summaries and case report forms submitted by the sponsor.

There were no SAEs of aplastic anemia, acute pancreatitis, acute respiratory failure, agranulocytosis, aplastic anemia, bone marrow depression, disseminated intravascular coagulation, hemolytic anemia, pancytopenia, rhabdomyolysis, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, sudden death/Torsade's, thrombotic thrombocytopenia purpura in migraine trials.

There were no SAEs of liver failure however there were "nonserious" cases that I discuss later in the laboratory section of this review.

SAEs in Phase 2 and 3 studies
In studies 301 and 302, there were 3 SAEs that occurred in 3 subjects (0.2%) who received placebo (b) (6) and 6 SAEs that occurred in 6 patients (0.2%) who had received lasmiditan. In study 202, there was one additional patient who experienced an SAE after taking lasmiditan.

I have organized the serious adverse events that occurred after drug administration by SOC for studies 202, 301 and 302 by dose in the table below.

Table 13. Serious Adverse Events in Studies 202, 301, and 302.

MedDRA system organ class Serious adverse events (preferred term)	50 mg N=736 n (%)	100 mg N=1347 n (%)	200 mg N=1329 n (%)	Placebo N=1347 n (%)
Gastrointestinal disorders	0	0	0	1 (0.1)
Intestinal obstruction	0	0	0	1 (0.1)
General /administration site conditions	0	0	0	1 (0.1)
Non-cardiac chest pain	0	0	0	1 (0.1)
Hepatobiliary disorders	0	0	0	1 (0.1)
Cholelithiasis	0	0	0	1 (0.1)
Neoplasm benign, malignant, and unspecified	1 (0.1)	0	0	0
Pituitary tumor benign	1 (0.1)	0	0	0
Nervous system disorders	0	0	2 (0.2)	0
Dizziness	0	0	1 (0.1)	0
Presyncope	0	0	1 (0.1)	0
Respiratory, thoracic, and mediastinal disorders	0	0	1 (0.1)	0
Asthma	0	0	1 (0.1)	0
Surgical and medical procedures	0	0	1 (0.1)	0
Surgery	0	0	1 (0.1)	0
Vascular disorders	0	1 (0.1)	1 (0.1)	0
Hypertension	0	0	1 (0.1)	0
Hypotension	0	1 (0.1)	0	0
Total # of SAEs	1 (0.1)	1 (0.1)	5 (0.4)	3 (0.2)
Total # of patients reporting an SAE	1 (0.1)	1 (0.1)	5 (0.4)	3 (0.2)

Reviewer created table from ISS dataset ADAE (numerator) where studyID=202, 302, 302, treatment=TRT01A for placebo and lasmiditan, AESER=Y, and AEFDOSEFL = Y, AESOC=Y, AEDECOD=Y and ADSL(denominator) with ASETAFL = Y and treatment=TRT01A. This table includes data from studies 202, 301, and 302.

Reviewer comment: Overall, the percentage of patients with SAEs in lasmiditan-treated patients for studies 202, 301, and 302 was low.

In study 305, there were a total of 75 unique SAEs occurring in 60 subjects in the safety population. After excluding one case of small intestinal obstruction and one case of nephrolithiasis that occurred prior to lasmiditan dosing, there were 75 unique SAEs occurring in 58 lasmiditan-treated subjects.

Thirty-five SAEs were reported in 28 subjects in the 100 mg dose group and 40 SAEs were reported in 30 subjects in the 200 mg dose group. The percentage of subjects with SAEs

occurring after lasmiditan dosing in the 100 mg group was 2.9% (25/963) and in the 200 mg group was 3.0% (30/1015).

The below table organizes SAEs by preferred term occurring in at least 2 subjects in study 305 after lasmiditan dosing.

Table 14. SAEs by Preferred Term and SOC in Study 305 in at Least 2 Subjects After Lasmiditan Dosing in the Post-Administrative Hold Period.

MedDRA System Organ Class	100 mg N=963 n (%)	L200 mg N=1015 n (%)	All N=1978 n (%)
Gastrointestinal disorders	1 (0.1)	5 (0.5)	6 (0.3)
Gastritis	0 (0.0)	2 (0.2)	2 (0.1)
Hiatus hernia	0 (0.0)	2 (0.2)	2 (0.1)
General disorders and administration site conditions	2 (0.2)	0 (0.0)	2 (0.1)
Non-cardiac chest pain	2 (0.2)	0 (0.0)	2 (0.1)
Infections and infestations	9 (0.9)	4 (0.4)	13 (0.7)
Cellulitis	2 (0.2)	0 (0.0)	2 (0.1)
Pneumonia	1 (0.1)	2 (0.2)	3 (0.2)
Injury, poisoning and procedural complications	2 (0.2)	4 (0.4)	6 (0.3)
Intentional overdose	0 (0.0)	2 (0.2)	2 (0.1)
Nervous system disorders	4 (0.4)	2 (0.2)	6 (0.3)
Seizure	1 (0.1)	1 (0.1)	2 (0.1)
Pregnancy, puerperium and perinatal conditions[a]	3 (0.4)	2 (0.2)	5 (0.3)
Abortion spontaneous	3 (0.4)	1 (0.1)	4 (0.2)
Renal and urinary disorders	2 (0.2)	2 (0.2)	4 (0.2)
Acute kidney injury	1 (0.1)	1 (0.1)	2 (0.1)
Vascular disorders	3 (0.3)	0 (0.0)	3 (0.2)
Hypertension	3 (0.3)	0 (0.0)	3 (0.2)

Reviewer created table from ISS IDB dataset ADAE (numerator) with studyID=305, AESER = Y, AEFLTNFL = Y, AESOC=Y. The denominator is the safety population for 305, IDB dataset ADSL with HLSAFFL = Y, treatment = TROL01A. This table includes data from study 305. If a subject experienced more than one AE with within an SOC, the subject was only counted once for the SOC. If a subject experienced the same preferred term more than once, the subject was only counted once for that preferred term. [a]Rates adjusted for female population.

Reviewer comment: No SOC had greater than 1% of the serious adverse events recorded in study 305.

In the pre-administrative hold population of study 305, 2 SAEs were reported in the Table of Significant Notable Patients submitted by the sponsor (pneumonia, intestinal obstruction). The

case of intestinal obstruction is summarized in the 120 Day Safety Update section of the SAE section.

SAEs in Phase 1 studies

There were 3 SAEs that occurred in Phase I studies in patients receiving lasmiditan. The 3 SAEs were anal abscess (b) (6), cerebellar hematoma (b) (6), and biliary colic (b) (6)

Narratives of Select SAEs in lasmiditan-exposed patients

I summarize select SAEs for studies 202, 301 and 302 in lasmiditan-exposed patients that were treatment-emergent SAEs. There were two SAEs of seizure and two SAEs of renal failure in study 305 that I summarize. Given the class warnings for ischemia with triptans, I also summarized SAEs in lasmiditan-exposed subjects with potential cardiovascular etiology for Phase 1 through 3 trials.

Narratives of SAEs in studies 202, 301, and 302

Dizziness (b) (6)

A 46-year-old woman with no prior history of bradycardia was hospitalized for dizziness of moderate severity which occurred 30 minutes after taking lasmiditan 200 mg. The patient was noted to have bradycardia of 40 beats per minute upon hospitalization (32 beats per minute lower than her baseline screening heart rate) and an ECG showing sinus bradycardia. She received normal saline by infusion and was discharged the next day. The following day, a repeat ECG showed sinus bradycardia at 52 beats per minute. Her only concomitant medication was ibuprofen.

Reviewer comment: *The AE of dizziness was likely caused by lasmiditan given that onset of dizziness occurred within 30 minutes of taking the drug. Given that the terminal elimination half-life of lasmiditan is 5.7 hours, it is conceivable that lasmiditan was still present the following day and could have contributed to the sinus bradycardia that was still observed.*

Hypertension (b) (6)

A 43-year-old woman with history of rheumatoid arthritis, tobacco use, and hypertension on nifedipine 100 mg daily took lasmiditan 200 mg for a migraine headache. The headache resolved however reoccurred and she presented to the emergency room with complaint of migraine within 12 hours of taking lasmiditan. She was hospitalized for 3 days for uncontrolled hypertension reportedly until her blood pressure was stable (blood pressure readings reportedly not recorded). Her blood pressure at her screening visit was 120/84 mmHg and her heart rate was 56 beats per minute. Her nifedipine dose was increased to 150 mg daily and her blood pressure was controlled. Concomitant medications included diclofenac 75 mg as needed for rheumatoid arthritis. At the study completion visit approximately 12 days after the event her blood pressure was 110/74 with a heart rate of 52 beats per minute.

Reviewer comment: A role for lasmiditan in the event of hypertension cannot be ruled out given the proximity between drug administration and onset of the event. Confounding factors such as pain may have contributed to blood pressure elevation. In addition, duration of the uncontrolled blood pressure of 3 days lasted longer than 5 times the half-life of the drug. Of note, she was recorded to be taking nifedipine 100 mg daily up until the day of the adverse event.

Hypotension/Dystonic Reaction (b) (6)
A 67-year-old woman was hospitalized for orthostatic hypotension and "dystonic jerky reaction" that occurred 20 minutes after taking lasmiditan 100 mg. While hospitalized, she experienced myoclonic twitching and underwent an MRI of the brain which showed "tiny focal hypersensitivities in the deep white matter." While hospitalized, she was treated with lorazepam and procyclidine. Her exit interview from the study was notable for a positive Romberg test. There was no information available about blood pressure during this event. The event of hypotension reportedly lasted 3 days and she was treated with ibuprofen and omeprazole. Of note the sponsor reports in the ISS that that the AE term was updated in the safety database to dystonic reaction.

Reviewer comment: Of note, blood pressure measurements were not provided, and lack of blood pressure measurements makes the event of orthostatic hypotension difficult to interpret. The role of lasmiditan in the event of orthostatic hypotension cannot be ruled out. The positive Romberg test could be sequelae from an anoxic event; however, the findings from the MRI of the brain are not suggestive of a stroke. It is unclear whether the myoclonic twitching or positive Romberg test are related to the study drug.

Presyncope (b) (6)
A 53-year-old woman developed lightheadedness, syncopal feeling, sweaty palms, general weakness, dry mouth, slowed speech, impaired concentration, and tiredness immediately after taking a 200 mg dose of lasmiditan. All of her symptoms except for fatigue resolved after 8 hours with no treatment. She remained hospitalized for persistent fatigue for 1 day.

Reviewer comment: No test results were available, such as blood pressure, that would assist in characterizing this event. These symptoms could be symptoms of a migraine, but a role for lasmiditan cannot be ruled out.

Pituitary Tumor (b) (6)
A 67-year-old man was diagnosed with a benign pituitary tumor. He had taken 2 doses of lasmiditan 50 mg but had not recorded the time for when he took the medications. Six weeks after his study enrollment, he reported that he had been diagnosed with a pituitary tumor in the interval time.

Reviewer Comment: This event is unlikely to be drug-related given the short time frame between lasmiditan and the diagnosis of the tumor.

Narratives of Select SAEs occurring in study 305

Acute Kidney Injury (b) (6)

A 56-year-old female with past medical history of diabetes mellitus, hypertension, reflux disease, hypothyroidism, hypokalemia and hypomagnesemia, and elevated creatinine (baseline creatinine in study 302 was 1.3 mg/dL) was hospitalized for acute renal failure (creatinine 3.0 although units were not reported), metabolic acidosis, and dehydration. She was treated with intravenous fluids and four days later her creatinine had decreased to 1.2 (units not reported). She developed hypocalcemia 4 days after the AE of renal failure which resolved 4 days later. Her most recent dose of lasmiditan had been 17 days prior to developing acute kidney injury and she had treated 8 migraine attacks before the SAE was reported.

Two months prior to the AE of acute kidney injury, the patient underwent surgery for multinodular goiter and was reported to have developed nausea, vomiting, and dehydration that reportedly had been going on since then and was ongoing at the time of the data cut off. No laboratory values are reported between the time of the surgery and the AE of acute kidney injury. The most recent creatinine recorded before the reported AE of acute kidney injury was 1.2 mg/dL and was three months prior to the AE. Concomitant medications included hydrochlorothiazide, omeprazole, magnesium and potassium.

Reviewer comment: A role of lasmiditan in the AE of acute kidney injury cannot be ruled out given that the most recent dose had occurred 17 days prior to the AE. Underlying risk factors for acute kidney injury include a history of elevated creatinine and post-operative complications of nausea, vomiting, and dehydration. Resolution with intravenous fluids supports a role for dehydration.

Possible Seizure, lethargy (b) (6)

A 34-year-old female with past medical history of obesity and tension headaches experienced bilateral numbness in her fingertips and face for 1 minute, followed by shaking of the whole body that lasted for 4 minutes. There was no loss of consciousness, bowel or bladder incontinence or tongue biting. She experienced lethargy three days later. She saw a neurologist who diagnosed her with pseudo seizure. Her most recent dose of lasmiditan had been 41 days prior to the possible seizure.

Reviewer comment: The description of the AE appears consistent with the diagnosis of pseudo seizure and lasmiditan is unlikely to be related in this case.

Seizure (b) (6)

A 50-year-old man with past medical history of cerebral palsy, depression, and anxiety was

hospitalized for seizure and presumed stroke. He presented to the hospital with aphasia, seizure, decreased appetite, fatigue, malaise, nausea, non-cardiac chest pain, blurred vision with his right eye and was also noted to have dehydration, hypernatremia, leukocytosis and muscle weakness. A CT and an MRI of the head showed no infarct. New medications upon discharge included aspirin and levetiracetam. The event occurred 99 days after his last dose of medication and he had treated 3 migraines prior to the adverse event.

Reviewer comment: The adverse event of seizure does not appear to be related to lasmiditan given that the event occurred 99 days after his most recent dose of lasmiditan.

Atrial fibrillation/angina pectoris (b) (6)
A 51-year-old woman with past medical history of rheumatic heart disease, mitral valve stenosis, diabetes mellitus type 2, hypertension, hyperlipidemia, gastroesophageal reflux disease, and chronic obstructive pulmonary disease was hospitalized for angina pectoris and atrial fibrillation with rapid ventricular response. On echocardiogram, she was noted to have moderate mitral valve stenosis with a mitral valve area of 1.8 cm^2. She was started on amiodarone 27 days later and the event resolved on the same day. Her most recent dose of lasmiditan prior to the event was 159 days beforehand and she received 9 doses prior to the event.

Reviewer comment: The event of atrial fibrillation and chest pain are unlikely to be related to lasmiditan as they occurred 5 months after her most recent dose of lasmiditan. Additionally, confounding factors for atrial fibrillation in this case exist including pre-existing mitral valve stenosis and hypertension.

Bradycardia/sinus node dysfunction (b) (6)
A 41-year-old man with past medical history of attention deficit hyperactivity disorder, depression, insomnia, and hypertension presented to the ER with vomiting and slurred speech. He was hospitalized for bradycardia (heart rate of 51 beats per minute and blood pressure of 104/56 mmHg upon presentation), diagnosed with sinus node dysfunction, and treated with pacemaker implantation 13 days later. Concomitant medications included aripiprazole, cetirizine, fluticasone spray, and guanfacine. His last dose of lasmiditan was 12 hours prior to the event and he had treated 7 migraines prior to the event. Of note, he had a mean heart rate of 49 beats per minute on his screening ECG in study 302 and his blood pressure at the time was 101/60 mm Hg. At his screening visit in study 305, his heart rate was 60 beats per minute and his blood pressure was 95/60 mmHg at the time.

Reviewer comment:
It seems unlikely that the event of bradycardia is related to lasmiditan as the patient had a similar degree of bradycardia at his screening visit in study 302. Additional confounding factors for bradycardia include guanfacine as this medication has been associated with worsening of

sinus node dysfunction.[5]

Stress cardiomyopathy (b) (6)
A 59-year-old woman with past medical history of anxiety, obesity, depression, hyperlipidemia, hypertension, atrial fibrillation, hypothyroidism, and edema was diagnosed with stress cardiomyopathy by cardiac catheterization. She received a total of 74 doses of lasmiditan prior to the event and the most recent dose had occurred 9 days before. She had normal coronary arteries on cardiac catheterization at the time of hospitalization. Medications prior to hospitalization included aspirin, escitalopram, losartan, omeprazole, pitavastatin, fish oil, magnesium oxide, multivitamin and verapamil. The event of stress cardiomyopathy was reported to have resolved 4 days later.

Reviewer comment: It seems unlikely that lasmiditan is related to stress cardiomyopathy in this case. Known risk factors for stress cardiomyopathy include female sex and history of anxiety. Additional potential confounding factors include the presence of verapamil which has been associated with severe left ventricular dysfunction.[6,7]

Non-cardiac chest pain/Hypertension/Acute Kidney Injury/Sepsis/Syncope/Potentially clinically significant high changes in vital signs (b) (6)
A 49-year-old woman with past medical history of hypertension, uterine cancer, depression, history of crack cocaine use, abnormal baseline ECG in study 301 (prolonged QTcB and non-specific t-wave abnormality), and elevated creatinine (1.1 mg/dL on screening lab in study 301) was hospitalized for hypertension and then again for sepsis, acute kidney injury, and syncope, all in study 305. The hospitalization for hypertension (blood pressure not reported) occurred 17 days after her most recent dose of lasmiditan. Her blood pressure readings at the 2 visits preceding hospitalization were 149/105 and 127/99. These readings were before her first dose of lasmiditan. Following hospitalization, her blood pressure was elevated at 3 out of 4 subsequent visits. Her blood pressure readings were 144/108 (most recent dose of lasmiditan 31 days prior), 155/117 (most recent dose of lasmiditan 33 days prior), and 145/116 mmHg (most recent dose of lasmiditan 12 days prior).

Her second hospitalization in study 305 was for sepsis, acute kidney injury, non-cardiac chest pain, and syncope. The hospitalization occurred 10 months after her first dose of lasmiditan and 15 days after her most recent dose of lasmiditan and approximately 4 days after experiencing

flu-like symptoms. She had treated a total of 8 migraine attacks prior to the event. At the time of hospitalization, concurrent symptoms included myalgias and upper respiratory congestion and a urine analysis positive for leukocyte esterase and oxalate crystals. Serum creatinine was 1.4 (reference value not available) and diagnosed as renal failure. The following day her fever subsided and repeat urine analysis and renal ultrasound were normal. She was treated with ceftriaxone and sulfamethoxazole-trimethoprim. Concomitant medications at the time included amlodipine, pravastatin, and hydrochlorothiazide.

Reviewer comment: For the event of hospitalization for hypertension, it is unlikely that this event was related to lasmiditan as the patient had uncontrolled hypertension at baseline as noted by her blood pressure readings at her previous study visits, and the event occurred 15 days after the most recent dose.

The event of hospitalization for sepsis, syncope, acute kidney injury and non-cardiac chest pain does not appear related to lasmiditan as the event appears to be due to a urinary tract infection and baseline renal insufficiency.

Non-cardiac chest pain/Hypertension (b) (6)
A 66-year-old woman with past medical history of idiopathic intracranial hypertension, anxiety, hypertension, gastroesophageal reflux disease, gastrectomy, and systemic lupus erythematosus was hospitalized for anxiety, non-cardiac chest pain and hypertension (blood pressure reading not reported). A cardiac catheterization at the time of hospitalization showed no coronary artery disease. She was started on amlodipine and her dosage of duloxetine was increased. The hospitalization occurred 19 days after her most recent dose of lasmiditan and after treating 19 migraine attacks. Her blood pressure readings in studies 302 and 305 prior to hospitalization had ranged between 120-140s/60-90s. Concomitant medications included duloxetine, meloxicam, omeprazole, ondansetron, fluticasone-salmeterol, and hydroxychloroquine.

Reviewer comment: The hospitalization for anxiety, hypertension and non-cardiac chest pain does not appear to be related to lasmiditan given that her last dose of lasmiditan had occurred 19 days prior to the event.

Ischaemic stroke (b) (6)
A 63-year-old woman with past medical history of ischemic stroke, hypertension, diabetes mellitus type 2, and hyperlipidemia was hospitalized for ischemic stroke. Her most recent dose of lasmiditan was 159 days beforehand and she had received 9 doses prior to the event.

Reviewer comment: The SAE of ischemic stroke is most likely not related to lasmiditan given that her most recent dose of lasmiditan was 5 months before. Additional risk factors for ischemic stroke in this case exist including hypertension, diabetes mellitus, hyperlipidemia, and history of stroke.

Transient Ischemic Attack (b) (6)
A 37-year-old woman with past medical history of hypertension, obesity, former tobacco use, and headache was hospitalized for transient ischemic attack. The hospitalization occurred 249 days after her first dose of lasmiditan and 19 days after her last dose. She treated 20 migraine attacks prior to the adverse event. Her blood pressure prior to the event ranged in the 130s/70-80s mmHg. Concomitant medications included lisinopril, tramadol, acyclovir, cetirizine, fluticasone, and ibuprofen.

Reviewer comment: It is unlikely that the event of transient ischemic attack was related to lasmiditan as it occurred 19 days after her most recent dose. Additional confounding factors for transient ischemic attack exist in this case including hypertension and history of tobacco use.

Hypertension (b) (6)
A 59-year-old woman with past medical history of hypertension, depression, and history of lacunar infarct was hospitalized for chest pain and hypertension (blood pressure reading not reported). This occurred 32 days after her most recent dose of lasmiditan and 325 days after her first dose. She had treated 32 migraines prior to the event. A stress test at the time of hospitalization did not show evidence of ischemia. Concomitant medications included hydrochlorothiazide, lisinopril and meloxicam. Of note, her blood pressure readings at her screening study visits were 96/75 mmHg and 120/83 mm Hg.

Reviewer comment: The event of hypertension and chest pain do not appear to be related to lasmiditan as her most recent dose of lasmiditan was 32 days prior to the event.

Pulmonary embolism (b) (6)
A 31-year-old woman with a past medical history of antithrombin III deficiency, history of recurrent pulmonary embolism, deep vein thrombosis, tobacco use, depression, anxiety, and reflux developed a pulmonary embolism nine days after her first dose of lasmiditan 200 mg in study 305 and 5 days after her most recent dose of lasmiditan. She had treated two migraine attacks in study 305. Three weeks prior to the pulmonary embolism, her blood pressure was 126/99 mmHg and pulse rate was 108 bpm. The AE of peripheral edema was also reported with the pulmonary embolism. Twenty days after her hospitalization, her blood pressure was 112/90 mmHg and her pulse rate was 104 bpm.

Five months after her first hospitalization, she was hospitalized for prescription drug abuse. She was discharged a month later for non-compliance with the study protocol.

Reviewer comment: A role for lasmiditan in the event of pulmonary embolism cannot be ruled out given proximity to dosing, however the subject's prior history of recurrent pulmonary embolism, antithrombin III deficiency, and tobacco use are likely contributing factors.

Altered mental status (b) (6)
A 46-year-old female with history of alcohol use was hospitalized due to alcohol intoxication and mental status change. The most recent dose of lasmiditan had been 38 days before and she had treated two migraine attacks prior to the SAE. Concomitant medications included gamma hydroxybutyrate. She also noted drug withdrawal syndrome from gamma hydroxybutyrate, severe agitation, severe alcohol withdrawal syndrome, and hyperglycemia on the same day as the mental status changes. She was treated with lorazepam while hospitalized and oxazepam on discharge. The SAE of mental status changes was recorded as lasting three days. The patient was discontinued from the study approximately six weeks later due to noncompliance with the study protocol. At that time, she had been rehospitalized for alcohol detoxification.

Reviewer comment: A role for lasmiditan is unlikely in the event of mental status changes as the subject had multiple confounding factors including alcohol withdrawal, hyperglycemia, and drug withdrawal syndrome from gamma hydroxybutyrate.

Subdural hematoma (b) (6)
A 77-year-old female with history of hypertension, hypothyroidism, chronic kidney disease, diabetes mellitus type 2, depression, anxiety, and peripheral neuropathy was hospitalized for a subdural hematoma. This occurred after she had hit her head against a sharp object on the wall while searching for light and had slipped and fallen down. She was admitted to the hospital on the same day for neurochecks and was noted to have a small subdural hematoma. Her most recent dose of lasmiditan had been 4.5 months before and she had treated three migraine attacks before the event had occurred. Concomitant medications included anastrozole, atorvastatin calcium, duloxetine hydrochloride, levothyroxine sodium, and tramadol hydrochloride.

Reviewer comment: The AE of subdural hematoma is not likely related to lasmiditan given that the most recent dose was 4.5 months before.

Deep Vein Thrombosis (b) (6)
A 38-year-old female was diagnosed with a right lower extremity deep vein thrombosis that started one day prior to receiving study drug.

Reviewer comment: The SAE is not related to lasmiditan given timing of dose and onset of AE.

Fall (b) (6)
A 47-year-old female with past medical history of hypotension was hospitalized for an intertrochanteric hip fracture occurring after a fall (date of fall unknown). Her most recent dose of lasmiditan had been four days before hospitalization and she had taken nine doses prior to the event. Concomitant medications included midodrine. Her blood pressure was recorded at

94/62 mmHg in study 302 prior to her first dose of lasmiditan. No changes were made to her medications at the time of hospitalization.

Reviewer comment: It is not known if the event of hospitalization for hip fracture is related to lasmiditan as the date of the fall that caused the hip fracture is unknown.

SAEs occurring in Phase 1 studies

There was 1 SAE with a potential cardiovascular etiology from Phase I studies which I review.

Cerebellar haematoma (b) (6)

A 34-year-old male with history of intolerance to ciprofloxacin (muscle aches), former tobacco use, and current alcohol drinker (3 units per week) was diagnosed with a cerebellar hematoma after experiencing a headache for eight days. His most recent dose of lasmiditan had occurred eight days before the onset of headache and he had received three doses prior to the event.

Reviewer comment: It is unlikely that the event of cerebellar hematoma was related to lasmiditan as he experienced a headache eight days before the hematoma and his most recent dose of lasmiditan had been eight days before the headache.

120 Day Safety Update Report for SAEs in study 305

There were an additional four SAEs reported by the sponsor in study 305 at the time of the 120 Day Safety Update. The SAEs included diverticulitis, endometriosis, pregnancy, and atrial flutter. The percentage of subjects who experienced an SAE after receiving a lasmiditan dose by treatment group was 3.0% (30/991) for the 100 mg group and 3.1% (32/1039) for the 200 mg group. The percentage of subjects who experienced an SAE after lasmiditan dosing for both dose groups combined was 3.1% (62/2030).

No SOC had greater than 1% of SAEs in study 305 at the time of the 120 Day Safety Update. There were two SAEs of diverticulitis (one occurring in the original submission and one occurring with the 120 Day Safety Update). I summarize those cases along with two SAEs of intestinal obstruction (one case coming from the pre-administrative hold period in study 305).

Intestinal obstruction (b) (6)

A 54-year-old female with past history of oophorectomy, cholecystectomy, urinary bladder suspension, and esophagogastric fundoplasty was hospitalized for intestinal obstruction. This occurred seven days after the most recent dose of lasmiditan 200 mg in the pre-administrative hold phase of study 305 and 17 days after the initial dose. At the time of hospitalization, she was also diagnosed with bilateral nonobstructing kidney stones. She had treated two migraine attacks in study 305 and had received placebo in study 301. Concomitant medications included buspirone, cyclobenzaprine hydrochloride, and mirabegron.

Reviewer comment: A role for lasmiditan cannot be ruled out given proximity of event onset to lasmiditan dosing; however, her history of multiple previous abdominal surgeries is a risk factor for developing intestinal obstruction.

Small intestinal obstruction (b) (6)
A 45-year-old female with history of hysterectomy was hospitalized for small intestinal obstruction. This occurred two months after her most recent dose of lasmiditan and she had treated 7 migraine attacks prior to the onset of the AE. The patient underwent an exploratory laparoscopic abdominal lysis of adhesions and had resolution of her abdominal pain.

Reviewer comment: A role for lasmiditan in the AE of intestinal obstruction is unlikely given that the most recent dose had been 2 months prior the event. Additionally, her previous history of abdominal surgery is a known risk factor for developing intestinal obstruction.

Diverticulitis (b) (6)
A 43-year-old female with history of tubal ligation experienced two SAEs of diverticulitis. In study 305, she was diagnosed with the AE of diverticulosis. Her most recent dose of lasmiditan had been 13 days before and she received two doses of lasmiditan prior to developing the AE. Eight days after the diagnosis of diverticulosis, she was recorded as having the AE of gastric ulcer due to helicobacter which reported as resolved three weeks later

Four months later, she was hospitalized for diverticulitis. Her most recent dose of lasmiditan had been 41 days before and she had treated five migraine attacks in study 305 prior to developing the AE. She was treated with amoxicillin/clavulanate potassium, ciprofloxacin, ertapenem sodium, metronidazole, hydromorphone, morphine, hydrocodone/acetaminophen, ondansetron, sodium chloride, and omeprazole. Six months later, she was hospitalized for diverticulitis and underwent surgical correction of diverticulitis with laparoscopic sigmoidectomy, mobilization of the splenic flexure, lysis of adhesions, and a colorectal anastomosis. She received unspecified antibiotics during her hospitalization. The most recent dose of lasmiditan had been five days before and she had treated a total of 10 migraine attacks prior to the second SAE of diverticulitis. Concomitant medications included omeprazole.

Reviewer comment: A role for lasmiditan in the SAE of diverticulitis is unlikely as she had the predisposing factor of diverticulosis. Her diagnosis of diverticulosis occurred three weeks after her first dose of lasmiditan and a role for lasmiditan in the AE of diverticulosis is unlikely.

Diverticulitis (b) (6)
A 57-year-old female with history of dyspepsia was hospitalized for diverticulitis of the sigmoid colon after experiencing abdominal discomfort for seven days. She was treated with ciprofloxacin and metronidazole and she was reported to have recovered two days later. The subject had multiple doses of lasmiditan however the dates of the doses were not recorded.

She took 71 doses of lasmiditan in study 305 and the last known recorded dose of lasmiditan was 16 days prior to the event. Concomitant medications include calcium carbonate, celecoxib, cholecalciferol, curcuma longa rhizome, dihydroergotamine mesilate, linum usitatissimum seed oil, Bioperin (active ingredient: piperine[8]), paracetamol, probiotic NOS, and Vitamin B complex.

Reviewer comment: A role for lasmiditan in the AE of diverticulitis cannot be ruled out given the multiple doses that she had received during study 305 and proximity to the onset of the event. Confounding factors for constipation include concomitant medication use of celecoxib.

One of the four SAEs from the 120 Day Safety Update had a potential cardiovascular etiology and I summarize the case here.

Atrial flutter (b) (6)
A 51-year-old male with past medical history of hypertension, depression, and hypertriglyceridemia, developed atrial fibrillation on an ECG at his fourth study visit on study day 182. His most recent dose of lasmiditan had occurred on study day 109. He was hospitalized on study day 366 for atrial fibrillation with atrial flutter. His most recent dose of lasmiditan prior to the event of hospitalization was on study day 358. He had treated four migraines prior to the onset of atrial fibrillation with atrial flutter at his fourth study visit and his ECG had been noted to be normal at his 3rd study visit (study day 91). Concomitant medications included acetylsalicylic acid, hydrochlorothiazide, ibuprofen, fenofibrate, metoprolol, mirtazapine, venlafaxine, and pantoprazole.

Reviewer comment: It is unlikely that lasmiditan contributed to the event of atrial flutter. Factors that are not supportive of an association between lasmiditan and atrial flutter include the most recent dose of lasmiditan prior to developing atrial fibrillation was 73 days prior to the event. Additional confounding factors in this case include pre-existing hypertension.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Criteria for premature withdrawal in studies 301, 302 and 305 included the following reasons: non-compliance with protocol requirements, pregnancy, death, adverse event, subject request, sponsor request, investigator request, or concern by the investigator that continuation in the study would pose a significant safety risk to the subject.

Criteria for withdrawal in study 202 included the following reasons: deterioration in the subject's signs or symptoms; development of a condition that in the opinion of the investigator would compromise the subject's safety; investigator's judgment; protocol violation; subject not treating a migraine attack within eight weeks of the screening visit.

8. Bioperine. www.bioperine.com. Accessed June 20, 2019.

The following table shows reasons for discontinuations in studies 202/301/302 and 305.

Table 15. Reasons for Discontinuations Due to AEs or Possibly AEs

Reasons for Discontinuation	Studies 202, 301, and 302		Study 305
	Placebo N=1347 n (%)	Lasmiditan N=3412 n (%)	Lasmiditan N=1978 n (%)
Adverse Event	0	1 (0)	254 (12.8)
Lost to Follow Up	18 (1.3)	39 (1.1)	181 (9.2)
Non-compliance with Protocol Requirement	7 (0.5)	13 (0.4)	14 (0.7)
Physician Decision	0	1 (0)	34 (1.7)
Protocol Deviation	4 (0.3)	30 (0.9)	109 (5.5)
Withdrawal by Subject	4 (0.3)	12 (0.4)	431 (21.8)

Reviewer created table from ISS IDB dataset ADSL. For studies 202, 301 and 302, ASETAFL=Y, treatment=TRT01A, DISCREAS=Y. For study 305, HLSAFFL=Y, HLDCREAS=Y. The denominator for studies 202, 301, and 302 the safety population by study drug, ISS IBD dataset ADSL where ASETAFL=Y and treatment=TRT01A. The denominator for study 305 is anyone who had received lasmiditan in 305, ISS IDB dataset ADSL where HLSAFFL=Y.

Reviewer comment: The number of AEs causing discontinuation in studies 202/301/302 is low and is likely due to the study design as subjects could take a minimum of one dose of study drug. The higher rate of withdrawal seen in study 305 is likely in part due to the longer duration of the study (12 months).

Only one subject (b) (6), 200 mg dose) withdrew due to an AE (dizziness and fatigue) in studies 202, 301, and 302.

In study 305, 408 AEs in 254 lasmiditan-exposed subjects were reported as reasons for discontinuation. One hundred and eight (11.2%) of subjects in the lasmiditan 100 mg dose group and 146 (14.4%) subjects in the lasmiditan 200 mg group discontinued due to an AE. At the time of the 120 Day Safety Update, 112 subjects (11.3%) in the 100 mg group and 148 subjects (14.2%) in the 200 mg dose group had discontinued due to an AE.

The table below lists AEs (and groupings of closely related AEs using the ODE-1 methodology) reported as causing discontinuation in study 305 with an incidence of at least 1% at the time of the 120 Day Safety Update. The incidence of AEs reported as causing discontinuation in the 120 Day Safety Update was similar to the incidence of AEs in the initial submission.

Table 16. AEs Reported as Causing Discontinuation with an Incidence of At Least 1% in Study 305 after 120 Day Safety Update, Grouped.[a]

MedDRA AEs (preferred term)	100 mg N=991 n (%)	200 mg N=1039 n (%)
Dizziness, light-headedness	28 (2.8)	44 (4.2)
Somnolence, sedation	16 (1.6)	12 (1.2)
Asthenia, fatigue, malaise, weakness	7 (0.7)	26 (2.5)
Paresthesia, hypoaesthesia	8 (0.8)	19 (1.8)
Nausea, vomiting	7 (0.7)	16 (1.5)
Confusion, delirium, altered mental status, disorientation	21 (2.1)	15 (1.4)

Reviewer created table from ISS IDB dataset ADAE 120 Day Safety Update (numerator) where STUDYID = 305, AELTNFL=Y, DISAEFL=Y, and treatment = TROL01A. The denominator is the safety population for 305 after 120 Day Safety Update. [a]The ODE-1 groupings were adjusted for preferred terms that primarily contributed to the groupings.

8.4.4. Significant Adverse Events

Severity of AEs in studies 301, 302, and 305, were assessed using the WHO Toxicity Criteria. Severity of AEs in study 202 were graded by the investigator using the following categories: mild, moderate, and severe. In my opinion, the categories for grading AE severity in study 202 were similar to the categories for grading AE severity using WHO Toxicity Criteria.

In general, approximately 35% of AEs were mild across the controlled studies and study 305. In Study 202, 22% to 36% of AEs were severe, in a dose-related fashion compared to approximately 18% severe for placebo. In studies 301 and 302, the most frequent severe AEs included dizziness/light-headedness, and were severe in 0.3% of 50 mg, 0.8% of 100 mg, and 1.4% of 200 mg vs 0.1% for placebo. Severe AEs of asthenia/fatigue/malaise, nausea/vomiting, confusion/delirium/ altered mental status/disorientation, somnolence/sedation, balance disorder, and vertigo/vestibular dysfunction were also among the most frequent, all occurring in less than 1%.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

I evaluated TEAEs reported in study 202 separately from TEAEs reported in phase 3 studies because the definition of a TEAE in study 202 was different from the definition of a TEAE in phase 3 studies and was based on the likelihood of the event being related to study drug.

In studies 301/302 combined, 25.5%, 36.3%, and 40.8% of lasmiditan 50 mg, 100 mg, and 200 mg-treated patients, respectively, and 13.9% of placebo-treated patients experienced at least one TEAE.

The following table lists TEAEs (and groupings of closely related TEAEs using the ODE-1 methodology) in studies 301 and 302 occurring after first dose with an incidence of at least 2% and at least 2% greater than placebo. Dizziness/balance disorder and somnolence/fatigue/sedation occurred in 18% and 11%, respectively, of subjects given lasmiditan 200 mg. Dose-responses are seen with all the groupings of TEAEs listed in the table suggesting that these effects are related to drug exposure.

Table 17. TEAEs after First Dose with an Incidence of At Least 2% and At Least 2% Greater than Placebo in Studies 301 and 302, Grouped.[a]

MedDRA AEs (preferred term), grouped	50 mg N=654 n (%)	100 mg N=1265 n (%)	200 mg N=1258 n (%)	All Lasmiditan N=3177 n (%)	Placebo N=1262 n (%)
Dizziness, balance disorder	57 (9)	201 (16)	227 (18)	485 (15)	37 (3)
Somnolence, fatigue, sedation	53 (8)	122 (10)	135 (11)	310 (10)	36 (3)
Confusion, delirium, altered mental status, disorientation, hallucinations[b]	42 (6)	86 (7)	102 (8)	230 (7)	29 (2)
Asthenia, fatigue, malaise, weakness	29 (4)	85 (7)	98 (8)	212 (7)	11 (1)
Paresthesia, hypoesthesia	16 (2)	73 (6)	95 (8)	184 (6)	23 (2)
Nausea, vomiting	22 (3)	48 (4)	56 (4)	126 (4)	28 (2)

Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 301 and 302, TRTEM1FL=Y. The denominator is the safety population for studies 301 and 302 (IDB ADSL dataset with ASETBFL=Y, TRT01A=Y). [a]The ODE-1 groupings were adjusted for preferred terms that primarily contributed to the groupings. [b]Includes the preferred terms of confusional state, delirium, disorientation, disturbance in attention, lethargy, mental impairment, mental status changes, somnolence, stupor, hallucination, visual hallucination, auditory hallucination, and hypnagogic hallucination.

The grouping of confusion/delirium/altered mental status/disorientation/hallucinations was primarily driven by the preferred terms somnolence and lethargy which are not included in the name of the grouping.

TEAE Groupings in the Label

In the label, the preferred term of dizziness is reported alone. The incidence of dizziness in the lasmiditan 50 mg, 100 mg, 200 mg, and placebo group was 8.6%, 15.3%, 17.2%, and 2.9%,

respectively. The grouping of confusion/delirium/altered mental status/disorientation/hallucinations does not appear in the label as the preferred terms somnolence and lethargy contributed to this grouping and are represented in other groupings in the label. In the label fatigue is grouped with grouped with asthenia and malaise. The incidence of fatigue/asthenia/malaise in the lasmiditan 50 mg, 100 mg, 200 mg, and placebo group was 3.5%, 5.1%, 5.6%, and 0.8%, respectively. In the label, paresthesias includes the preferred terms paresthesias, oral paresthesias, hypoesthesia, and oral hypoesthesia and had an incidence in the lasmiditan 50 mg, 100 mg, 200 mg, and placebo group of 2.8%, 7.0%, 9.0%, and 1.9%, respectively. In the label, the grouping of Sedation/Somnolence does not contain the preferred term fatigue. The incidence of the combined terms of sedation and somnolence in the lasmiditan 50 mg, 100 mg, 200 mg, and placebo group was 5.5%, 5.6%, 6.8%, and 2.2%, respectively. The preferred term of muscle weakness is reported alone. The incidence of muscle weakness in the lasmiditan 50 mg, 100 mg, 200 mg, and placebo group was 1.1%, 1.3%, 1.5%, and 0%, respectively. The incidence of cognitive changes and confusion which includes the preferred terms confusional state, delirium, disorientation, mental status changes, disturbance in attention, mental impairment, and stupor in the lasmiditan 50 mg, 100 mg, 200 mg, and placebo group was 0.5%, 0.6%, 1.0%, and 0.1%, respectively.

In Study 305, overall, 45.1% of lasmiditan 100 mg-treated patients and 52.2% of lasmiditan 200 mg-treated patients experienced at least one TEAE. The table below lists TEAEs occurring in study 305 after first dose with an incidence of at least 2%. Additional groupings of TEAEs are present in study 305 that are not seen in study 301 and 302 including infection, vertigo/vestibular dysfunction, and URI/cold/rhinitis/flu-like illness.

Table 18. TEAEs after First Dose of Lasmiditan with an Incidence of At Least 2% in Study 305, Grouped.[a]

MedDRA AEs (preferred term), grouped	100 mg N=963 n (%)	200 mg N=1015 n (%)	All N=1978 n (%)
Dizziness, light-headedness	151 (16)	215 (21)	366 (19)
Somnolence, fatigue, sedation	117 (12)	156 (15)	273 (14)
Confusion, delirium, altered mental status, disorientation	95 (10)	119 (12)	214 (11)
Asthenia, fatigue, malaise, weakness	70 (7)	100 (10)	170 (9)
Paresthesia, hypoesthesia	53 (6)	84 (8)	137 (7)
Nausea, vomiting	49 (5)	60 (6)	109 (6)
Infection, all	35 (4)	44 (4)	79 (4)
Vertigo; vestibular dysfunction	14 (1)	28 (3)	42 (2)
URI, cold, rhinitis, flu-like illness	19 (2)	20 (2)	39 (2)

Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 305, TRTEM4FL=Y. The denominator is the safety population for study 305 (IDB ADSL dataset with LAHLFL=Y, HLSAFFL=Y, TROL01A=Y).
[a]The ODE-1 groupings were adjusted for preferred terms that primarily contributed to the groupings.

In the above table, fatigue is represented in the somnolence/fatigue/sedation grouping and in the asthenia/fatigue/malaise/weakness grouping. The incidence of the combined terms of sedation and somnolence in Study 305 in the lasmiditan 100 mg, 200 mg, and all-lasmiditan group was 8.1%, 9.8%, and 8.9%, respectively.

The below table lists TEAEs (and groupings of closely related TEAEs using the ODE-1 methodology) reported after first or recurrent doses of lasmiditan with an incidence of at least 2% and at least 2% greater than placebo in studies 301, 302, and 305 combined. The groupings of TEAEs reported in the combined studies are similar to TEAEs reported in studies 301/302 and study 305 separately after the first dose of lasmiditan.

Table 19. TEAEs with an Incidence of At Least 2% for Any Dose of Lasmiditan and At Least 2% Greater than Placebo in Studies 301, 302, and 305, Grouped.[a]

MedDRA AEs (preferred term)	50 mg N=654 n (%)	100 mg N=2228 n (%)	200 mg N=2273 n (%)	All Lasmiditan N=5155 n (%)	Placebo N=1262 n (%)
Dizziness, balance disorder	57 (9)	357 (16)	453 (20)	867 (17)	37 (3)
Somnolence, fatigue, sedation	53 (8)	239 (11)	291 (13)	583 (11)	36 (3)
Confusion, delirium, altered mental status, disorientation	42 (6)	180 (8)	218 (10)	440 (9)	29 (2)
Asthenia, fatigue, malaise, weakness	29 (4)	155 (7)	198 (9)	382 (7)	11 (1)
Paresthesia, hypoesthesia	16 (2)	126 (6)	179 (8)	321 (6)	23 (2)
Nausea, vomiting	22 (3)	97 (4)	116 (5)	235 (5)	28 (2)
Vertigo; vestibular dysfunction	4 (1)	25 (1)	39 (2)	68 (1)	3 (0)

Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 301, 302, TRTEM1FL=Y, and Study ID= 305 TRTEM4FL=Y. The denominator is the total number of TEAEs by dose in studies 301, 302, and 305. The denominator is the safety population in study 301, 302, and 305. [a]The ODE-1 groupings were adjusted for preferred terms that primarily contributed to the groupings.

The following table shows TEAEs occurring in Studies 301 and 302 in either lasmiditan 200 mg with incidence of at least 0.4% and with incidence in placebo of ≤0.1% or lasmiditan 200 mg arm with incidence of 0.3% and with incidence in placebo of 0%.

Table 20. TEAEs by Preferred Term with Incidence of at Least 0.4% and with Incidence in Placebo of **≤0.1%** or Lasmiditan 200 mg Arm with Incidence of 0.3% and with Incidence in Placebo of 0% in Study 301 and 302.

MedDRA AEs (preferred term)	50 mg N=654 n (%)	100 mg N=1265 n (%)	200 mg N=1258 n (%)	All Lasmiditan N=3177 n (%)	Placebo N=1262 n (%)
Insomnia, Sleep Disturbance, Abnormal Dreams[a]	3 (0.5)	6 (0.5)	15 (1.2)	24 (0.8)	0
Visual Disturbance[b]	3 (0.5)	7 (0.6)	14 (1.1)	24 (0.8)	1 (0.1)
Lethargy	4 (0.6)	13 (1)	12 (1)	29 (0.9)	1 (0.1)
Restlessness, Agitation, Hyperkinesia[c]	2 (0.3)	9 (0.7)	12 (1)	23 (0.7)	1 (0.1)
Muscle spasm[d]	1 (0.2)	8 (0.6)	13 (1)	22 (0.7)	0
Tremor	1 (0.2)	8 (0.6)	10 (0.8)	19 (0.6)	1 (0.1)
Feeling abnormal	2 (0.3)	9 (0.7)	9 (0.7)	20 (0.6)	1 (0.1)
Anxiety	3 (0.5)	8 (0.6)	8 (0.6)	19 (0.6)	1 (0.1)
Limb discomfort	3 (0.5)	5 (0.4)	7 (0.6)	15 (0.5)	1 (0.1)
Dysarthria	0	3 (0.2)	6 (0.5)	9 (0.3)	0
Vertigo	2 (0.3)	11 (0.9)	6 (0.5)	19 (0.6)	1 (0.1)
Palpitations	2 (0.3)	4 (0.3)	6 (0.5)	12	1 (0.1)
Restless legs syndrome	0	0	5 (0.4)	5 (0.2)	0
Tachycardia[e]	1 (0.2)	6 (0.5)	4 (0.3)	11 (0.3)	1 (0.1)
Ataxia[f]	1 (0.2)	4 (0.3)	4 (0.3)	9 (0.3)	0

[a]Includes Abnormal Dreams, Nightmare, Insomnia, Hypersomnia, Sleep Disorder, Sleep Terror. [b]Includes includes Vision Blurred, Visual impairment, Visual field defect, Visual Acuity Reduced, Tunnel vision. [c]Includes Restlessness, Feeling Jittery, Agitation. [d]Includes muscle twitching. [e]Includes Heart Rate Increased. [f]Includes Abnormal Coordination. Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 301 and 302, SAFFL=Y, TRTEM1FL=Y. The denominator is the safety population for studies 301 and 302 (IDB ADSL dataset with ASETBFL=Y, TRT01A=Y).

The following table shows incidence of dyspnea and non-cardiac chest pain as these were TEAEs of potential concern.

Table 21. Select TEAEs by Preferred Term in Study 301 and 302.

MedDRA AEs (preferred term)	50 mg N=654 n (%)	100 mg N=1265 n (%)	200 mg N=1258 n (%)	All Lasmiditan N=3177 n (%)	Placebo N=1262 n (%)
Dyspnoea	0	2 (0.2)	2 (0.2)	4 (0.1)	0
Chest pain, non-cardiac[c]	3 (0.5)	0	7 (0.6)	10 (0.3)	4 (0.3)

[a]Includes non-cardiac chest pain, musculoskeletal chest pain, chest discomfort. Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 301 and 302, SAFFL=Y, TRTEM1FL=Y. The denominator is the safety population for studies 301 and 302 (IDB ADSL dataset with ASETBFL=Y, TRT01A=Y).

In Study 202, overall, 67.1%, 72%, and 85.9% of lasmiditan 50 mg, 100 mg, and 200 mg-treated patients, respectively, and 23.5% of placebo-treated patients experienced at least 1 TEAE. The table below shows TEAEs (and groupings of closely related TEAEs using the ODE-1 methodology) after first dose in study 202 with an incidence of at least 2% and at least 2% greater than placebo. I note similar TEAE groupings in study 202 as in studies 301/302 and study 305. Additional TEAEs reported in study 202 with incidence of at least 2% and at least 2% greater than placebo not reported in Phase 3 studies include anxiety, nervousness, panic attacks, restlessness, agitation, hyperkinesia, insomnia, depression, tremor, shakiness, and ataxia.

Table 22. TEAEs after First Dose of Lasmiditan with an Incidence of At Least 2% and At Least 2% Greater than Placebo in Study 202, Grouped.[a]

MedDRA AEs (preferred term)	50 mg N=82 n (%)	100 mg N=82 n (%)	200 mg N=71 n (%)	All Lasmiditan N=235 n (%)	Placebo N=85 n (%)
Dizziness, balance disorder	20 (24)	23 (28)	31 (44)	74 (31)	1 (1)
Somnolence, fatigue, sedation	18 (22)	24 (29)	22 (31)	64 (27)	4 (5)
Asthenia, fatigue, malaise, weakness	19 (23)	28 (34)	21 (30)	68 (29)	2 (2)
Confusion, altered mental status, disorientation	9 (11)	13 (16)	12 (17)	34 (14)	4 (5)
Paresthesia, hypoesthesia	2 (2)	9 (11)	12 (17)	23 (10)	2 (2)
Nausea, vomiting	7 (9)	8 (10)	4 (6)	19 (8)	0
Visual disturbance	1 (1)	2 (2)	4 (6)	7 (3)	0
Abdominal pain, distension, bloating, spasm	0	1 (1)	3 (4)	4 (2)	1 (1)
Hypertension, BP increased	0	0	2 (3)	2 (1)	0

MedDRA AEs (preferred term)	50 mg N=82 n (%)	100 mg N=82 n (%)	200 mg N=71 n (%)	All Lasmiditan N=235 n (%)	Placebo N=85 n (%)
Anxiety, nervousness, panic attacks	0	1 (1)	2 (3)	3 (1)	0
Restlessness, agitation, hyperkinesia, akathisia	1 (1)	0	2 (3)	3 (1)	0
Insomnia, sleep disturbance, abnormal dreams	1 (1)	1 (1)	2 (3)	4 (2)	1 (1)
Gait disturbance, difficulty walking	0	1 (1)	2 (3)	3 (1)	0
Depression	0	2 (2)	0	2 (1)	0
Tremor, shakiness, trembling	3 (4)	3 (4)	0	6 (3)	1 (1)
Ataxia, cerebellar syndrome	1 (1)	2 (2)	0	3 (1)	0
Fever, rigors	2 (2)	1 (1)	0	3 (1)	0
Chest pain (non-cardiac or unknown)	3 (4)	2 (2)	1 (1)	6 (3)	1 (1)
Headache	3 (4)	1 (1)	0	4 (2)	0
Migraine	2 (2)	0	0	2 (1)	0

Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 202, TRTEM1FL=Y. The denominator is the safety population for study 202 (IDB ADSL dataset with study ID= 202, SAFFL=Y, TRT01A=Y).
[a]The ODE-1 groupings were adjusted for preferred terms that primarily contributed to the groupings.

The following table shows the incidence of subjects taking one or two doses of study drug who experienced at least one TEAE in studies 301/302. A lower incidence of subjects experiencing at least one TEAE was seen in subjects who took two doses compared to one dose. This can in part be explained by a selection bias where subjects who experienced one TEAE would be less likely to take an additional dose.

Table 23. Incidence of Subjects who took One or Two Doses Experiencing at Least One TEAE in Studies 301/302.

Number of Doses	50 mg N=654 n (%)	100 mg N=1265 n (%)	200 mg N=1258 n (%)	All-lasmiditan N=3177 n (%)	Placebo N=1262 n (%)
1	93 (14.2)	287 (22.7)	354 (28.1)	734 (23.1)	76 (6.0)
2	74 (11.3)	172 (13.6)	159 (12.6)	405 (12.7)	100 (7.9)

The reviewer created this table using the IBD ADAE dataset, studyID = 301 and 302, SAFFL=Y, TRTEMFL=Y, SAF2FL=N for 1 dose, SAF2FL=Y for 2 doses, grouped by USUBJID and TRT01A.

Mean number of TEAEs reported after one versus two doses

I compared the mean number of TEAEs reported by subject after one dose of lasmiditan with mean number of TEAEs reported after two doses of lasmiditan of the same strength. The table

below shows that subjects in study 301 and 302 who took two doses did not report higher rates of TEAEs compared to subjects who took one dose.

Table 24. Mean Number of TEAEs Reported After One or Two Doses of Study Drug Per Subject in Studies 301 and 302.

Number of Doses	Parameter	50 mg N=654	100 mg N=1265	200 mg N=1258	Placebo N=1262
One dose	# of TEAEs reported	134	499	651	110
	# of subjects	352	716	802	500
	Mean # of TEAEs reported after one dose per subject	0.38	0.70	0.81	0.22
Two doses	# of TEAEs reported	47	90	75	80
	# of subjects	206	380	303	762
	Mean # of TEAEs reported after two doses per subject	0.23	0.24	0.25	0.10

Reviewer created table from ISS IDB dataset ADAE (numerator) where for one dose STUDYID = 301 and 302, SAFFL=Y, TRTEMFL = Y, TRTEM1FL= Y, SAF2FL=N and treatment = TRT01A. The denominator is IDB ADSL dataset, studyID = 301 and 302, SAFFL=Y, SAF2FL=N, treatment = TRT01A. For two doses, STUDYID = 301 and 302, SAFFL=Y, TRTEMFL = Y, TRTEM2FL= Y, and treatment = TRTSEQA. The denominator is IDB ADSL dataset, studyID = 301 and 302, SAFFL=Y, SAF2FL=Y, treatment = TRTSEQA.

TEAEs and SAEs in the pre-administrative hold population

In the pre-administrative hold population there were 64 AEs occurring in the 63 subjects who did not enter into the post-administrative hold period of study 305. There was one SAE which was pneumonia (b) (6) and occurred 35 days after most recent dose of lasmiditan. The subject also had severe nasopharyngitis, pneumonia and bronchitis which occurred 29 days after the most recent dose of lasmiditan. These events are not likely due to lasmiditan.

In terms of severity of the 64 AEs, 57.8% of the AEs were categorized as mild, 35.9% were moderate, and 6.35% were severe. The four severe AEs were nasopharyngitis, pneumonia and bronchitis, and dizziness. The adverse events were consistent with those observed in the entire database. The most common were dizziness, fatigue, somnolence, paresthesias and lethargy. I note the following potentially medically important adverse event.

Tongue swelling (b) (6)

A 51-year-old female with history of seizures developed dizziness, swollen tongue, and muscle twitching that were mild in severity 2 hours after her first dose of lasmiditan 200 mg, and nightmare that was mild in severity 4 hours after her first dose. The tongue swelling lasted for three hours and resolved without

treatment. The muscle twitching and dizziness lasted for 2 hours. Concomitant medications included cyclobenzaprine hydrochloride. The subject discontinued the study due to the AEs. In study 301, she had received placebo.

8.4.6. Laboratory Findings

Method

The sponsor evaluated mean change from baseline and performed analyses of high, low, or abnormal laboratory test results at any time in subjects treated with lasmiditan compared to placebo. The analyses were pooled into the following groups: 301/302; 202/301/302; 202/301/302/305.

The sponsor also performed a separate analysis for hepatic safety that included an evaluation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥3X and ≥5X upper limit of normal (ULN) and alkaline phosphatase (ALK PHOS) greater than 2X times the ULN for studies 202, 301, 302, and 305. The sponsor also searched for SMQs related to hepatic injury and function with the following terms: broad and narrow terms in the liver-related investigations, signs, and symptoms; broad and narrow terms in the cholestasis and jaundice of hepatic origin, broad and narrow terms in the hepatitis, noninfectious, broad and narrow terms in the hepatic failure, fibrosis, cirrhosis, and other liver damage; narrow terms in the liver-related coagulation and bleeding disturbances.

Overall, I found the sponsor's approach to laboratory analyses to be acceptable; however, as previously noted, laboratory findings were only available at screening/baseline and then within seven days after a dose of lasmiditan in studies 301 and 302 and end of study, and in Study 305 at months 1, 3, 6, 9, and end of study, without a relationship to a recent dose. Therefore, I reviewed laboratory analysis from clinical pharmacology studies to further assess the effect of lasmiditan on laboratory findings.

Results for mean change from baseline and abnormal values in studies 202, 301, 302, and 305
The sponsor found a mean increase in serum triglycerides of 1.5 mg/dL in lasmiditan-treated subjects in studies 202/301/302/305. I did not think that this change was clinically meaningful due to the small magnitude of change in the serum triglyceride level. I also examined the sponsor's analysis of mean change from baseline for other laboratory values and did not find any clinically meaningful changes.

There were two statistically significant differences between lasmiditan and placebo-exposed subjects in studies 301 and 302 for abnormal lab values; low hemoglobin and an elevated neutrophil/leukocyte fraction of 1. A greater proportion of subjects had low hemoglobin values in the lasmiditan group compared to placebo (lasmiditan n=89, 3.2%; placebo n=23, 2.0%) and a greater proportion of subjects had a high neutrophil/leukocyte ratio at any time in the placebo compared to lasmiditan exposed group (lasmiditan n=45, 1.5%, placebo n=33, 2.8%). The lowest

post-baseline hemoglobin recorded among lasmiditan-exposed subjects was 10.0 g/dL. Subjects who received lasmiditan and subjects who received placebo had the same incidence of low hematocrit values (2.0%).

The pool of studies 202/301/302 showed similar results to 301/302 except for a statistically significant increase in hyaline casts noted in the urine analysis for placebo-exposed subjects compared to lasmiditan-exposed subjects (n=2, 0.7% and n=0, 0%, respectively).

Hepatic-Related Events

Differences between the maximum post-dose AST, ALT, ALK PHOS, and total bilirubin (TBIL) values compared to baseline values in either lasmiditan and placebo treated subjects for studies 202/301/302 or 305 were not clinically meaningful due to the small magnitude of change seen (data not shown here).

The following tables show that a similar percentage of subjects exposed to lasmiditan and placebo had AST and ALT values ≥3, 5, and 10 times ULN. For studies 202/301/302, there were no cases of bilirubin greater than 2 times ULN. For studies 202/301/302/305, there were an isolated case of bilirubin elevation of greater than 2 times ULN.

Table 25. Shift of AST from Maximum Baseline to Maximum Postbaseline for Safety Population for Studies 202/301/302 and 202/301/302/305.

Category	202/301/302		202/301/302/305
	All Lasmiditan N= 3297 n (%)	Placebo N=1313 n (%)	All Lasmiditan N= 3951 n (%)
AST ≥ 3x ULN	2 (0.1)	2 (0.2)	13 (0.3)
AST ≥ 5x ULN	2 (0.1)	1 (0.1)	6 (0.2)
AST ≥ 10x ULN	1 (0)	1 (0.1)	3 (0.1)

Data in table taken from table submitted by sponsor in ISS appendix: Table ISS. APP.18.43 and 18.48.

Table 26. Shift of ALT from Maximum Baseline to Maximum Postbaseline for Safety Population for Studies 202/301/302 and 202/301/302/305.

Category	202/301/302		202/301/302/305
	All Lasmiditan N= 3299 n (%)	Placebo N=1313 n (%)	All Lasmiditan N= 3952 n (%)
ALT ≥ 3x ULN	10 (0.3)	4 (0.3)	28 (0.7)
ALT ≥ 5x ULN	2 (0.1)	1 (0.1)	7 (0.2)

Category	202/301/302		202/301/302/305
	All Lasmiditan N= 3299 n (%)	Placebo N=1313 n (%)	All Lasmiditan N= 3952 n (%)
ALT ≥ 10x ULN	1 (0)	1 (0.1)	1 (0)

Data in table taken from table submitted by sponsor in ISS appendix: Table ISS. APP.18.44 and 18.49.

I reviewed AST, ALT, and TBIL values from studies 202, 301, 302, and 305 and found no cases that met Hy's Law (elevation of AST or ALT of 3-fold or higher than ULN and total bilirubin greater than 2 times ULN without initial findings of cholestasis).

I performed a search for SMQ terms related to hepatic safety and found no terms with a frequency > 1.1% in the all-lasmiditan treated group for studies 202/301/302/305. For studies 202/301/302 combined, I found no SMQ terms related to hepatic safety with frequency greater than 0.5% above placebo by 50, 100, 200 mg doses or by all doses of lasmiditan combined.

Narratives

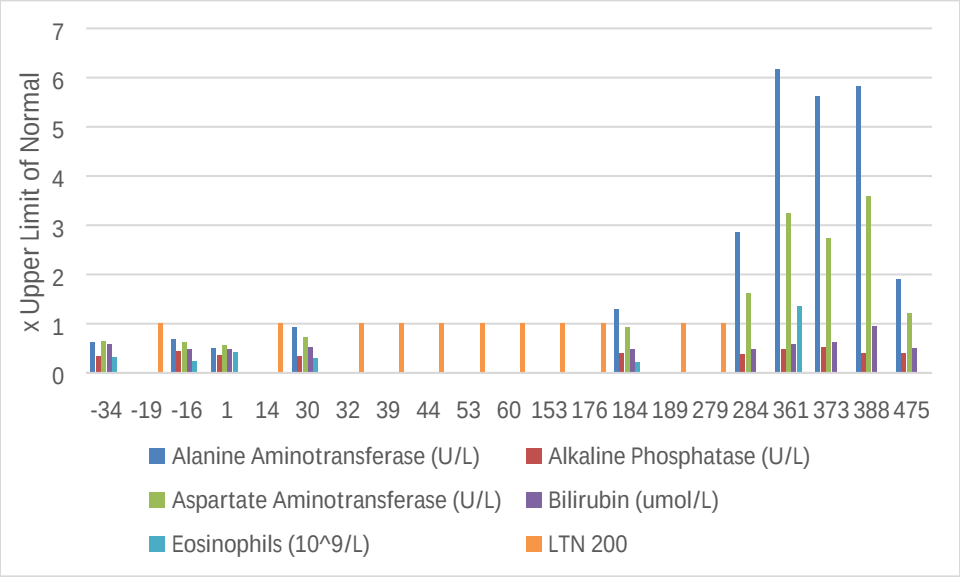
I reviewed the narratives of subjects with hepatic injury or abnormal hepatic enzymes in studies 202, 301, 302, and 305 and found confounding factors in most narratives. The most common confounders included previous history of liver or gallbladder disease, baseline liver enzyme elevation, and concomitant medication use associated with hepatic injury. I summarize a case that had minimal confounding factors of a subject from 305 who developed abnormal hepatic enzymes.

Abnormal Hepatic Laboratory Result (b) (6)

A 46-year-old female with normal AST, ALT, ALK PHOS, and TBIL at baseline took 9 doses of lasmiditan 200 mg in study 305 and developed ALT elevation to 53 U/L (ULN of 41 U/L) at the fourth study visit, two days after the most recent dose of lasmiditan. She also reported the AE of tiredness three weeks prior to the fourth study visit and noted that the AE had lasted for two weeks. Approximately three months later, after taking an additional two doses of lasmiditan, her ALT had further elevated to 117 U/L and her AST to 60 U/L (ULN of 37 U/L). Two months later, her ALT was further elevated to 253 U/L, AST to 120 U/L, and her eosinophil count was elevated to 0.76 x 10^9/L (ULN of 0.56 x 10^9/L). Two weeks later, her ALT had decreased to 239 U/L and her AST remained elevated at 133 U/L. Her bilirubin had increased to 20 umol/L (upper limit of normal 21 umol/L), and her alkaline phosphatase remained normal. Per the 120 Day Safety Update, at her last study visit (three months later) her ALT had decreased to 78 U/L and her AST to 45 U/L and her total bilirubin had returned to normal levels. Concomitant medication usage included oral minoxidil as needed for acne. She had no significant prior medical history and there was no report of symptoms including fever or rash. In response to an information request, the sponsor noted that one year after her last study, her ALT, AST, ALK PHOS, and TBIL were all within normal limits. They also note that she did not have viral hepatitis

serologies performed at the time of the abnormal hepatic laboratory results. She had not traveled prior to the developing the AE and had not used alcohol or recreational drugs. She had not taken any herbal products, dietary supplements, or additional nonprescription medications. The following figure shows liver function tests and eosinophil counts in relation to lasmiditan dosing.

Figure 1. Abnormal Hepatic Enzyme Case.



Reviewer created figure from ISS IDB ADLB dataset.

Reviewer comment: A role for lasmiditan cannot be ruled out for the event of the hepatic laboratory abnormality given the time of onset of AE from dose administration as well as the lack of confounding factors. My review of Livertox.nih.gov notes that serum aminotransferase elevations during minoxidil therapy are uncommon and that oral minoxidil has not been implicated in convincing cases of clinically apparent acute liver injury.[9]

Clinical Laboratory Evaluation in Phase I studies

Subjects in study LAHE were given lasmiditan 200 mg daily or 400 mg daily for 7 days and had laboratory values measured at baseline, study day 2 and study day 6. No clinically meaningful changes to mean values for chemistry or hematology laboratory measurements were seen after dosing with lasmiditan due to the small magnitude of change seen (see Appendix).

Study LAHQ, performed in healthy subjects, had laboratory measurements at -1 day, day 1, and day 2 in relation to lasmiditan 50, 100, and 200 mg dosing. The sponsor analyzed mean changes

in chemistry, hematology, urine analysis and coagulation parameters. I did not find any clinically significant differences between baseline values and post-dose values. Study LAHP was a study performed in healthy volunteers given lasmiditan 100 mg and 400 mg doses. Chemistry, hematology, and urine analysis were measured at -2 day and day 2 after dosing. I did not find any clinically significant differences in mean pre- and post-dose laboratory values.

The sponsor identified two subjects who experienced three TEAEs related to laboratory evaluations in the clinical pharmacology studies. One subject experienced increase in blood creatinine and blood urea after lasmiditan 200 mg and another subject experienced hypocalcemia after lasmiditan 200 mg.

An additional subject was noted to have the TEAE of increased ALT and is summarized in the Hepatically Impaired and Renally Impaired section of this review.

8.4.7. Vital Signs

Lasmiditan appears to be associated with small increases in systolic and diastolic blood pressure and decreases in heart rate when compared to placebo.

Vital sign mean changes from baseline, outlier analysis, and orthostatic changes.
The mean difference from baseline between lasmiditan and placebo groups was not meaningfully different for either blood pressure or pulse rate values for pools 301/302 and 202/301/302. However, because vital signs measurements were not obtained at the time of lasmiditan dosing in studies 202, 301, 302, and 305, but within 7 days after a dose, the results of these studies do not meaningfully contribute to the evaluation of vital sign changes. Evaluation of the effect of lasmiditan on vital signs relies on results of the clinical pharmacology studies.

Healthy non-elderly subjects
In the 28/05/2019 response to an information requested dated 22/05/2019, the sponsor provided the vital signs for Day 1, 200 and 400 mg lasmiditan and placebo from Study LAHE in which vital signs were collected hourly. Those results for supine systolic and diastolic blood pressure and for pulse rate are shown in the table below for predose, and for the time of maximal change. SBP and DBP increased, with a maximum mean increase of 7.1 mmHg for SBP at 1 hour and a maximum mean increase of 4.3 mmHg for DBP at 1 hour for lasmiditan 200 mg. Blood pressure returned to baseline between 3 to 6 hours after dosing. Pulse rate decreased, with a maximum mean decrease of 10.1 beats per minute at 3 hours for lasmiditan 200 mg. Subjects who received placebo had a mean decrease in pulse rate of 6.0 bpm at the same timepoint. In my opinion, the changes seen in pulse rate were not clinically significantly different between lasmiditan 200 mg and placebo due to the small magnitude of difference between lasmiditan and placebo groups. By 6 hours, the maximum decrease in pulse rate was

2.2 beats per minute and by 12 hours, the maximum decrease in pulse rate was 1.2 beats per minute for lasmiditan 200 mg.

Table 27. Vital Signs Change from Baseline in Study LAHE.

Time[a]	Parameter	Placebo N=26-27	200 mg N=28	400 mg N=15
Systolic Blood pressure (mmHg)				
Predose	Mean	110.3	111.9	112.0
	Median	111.7	110.8	113.3
	Minimum	97	95	91
	Maximum	125	146	131
1 hour	Mean	1.1	7.1	3.7
	Median	1.0	6.3	4.4
	Minimum	-8	-5	-23
	Maximum	14	23	22
Diastolic Blood Pressure (mmHg)				
Predose	Mean	69.3	68.6	66.9
	Median	69.3	67.3	65.7
	Minimum	59	57	50
	Maximum	84	81	86
1 hour	Mean	-0.2	4.3	1.9
	Median	1.0	4.7	3.3
	Minimum	-8	-9	-21
	Maximum	8	17	20
Pulse (beats per minute)				
Predose	Mean	64.4	66.4	62.2
	Median	65.0	67.2	57.0
	Minimum	45	52	48
	Maximum	83	101	91
3 hour	Mean	-6.0	-10.1	-10.9
	Median	-5.4	-8.2	-6.6
	Minimum	-18	-35	-37
	Maximum	3	-1	2

Data is taken from the 28/05/2019 response to an information requested dated 22/05/2019. Vitals reported were taken in the supine position on Day 1 of study. [a]Predose timepoints reflect actual SBP, DBP, and pulse rate measurements. Other timepoints reflect the change from predose values.

Similar findings for the increase in SBP and DBP and decrease in pulse rate, with a similar time course, were observed in studies LAHU and LAIF (data not shown). Study LAHU was a 24-hour ambulatory blood pressure monitoring study and also showed similar increases in blood

pressure and heart rate in subjects treated with lasmiditan 200 mg compared to placebo at similar timepoints.

Outlier analysis as requested by the Agency showed a higher percentage of subjects treated with lasmiditan with pulse rate less than 60 beats per minute compared to placebo across all studies in healthy non-elderly subjects. Representative results from study LAHE are shown in the table below.

Table 28. Vital Signs Outlier Analysis in Study LAHE for Days 1 and 2.

Vital Sign	Category	Placebo N=25-27 n (%)	Lasmiditan 200 mg N=28 n (%)	Lasmiditan 400 mg N=14-15 n (%)
Day 1				
SBP	< 90 mmHg	0	1 (3.6)	1 (6.7)
	>140 mmHg	0	2 (7.1)	0
	>160 mmHg	0	0	0
DBP	<50 mmHg	1 (3.7)	1 (3.6)	1 (6.7)
	>90 mmHg	0	0	0
	>100 mmHg	0	0	0
Pulse Rate	<60 bpm	18 (66.7)	22 (78.6)	14 (93.3)
	>100 bpm	0	0	0
Day 2				
SBP	< 90 mmHg	0	0	0
	>140 mmHg	0	0	0
	>160 mmHg	0	0	0
DBP	<50 mmHg	1 (4.0)	0	0
	>90 mmHg	0	0	0
	>100 mmHg	0	0	0
Pulse Rate	<60 bpm	11 (44.0)	13 (46.4)	9 (64.3)
	>100 bpm	0	0	0

Data is taken from the 28/05/2019 response to an information requested dated 22/05/2019. Vitals were taken in the supine position.

Reviewer comment: The high percentage of subjects in placebo and lasmiditan arms with heart rate less than 60 beats per minutes in study LAHE is likely due in part to baseline bradycardia as the baseline incidence of bradycardia in these healthy subjects was 39%.

Orthostatic changes

Orthostatic blood pressure and pulse rate measurements were evaluated in non-elderly healthy subjects in studies 113, 114, LAHA, LAHD, LAHE, LAHI, and LAHT. I reviewed the method for

measuring orthostatic vital signs (measured after subjects had been laying down for five minutes and then again after they had been standing for two minutes[10]) and the method appears to be adequate. I considered subjects to be orthostatic if there was a decrease in SBP of > 20 mmHg, decrease in DBP of > 10 mmHg, or an increase in pulse of > 20 bpm between lying and standing values measured at the same timepoint.

The two trials that measured mean orthostatic changes in placebo and lasmiditan treated subjects (LAHT and LAHE) did not show evidence of orthostasis in lasmiditan-treated subjects. Mean change in orthostatic vital signs at various timepoints in Study LAHE are shown in the table below.

Table 29. Mean Change in Orthostatic Vital Signs in Study LAHE.

Timepoint (hours)	Placebo N=14-27	Lasmiditan 200 mg N=28	Lasmiditan 400 mg N=14-15
Systolic Blood Pressure (mmHg)			
Baseline	11.8	13.3	8.5
0.5	9.5	9.4	8.7
1	7.7	11.6	8.5
2	9.1	8.1	7.5
Diastolic Blood Pressure (mmHg)			
Baseline	11.7	13.4	12.2
0.5	10.1	11.3	5.9
1	10.4	10.1	10.6
2	10.6	9.1	6.8
Pulse Rate (beats per minute)			
Baseline	13.9	13.9	11.5
0.5	14.3	14.8	17.5
1	18.2	10.6	9.5
2	18.4	11.7	10.7

Data is taken from the 28/05/2019 response to an information requested dated 22/05/2019. Vital signs are reported for Day 1. Results show mean increases in systolic and diastolic blood pressure and pulse rate.

In studies lacking a placebo arm (LAHN, LAHF, LAHI, LAHC, LAHD), no evidence of orthostasis was noted in lasmiditan-treated subjects at timepoints 1, 2, 4, 8, and 24 hours.

The sponsor submitted an outlier analysis of vital sign changes consistent with orthostasis in studies that measured orthostatic vital signs. In the placebo-controlled studies, the incidence of

subjects with orthostatic vital signs was in similar to placebo-treated subjects. Outlier analysis of vital signs consistent with orthostasis from Study LAHE are shown in the table below. Overall, there was a higher percentage of subjects in the lasmiditan 400 mg arm who were orthostatic by pulse at 0.5 hours compared to placebo (33.3% versus 25.9%, respectively). Given the small number of subjects enrolled within that treatment arm (n=15), the significance of this finding unknown.

Table 30. Outlier Analysis of Orthostatic Vital Sign Changes in Study LAHE.

Parameter	Timepoint (hours)	Placebo N=27 n (%)	Lasmiditan 200 mg N=28 n (%)	Lasmiditan 400 mg N=15 n (%)
Decrease in SBP > 20 mm Hg	Baseline	0	0	0
	0.5	0	0	0
	1	0	0	0
	2	0	0	0
Decrease in DBP > 10 mm Hg	Baseline	0	0	0
	0.5	1 (3.7)	0	1 (6.7)
	1	0	0	0
	2	1 (3.7)	0	0
Increase in pulse rate > 20 bpm	Baseline	5 (18.5)	7 (25.0)	3 (20.0)
	0.5	7 (25.9)	7 (25.0)	5 (33.3)
	1	9 (33.3)	3 (10.7)	0
	2	11 (40.7)	4 (14.3)	2 (13.3)

Data is taken from the 28/05/2019 response to an information requested dated 22/05/2019. Vital Signs are reported for Day 1.

Healthy elderly subjects

In the 28/05/2019 response to an information requested dated 22/05/2019, the sponsor provided the vital signs for placebo and lasmiditan-200 mg dose arms from study LAHA in which vital signs were collected hourly in elderly (at least 65-year-old) and non-elderly (45-year-old or less) healthy subjects following single 200 mg doses of lasmiditan vs placebo. The results for supine systolic and diastolic blood pressure and for pulse rate are shown in the table below predose and for the time of the maximum change. Overall, SBP increases were higher in elderly subjects compared to non-elderly subjects. Mean pulse rate decreased less in elderly compared to non-elderly subjects. Overall, differences in vital signs from baseline had returned to baseline for elderly lasmiditan 200 mg group by 4 hours.

Table 31. Vital Signs Change from Baseline in Study LAHA.

Time[a]	Parameter	Elderly Placebo N=18	Non-Elderly Lasmiditan 200 mg N=17	Elderly Lasmiditan 200 mg N=18
Systolic Blood pressure (mmHg)				
Predose	Mean	125.3	108.7	123.0
	Median	124.3	106.3	122.5
	Minimum	103	96	100
	Maximum	153	123	146
1 hour	Mean	-0.9	4.3	11.5
	Median	0.5	5.4	10.5
	Minimum	-17	-16	-4
	Maximum	11	13	30
1.5 hour	Mean	2.4	1.8	14.5
	Median	2.5	2.7	15.2
	Minimum	-19	-22	-5
	Maximum	21	14	42
Diastolic Blood Pressure (mmHg)				
Predose	Mean	73.1	63.2	71.3
	Median	72.3	64.0	71.8
	Minimum	59	53	54
	Maximum	90	72	85
1 hour	Mean	-1.7	5.4	3.8
	Median	-1.4	4.7	4.2
	Minimum	-8	-6	-6
	Maximum	5	15	12
Pulse (beats per minute)				
Predose	Mean	63.4	60.7	60.2
	Median	61.3	57.7	59.0
	Minimum	50	46	49
	Maximum	81	82	76
1.5 hour	Mean	-5.0	-8.0	-5.7
	Median	-3.8	-7.0	-5.7
	Minimum	-29	-27	-15
	Maximum	6	8	1

Data is taken from the 28/05/2019 response to an information requested dated 22/05/2019. Vitals were taken in the supine position. [a]Predose timepoints reflect actual SBP, DBP, and pulse rate measurements. Other timepoints reflect the change from predose values.

Similar findings of an increase in SBP and a decrease in pulse rate, with a similar time course, were observed in Study LAIG with ambulatory blood pressure monitoring in elderly healthy subjects (data not shown). In study LAIG, the maximum LS means increase from baseline for lasmiditan 200 mg for SBP occurred at 1 hour with an increase of 7.3 mmHg as compared to placebo of an increase of 3.5 mmHg at the same timepoint. The maximum LS means difference from baseline for lasmiditan 200 mg for pulse rate was a decrease of 6.4 beats per minute occurring at 2 hours compared to placebo with a decrease of 0.9 beats per minute at the same timepoint. A maximum LS means increase from baseline for lasmiditan 200 mg for DBP was an increase of 2.8 mmHg at 1 hour compared to an increase of 3.0 mmHg with placebo at the same timepoint.

Outlier analysis as requested by the Agency in study LAHA showed that a higher incidence of elderly subjects had systolic blood pressure > 140 mmHg and > 160 mmHg as compared to non-elderly subjects. Rates were similar between elderly and non-elderly for diastolic blood pressure and pulse rate. The following table shows systolic blood pressure outlier analysis in study LAHA.

Table 32. Systolic Blood Pressure Outlier Analysis in Elderly and Non-elderly in Study LAHA.

SBP Category	Non-elderly N=17 n (%)	Elderly N=18 n (%)
< 90 mmHg	0	0
>140 mmHg	0	10 (55.6)
>160 mmHg	0	2 (11.1)

Data is taken from the 28/05/2019 response to an information requested dated 22/05/2019. Vitals were taken in the supine position.

Mean change in orthostatic vital signs in healthy elderly subjects treated with lasmiditan in study LAHA did not indicate orthostasis. An analysis of outliers with orthostatic vital sign changes in study LAHA showed that lasmiditan-treated elderly subjects had higher incidence of orthostasis compared to placebo at 0.5, 2 and 24 hours after dosing. The following table shows orthostatic vital sign outliers in lasmiditan arm with incidence greater than placebo arm for study LAHA. The significance of this finding is unknown given the small number of subjects in each of the treatment arms (n=18).

Table 33. Orthostatic Vital Sign Outlier Analysis in Lasmiditan-treated Subjects LAHA with Incidence Greater Than Placebo in Study LAHA.

Vital Sign Parameter	Time Point (hours)	Elderly Placebo N=18 n (%)	Elderly Lasmiditan 200 mg N=18 n (%)
Orthostatic SBP Decrease > 20 mmHg	0.5	0	1 (5.6%)
Orthostatic DBP Decrease > 10 mmHg	2	0	3 (16.7)
Orthostatic pulse rate > 10 bpm	0.5	0	1 (5.6)
	24	1 (5.6)	3 (16.7)

Data is taken from the 28/05/2019 response to an information requested dated 22/05/2019.

Pulse Rate in Thorough QT Study

I reviewed the Interdisciplinary Review team consult of the thorough QT study. The study showed similar decreases in heart rate in subjects given lasmiditan 100 mg and 400 mg compared to placebo. The mean maximum difference in heart rate between lasmiditan 400 mg and placebo occurred 6 hours after dosing and resulted in a decrease in heart rate of 6.6 beats per minute. Lasmiditan 100 mg resulted in a similar decrease in heart rate of 4.5 bpm compared to placebo at the same timepoint. By 24 hours, the difference between lasmiditan and placebo had resolved.

Temperature, body weight, and respiratory rate

Evaluations of temperature, body weight, and respiratory rate, when they were collected in Phase 1 studies, do not contribute meaningfully to the assessment of safety.

In conclusion, I note that healthy, non-elderly subjects had mean increases in systolic and diastolic blood pressure and mean decreases in pulse rate within one hour of lasmiditan dosing that resolved within 12 hours of dosing. Outlier analysis of vital signs showed that a higher incidence of subjects who received lasmiditan 200 mg had pulse rates less than 60 bpm compared to subjects who received placebo (79 % versus 67%, respectively). There was no evidence of orthostasis in non-elderly subjects by mean change in orthostatic vital signs. An outlier analysis of orthostatic vital signs showed a higher incidence of subjects with orthostatic vital signs in the lasmiditan 400 mg arm compared to placebo arm at 0.5 hours; however, the significance of this finding is unknown given the low number of subjects in the 400 mg treatment arm.

In healthy, elderly subjects, an analysis of mean change in vital signs showed higher mean maximum increases in SBP and lower mean maximum decreases in pulse rate within 2 hours of

dosing compared to healthy, non-elderly subjects. An outlier analysis of orthostatic vital sign changes in study LAHA showed that healthy, elderly subjects had a higher incidence of orthostatic vital signs within 2 hours of dosing and at 24 hours after dosing compared to healthy, non-elderly subjects; however, the significance of these findings is unknown given the low number of subjects in each treatment arm (n=18).

8.4.8. Electrocardiograms (ECGs)

Because ECGs were not obtained at the time of lasmiditan administration in studies 202, 301, 302, or 305, ECG results from those studies do not contribute meaningfully to characterizing the safety of lasmiditan. I also reviewed ECG parameters measured in the thorough QT study which compared lasmiditan 100 mg and lasmiditan 400 mg to placebo. The mean change from baseline and difference in LS means between placebo and lasmiditan 100 mg or lasmiditan 400 mg groups for PR and QRS intervals were presented in Tables 16-19 of the QT- IRT consult dated August 21, 2012. The largest upper limit for the 90% CI for mean differences for the PR interval were 2.0 msec and 5.2 msec for the 100 mg and 400 mg doses of lasmiditan, respectively. The largest upper limit of the 90% CI for the mean differences for the QRS interval were 0.7 msec and 1.1 msec for lasmiditan 100 mg and lasmiditan 400 mg, respectively. I conclude that lasmiditan did not have a meaningful effect on mean PR or QRS intervals.

AEs related to ECG changes occurring in Phase 1 through 3 studies are summarized in the Cardiovascular Safety Section of this review.

8.4.9. QT

The sponsor conducted a thorough QT study (Study LAHP) that evaluated the effects of a single dose of lasmiditan 100 mg, lasmiditan 400 mg, moxifloxacin 400 mg or placebo on the QT interval in 51 non-elderly volunteers in a 4-way crossover study.

I reviewed the interdisciplinary review team's (IRT) consult dated August 21, 2012 and their conclusion was "no significant QTc prolongation effect of lasmiditan (100 mg and 400 mg) was detected in this TQT study." At the time of the review, the consult noted that that it was not known whether the concentrations covered in the study represented the expected highest clinical exposure scenario given that other factors such as food effect, renal/hepatic impairment or drug-drug interactions had yet to be reported. A subsequent review by clinical pharmacology has suggested that these factors do not contribute to meaningfully increases in plasma levels.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Cardiovascular Safety

Current migraine therapies include triptans which act on $5HT_{1B/1D}$ receptors of intracranial vessels and presumably induce vasoconstriction. Ischemic events have been associated with triptans and because of this, triptans carry a class warning contraindicating their use in patients with cardiovascular disease. Lasmiditan is an agonist of $5HT_{1F}$ receptors and the proposed label by the sponsor does not include the class warning for ischemia noted with triptan labeling; therefore, the cardiovascular safety profile of lasmiditan was evaluated. The sponsor provided a review of adverse events with potential cardiovascular etiology and did not find increased cardiovascular risk. In this section I consider cardiovascular risk from the combined available findings.

Baseline demographics of the population enrolled with cardiovascular disease is reviewed in the section on relevant characteristics of the safety population. Of note, a low number of subjects with ischemic heart disease enrolled in studies 301 and 302 potentially limit the interpretability of safety in patients with ischemic heart disease.

The sponsor searched for AEs with potential cardiovascular etiology. An AE with potential cardiovascular etiology was an AEs occurring after first dose of lasmiditan and having the preferred terms of abdominal pain, abdominal pain upper, and abdominal pain lower or belonging to the following SMQs:

- Cardiac arrhythmias
- Cardiac failure
- Cardiomyopathy
- Central nervous system vascular disorders
- Embolic and thrombotic events
- Hypertension
- Ischaemic heart disease
- Pulmonary hypertension
- Torsade de pontes/QT prolongation

In studies 202/301/302, there were 2 SAEs with potential cardiovascular etiology however only one of the SAEs occurred after administration of study drug (301-137-0001, worsening hypertension). In the open-label extension study, the incidence of SAEs with potential cardiovascular etiology was 0.7% (7/991) in the lasmiditan 100 group compared to 0.6% (6/1039) in the lasmiditan 200 mg group. No SAEs of potential cardiovascular etiology led to discontinuation.

The following table lists subjects with SAEs with potential cardiovascular etiology in studies 202, 301, 302, and 305 at the time of the 120 Day Safety Update.

Table 34. Subject Listing of SAEs with Potential Cardiovascular Etiology After Study Drug Dosing Occurring in Studies 202, 301, 302, and 305 after 120 Day Safety Update.

Study ID	Subject ID	Preferred Term	Treatment
Study 301	(b) (6)	Worsening of HTN	200 mg
Study 305		Hypertension	100 mg
		Atrial fibrillation	200 mg
		Transient ischaemic attack	100 mg
		Hypertension	100 mg
		Subdural Hematoma	200 mg
		Stress cardiomyopathy	100 mg
		Pulmonary embolism	200 mg
		Altered mental status	L100 mg
		Bradycardia, sinus node dysfunction	200 mg
		Atrial flutter	100 mg
		Ischaemic stroke	200 mg
		Hypertension	100 mg

The reviewer created this table using the IDB ADAE dataset where studyID = 202, 301, 302, or 305, AESER=Y.

The narratives of subjects with SAEs of potential cardiovascular etiology are summarized in the SAEs section of this review. In the summary of narratives of SAEs of potential cardiovascular etiology, I include one SAE of hypotensive reaction and one SAE of presyncopal episode as I considered them to have potential cardiovascular etiology. In most cases I considered these events not likely related because of the delay between lasmiditan and the event and in some cases likely related to a pre-existing condition or confounded by other medications.

In studies 202/301/302, there was only one subject that discontinued due to an AE (dizziness and fatigue). In study 305, at the time of the 120 Day Safety Update, 5 subjects (0.5%) in the 100 mg group and 11 subjects (1.1%) in the 200 mg group discontinued due to an AE with potential cardiovascular etiology. The rate of discontinuation due to an AE with potential cardiovascular etiology for both arms combined was 0.8% (16/2030).

The following tables show the incidence of subjects experiencing at least one AE with potential cardiovascular etiology. A higher incidence of subjects reporting AEs with potential cardiovascular etiology was observed with increasing doses of lasmiditan in studies 202/301/302 and 305.

Table 35. Incidence of Subjects Experiencing at Least One AE with Potential Cardiovascular Etiology in Studies 202/301/302.

50 mg N=736 n (%)	100 mg N=1347 n (%)	200 mg N=1329 n (%)	All-lasmiditan N=3412 n (%)	Placebo N=1347 n (%)
16 (2.2)	36 (2.7)	37 (2.8)	89 (2.6)	12 (0.9)

The reviewer created this table using the IBD ADAE dataset, studyID = 202, 301 and 302, SAFFL=Y, AEFDOSFL=Y, PCARDFL=Y, grouped by USUBJID and TRT01A.

Table 36. Incidence of Subjects Experiencing at Least One AE of Potential Cardiovascular Etiology by Dose in Study 305 After the 120 Day Safety Update.

L100 mg N=991 n (%)	L200 mg N=1039 n (%)	All LTN N=2030 n (%)
69 (7.0)	96 (9.2)	165 (8.1)

The reviewer created this table using the IDB ADAE dataset 120 Day Safety Update, study 305, HLSAFFL=Y, PCARDFL=Y, AEFLTN=Y, grouped by USUBJID and TROL01.

The following tables show incidence of AEs grouped by the categories of arrhythmia, ECG changes, and blood pressure changes for studies 202/301/302 and 305. A higher incidence was seen in subjects who received lasmiditan compared to subjects who received placebo although the difference was no greater than 0.4%.

Table 37. Incidence of Subjects Experiencing AEs Related to Arrhythmia, ECG Changes, or Blood Pressure Changes in Studies 202/301/302.

Preferred Term, grouped	50 mg N=736 n (%)	100 mg N=1347 n (%)	200 mg N=1329 n (%)	All-LTN N=3412 n (%)	Placebo N=1347 n (%)
Arrhythmias					
Bradycardia	0	1 (0.1)	0	1 (0)	1 (0.1)
Extrasystoles	1 (0.1)	0	0	1 (0)	0
Sinus bradycardia	0	0	2 (0.2)	2 (0.1)	1 (0.1)
Sinus tachycardia	0	0	0	0	1 (0.1)
Tachycardia	1 (0.1)	3 (0.2)	4 (0.3)	8 (0.2)	0
Ventricular extrasystoles	1 (0.1)	0	0	1 (0)	0
Total	3 (0.4)	4 (0.3)	6 (0.5)	13 (0.4)	3 (0.2)
ECG changes					
Electrocardiogram abnormal	0	2 (0.1)	0	2 (0.1)	0
Electrocardiogram QT prolonged	0	2 (0.1)	1 (0.1)	3 (0.1)	0
Electrocardiogram ST segment depression	0	1 (0.1)	0	1 (0)	0

Total	0	5 (0.4)	1 (0.1)	6 (0.2)	0
Blood pressure changes					
Blood pressure diastolic increased	1 (0.1)	0	0	1 (0)	0
Blood pressure increased	1 (0.1)	1 (0.1)	2 (0.2)	4 (0.1)	0
Hypertension	0	3 (0.2)	2 (0.2)	5 (0.1)	2 (0.1)
Total	2 (0.3)	4 (0.3)	4 (0.3)	10 (0.3)	2 (0.1)

The reviewer created this table using the IBD ADAE dataset, studyID = 202, 301 and 302, SAFFL=Y, AEFDOSFL=Y, PCARDFL=Y, grouped by USUBJID, AEDECOD and TRT01A.

Table 38. Incidence of Subjects Experiencing AEs Related to Arrhythmia, ECG Changes, or Blood Pressure Changes in Study 305 after the 120 Day Safety Update.

Preferred Term, grouped	L100 mg N=991 n (%)	L200 mg N=1039 n (%)	All LTN N=2030 n (%)
Arrhythmias			
Atrial fibrillation	1 (0.1)	1 (0.1)	2 (0.1)
Atrial flutter	1 (0.1)	0	1 (0)
Bradycardia	1 (0.1)	1 (0.1)	2 (0.1)
Heart rate irregular	1 (0.1)	1 (0.1)	2 (0.1)
Sinus bradycardia	1 (0.1)	0	1 (0)
Sinus node dysfunction	0	1 (0.1)	1 (0)
Supraventricular tachycardia	0	1 (0.1)	1 (0)
Ventricular extrasystoles	1 (0.1)	1 (0.1)	2 (0.1)
Total	6 (0.6)	6 (0.6)	12 (0.6)
ECG changes			
Bundle branch block left	1 (0.1)	1 (0.1)	2 (0.1)
Bundle branch block right	0	1 (0.1)	1 (0)
Electrocardiogram abnormal	0	2 (0.2)	2 (0.1)
Electrocardiogram QT prolonged	2 (0.2)	3 (0.3)	5 (0.2)
Electrocardiogram T wave abnormal	2 (0.2)	2 (0.2)	4 (0.2)
Electrocardiogram T wave inversion	0	1 (0.1)	1 (0)
Total	5 (0.5)	10 (1.0)	15 (0.7)
Blood pressure changes			
Essential hypertension	0	2 (0.2)	2 (0.1)
Hypertension	17 (1.7)	20 (1.9)	37 (1.8)
Hypertensive crisis	0	1 (0.1)	1 (0)
Blood pressure diastolic increased	1 (0.1)	3 (0.3)	4 (0.2)
Blood pressure increased	6 (0.6)	8 (0.8)	14 (0.7)
Total	24 (2.4)	34 (3.3)	58 (2.9)

The reviewer created this table using the IDB ADAE dataset 120 Day Safety Update, study 305, HLSAFFL=Y, PCARDFL=Y, AEFLTN=Y, grouped by USUBJID, AEDECOD, and TROL01.

The following tables shows the incidence of subjects experiencing at least 1 TEAE with potential cardiovascular etiology in studies 301/302, 202/301/302, and 305. A higher incidence of subjects reporting TEAEs with potential cardiovascular etiology was observed with increasing doses of lasmiditan in studies 301/302, 202/301/302, and 305.

Table 39. Incidence of Subjects Experiencing at Least One TEAE with Potential Cardiovascular Etiology in Studies 301/302.

50 mg N=654 n (%)	100 mg N=1265 n (%)	200 mg N=1258 n (%)	All-lasmiditan N=3177 n (%)	Placebo N=1262 n (%)
7 (1.1)	25 (2.0)	26 (2.1)	58 (1.8)	6 (0.5)

The reviewer created this table using the IBD ADAE dataset, studyID = 301 and 302, SAFFL=Y, TRTEMFL=Y, PCARDFL=Y, grouped by USUBJID and TRT01A.

Table 40. Incidence of Subjects Experiencing at Least One TEAE with Potential Cardiovascular Etiology in Studies 202/301/302.

50 mg N=736 n (%)	100 mg N=1347 n (%)	200 mg N=1329 n (%)	All- Lasmiditan N=3412 n (%)	Placebo N=1347 n (%)
11 (1.5)	28 (2.1)	34 (2.6)	73 (2.1)	8 (0.6)

The reviewer created this table using the IBD ADAE dataset, studyID = 202, 301, and 302, SAFFL=Y, TRTEMFL=Y, PCARDFL=Y, grouped by USUBJID and TRT01A. The above table does not include the 400 mg treatment arm of study 202.

Table 41. Incidence of Subjects Experiencing at Least One TEAE of Potential Cardiovascular Etiology by Dose in Study 305 After the 120 Day Safety Update.

L100 mg N=991 n (%)	L200 mg N=1039 n (%)	All N=2030 n (%)
18 (1.8)	26 (2.5)	44 (2.2)

The reviewer created this table using the IDB ADAE dataset 120 Day Safety Update, study 305, HLSAFFL=Y, PCARDFL=Y, TRTEM3FL=Y, grouped by USUBJID and TROL01.

The most commonly reported cardiovascular TEAEs that occurred more frequently in lasmiditan than in placebo in studies 202/301/302 were palpitations and tachycardia/heart rate increased. The following table shows the incidence of subjects experiencing at least one of those TEAEs in

studies 202/301/302 and 305.

Table 42. Incidence of Subjects Experiencing the TEAEs of Palpitations and Heart Rate Increased/Tachycardia for Studies 202/301/302 and 305 after 120 Day Safety Update.

MedDRA TEAEs (preferred term)	Studies 202/301/302		Study 305
	All-Lasmiditan N=3412 n (%)	Placebo N=1347 n (%)	All-Lasmiditan N=2030 n (%)
Palpitations	15 (0.4)	2 (0.1)	8 (0.4)
Heart rate Increased/Tachycardia	12 (0.4)	1 (0.1)	5 (0.2)

The reviewer created this table using the 120-Day Safety Update IDB ADAE dataset. For study 305: studyID=305, HLSAFFL=Y, AEFLTNFL=Y, TRTEM3FL=Y grouped on USUBJID. For studies 202/301/302 studyID=202, 301, and 302, SAFFL=Y, AEFDOSFL=Y, TRTEMFL=Y grouped on USUBJID and TRT01A.Data does not include 400 mg arm in Study 202.

I compared the incidence of subjects with at least one TEAE with potential cardiovascular etiology by treatment arm and by number of cardiovascular risk factors and note a higher incidence in subjects with 1 or ≥ 2 cardiovascular risk factors compared to no risk factors in lasmiditan-treated subjects.

Table 43. Incidence of TEAEs with Potential Cardiovascular Etiology by Dose by Cardiovascular Disease Risk Factor for Studies 202/301/302.

Number of CVD risk factors	50 mg N=736 n (%)	100 mg N=1347 n (%)	200 mg N=1329 n (%)	Placebo N=1347 n (%)
0 (n= 1,119)	1 (0.1)	6 (0.4)	9 (0.7)	3 (0.2)
1 (n= 1,837)	8 (1.1)	14 (1.0)	15 (1.1)	2 (0.1)
≥2 (n= 1,873)	2 (0.3)	8 (0.6)	10 (0.8)	3 (0.2)

The reviewer created this table using the 120 day safety IDB ADAE dataset, SAFFL=Y, AEFDOSEFL=Y, TRTEMFL=Y, PCARDFL=Y, grouped on USUBJID and TRT01A and CVDFACT.

The sponsor also performed an analysis of change in dose or addition of a cardiovascular medication with drugs in the following classes of cardiac therapy: antihypertensives; diuretics; peripheral vasodilators; vasoprotectives; beta-blocking agents; calcium channel blockers; agents acting on the renin-angiotensin system; lipid-modifying agents; antithrombotics.

Given the design of studies 202, 301, and 302, very few subjects had changes in their

medications. In study 305, I note that 6.0% of subjects had either addition of a cardiovascular medication or change to a cardiovascular medication during the study and rates were similar between 100 and 200 mg doses.

A review of vital signs in the Phase 2 and 3 studies is located in the Vital Signs section of this review.

I summarize select narratives of subjects related to cardiovascular safety from Phase 2/3 studies.

Palpitations

Palpitations (b) (6)

A 26-year-old female experienced the AEs of mild palpitations and dizziness which occurred 4 hours after taking lasmiditan 100 mg and lasted for 50 minutes. Concomitant medications included domperidone, naratriptan, and sumatriptan. At her screening visit, her blood pressure was 110/70 mmHg and pulse rate was 53 bpm and her ECG was normal with QTC_B interval of 384 msec. At her follow up visit, her blood pressure was 90/70 mmHg and her pulse rate was 68 bpm and her ECG showed a QTC_B interval increase to 396 msec.

Reviewer comment: A role for lasmiditan in the event of palpitations cannot be ruled out given proximity of the event to lasmiditan administration.

ECG-related changes of interest

Change in baseline ECG (b) (6)

A 56-year-old female with no contributory medical history took two doses of lasmiditan 100 mg in study 301 and developed a prolonged QRS duration of 154 msec that was noted at her completion visit. Her screening visit ECG showed sinus arrhythmia with pulse of 52 bpm and QRS duration of 106 msec and her blood pressure at the visit was 124/78 mmHg and pulse rate of 66 bpm. At her completion visit, her ECG showed right bundle branch block with a left axis deviation, and QRS duration of 154 msec. Her blood pressure was 117/78 mmHg and pulse rate of 78 bpm at the completion visit. Her most recent dose of lasmiditan had occurred 15 days prior to the event. Concomitant medications included acetylsalicylic acid, conjugated estrogen, ibuprofen, and loratadine.

Reviewer comment: A role for lasmiditan cannot be ruled out in the event. Evaluation of causal association is complicated by the fact that ECGs were intermittently recorded and therefore do not allow for determination of when the event occurred in relation to lasmiditan dosing.

ECG QT Prolonged (b) (6)

A 57-year-old female with history of hypothyroidism, hyperlipidemia, reflux disease, depression and myocardial infarction was noted to develop ECG QT prolongation at her completion visit

after taking one dose of lasmiditan 100 mg eight days before. Concomitant medications given prior to the event were atorvastatin calcium, levothyroxine sodium, pantoprazole, and sertraline. At her screening visit, her blood pressure was 127/71 mmHg and pulse rate of 95 bpm. Her baseline ECG showed QTC_F interval of 385 msec and QTC_B interval of 406 msec. At her follow up visit 3 weeks later, her ECG showed QTC_F interval of 432 msec and QTcB of 467 msec, non-specific T wave abnormality, and old or age indeterminate inferior myocardial infarction. Her blood pressure was 136/65 mmHg and pulse rate was 112 bpm.

Reviewer comment: A role for lasmiditan cannot be ruled out in the event of ECG QT prolonged. Confounding factors in this case exist and include the risk factor of previous myocardial infarction to predispose her to the event. Additionally, given that ECGs were intermittently recorded, evaluation of causal association is complicated by lack of knowledge of when the event occurred in relation to lasmiditan dosing.

CNS Vascular Events

Dysarthria (b) (6)

A 56-year-old male with history of hypertension and overweight reported dysarthria on Study Day 7 and also the same day as lasmiditan administration in study 305 (exact timing of the symptom in relation to the dose is unknown). The event was reported as resolved on the day of onset. Three weeks later, at his study 5 visit, his blood pressure was 130/90 mmHg and his pulse rate was 80 bpm. At his screening visit in study 305, his blood pressure had been 138/75 mmHg and his pulse rate 62 bpm.
Concomitant medications included ibuprofen, amitriptyline, dextromethorphan hydrobromide, acetaminophen-dextromethorphan, hydrobromide-phenylephrine hydrochloride, lisinopril, metoprolol, omeprazole, and sildenafil citrate.

Reviewer comment: A role for lasmiditan in the event of dysarthria is uncertain given that it is not known if the event occurred before or after the administration of lasmiditan.

Cardiomyopathy/Elevated Blood Pressure (b) (6)

A 44-year-old female with history of attention deficit hyperactivity disorder, overweight, left bundle branch block, asthma, and hypothyroidism who experienced elevated blood pressure of moderate severity on Study Day 151 and cardiomyopathy of mild severity on Study Day 171. The patient discontinued the study due to cardiomyopathy. She had received 5 doses of lasmiditan 100 mg prior to the onset of the AEs. The events of hypertension and cardiomyopathy occurred 13 days and approximately one month, respectively, after the most recent dose. At her screening visit in study 301, her blood pressure was 116/89 mmHg and her pulse rate was 104 bpm. The AE of blood pressure was considered resolved after two days and the AE of cardiomyopathy was ongoing. She reported dizziness of mild severity on Study Day 180 and 181. She was started on acetylsalicylic acid and metoprolol succinate. Concomitant medications were bupropion, hydrochloride/naltrexone hydrochloride,

amphetamine/dextroamphetamine, linaclotide, oxytocin, levothyroxine, and salbutamol sulfate. Further details such as echocardiogram and cardiac catheterization reports were not reported.

Study Day	Blood Pressure	Pulse
-18	116/89	104
1	133/89	100
31	131/86	86
95	125/88	84
186	121/75	98
205	120/81	84

Reviewer comment: A role for lasmiditan in the event of cardiomyopathy and elevated blood pressure is unlikely given that the most recent dose of lasmiditan occurred 13 days prior to the onset of hypertension and the hypertension resolved within two days. Confounding factors in this case exist as well including use of amphetamine/dextroamphetamine which has been associated with the development of cardiomyopathy.

Hypertensive Crisis (b) (6)
A 35-year-old female with history of congenital cystic kidney disease and depression experienced hypertensive urgency of moderate severity which occurred on Study Day 306 of study 305. This occurred 15 days after her most recent dose of lasmiditan 200 mg and she had treated 11 migraine attacks prior to the event. At her screening visit in study 301, her BMI was 28.4 kg/m^2, her blood pressure was 146/89 mmHg, and her pulse was 83 bpm. The most recent blood pressure reading prior to the event of hypertensive crisis was 128/88 mmHg (Study Day 269). Concomitant medication use included levonorgestrel, phentermine, and venlafaxine. She was started on losartan-hydrochlorothiazide four days after the event of hypertensive crisis. At her end of study visit (Study Day 358), her blood pressure was 114/78 mmHg and her pulse rate was 90 bpm. The event was considered resolved at that time.

Reviewer comment: A role for lasmiditan in the event of hypertensive crisis is unlikely given that the event occurred 15 days after her last dose and the subject had underlying risk factors for the event including cystic kidney disease, elevated blood pressure (noted at her screening visit in study 301), overweight, and concomitant medication use with phentermine and venlafaxine.

Cardiovascular Safety in Clinical Pharmacology Studies
One SAE with potential cardiovascular etiology (cerebellar hematoma) is reviewed in the SAE section of this review.

The sponsor identified 50 TEAEs in 42 subjects with potential cardiovascular etiology in the

clinical pharmacology studies. Of the 50 TEAEs, the sponsor assessed 38 as likely cardiovascular in etiology.

I reviewed TEAEs occurring in healthy non-elderly subjects after a single dose in clinical pharmacology studies reported by the sponsor in Table ISS.APP.19.4 and note the following TEAEs with potential cardiovascular etiology: AV block (n=2); orthostatic hypotension (n=2); postural dizziness (n=2); ECG change (n=2); ECG abnormal; nodal rhythm; hypotension. Per the sponsor's analysis in Table ISS.APP.19.4, dizziness occurred in 63.7% of non-elderly subjects treated with a single dose of lasmiditan compared to 18.1% with placebo.

I reviewed the sponsor's submission of TEAEs occurring in elderly subjects after a single dose (Table ISS.APP.19.4), and I consider the following TEAEs as having potential cardiovascular etiology: dizziness (n=20); chest discomfort; postural dizziness; presyncope. The rate of dizziness calculated by the sponsor was 14.3% (5/35) for the 100 mg dose and 27.8% 15/54) for the 200 mg dose.

In special populations of clinical pharmacology studies, there was were 5 TEAEs that I considered as having potential cardiovascular etiology (QT prolonged, ECG T wave abnormal, postural orthostatic tachycardia syndrome, syncope, presyncope). These occurred after a single dose of lasmiditan.

I review select narratives from the clinical pharmacology studies.

ECG-Related Changes in Clinical Pharmacology Studies.

Five subjects had first degree AV block occurring in study LAHI after lasmiditan dosing. In this study, subjects were exposed to 200 mg lasmiditan 200 mg + placebo, 200 mg lasmiditan + 100 mg sumatriptan, and 100 mg sumatriptan + placebo in a 3-period crossover study. AV block occurred in five of the subjects during the 200 mg lasmiditan + 100 mg sumatriptan period. Of the five subjects, three experienced AV block occurring during the 200 mg lasmiditan + placebo period. Of the five subjects, two experienced AV block occurring during 100 mg sumatriptan + placebo period.
In all the cases, the PR intervals were no greater than 208 msec and no greater than 13 msec above the subject's baseline. The events occurred within 8 hours of dosing of lasmiditan and were all noted to be resolved within hours to up to 3 weeks. I summarize select narratives related to ECG changes from that study.

Atrioventricular block, first degree (b) (6)
A 24-year-old female with no previous medical history developed first degree AV block (mean PR interval of 200 msec, 6 ms increase from baseline) 4 hours after dosing with lasmiditan 200 mg and sumatriptan 100 mg on Study Day 1. This was accompanied by sinus bradycardia of 46

beats per minute (mean decline from baseline of 16 bpm). The event resolved after 4 hours.

She developed an inverted T wave in lead V2, sinus arrhythmia, and sinus bradycardia of 53 bpm (mean decline of 31 beats per minute from baseline) on Study Day 12 which occurred 8 hours after receiving lasmiditan 200 mg and placebo. Sixteen hours later, her ECG was noted to have resolution of the T wave inversion and persistent sinus bradycardia and sinus arrhythmia. She had also received sumatriptan 100 mg and placebo on Study Day 5.

Reviewer comment: A role for lasmiditan in the event of sinus bradycardia cannot be ruled out given onset of the AE at the time of lasmiditan administration and reoccurrence of the AE with rechallenge.

T wave inversion lead III (b) (6)
A 27-year-old woman with allergic rhinitis developed T wave inversion in lead III one hour after taking lasmiditan 200 mg and placebo. The event was considered resolved after three hours. Within 45 minutes of dosing, the patient also experienced hypersomnia, euphoric mood and dizziness which were mild in severity and resolved after 5.5 hours. Twenty-four hours after dosing, her ECG showed T wave inversion in lead III with resolution after 1.5 hours later. In the next study period six days later, she received lasmiditan 200 mg and sumatriptan and developed T wave inversions in lead III and bradycardia of 59 beats per minute (decrease of 4 beats per minute from baseline) 4 hours after dosing. The changes resolved 4 hours later. On the same day and 15 minutes after dosing, she reported dizziness, auditory disorder, and hypersomnia. These symptoms were rated as mild and resolved within 4 hours.

Reviewer comment: A role for lasmiditan in the event of ECG changes cannot be ruled out given proximity to dosing and reoccurrence of the AE with rechallenge.

<u>AEs related to bradycardia, dizziness, or orthostatic hypotension</u>

Orthostatic hypotension (b) (6)
A 43-year-old female with no previous past medical history experienced dizziness with reported orthostatic hypotension 1.5 hours after taking lasmiditan 200 mg. At the time of the AE, her blood pressure was 110/65 mmHg (13/15 mmHg decrease from her blood pressure measured 3 minutes earlier in a half-seated position) and her pulse rate was 54 beats per minute (8 bpm decrease from pulse rate measured 3 minutes before in a half-seated position). The event resolved within 1 minute. Two and a half hours later, the patient was experienced orthostasis again. Her standing blood pressure was 97/51 mmHg (decrease of 20/22 mmHg from a half-seated position 3 minutes before) and pulse rate 52 bpm (15 bpm decrease from a half-seated position 3 minutes before). The event resolved after one minute. The patient also experienced somnolence 1.5 hours after dosing which resolved without treatment five hours later.

Reviewer comment: A role for lasmiditan in the event is reasonable given proximity to dosing administration, and absence of confounding factors such as previous medical history or concomitant medication use. The event appears to be more consistent with a vasovagal event rather than orthostatic hypotension given the pulse rate decrease.

Syncope (Vasovagal syncope) (b) (6)
A 42-year-old male with medical history of bradycardia, dizziness, sleep apnea syndrome, rhinoplasty, anxiety, and hyperlipidemia experienced syncope 12 hours after taking lasmiditan 200 mg. The event was recorded as lasting for 8 minutes. He was taken to the hospital and observed for a period of 15 hours. He received 1 liter of sodium chloride intravenously while hospitalized. One minute after the stop time of the event, the patient had a sitting blood pressure of 91/59 (48/25 mmHg decrease from the mean of the supine triplicate predose measurement of 139/84 mmHg). His pulse 1 minute after end time of the event was 62 beats per minute (4 bpm higher than mean supine predose pulse measurement). According to the narrative, the patient had recalled a disturbing memory just before the event. The patient also noted decreased oral intake the day prior to the study. The patient also experienced paresthesias 1 hour after study drug dosing which resolved after 2 minutes. The patient reported that during the observation period he had the following test results: normal chest x-ray, ECG, carotid ultrasound and MRI scan (unspecified type). Concomitant medications included atorvastatin, acetylsalicylic acid, cetirizine, ibuprofen, paracetamol, and sumatriptan.

Reviewer comment: A role for lasmiditan cannot be ruled out given the proximity of the event to lasmiditan administration. Confounding factors in this case include dehydration and occurrence of a disturbing memory.

Orthostatic hypotension (b) (6)
A 36-year-old woman with past medical history of migraine and overweight was reported to have orthostatic hypotension 8 hours after taking lasmiditan 200 mg. Five minutes prior to the onset of symptoms, her supine blood pressure was 106/75 mmHg with a pulse rate of 73 beats per minute. At the onset of the event, her standing blood pressure was 78/28 mmHg with a heart rate of 53 beats per minute. The event was recorded as resolved without treatment after 5 minutes however the CSR notes that the subject was unable to stand for repeat orthostatic vital signs. Concomitant medications include ibuprofen.

Reviewer comment: A role for lasmiditan in the event cannot be ruled out given proximity to dosing. The event appears to be more consistent with a vasovagal event rather than orthostatic hypotension given the pulse rate decrease.

Orthostatic hypotension (b) (6)
A 61-year-old male with past medical history of coronary artery disease, hypertension, hyperlipidemia, hyperphosphatemia, hypertensive retinopathy, hypertensive encephalopathy,

hyperparathyroidism, and chronic kidney disease on hemodialysis experienced orthostatic hypotension 4 hours after taking lasmiditan 200 mg. His blood pressure was 83/50 mmHg (34/21 mmHg decrease from predose standing baseline) and his heart rate was 86 beats per minute (6 beat per minute increase from predose standing baseline). The event resolved after 6 minutes (blood pressure 107/65 mmHg, pulse rate 75 bpm). Concomitant medications included glyceryl trinitrate, acetylsalicylic acid, calcium carbonate, alfacalcidol, atorvastatin calcium, irbesartan, and metoprolol tartrate. The patient also experienced fatigue 3 hours after study drug which resolved 4 hours later without treatment

Reviewer comment: A role for lasmiditan in the event of orthostatic hypotension cannot be ruled out. Other predisposing factors for orthostatic hypotension in this narrative include end stage renal disease and concomitant medications use that included glyceryl trinitrate, irbesartan, and metoprolol tartrate.

Clinically Significant Changes in Vital Signs

Potentially clinically significant high changes in vital signs (b) (6)

A 59-year-old man with past medical history of hypertension, hepatitis C with moderate hepatic impairment, ascites, hepatosplenomegaly, and tremor experienced an increase in his sitting heart rate to 115 bpm (49 bpm increase from predose baseline). The event occurred 2 hours after dosing with lasmiditan 200 mg. At the same timepoint, his blood pressure was 80/64 mmHg (39/21 mmHg decrease from his predose baseline). Four hours post dose, his sitting heart rate remained elevated at 122 bpm and his blood pressure low at 80/70 mmHg. On Day 2, his sitting heart rate remained 14 beats per minute above his baseline value from the previous day and his blood pressure was 126/93 mmHg.

Reviewer comment: The event of elevated heart rate appears likely related to lasmiditan use given onset within 2 hours of taking lasmiditan.

Feeling of Heart Racing/Palpitations (b) (6)

A 24-year-old man with history of drug abuse experienced palpitations “feeling of heart racing” 5 hours after taking lasmiditan 200 mg. Fifteen minutes later he experienced postural orthostatic tachycardia with a standing pulse of 134 bpm (38 bpm higher than his supine heart rate 3 minutes before). The palpitations resolved after 1.5 hours and the postural orthostatic tachycardia syndrome resolved after 5 hours. At the time of the palpitations, the patient also experienced the AE of mild presyncope which resolved 5 minutes later and mild tinnitus which resolved after 1.5 hours.

The patient also experienced the AE of visual hallucination and mild paresthesias 30 minutes after dosing, mild dysphoria 1.5 hours after dosing, and mild euphoric mood 4.5 hours after dosing. The visual hallucination resolved after 1 hour, paresthesias after 6 hours, dysphoria after 3 hours, and euphoria after 2 hours.

Reviewer comment: The event of postural orthostatic hypotension and palpitations appear related to lasmiditan as does the visual hallucination, paresthesias and mood changes given timing of AEs with lasmiditan administration.

In summary, a low number of subjects with ischemic heart disease was enrolled in Phase 3 studies which potentially limits interpretation of safety for patients with ischemic heart disease. The rate of SAEs with potential cardiovascular etiology in studies 202/301/302/305 was low. A higher percentage of subjects who received lasmiditan reported at least one TEAE with potential cardiovascular etiology compared to subjects treated with placebo in studies 202, 301, and 302. The overall risk difference between the groups was not greater than 2%. The thorough QT study evaluated lasmiditan 100 mg and 400 mg doses and showed no significant QTc prolongation effect of lasmiditan at 100 mg and 400 mg doses. A review of vital signs from the clinical pharmacology studies showed evidence of increases in systolic and diastolic blood pressure within one hour of lasmiditan dosing along with decreases in pulse rate. Cases of orthostatic hypotension, palpitations, and ECG changes were also noted to occur within hours of lasmiditan dosing in clinical pharmacology studies. Two clinical pharmacology studies (LAHT and LAHE) did not show evidence of orthostasis by mean orthostatic changes in subjects who received lasmiditan. Overall, the current database does not support increased cardiovascular risk with lasmiditan.

8.5.2. Evaluation of Injuries and Accidents Secondary to Neurologic Adverse Events

The sponsor's analysis did not demonstrate that patients with neurological adverse events experienced an increased risk of injuries. The most frequently reported TEAEs in Phase 3 studies are CNS in nature and therefore, the effects of lasmiditan in contributing to the development of an injury or accident was of special interest. The sponsor searched for injuries and accidents in the Injury, Poisoning, and Procedural Complications SOC and then evaluated whether the AE was preceded or occurred concurrently with an AE belonging to the Nervous system disorders SOC.

In studies 301 and 302, an increased rate of AEs in the Injury, Poisoning, and Procedural Complications SOC and CNS TEAEs was seen in subjects who received lasmiditan compared to subjects who received placebo (0.3% versus 0.1%). The following table shows incidence of subject experiencing CNS TEAEs and AEs in the Injury, Poisoning, and Procedural Complications SOC.

Table 44. CNS TEAEs with AEs related to Injury, Poisoning, and Procedural Complications SOC in Studies 301 and 302.

Category	All LTN N=3177 n (%)	Placebo N=1262 n (%)
Subjects with at least one CNS TEAE	827 (26.0)	87 (6.9)
Subjects with at least one AE in the Injury, Poisoning, and Procedural Complications SOC	31 (1.0)	6 (0.5)
Subjects with at least on CNS TEAE and one AE in the Injury, Poisoning, and Procedural Complications SOC	9 (0.3)	1 (0.1)

The above data was submitted by the sponsor in the ISS Table ISS.18.19.

In subjects who received lasmiditan in studies 301 and 302, nine subjects experienced both an AE related to the Injury, Poisoning, and Procedural Complications SOC and a CNS TEAE. In studies 301 and 302, nine subjects experienced both an AE related to the Injury, Poisoning, and Procedural Complications SOC and a CNS TEAE. Five of the nine subjects experienced the AE related to the Injury, Poisoning, and Procedural Complications SOC before receiving lasmiditan. Two of the nine subjects experienced an AE of arthropod sting one day after dosing. Of the remaining 2 subjects, both subjects reported the TEAE of dizziness on the same day of lasmiditan dosing with resolution of the TEAE on the same day. One of the two subjects experienced a laceration 9 days after dosing and the other subject reported a sprained Achilles tendon 2 days after dosing.

Reviewer comment: It is unlikely that lasmiditan contributed to the development of the injury in these cases as the most recent dose of lasmiditan and the CNS TEAE had occurred at least 2 days prior to the injury.

In study 202, there were an additional three subjects who experienced an AE related to the Injury, Poisoning, and Procedural Complications SOC and a CNS TEAE. The three subjects experienced dizziness on the day of lasmiditan dosing with resolution of the dizziness on the same day. One of the three subjects experienced a motor vehicle accident 4 days after dosing. Another subject experienced rib fracture, weakness and fatigue 4 days after dosing. The third subject experienced concussion of the brain 10 days after dosing.

Reviewer comment: A role for lasmiditan is unlikely in these cases as the most recent dose was at least 4 days prior to the injuries.

In study 305, there were 52 subjects who experienced both an AE related to the Injury, Poisoning, and Procedural Complications SOC and a CNS TEAE. Of the 52 subjects, 15 had injuries prior to lasmiditan dosing. Thirty-two of the 52 subjects experienced an AE related to

the Injury, Poisoning, and Procedural Complications SOC that occurred 2 days to several months after resolution of the CNS TEAE.

Of the remaining 4 subjects, one subject (b) (6) experienced post-surgery hernia pain in the setting of the lethargy which had started 9 days before. Another subject (b) (6) (b) (6) reported pain from cholecystectomy in the setting of mild balance disorder that was reported as starting 1.5 months before. A third subject (b) (6) experienced back strain in the setting of drowsiness that had started 3 months before. The fourth case ((b) (6) is summarized in the Impairment of Mental Ability section of this review.

Reviewer comment: A role for lasmiditan is unlikely in these four cases. In two of the four cases the injuries were due to previous surgeries. In one of the four cases, the CNS TEAE had been present for 3 months and was unlikely to be related to lasmiditan. In the fourth case, the event of Road Traffic Accident had occurred 2 days after the most recent dose of lasmiditan and was unlikely to be related.

In the clinical pharmacology studies, the sponsor notes that there were no AE related to the Injury, Poisoning, and Procedural Complications SOC that occurred in the setting of a CNS TEAE.

Overall, there was a higher incidence of AEs related to the Injury, Poisoning, and Procedural Complications SOC that occurred in the setting of a CNS TEAE in lasmiditan-treated subjects compared to placebo-treated subjects in the Phase 2/3 studies; however, the number of reported events was low and the difference in incidence between lasmiditan and placebo was no higher than 0.3%.

8.5.3. Impairment of Mental Ability

The sponsor's analysis did not find increased adverse events related to accidents although higher rates of adverse events with possible effects on mental ability were noted. The most frequently reported TEAEs in Phase 3 studies are CNS in nature; therefore, the effects of lasmiditan on impairment of mental ability and on the ability to drive were areas of special interest. For a review of lasmiditan on the ability to drive, the reader is referred to the driving studies section of this review.

To assess impairment of mental ability, the sponsor evaluated TEAEs in Phase 2 and 3 studies with preferred terms in the Nervous system and Psychiatric disorders SOC that primarily reflected attentional, perceptual, or executive functioning impairments or changes in sensorium.

In studies 301/302, a higher percentage of subjects who received lasmiditan (21.2%) reported at least one TEAE in the above-referenced search compared to subjects who received placebo

(5.1%). Studies 202/301/302 showed similar incidence between lasmiditan- and placebo-treated subjects.

The following table lists preferred terms in the above-referenced search for studies 202/301/302 occurring in lasmiditan-treated subjects with incidence greater than placebo and occurring in at least 3 subjects.

Table 45. TEAEs Within SOCs Representing Possible Effects on Mental Ability for Studies 202/301/302.

Preferred Terms	Placebo N=1347 n (%)	All-Lasmiditan N=3412 n (%)
Dizziness	38 (2.8)	534 (15.7)
Somnolence	29 (2.2)	201 (5.9)
Lethargy	1 (0.1)	31 (0.9)
Sedation	1 (0.1)	20 (0.6)
Disturbance in Attention	0	10 (0.3)
Hypersomnia	0	4 (0.1)
Cognitive Disorder	0	3 (0.1)
Mental Impairment	0	3 (0.1)
Vertigo	2 (0.1)	51 (1.5)
Confusional State	2 (0.1)	7 (0.2)
Disorientation	1 (0.1)	6 (0.2)

The above data was submitted by the sponsor in the ISS Appendix, Table ISS.APP.16.3.

As part of the assessment for mental impairment occurring with lasmiditan, the sponsor assessed the effect on ability to drive or operate heavy machinery. The sponsor searched for TEAEs and AEs occurring in studies 202, 301, 302 and 305 under the following SOCs: Road Traffic Accident; Impaired Ability to Use Machinery; Accident or Injury, Poisoning and Procedural Complications. Protocols in studies 301 and 302 specified that subjects should be advised to not drive or operate machinery until 12 hours after treatment. In study 305, subjects were advised not to drive or operate machinery until they knew how they would react to lasmiditan.

In the Phase 3, placebo-controlled studies, there were no AEs or TEAEs of Road Traffic Accident, Impaired Ability to Use Machinery, or Accident in subjects who received study drug.

In the oral Phase 2/3, placebo-controlled trials, one AE of Road Traffic Accident was reported in a subject who received lasmiditan 100 mg (b) (6).

AE: Road Traffic Accident (b) (6)
A 20-year-old woman experienced a road traffic accident 4 days after taking lasmiditan 100 mg. The patient also noted severe dizziness that started prior to the accident and a moderate headache that started the day of the accident.

Reviewer comment: A role for lasmiditan in the AE of traffic accident is unlikely as the accident was separated from the last dose of lasmiditan by 4 days.

In the open-label extension study, there were two TEAEs of Road Traffic Accident, two AEs of Road Traffic Accident, and one AE of posttraumatic neck syndrome due to a car accident. The two AEs of Road Traffic Accident (b) (6) occurred 43 and 50 days after the most recent dose of lasmiditan and are unlikely to be related to the drug. The AE of posttraumatic neck syndrome (b) (6) due to car accident occurred 13 days after the most recent dose of study drug and is unlikely to be related. I summarize the two TEAEs of Road Traffic Accident here.

TEAE: Road Traffic Accident (b) (6)
A 40-year-old woman with past medical history of bipolar disorder experienced a road traffic accident 2 days after taking her most recent dose of lasmiditan (100 mg). It is not known if the patient was the driver of the vehicle. She also reported sciatica on the same day as the accident. Concomitant medications were lithium and quetiapine.

Reviewer comment: A role for lasmiditan is unlikely in the event of motor vehicle accident as the accident occurred two days after her most recent dose of lasmiditan.

TEAE: Road Traffic Accident (b) (6)
A 40-year-old female with anxiety, bilateral deafness, depression, and Meniere's disease was the driver of a vehicle in a motor vehicle accident. The event was categorized as treatment emergent as the patient was recorded as taking a dose of lasmiditan with a start and stop time that spanned three months. Concomitant medications included cetirizine, diphenhydramine, duloxetine, levothyroxine, alprazolam, candesartan, metoprolol succinate, phentermine, hydrocodone-acetaminophen, and Migramaxx.

Reviewer comment: It is not known if the accident occurred close to the time of the dose of lasmiditan. A role for lasmiditan in the AE of Road Traffic Accident cannot be drawn due to a lack of information regarding the timing of the dose.

In summary, higher rates of TEAEs within SOCs representing possible effects on mental ability were noted in lasmiditan-treated subjects compared to placebo-treated subjects. A low number of AEs of Road Traffic Accident occurred in Phase 2/3 studies and a role for lasmiditan in these AEs could not be established.

8.5.4. Hypersensitivity Reaction

The sponsor's analysis showed cases of hypersensitivity occurring in lasmiditan-treated subjects. I searched AEs in studies 301/302 and study 202 belonging to the SMQs Hypersensitivity and Anaphylactic Reaction. In studies 301/302, higher rates of AEs related to hypersensitivity and anaphylactic reaction occurred in lasmiditan 200 mg-dose group compared to placebo. The difference in the rates was not greater than 1%. Study 202 was similar to studies 301/302 in that a higher percentage of AES belonging to the Hypersensitivity Broad or Anaphylactic Reaction Broad occurred in lasmiditan-treated subjects compared to placebo. There were no cases of anaphylaxis related to lasmiditan.

Table 46. Incidence of AEs Belonging to the Hypersensitivity SMQs for Studies 301/302.

SMQ category	Lasmiditan 50 mg N=654 n (%)	Lasmiditan 100 mg N=1265 n (%)	Lasmiditan 200 mg N=1258 n (%)	All-Lasmiditan N=3177 n (%)	Placebo N=1262 n (%)
Hypersensitivity (Broad)	0	6 (0.5)	13 (1.0)	19 (0.6)	10 (0.8)
Hypersensitivity (Narrow)	0	3 (0.2)	4 (0.3)	7 (0.2)	1 (0.1)
Anaphylactic reaction (Broad)	3 (0.5)	13 (1.0)	18 (1.4)	34 (1.1)	10 (0.8)
Anaphylactic reaction (Narrow)	0	0	1 (0.1)	1 (0)	0

The reviewer created this table using ISS ADSL and ADAE datasets. For ADSL, SAFFL=Y and studyID=301 or 302. For ADAE, study ID=301 or 302. AEFDOSEFL=Y. The numerator is the number of subjects with AEs within SMQ category and the denominator is number of subjects in the treatment arm of the safety population.

Table 47. Incidence of AEs Belonging to the Hypersensitivity SMQ (Narrow) for Studies 301/302.

SMQ category	Lasmiditan 50 mg N=654 n (%)	Lasmiditan 100 mg N=1265 n (%)	Lasmiditan 200 mg N=1258 n (%)	All-Lasmiditan N=3177 n (%)	Placebo N=1262 n (%)
Face oedema	0	0	1 (0.1)	1 (0)	0
Hypersensitivity	0	0	1 (0.1)	1 (0)	0
Rash	0	2 (0.2)	1 (0.1)	3 (0.1)	0
Rhinitis allergic	0	1 (0.1)	0	1 (0)	0
Contact dermatitis	0	0	0	0	1 (0.1)
Circulatory Collapse	0	0	1 (0.1)	1 (0)	0

SMQ category	Lasmiditan 50 mg N=654 n (%)	Lasmiditan 100 mg N=1265 n (%)	Lasmiditan 200 mg N=1258 n (%)	All-Lasmiditan N=3177 n (%)	Placebo N=1262 n (%)
Hypersensitivity (Narrow)	0	3 (0.2)	4 (0.3)	7 (0.2)	1 (0.1)

The reviewer created this table using ISS ADAE datasets with study ID=301 or 302, SAFFL=Y, AEFDOSEFL=Y, and preferred terms = face oedema, hypersensitivity, rash, rhinitis allergic, circulatory collapse, contact dermatitis.

For the label, after excluding a case of circulatory collapse and a case of contact dermatitis as they were not considered related to drug, the percentage of subjects with AEs belonging to the Hypersensitivity SMQ was 0.2% for lasmiditan and 0% for placebo. The case of circulatory collapse is discussed later in this section.

Table 48. Incidence of AEs Belonging to the Hypersensitivity SMQs for Study 202.

SMQ category	Lasmiditan 50 mg N=82 n (%)	Lasmiditan 100 mg N=82 n (%)	Lasmiditan 200 mg N=71 n (%)	All-Lasmiditan N=235 n (%)	Placebo N=85 n (%)
Hypersensitivity (Broad)	1 (1.2)	3 (3.7)	1 (1.4)	5 (2.1)	0
Hypersensitivity (Narrow)	1 (1.2)	0	0	1 (0.4)	0
Anaphylactic reaction (Broad)	5 (6.1)	6 (7.3)	3 (4.2)	14 (6.0)	1 (1.2)

The reviewer created this table using ISS ADSL and ADAE datasets. For ADSL, SAFFL=Y and studyID=202. For ADAE, study ID=202, AEFDOSEFL=Y. The numerator is the number of subjects with AEs within SMQ category and the denominator is number of subjects in the treatment arm of the safety population.

In studies, 202, 301, and 302, there were 22 TEAEs that were potentially related to hypersensitivity occurring in lasmiditan-treated subjects. No cases led to discontinuation. The following table shows severity of TEAEs with potential hypersensitivity etiology by dose in studies 202, 301, and 302. Most TEAEs were mild or moderate in severity. The TEAEs included asthma, conjunctivitis, flushing, hypersensitivity, pruritis generalized, rash, and rash pruritic. One case was coded as circulatory collapse; however, in the 29/05/2019 response to an information request dated 22/05/2019, the investigator noted that the case was better described as poor peripheral circulation.

Table 49. Severity of Hypersensitivity-Related TEAEs by Dose in Studies 202, 301, and 302.

AE Severity	Lasmiditan 50 mg N=1	Lasmiditan 100 mg N=7	Lasmiditan 200 mg N=14	Placebo N=10
Mild	0.0	57.1	35.7	80.0
Moderate	100.0	28.6	57.1	22.2
Severe	0.0	14.3	7.1	0.0

Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 202, 301 and 302, TRTEMFL=Y. The denominator is the total number of hypersensitivity-related TEAEs by dose occurring in studies 202, 301, and 302. The reviewer searched for the following hypersensitivity-related preferred terms: allergic sinusitis, asthma, bronchospasm, circulatory collapse, conjunctivitis, conjunctivitis, allergic, dermatitis contact, dermatitis, drug hypersensitivity, face oedema, flushing, hypersensitivity, mouth ulcerations, pruritus, pruritus generalized, rash, rash pruritic, rash generalized, rhinitis allergic, seasonal allergy, skin oedema, swelling face, swollen tongue, throat tightness, upper airway obstruction.

In study 305, I identified 30 TEAEs with potential hypersensitivity etiology that included blister, conjunctivitis, allergic conjunctivitis, dermatitis, contact dermatitis, flushing, pruritis, rash, rash generalized, rhinitis allergic, seasonal allergy, swelling face, swollen tongue, throat tightness, and urticaria. They were of mild or moderate severity. Five of the 30 TEAEs led to discontinuation.

None of the potential cases of hypersensitivity cases met criteria for an SAE however several were potentially medically significant including swelling face and swollen tongue. I summarize cases of potential hypersensitivity here.

Swollen tongue/abdominal pain/muscle spasms/hypoesthesia (b) (6)
A 27-year-old female with history of anxiety and seasonal allergic rhinitis, who received placebo in study 302, was randomized to receive lasmiditan 200 mg in study 305. On Study Day 16, she developed a swollen tongue, abdominal pain, and hypoesthesia within 37 minutes of taking lasmiditan 200 mg and developed muscle spasms approximately two hours later. The swollen tongue, abdominal pain, and hypoesthesia lasted one hour and the muscle spasms lasted 14 hours. She did not receive any treatment for the events. In study 305, her first dose of lasmiditan had occurred on Study Day 8 and her second dose on Study Day 11. Concomitant medications included loratadine and clindamycin. She discontinued study 305 due to the AEs.

Reviewer comment: A role for lasmiditan cannot be ruled out for the AEs based on timing of the events and administration of lasmiditan and the occurrence after previous exposure to lasmiditan.

Swelling to face (b) (6)
A 30-year-old female with past medical history of asthma developed swelling to the left side of her face 0.3 hours after her first dose of lasmiditan 200 mg in study 305. She had received placebo in study 302. She also developed worsening aura with a kaleidoscope effect at the

same time as the facial swelling. Both AEs resolved after two hours. Concomitant medications included salbutamol PRN. The subject discontinued the study due to the AEs.

Reviewer comment: The event of facial swelling is unlikely to be an allergic reaction to lasmiditan given absence of previous exposure to lasmiditan. The subject may have developed hypersensitivity to an excipient, a non-allergic hypersensitivity reaction to lasmiditan cannot be ruled out.

Swelling to face (b) (6)
A 25-year-old female with history of seasonal allergy disorder and food allergy experienced the TEAE of swelling to right side of her face in study 305 two hours after her ninth dose of lasmiditan 200 mg. She had received two doses of lasmiditan 100 mg in study 301. She experienced a second episode of swelling to her face, 24 days after her 11th dose of lasmiditan in study 305. The first event resolved after 19 hours and the second event resolved after 26 hours. She also reported concurrent facial pain with the facial swelling for both episodes. She received an additional four doses of study medication in study 305 however no further episodes of swelling to her face or other hypersensitivity events were reported.

Reviewer comment: The role of lasmiditan in the event of facial swelling cannot be ruled out given the prior exposure to drug and the timing of the event. Factors not supportive of an allergic reaction to lasmiditan are absence of similar responses for subsequent doses in study 305, although a non-allergic hypersensitivity reaction cannot be ruled out.

Swelling face (b) (6)
A 40-year-old male with history of seasonal allergy developed swelling to face, of moderate severity 33 minutes after taking his second dose of lasmiditan 100 mg in study 305. His first dose of lasmiditan had occurred two hours before the second dose. He had received placebo in study 301. He also developed the AE of dizziness of moderate severity 18 minutes after his second dose of lasmiditan. The swelling to his face lasted for 15 minutes and the dizziness lasted for 30 minutes. The subject discontinued the study due to dizziness and swelling to his face.

Reviewer comment: The role of lasmiditan in the event of facial swelling cannot be ruled out given the timing of the event.

Flushing (b) (6)
A 51-year-old female with history of eczema, urticaria, psoriasis, and seborrheic dermatitis developed flushing of moderate severity 20 minutes after taking lasmiditan 200 mg in study 305. She had treated two migraine attacks in the preadministrative hold period of study 305 and six migraine attacks in study 305 prior to developing the AE. The flushing lasted for three hours and the subject discontinued the study due to the adverse event.

Reviewer comment: The role of lasmiditan in the event of flushing cannot be ruled out given her previous exposure to the drug and the timing of the event.

Pruritis (b) (6)
A 58-year-old female with history of allergic rhinitis developed itching of moderate severity two days after taking her most recent dose of lasmiditan 100 mg in study 305. She had treated 33 migraine attacks prior to the onset of the AE. Concomitant medications included mometasone furoate. She was treated with diphenhydramine hydrochloride and the event resolved after eight days. She discontinued the study due to the AE.

Reviewer comment: The role of lasmiditan in the event of pruritis cannot be ruled out given her previous exposure to the drug and the timing of the event. Although the event was separated from lasmiditan administration by two days, the subject may have experienced a delayed hypersensitivity reaction.

Circulatory collapse (b) (6)
A 32-year-old female with history of hypothyroidism was recorded as having circulatory problems (circulatory failure [no collapse or shock]), "severe feeling (abnormal feeling)" and paresthesia ("tingling at the body") between 8 to 32 hours after taking her first dose of lasmiditan 200 mg in study 302 (exact time of AE not recorded). The sponsor communicated with the investigator who noted that the event was incorrectly coded as circulatory failure and that "a more appropriate code would have been 'poor peripheral circulation.'" There was no event of collapse although the subject felt like "being near to it." The symptoms resolved after one hour. She was not assessed by a medical provider on the day of the event and did not have vital signs measured on the day of the event. The exact time of the day of lasmiditan administration in relation to the event was not provided by the subject. Concomitant medications were levothyroxine sodium, acetylsalicylic acid, rizatriptan and dimethyl fumarate.

During the study, the subject also experienced mild abdominal pain that lasted 4 day and renal pain that was ongoing at the time of study completion. At her screening visit, her blood pressure was 116/79 mmHg and pulse was 70 beats per minute. At her second visit, her blood pressure was 130/84 mmHg and pulse of 79 beats per minute.

Reviewer comment: A role for lasmiditan cannot be ruled out for the abnormal feeling/paresthesias/feeling of being close to collapse given the onset of the symptoms with lasmiditan administration. In this reviewer's opinion, the event appears to be characteristic of presyncope or paresthesias.

Rashes
In the 07/06/2019 response to an information requested dated 04/06/2019, the sponsor

provided a summary of cases of rash occurring in studies 202, 301, 302, and 305. The sponsor noted 15 cases of rash. Eight of the 15 are described in the ISS. The sponsor noted the other seven cases did not have medical summaries as the cases had been assessed by the sponsor as not likely related to lasmiditan because of confounding factors. Of the eight cases described in the ISS, six cases were mild and two were moderate in severity. Six of the eight cases reported a rash that included the arms and two of the eight cases reported a rash that included the face. In cases where time from most recent lasmiditan dose was reported, the range was between one and 23 hours. In cases where the duration of the rash was reported, the range was between 21 to 24 hours. Treatments for the rash were listed in four cases and included oral diphenhydramine, topical hydrocortisone, and clindamycin gel. I summarize the narrative of a case of rash here.

Rash (b) (6)
A 35-year-old female with history of drug hypersensitivity to codeine received two doses of lasmiditan 100 mg in study 301 on Study Day 8. The second dose was taken 14 hours after the first dose. She developed a rash to her face and trunk 3 hours after the second dose of study drug. The subject was treated with oral diphenhydramine and the AE was reported as recovering/resolving.

In the clinical pharmacology studies, the sponsor noted five lasmiditan-treated subjects who experienced TEAEs belonging to the Hypersensitivity SMQ (narrow). The TEAEs were: skin reaction, mild; contact dermatitis, mild (n=3), eye swelling, mild.

120 Day Safety Update
In the 120 Day Safety Update, the All-lasmiditan Phase 2/3 pool had five additional potential non-immediate hypersensitivity events within the hypersensitivity SMQ: allergic rhinitis, asthma, dyspnea, edema, and photosensitivity reaction.

Photosensitivity (b) (6)
A 23-year-old female with history of eczema developed photosensitivity reaction of mild severity on Study Day 34, four days after taking her most recent dose of lasmiditan 200 mg in study 305. She had treated two migraine attacks prior to the onset of the adverse event. The event was considered resolved after 3 hours. No concomitant medication use was reported.

Reviewer comment: A role for lasmiditan in the event of photosensitivity cannot be ruled out given timing of the AE with her most recent dose of lasmiditan.

8.5.5. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose
The sponsor searched for cases of overdose using the following preferred terms: accidental overdose, antemortem blood drug level abnormal, antemortem blood drug level increased,

drug level above therapeutic, drug level increased, extra dose administered, intentional overdose, overdose, postmortem blood drug level abnormal, postmortem blood drug level increased, and prescribed overdose.

There were no cases of overdose across the clinical development program. The sponsor noted one subject (b) (6) who had an affirmative response on the C-SSRS of taking pills above the prescribed dose. In this case, the subject "used her own medications." The last dose of lasmiditan recorded was 43 days prior to the affirmative response and no additional information regarding whether the subject had taken lasmiditan above the prescribed dose was included.

In the Phase 2/3 studies, the sponsor searched for subjects taking maximum protocol-allowed doses in a 24-hour period. The maximum dose received within 24 hours was 600 mg and occurred in three subjects. One of the three subjects took a cumulative of 600 mg in 24 hours on five separate occasions. No TEAEs were reported in any of these cases.

Drug Abuse Potential

Because lasmiditan penetrates the CNS, an assessment of the abuse potential of lasmiditan was performed. A human abuse liability study (study LAHB) was conducted by the sponsor with 100 mg and 200 mg doses of lasmiditan in comparison to placebo in recreational drug users. For further details regarding the results of this study, the reader is referred to the review by the Controlled Substance Staff.

The sponsor's analysis showed increased adverse events related to abuse potential. The sponsor assessed abuse potential in Phase 2/3 studies by searching for TEAEs using the SMQ of Drug Abuse and Dependence (v21.0). The sponsor also searched for TEAEs related to abuse potential using a sponsor-generated list of preferred terms related to abuse potential. The sponsor-generated list included preferred terms related to the following: feeling abnormal; euphoric mood; feeling drunk; abnormal dreams; mental impairment; dysphoria; apathy; hallucination; hallucination, visual; hallucination, auditory; depersonalization/derealization disorder; illusion. I considered the sponsor-generated list to be in alignment with the Assessment of Abuse Potential of Drugs: Guidance for Industry (FDA). The SMQ of Drug Abuse and Dependence did not include preferred terms related to abuse potential identified in the FDA guidance. One TEAE related to abuse potential was identified across studies 202, 301, 302, and 305 using the SMQ of Drug Abuse and Dependence. I summarize the results of the search for TEAEs related to abuse potential using the sponsor-generated list for this review.

In study 305, due to the longer duration of the study, the sponsor performed a search for AEs using the SMQ of Drug Abuse and Dependence. Cases were assessed for stolen or diverted drug. I considered the sponsor's search method to be adequate.

In studies 301 and 302, 28.5% of lasmiditan-exposed subjects reported at least one TEAE belonging to the sponsor-generated list of terms related to abuse potential compared to 7.6% of placebo-exposed subjects. The following table shows TEAEs with incidence of greater than 0.2% above placebo for lasmiditan-treated subjects in studies 301 and 302.

Table 50. TEAEs Related to Abuse Potential (Sponsor-generated List) with Incidence > 0.2% Above Placebo for Studies 301 and 302.

Preferred Term	Placebo N=1262 %	All Lasmiditan N=3177 %
Dizziness	2.9	14.7
Paresthesias	1.5	5.7
Somnolence	2.1	5.5
Fatigue	0.6	3.8
Asthenia	0.2	1.1
Feeling Abnormal	0.1	0.6
Anxiety	0.1	0.6
Balance disorder	0	0.6
Sedation	0.1	0.6
Euphoric mood	0	0.4
Restlessness	0	0.4
Feeling jittery	0.1	0.3
Dysarthria	0	0.3
Ataxia	0	0.2
Confusional state	0	0.2
Abnormal dreams	0	0.2
Disturbance in attention	0	0.2

The above data was submitted by the sponsor in the ISS, Table.14.1.

Analysis of TEAEs belonging to the sponsor-generated list of terms related to abuse potential for studies 202/301/302 showed similar incidences compared to studies 301/302. In the All-lasmiditan Pool, a higher incidence of lasmiditan-exposed subjects (39.5%) reported at least one TEAE belonging to the sponsor-generated list of terms related to abuse potential. The higher of incidence is likely in part due to the longer duration of study 305. The following terms are additional terms with incidence >0.2% that were present in the All-lasmiditan Pool and not in the placebo-controlled pools: hot flush (0.4%), disorientation (0.3%), abnormal dreams (0.3%), dysarthria (0.2%), cognitive disorder (0.2%), hallucinations (0.4%) (includes the preferred terms of hallucination, visual hallucination, auditory hallucination and hypnagogic hallucination), coordination abnormal (0.2%).

The sponsor noted that for lasmiditan-treated subjects across the Phase 2/3 studies, TEAEs related to abuse potential had median time of onset of less than one hour and median duration of five hours or less. The majority of TEAEs were mild to moderate in severity and none caused discontinuation.

With regards to incidence of abuse, the sponsor noted that there were no reports of TEAEs from within the SMQ of Drug Abuse and Dependence in studies 201, 202, 301, or 302. One TEAE was reported in study 305 with preferred term medication overuse headache. I reviewed the case and did not find it consistent with medication overuse headache from lasmiditan as the subject did not take more than 200 mg of lasmiditan in a 24-hour period of time.

Three AEs related to abuse were reported in study 305. Two of the three cases were cases of intentional overdose that did not involve overdose with lasmiditan and are described in the Suicidal Ideation section of this review (b) (6). The third case of abuse did not involve abuse with lasmiditan.

The sponsor did not identify any cases of drug diversion, unusual dispensing, or dosing activities in study 305. Five subjects each reported one episode of stolen medication.

In conclusion, increased incidence of TEAEs that could be associated with abuse potential in studies 301 and 302 occurred in subjects who received lasmiditan compared to subjects who received placebo. The reader is referred to the CSS review for the results of their review of lasmiditan and abuse potential.

Withdrawal and Rebound
The reader is referred to the review by the Controlled Substance Staff.

8.5.6. Suicidal Ideation

The sponsor provided a review of suicidality cases and assessments of patients with questionnaires and did not find evidence that lasmiditan increases the risk for suicidality. Suicidal ideation and behavior were assessed in Phase 3 studies using the Columbia-Suicide Severity Rating Scale (C-SSRS). The sponsor noted that the C-SSRS was not collected in Phase 2 trials as these trials occurred prior to the FDA recommendations for suicidal assessment.

In studies 301 and 302, two lasmiditan-exposed subjects reported affirmative responses to any question of the C-SSRS that had been answered with a negative response at baseline. Both subjects had previous history of mental health disorders and one other positive affirmative response to the C-SSRS at baseline.

In the All-Lasmiditan Pool, 22 subjects responded affirmatively to any items on the C-SSRS at any time post baseline. Of these, 21 subjects (0.5%) responded affirmatively to items reflecting

suicidal ideation and 20 subjects had treatment-emergent suicidal ideation. Of the 20 subjects, six subjects had serious suicidal ideation (active suicidal ideation with either intent or some intent to act). Of these six subjects, four subjects had not reported suicidal ideation in the past six months. Two of the four subjects developed suicidal behavior. Of the 22 subjects who had responded affirmatively to any items on the C-SSRS post-baseline, four subjects (0.1%) responded affirmatively to items reflecting suicidal behavior. Twenty of the 22 subjects who had responded affirmatively to any items on the C-SSRS post-baseline had a previous history of mental health disorder or had responded affirmatively at baseline to at least one question on the C-SSRS.

The sponsor performed an analysis of treatment-emergent suicidal ideation. Treatment-emergent suicidal ideation was defined as an affirmative response to the C-SSRS postbaseline compared to no affirmative responses at baseline or a response at baseline that was lower in severity.

The sponsor searched for AEs related to suicidal ideation using the Suicide and Self-Injury-Related SMQ. In studies 202, 301, 302, one lasmiditan-treated subject reported an event related to the Suicide and Self-Injury-Related SMQ compared to no subjects who received placebo. In the All lasmiditan-treated phase 2/3 pool, eight subjects reported at least one AE belonging to the Suicide and Self-Injury-Related SMQ.

Three of the AEs were SAEs and I summarize them here.

Intentional Overdose (b) (6)
A 35-year-old female with history of anxiety and depression was hospitalized for an intentional overdose (with quetiapine) which occurred 13 days after taking her most recent dose. The event lasted for nine days. She was treated with quetiapine, valproate semi-sodium, fluoxetine, and hydroxyzine. She was also noted to experience the SAEs of severe obsessive-compulsive disorder and schizoaffective disorder bipolar type which prolonged the hospitalization and occurred 15 days after her most recent dose of lasmiditan. She had treated 17 migraine attacks prior to the onset of these disorders. At baseline, she had no affirmative responses to the C-SSRS at Visit 1 or 2 of study 301. Eleven days after her hospitalization on her 5th study visit, she responded affirmatively on the C-SSRS to "wish to be dead" and reported wishing to relieve stress and going to sleep without intention of killing herself. At her 6th study, she had no affirmative responses on the C-SSRS and was discontinued from the study due to sponsor request. Concomitant medications included fluoxetine hydrochloride, hydroxyzine, hydrocodone, paracetamol, and risperidone.

Reviewer comment: It is unlikely that lasmiditan contributed to the SAEs of hospitalization for overdose, obsessive-compulsive disorder and schizoaffective disorder bipolar type given that the most recent dose of lasmiditan had been 13 to 15 days prior to onset of the AEs.

Suicidal Ideation (b) (6)
A 19-year-old female with history of bipolar disorder, depression, and anxiety experienced the SAE of suicidal ideation at Visit 6 in study 305 (affirmative responses on the C-SSRS to: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with some intent to act without specific plan, and preparatory acts/behavior). Her most recent dose of lasmiditan had been five days before and she had treated two migraine attacks prior to the SAE. At her screening visit in study 302, she had responded affirmatively to the C-SSRS items: wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods without intent to act. At her screening visit in study 305, she had responded affirmatively to the C-SSRS items: non-specific active suicidal thoughts, preparatory acts/behavior.

Reviewer comment: A role for lasmiditan in the event of suicidal ideation cannot be established as the subject had positive affirmative responses of suicidal ideation at baseline in study 302.

Intentional Overdose (b) (6)
A 23-year-old female with history of Tourette's disorder, rheumatoid arthritis, Ehlers-Danlos syndrome, nightmare, autonomic neuropathy, and fibromyalgia was hospitalized for respiratory failure and suicide attempt. She was found unresponsive after an intentional medication overdose (consumed all accessible medications except for lasmiditan) and had sustained an intentional right wrist laceration. Her most recent dose of lasmiditan had been six days before hospitalization. She did not have affirmative responses on the C-SSRS at baseline or at subsequent visits and withdrew from the study 2.5 months later.

Reviewer comment: It is unlikely that lasmiditan contributed to this event as the most recent dose of lasmiditan had been six days prior.

I summarize select narratives reporting TEAEs related to suicidal ideation here.

Suicidal Ideation (b) (6)
A 42-year-old female with history hypothyroidism developed the TEAE of suicidal ideation ("wanting to die") 39 minutes after taking the most recent dose of lasmiditan. The event lasted for four hours. On the same day, the subject also reported anxiety, fatigue, depressed mood and dizziness. Concomitant medications included levothyrodine, liothyronine, and valacyclovir. She had taken one dose of lasmiditan prior to the event occurring. The subject did not have any affirmative responses to the items in the C-SSRS during the study.

Reviewer comment: A role for lasmiditan in the AE of suicidal ideation cannot be ruled out given timing of the event to administration of drug. A confounding factor in this case is concomitant medication use with valacyclovir as depression and dizziness were among the most common AEs for valacyclovir in a clinical study for suppression of recurrent genital herpes infection.

Suicidal ideation (b) (6)
A 40-year-old female with history of anxiety, depression, hypothyroidism, and insomnia developed the TEAE of suicidal ideation one day after her most recent dose of lasmiditan which led to discontinuation from the study. She had taken 40 doses of lasmiditan prior to the AE. Concomitant medications included bupropion, clonazepam, levothyroxine, melatonin, linaclotide, and sertraline. Affirmative responses related to suicidal ideation were noted on the C-SSRS at study visit 4 which preceded the TEAE by three months.

Reviewer comment: A role for lasmiditan in the AE of suicidal ideation cannot be established given that the subject had affirmative responses to the C-SSRS for suicidal ideation three months before to the event. Confounding factors in this case include previous history of anxiety and depression.

C-SSRS Affirmative Response/Discontinued due Depression (b) (6)
A 19-year-old female with history of depression and anxiety was hospitalized for the SAE of depression which occurred 45 days after the most recent dose of lasmiditan. She had treated three migraines in study 305 and three migraines in the pre-administrative hold period of study 305. At her end of study visit (twenty-two days after the hospitalization), she was noted to have affirmative responses on the C-SSRS of: wish to be dead; non-specific active suicidal thoughts; active suicidal ideation with specific plan and intent; preparatory acts or behavior; non-fatal suicide attempt. She discontinued from study 305 due to the event of depression. Relevant concomitant medications included sertraline, trazodone, levonorgestrel, and prazosin.

Reviewer comment: A role for lasmiditan cannot be established in the event of suicidal ideation as indicated by affirmative responses on the C-SSRS. Her history of depression and anxiety as well as her recent hospitalization for depression are confounding factors in this case.

In the clinical pharmacology studies, the sponsor did not identify any TEAEs related to suicidal ideation or behaviors or self-injurious behavior after using the Suicide and Self-Injury-Related SMQ. Additionally, there were no affirmative responses to the C-SSRS in the studies where this data was collected (Studies LAHR, LAHG, LAHH, LAHN, LAHF, LAHI, LAHB, LAHC, LAHE, LAIG, and LAHT).

In Study 305, 1 SAE each of depression and suicidal ideation led to discontinuation.

The following table shows TEAEs belonging to the SMQ of Depression excluding suicide and self-injury. No lasmiditan arm in the placebo-controlled trials had an incidence greater than 1%.

Table 51. TEAEs Belonging to SMQ of Depression[a] in Studies 202/301/302 and 305 after 120 Day Safety Update.

202/301/302					305		
50 mg N=736 n (%)	100 mg N=1347 n (%)	200 mg N=1329 n (%)	All-LTN N=3412 n (%)	Placebo N=1347 n (%)	100 mg N=991 n (%)	200 mg N=1039 n (%)	All-LTN N=2030 n (%)
1 (0.1)	11 (0.8)	10 (0.8)	22 (0.6)	1 (0.1)	15 (1.5)	17 (1.6)	32 (1.6)

Reviewer created table from ISS dataset ADSL for studies 202, 301, and 302: studyID=202, 302, 302,treatment=TRT01A, ADAE: TRTEMFL = Y. For study 305: ADSL with HLSAFFL=Y, ADAE with studyID = 305, TRTEM3FL=Y. [a]Excluding suicide and self-injury.

Overall, a role for lasmiditan cannot be established in the development of suicidal ideation.

8.5.7. Serotonin Syndrome

Two cases of potential serotonin syndrome were identified in lasmiditan-treated subjects. Given that lasmiditan acts on 5-HT receptors and could potentially cause effects seen with serotonin excess, assessing for cases of serotonin syndrome was an area of special interest. The sponsor identified potential cases across the clinical development program by searching for TEAEs within the SMQ of Neuroleptic Malignant Syndrome and by searching for the following preferred terms: orthostatic hypotension, urinary incontinence, urinary retention, oesophageal dysmotility, gastroparesis, diarrhoea, faecal incontinence, constipation, muscle twitching, muscle stiffness, and muscle spasm. The cases were medically reviewed by physicians and nine cases were determined to require further review. Cases were assessed for Serotonin Syndrome using Hunter and Sternbach criteria.

Of the nine cases that were identified by the sponsor as requiring further review, six cases did not meet Hunter or Sternbach criteria. The three other cases met Sternbach criteria, but not Hunter criteria for Serotonin Syndrome and I summarize them here.

Moderate Serotonin Syndrome/Flushing (b) (6)
A 52-year-old female (past medical history unknown) experienced the TEAEs of moderate serotonin syndrome and moderate flushing three minutes after dosing with 45 mg lasmiditan intravenously. The TEAEs resolved within 12 minutes. The subject experienced mild dizziness 17 hours after the dose which lasted for 10 hours. Baseline blood pressure was 138/96 mmHg and pulse rate 62 bpm. At 10 and 20 minutes after dosing her blood pressure was 152/92 mmHg and 150/97 mmHg, respectively. Her pulse rate at 10 and 20 minutes after dosing was 52 bpm and 56 bpm, respectively. No concomitant medications were taken.

Reviewer comment: The case did not meet Hunter's or Sternbach's criteria for serotonin syndrome (the case lacked reports of clonus, tremor, hyperreflexia, temperature above 38°C, mental status changes, agitation, myoclonus, diaphoresis, diarrhea, or incoordination). Given the lack of reported symptoms except for flushing and resolution of the symptoms within 12 minutes, the case is not supportive of a diagnosis of serotonin syndrome.

Muscle Twitching/Tremor/Agitation (b) (6)
A 61-year-old female with history of depression, hypertension, and neck pain developed twitching muscles, tremor, and agitation within 1.5 hours of dosing with lasmiditan 100 mg. The TEAEs were moderate in severity. The muscle twitching lasted for 10 minutes, and the tremor and agitation lasted for one hour. She had treated eight migraine attacks prior to developing these TEAEs. Amoxicillin/clavulanic acid was a concomitant medication. She treated one additional migraine in the study and discontinued from the study due to the TEAEs of somnolence, fear, and agitation.

Reviewer comment: The case did not meet Hunter's criteria for serotonin syndrome but did meet Sternbach criteria. It is possible that this case could represent Serotonin Syndrome. Notably, additional treatment for the symptoms of tremor, agitation and twitching muscles was not required, and symptoms resolved within 1.5 hours of dosing.

Tremor/Agitation/Ataxia (b) (6)
A 39-year-old female with history of hypothyroidism experienced tremor, nightmare, perceptual distortion, muscle weakness of the jaw and eyes, derealization, and agitation which were categorized as moderate in severity and dizziness and ataxia that were categorized as severe. The onset of the symptoms occurred within 25 minutes of dosing with lasmiditan 400 mg and resolved within six hours except for agitation and nightmare which lasted 36 hours. Concomitant medications included frovatriptan (taken 25 hours after dosing with lasmiditan) and dimenhydrinate.

Reviewer comment: The case did not meet Hunter's criteria for serotonin syndrome but did meet Sternbach criteria given the symptoms of tremor, agitation, and ataxia. It is possible that this case could represent Serotonin Syndrome caused by lasmiditan.

In conclusion, two cases met Sternbach criteria for Serotonin Syndrome. The majority of symptoms experienced by the two subjects resolved within 6 hours of dosing without treatment.

8.6. Safety Analyses by Demographic Subgroups

8.6.1. Sex, Age, Ethnicity and Race

I evaluated the incidence of common TEAEs (dizziness, fatigue, nausea, paresthesias, somnolence and vomiting) reported in studies 301/302 by the following demographics: sex; age; ethnicity; race.

For the analysis of the demographic of sex, the incidence of common TEAEs was similar in female compared to male subjects treated with lasmiditan.

For analysis of the demographic of age, dizziness was reported at a higher incidence in lasmiditan-treated subjects in the age group greater than 65 years (lasmiditan 18.9%, placebo 1.9%) compared to less than 65 years (lasmiditan 14.5%, placebo 3.0%). The incidence of paresthesias increased with increasing age groups. The following table shows common TEAEs reported in studies 301 and 302 by age group.

Table 52. Common TEAEs by Age Group in Studies 301 and 302.

Preferred Term	Age < 30 years		≥ 30 to <50 years		≥ 50 to <65 years		≥ 65 years	
	All LTN N = 560 %	PBO N=234 %	All LTN N=1666 %	PBO N=639 %	All LTN N=819 %	PBO N=335 %	All LTN N=132 %	PBO N=54 %
Dizziness	17.3	3.8	13.9	3.0	13.8	2.4	18.9	1.9
Fatigue	2.9	0.4	3.8	0.6	4.6	0.6	2.3	1.9
Nausea	3.6	1.3	3.2	2.0	3.7	0.6	3.0	3.7
Paresthesia	3.8	0.9	5.2	1.4	7.6	1.8	7.6	3.7
Somnolence	5.7	0.9	5.5	2.5	5.9	2.7	2.3	0.0
Vomiting	0.7	0.9	1.3	0.6	0.6	0.6	0.8	0.0

Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 301 and 302, TRTEM1FL=Y. The denominator is the safety population for studies 301 and 302 (IDB ADSL dataset with ASETBFL=Y, TRTAG1=Y. LTN= lasmiditan, PBO=placebo.

For analysis of the demographic of ethnicity, the Hispanic subgroup had a lower incidence of dizziness compared to non-Hispanics subgroup in subjects who received lasmiditan (9.2% versus 15.8%).

For analysis of the demographic of race, differences in incidence of common TEAEs reported in lasmiditan-treated subjects were noted however the number of subjects in some race categories was low. The following table shows incidence of common TEAEs occurring in studies

301 and 302 by race and treatment arm. A higher incidence of dizziness, paresthesias, nausea, and fatigue was seen in white subjects compared to black subjects.

Table 53. Incidence of Common TEAEs Occurring in Studies 301 and 302 by Race.

Preferred Term	American Indian or Alaska Native		Asian		Black or African American		Multiple		Other		White	
	All LTN N=21 %	PBO N=6 %	All LTN N=26 %	PBO N=5 %	All LTN N=563 %	PBO N=229 %	All LTN N=35 %	PBO N=11 %	All LTN N=46 %	PBO N=12 %	All LTN N=2476 %	PBO N=995 %
Dizziness	9.5	0	15.4	0	9.9	4.8	14.3	9.1	15.2	16.7	15.8	2.3
Fatigue	4.8	0	3.8	0	2.7	0	0	0	2.2	0	4.1	0.8
Nausea	9.5	0	3.8	0	2.8	1.7	0.0	9.1	2.2	8.3	3.5	1.4
Paresthesia	4.8	0	0	0	1.1	1.3	2.9	0	8.7	0	6.8	1.6
Somnolence	9.5	0	15.4	0	6.0	1.7	11.4	0	10.9	0	5.1	2.3
Vomiting	4.8	0	0	0	1.1	0	0	0	0	0	1.0	0.8

LTN: Lasmiditan, PBO: placebo. Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 301 and 302, TRTEM1FL=Y. The denominator is the safety population for studies 301 and 302 (IDB ADSL dataset with ASETBFL=Y, TRTAG1=Y.

8.6.2. Hepatically Impaired and Renally Impaired

Study 114 evaluated a single dose of lasmiditan 200 mg in subjects with mild and moderate hepatic impairment compared to healthy subjects. Each treatment arm had eight subjects. Hepatically-impaired subjects reported similar rates of TEAEs as compared to healthy subjects. The most commonly reported TEAEs in hepatically-impaired subject was somnolence.

In the Phase 1 studies, one subject (study LAHB) experienced the TEAE of increased ALT and I summarize the narrative here.

Increased ALT (b) (6)
A 29-year-old male with history of polyrecreational drug use experienced ALT elevation up to 215 U/L (ULN 46 U/L) and AST elevation up to 125 U/L (ULN 40 U/L) with normal bilirubin and alkaline phosphatase levels after receiving alprazolam 2 mg five days before in the human abuse liability study. He had also received placebo and lasmiditan 100, 200, and 400 mg in previous dosing periods of the study. Two days later, his ALT had decreased to four times the ULN and seven days later, the event was considered resolved by the investigator. The subject reported occasional use of tetrahydrocannabinol, Xanax, and cocaine. A urine drug screen at a follow up visit was positive for benzodiazepine and marijuana metabolites.

Reviewer comment: A role for lasmiditan in the event of increased ALT cannot be established given the predisposing risk factors of recreational drug use.

Overall, I did not identify a signal for hepatic injury. Cases of hepatic laboratory abnormalities were missing diagnostic evaluations to rule out alternate etiologies or had multiple other confounding factors which made it difficult to establish a relationship between lasmiditan and the adverse events.

Study 113 evaluated the effects of a single dose of lasmiditan 200 mg in renally impaired subjects and normal renal function subjects. Renally-impaired subjects reported similar rates of TEAEs as compared to normal-renal function subjects. Higher rates for the following TEAEs were reported in renally-impaired subjects compared to no reports in normal renal function subjects: fatigue (n=3), hypoesthesia n=2), paresthesia (n=2), orthostatic hypotension (n=2). The low number of subjects enrolled in each treatment arm (n=8) make it difficult to draw further conclusions regarding TEAEs reported in this study.

8.7. Specific Safety Studies/Clinical Trials

8.7.1. Driving studies

The sponsor's analysis demonstrated driving impairment in healthy subjects in a simulated driving experience. The sponsor conducted two simulated driving studies in healthy volunteers to evaluate the effects of lasmiditan on driving. Study 106 examined the effects of a single dose of lasmiditan 50 mg, 100 mg, and 200 mg and alprazolam 1 mg (positive control) compared to placebo on standard deviation of lateral position (SDLP). Study LAIF examined the effects of lasmiditan 100 mg and 200 mg and diphenhydramine 50 mg (positive control) on SDLP difference from placebo at 8, 12, and 24 hours after dosing. The studies were conducted consistent with the guidance Evaluating Drug Effects on the Ability to Operate a Motor Vehicle. The two studies are summarized here.

Study 106
Study 106 was a double-blinded, randomized, placebo-controlled study where subjects were given a single dose of lasmiditan 50 mg, 100 mg, 200 mg, placebo, or alprazolam 1 mg and then asked to participate in a simulated driving experience that started 90 minutes after dosing.

The study included a 5-period crossover where subjects were randomized to different treatment sequences. Each period within the treatment sequence consisted of exposure to study drug on the first day followed by a 5-day washout period. Subjects could be enrolled if they were between 21 and 50 years of age.

The primary endpoint was to determine the effects of study drug on standard deviation of lateral position (SDLP) using the Cognitive Research Corporation Driving Simulator-MiniSim (CRCDS-MiniSim).

Secondary endpoints included determining the effect of study drug on: subject sleepiness as measured by the Karolinska Sleepiness Scale; self-perceived safety to drive, assessment of subject's motivation and self-appraisal by Visual Analog Scale; performance, reaction time and accuracy as measured on the CogScreen Symbol Digit Coding and driving performance.

See Section 13.3 of the appendix for further descriptions of the driving assessments performed.

In terms of statistical analysis, pair-wise comparison of differences in least squared means and 95% confidence intervals of the differences were performed for lasmiditan 50 mg, 100 mg, 200 mg, and alprazolam 1 mg compared to placebo and lasmiditan 50 mg, 100 mg, or 200 mg compared to alprazolam 1 mg for the primary endpoint.

The prespecified inferiority margin was 4.4 centimeters and is what has been previously identified on the CRCDS as the difference in SDLP between subjects given placebo and subjects

with a blood alcohol concentration of 0.05%. Doses of lasmiditan were considered non-inferior to placebo if the upper 95% confidence limit of the difference in SDLP compared to placebo was less than 4.4 centimeters and lower doses did not exceed the inferiority margin. Pair-wise within-subject differences in SLDP greater than 4.4 cm in absolute value were compared using the McNemar test and tested for symmetry about zero using maximally-selected McNemar's test.

Results of Study 106

Ninety subjects were randomized (44 male, 46 female) and 84 subjects completed the study. One subject withdrew due to an AE (shoulder dislocation while playing hockey which occurred 3 days after taking lasmiditan). The AE was not thought to be related to study drug based on timing. The mean age of subjects was 34.9 years.

Primary endpoint

Alprazolam had a difference in least squared (LS) means in SDLP from placebo of 22.7 centimeters (95% CI 20.2, 25.2). Given that the confidence interval for the difference in LS means for alprazolam was greater than the pre-specified inferiority margin of 4.4 cm, the sensitivity of the driving simulator was established.

The table below shows differences in LS means in SDLP between lasmiditan 50 mg, 100 mg, and 200 mg and alprazolam 1 mg compared to placebo.

Table 54. Difference in LS Means in SDLP (cm) Compared to Placebo in Study 106.

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	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)

Data from the above table was taken from Table 11-3 of Study 106 report submitted by the sponsor. CI: confidence interval.

Reviewer comment: The table shows that the difference in LS means for all doses tested for lasmiditan compared to placebo is greater than 4.4 centimeters indicating that lasmiditan was inferior to placebo.

Secondary Endpoints

Lasmiditan at all doses was inferior to placebo in the following secondary endpoints: Cogscreen Symbol Digit Coding (# of correct responses in 120 seconds and reaction time variability); Karolinska Sleepiness Scale; Visual Analog Scale for Motivation and Self Appraisal for Driving; Number of Lane Exceedances; Maximum Lane Exceedance; Lane Exceedance Duration; Speed

Deviation; Excessive speeding around corners; Collisions; Errors of omission, reaction time, and reaction time variability with divided attention. Subjects given lasmiditan 100 mg and 200 mg doses performed worse than subjects given placebo with tests of speeding and correct responses with divided attention. Lasmiditan 200 mg was inferior to placebo on errors of commission with divided attention. Alprazolam was inferior to placebo for all secondary endpoints tested except for average speed.

The following table shows results of tests related to speed and collision in Study 106. A dose-dependent response is seen with the parameters of mean excessive speeding around corners, mean speed deviation, and mean speedings count.

Table 55. Secondary Endpoints Related to Collision and Speed in Study 106.

Parameter	LTN 50 mg N=87	LTN 100 mg N=86	LTN 200 mg N=89	Alprazolam 1 mg N=85	Placebo N=85
Mean Average Speed (m/sec)	26.4	26.3	26.4	26.4	26.3
Mean Excessive Speeding Around Corners (lateral g force)	196.0	231.5	275.3	197.7	116.0
Mean Speed Deviation (m/sec)	0.8	0.9	1.0	1.2	0.6
Mean Speedings Count	3.3	5.0	7.9	12.3	1.0
Mean Total Collisions	0	0	0.1	0.1	0

Reviewer created table from Study 106 dataset ADXD dataset, SAFFL=Y.

AEs and TEAEs in Study 106

There were no deaths. One patient had an SAE of cerebellar hematoma that has been described previously in the Safety Results SAE section (Section 8.4.2.), and I considered to be unrelated to study drug. The below table indicates the most frequently occurring TEAEs in Study 106.

Table 56. TEAEs With an Incidence of At Least 8% and 8% Greater than Placebo in Study 106.

Preferred Term	Lasmiditan 50 mg n=87 %	Lasmiditan 100 mg n=86 %	Lasmiditan 200 mg n=89 %	Alprazolam 1 mg n=85 %	Placebo n=85 %
Somnolence	11	27	43	53	2

Preferred Term	Lasmiditan 50 mg n=87 %	Lasmiditan 100 mg n=86 %	Lasmiditan 200 mg n=89 %	Alprazolam 1 mg n=85 %	Placebo n=85 %
Dizziness	16	20	40	31	1
Fatigue	17	12	8	16	2
Lethargy	3	5	8	4	0

Reviewer created table from Study 106 dataset ADAE, TRTEMFL=Y, SAFFL=Y, TRT01A=Y, TEAEs grouped by USUBJID.

Reviewer comment: The most frequently occurring TEAEs in Study 106 could potentially be contributing to the driving impairment seen in lasmiditan-exposed subjects.

Study LAIF

Study LAIF was a double-blinded study that evaluated the effect of a single dose of lasmiditan 100 mg or 200 mg on SDLP at 8, 12, and 24 hours after dosing. Diphenhydramine 50 mg was used as a positive control and was administered 2 hours prior to each driving assessment.

The study included a 4-period crossover where subjects were randomized to one of four treatment sequences. Each period within the treatment sequence consisted of exposure to study drug on the first day followed by a 3-day washout period. Subjects could be enrolled if they were between 21 and 50 years of age.

The primary endpoint was to determine the effects of study drug on SDLP.

Secondary endpoints included determining the effects of study drug on: subject sleepiness as measured by the Karolinska Sleepiness Scale; self-perceived safety to drive, assessment of subject's motivation and self-appraisal by Visual Analog Scale; performance, reaction time and accuracy as measured on the CogScreen Symbol Digit Coding and driving performance.

In terms of statistical methods, raw and change from baseline values for primary and secondary endpoints for each time point and treatment group were summarized using descriptive statistics. For primary and secondary endpoints, pairwise comparison of differences in LS means and 95% confidence intervals were evaluated at each timepoint for lasmiditan 100 mg, lasmiditan 200 mg, and diphenhydramine compared to placebo. Pairwise within-subject differences in SDLP greater than 4.4 centimeters in absolute values were compared using McNemar's test and were also tested for symmetry about zero using maximally-selected McNemar's test.

Results of Study LAIF

Sixty-eight subjects were randomized (40 male and 28 female subjects) and 67 subjects completed the study. The mean age of subjects was 32.8 years. There were no withdrawals due to an AE.

Two protocol deviations occurred where two subjects had assessments of AEs performed by an unblinded study investigator. Adverse events of those patients were subsequently reassessed by a blinded investigator.

Primary Endpoint

The table below shows differences in LS means in SDLP between lasmiditan 100 mg, lasmiditan 200 mg, diphenhydramine 50 mg and placebo at 8, 12, and 24 hours.

Table 57. Difference in LS Means in SDLP (cm) Compared to Placebo in Study LAIF.

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)

Data from the above table was taken from Table LAIF.7.10 submitted by the sponsor. CI: confidence interval

Reviewer comment: A discussion on 25/04/2019 with Statistical Reviewer Dr. Eugenio Andraca-Carrera confirmed that the results of the diphenhydramine arm (positive control) indicate that the trial is sensitive enough to detect a difference in SDLP of >4.4 cm at any given timepoint. The difference in LS means in SDLP from placebo for 100 mg and 200 mg lasmiditan doses at 8, 12, and 24 hours demonstrated noninferiority to placebo.

The table below shows the percentage of subjects by treatment arm with a difference in SDLP compared to placebo of greater than 4.4 cm at 8, 12, and 24 hours after dosing.

Table 58. Percentage of Subjects by Treatment Arm with Difference in SDLP Compared to Placebo of Greater Than 4.4 cm in Study LAIF.

Treatment	8 hours N = 67 %	12 hours N = 67 %	24 hours N= 67 %
Lasmiditan 100 mg	21	15	9
Lasmiditan 200 mg	25	13	13
Diphenhydramine 25 mg	44	38	49

Data for this table was taken from the sponsor's submission table LAIF.7.13.

Reviewer comment: This table shows that at 8 hours after dosing, approximately 21% of subjects given lasmiditan 100 mg and 25% given lasmiditan 200 mg had a difference in SDLP

compared to placebo greater than 4.4 cm. At 12 hours after dosing, the number of subjects with a difference in SDLP compared to placebo greater than 4.4 cm decreased to 15% and 13%, respectively.

Dr. Priya Brunson, FDA clinical pharmacologist, evaluated the exposure-response relationship in lasmiditan-treated subjects with impaired driving at 8, 12, and 24 hours and did not find differences in exposure that correlated with subjects with SDLPs greater than 4.4 centimeters. Please see the Clinical Pharmacology summary for further details. These findings suggest that other factors such as variable performance on the driving test not related to lasmiditan concentrations may affect subjects at later timepoints.

I evaluated the gender of subjects with a difference in SDLP compared to placebo of greater than 4.4 cm at timepoints 8, 12, and 24 hours after dosing to determine if changes in SDLP correlated with gender. The table below shows the percentage of subjects with difference in SDLP compared with placebo of greater than 4.4 cm by treatment arm and gender.

Table 59. Percentage of Subjects by Treatment Arm and Gender with Difference in SDLP Compared with Placebo > 4.4 cm at 8, 12, and 24 Hours Post Dose in Study LAIF.

Treatment	8 hours		12 hours		24 hours	
	Female N=28 n (%)	Male N=39 n (%)	Female N=28 n (%)	Male N=39 n (%)	Female N=28 n (%)	Male N=39 n (%)
Lasmiditan 100 mg	8 (28.6)	6 (15.4)	5 (18.5)	5 (12.8)	2 (7.1)	4 (10.3)
Lasmiditan 200 mg	10 (35.7)	6 (15.4)	7 (25.0)	1 (2.6)	3 (10.7)	5 (12.8)
Diphenhydramine 50 mg	13 (46.4)	16 (41.0)	11 (39.3)	15 (38.5)	14 (50.0)	18 (46.2)

Data is taken from the 13/06/2019 response to an information requested dated 11/06/2019.

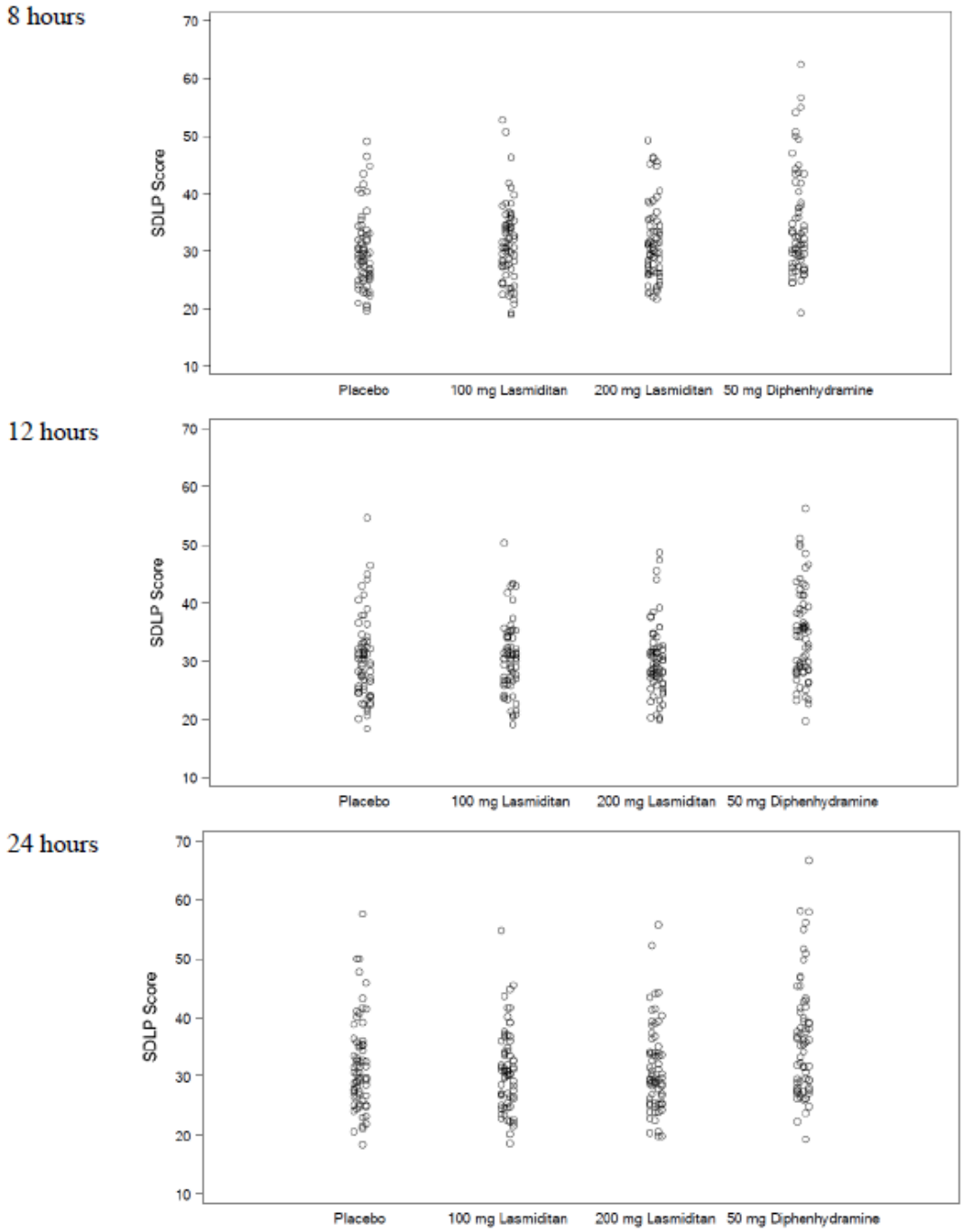
Reviewer comment: The table shows that female subjects exposed to lasmiditan are more likely to have an SDLP greater than 4.4 cm at 8 and 12 hours after dosing compared with male subjects. At 12 hours after dosing, greater than 10% of subjects treated with lasmiditan 100 mg continued to experience driving impairment. The low percentage of male subjects in the lasmiditan 200 mg treatment arm appears to be a spurious result and could be due to the low number of subjects enrolled in the study. The result demonstrates the difficulty in interpreting data from a small sample population.

As per the Clinical Pharmacology summary, no gender differences in exposure were seen in subjects who received lasmiditan. The reader is referred to the Clinical Pharmacology summary for further details on the effects of gender on exposure.

The sponsor performed an analysis of variation in SLDP in subjects who received lasmiditan and diphenhydramine compared to placebo at 8, 12, and 24 hours. The following figure shows that

the lasmiditan 100 mg and 200 mg arms had a distribution of SDLP scores that was more similar to placebo at 8, 12, and 24 hours than to the positive control arm.

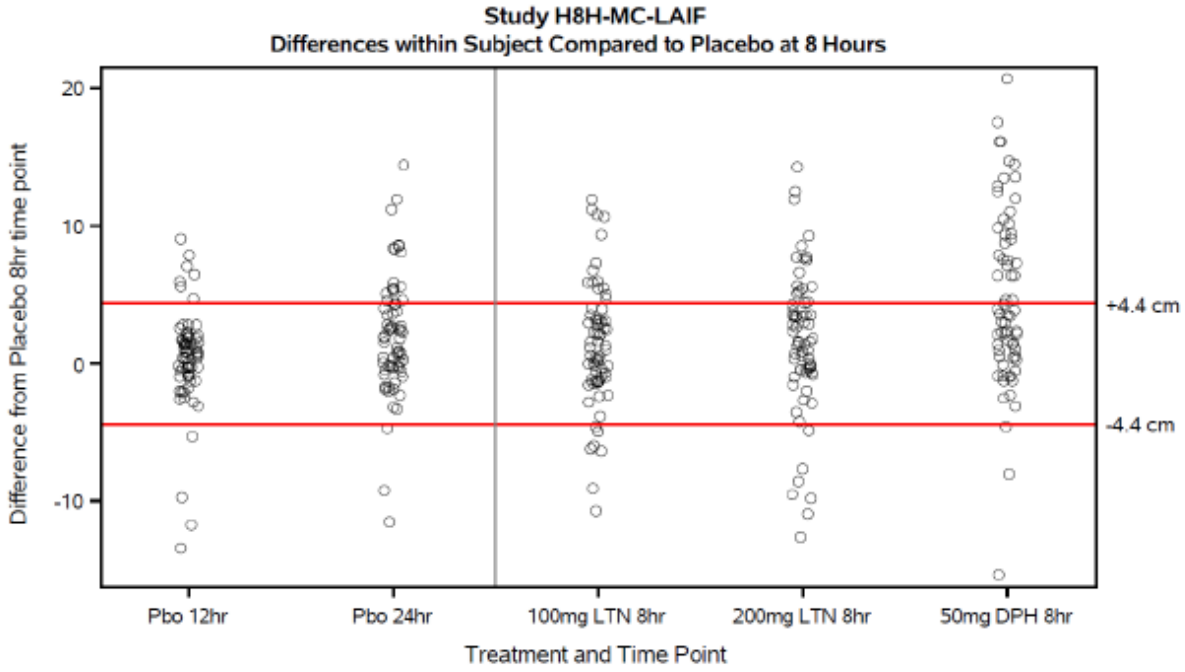
Figure 2. Distribution of Observed SDLP Values at 8, 12, and 24 Hours in Study LAIF.



The above figure was taken from the 25/09/2019 sponsor's Regulatory Response Requests Regarding Labeling.

The sponsor assessed within-subject variations in SDLP scores in study LAIF by performing a comparison of 8-hour placebo-subtracted SDLP scores between 12- and 24-hour placebo arms and 8-hour lasmiditan 100 mg, 200 mg, and diphenhydramine arms. Lasmiditan 100 mg and 200 mg arms had a distribution of SDLP scores that was similar to placebo arms at 12 and 24 hours and different from the positive control of diphenhydramine.

Figure 3. Within-Subject Differences in SDLP Compared to Placebo in Study LAIF



Abbreviations: DPH = diphenhydramine; LTN = lasmiditan; Pbo = placebo.

The above figure was taken from the 25/09/2019 sponsor's Regulatory Response Requests Regarding Labeling.

Reviewer comment: The figures show that variability in SDLP scores exist even in subjects exposed to placebo. The distribution of SDLP scores in lasmiditan-exposed subjects appears similar to placebo which suggests that variations in SDLP score in lasmiditan-exposed subjects were not due to the effects of drug.

Results of Secondary Endpoints for Study LAIF

Cogscreen Symbol Digit Coding Mean Speed: Subjects given lasmiditan 200 mg at 8 hours had a slightly higher mean speed (worse performance) compared to subjects given placebo (1.6 vs 1.5 seconds).

Karolinska Sleepiness Scale: Subjects given lasmiditan 200 mg at 8 hours had a statistically significant increase in sleepiness compared to placebo. The mean KSS rating for subjects taking

diphenhydramine showed increased sleepiness compared to placebo that was statistically significantly at 8 and 12 hours.

Self-Perceived Safety to Drive: No subjects receiving lasmiditan 100 mg or 200 mg felt unsafe to drive at any time point. One subject 8 hours after receiving placebo and two subjects 2 hours after receiving diphenhydramine felt unsafe to drive.

Reviewer comment: The results of the Self-Perceived Safety to Drive question demonstrate that subjects lacked insight into when they may have been driving impaired.

Driving Performance: At 12 hours post-dosing, a decrease in performance in subjects given lasmiditan 100 mg was noted that appeared to be driven by an outlier who reported decreased motivation compared to baseline in performing the task.

Number of lane exceedances: There was a statistically significant increase in lane exceedances in subjects who received lasmiditan 200 mg at 8 hours. At 12 hours, there was a significantly increased amount of lane exceedances for subjects who received lasmiditan 100 mg and a small but not statistically significant increase in subjects who received lasmiditan 200 mg. Subjects who received diphenhydramine had a statistically significant increase in the number of lane exceedances at 8, 12, and 24 hours.

The following table shows results of tests related to speed and collision in study LAIF. Subjects who received lasmiditan performed worse with mean speedings count compared to subjects who received placebo at 8, 12, and 24 hours. The significance of the observed difference in mean speedings is not known as differences between lasmiditan and placebo arms was not seen with other measures related to collision and speed.

Table 60. Secondary Endpoints Related to Collision and Speed in Study LAIF.

Parameter	Time Period Post-dosing (hours)	LTN 100 mg N=68	LTN 200 mg N=68	Diphenhydramine 50 mg N=68	Placebo N=67
Mean Average Speed (m/sec)	8	27.5	27.8	27.9	27.7
	12	27.8	27.9	28.1	27.9
	24	27.8	27.9	27.9	27.8
Mean Excessive Speeding Around Corners (lateral g force)	8	127.9	139.5	142.0	128.5
	12	121.0	122.1	125.1	121.7
	24	117.6	119.2	125.8	122.7
Mean Speed	8	0.9	1.0	1.1	0.9

Parameter	Time Period Post-dosing (hours)	LTN 100 mg N=68	LTN 200 mg N=68	Diphenhydramine 50 mg N=68	Placebo N=67
Deviation (m/sec)	12	1.0	0.9	1.1	1.0
	24	0.9	1.1	1.2	1.0
Mean Speedings Count	8	13.1	11.9	10.9	9.5
	12	14.4	13.5	12.1	10.4
	24	17.0	17.7	13.2	13.6
Mean Total Collisions	8	0.0	0.0	0.4	0.1
	12	0.0	0.1	0.2	0.1
	24	0.0	0.2	0.6	0.2

Reviewer created table from Study LAIF dataset ADXD dataset, SAFFL=Y.

For a listing of the results of additional secondary endpoints in study LAIF, see Section 13.3 of the appendix.

The most commonly reported TEAEs in study LAIF (reported by more than 3 subjects) were dizziness, somnolence, fatigue, headache, and paresthesias. Four subjects reported TEAEs within 8 hours of dosing that had not resolved by 8 hours after dosing. The reported TEAEs included somnolence, dizziness, and insomnia.

Conclusion of Driving Studies

In study 106, subjects exposed to lasmiditan had impaired driving as evidenced by a mean SDLP score of greater than 4.4 centimeters at 90 minutes after dosing. In study LAIF at 8, 12, and 24 hours after dosing, difference in mean SDLP scores for lasmiditan 100 mg and 200 mg were not greater than the pre-specified inferiority margin of 4.4 centimeters. Although a percentage of lasmiditan-exposed subjects had SDLP scores greater than 4.4 centimeters at each timepoint, this was not considered to be clinically meaningful by the team primarily because interpretation of SDLP scores at the individual level has not been validated.[11] Other factors that are supportive of a population effect not related to drug include that lasmiditan-exposed treatment arms had similar patterns of distribution of SDLP scores as placebo arms at 8, 12, and 24 hours. Additionally, lasmiditan-exposed subjects had similar distributions of 8-hour placebo-subtracted SDLP scores as compared to placebo. Lastly, mean number of collisions occurring in the driving study in lasmiditan arms was more similar to placebo than to positive control.

[11] Jongen S, Vermeeren A, van der Sluiszen NJJM, Schumacher MB, Theunissen EL, Kuypers KPC, Vuurman EFPM, Ramaekers JG. A pooled analysis of on-the-road highway driving studies in actual traffic measuring standard deviation of lateral position (i.e., "weaving") while driving at a blood alcohol concentration of 0.5 g/L. Psychopharmacology (2017) 234:837–844. DOI 10.1007/s00213-016-4519-z

Overall, I support a Warnings and Precautions Statement be added to labeling to indicate that patients should not drive for at least 8 hours after taking lasmiditan. Subjects appeared to lack insight into when they may be impaired to drive as indicated by the Self-Perceived Safety to Drive question and I recommend that this be added to the label.

8.7.2. Drug-Drug Interactions Studies

The reader is referred to the Clinical Pharmacology review for further details regarding the clinical pharmacology studies. Drug-drug interactions were evaluated in individual in vitro studies and studies in healthy volunteers.

Sumatriptan

The sponsor conducted a drug-drug interaction study with sumatriptan and lasmiditan and did not find clinically significant changes in vital sign or ECG changes. Sumatriptan is an acute treatment for migraine and could potentially be administered with lasmiditan; therefore, the effect of sumatriptan in combination with lasmiditan was an area of interest. Studies LAHU and LAHI assessed the effects of co-administration of sumatriptan 100 mg with a single dose of lasmiditan 200 mg.

In study LAHU, vital signs were collected at baseline, 1, 2, 4, and 24 hours after study drug. The four treatment arms of the study included 100 mg sumatriptan, 200 mg lasmiditan, 200 mg lasmiditan + 100 mg sumatriptan, and placebo. The results for supine systolic and diastolic blood pressure and for pulse rate are shown in the table below for timepoints after baseline. Lasmiditan 200 mg + sumatriptan 100 mg in comparison to lasmiditan 200 mg treatment arm had a higher maximum mean increase in systolic blood pressure (6.0 mmHg versus 2.4 mmHg), a higher maximum mean increase in diastolic blood pressure (4.6 mmHg versus 2.8 mmHg), and a lower maximum mean decrease in pulse rate (-8.3 bpm versus -9.9 bpm).

Table 61. Vital Signs Mean Change from Baseline in Study LAHU.

Parameter and Timepoint	Placebo N=40	100 mg Sumatriptan N=39	LTN 200 mg N=39	LTN 200 mg + 100 mg Sumatriptan N=39
Systolic Blood pressure (mmHg)				
1 hour	0.4	4.1	2.4	5.9
2 hour	1.5	4.8	1.7	6.0
4 hour	-0.1	3.1	-0.1	3.4
24 hour	-1.8	-2.6	-1.2	-0.1
Diastolic Blood Pressure (mmHg)				
1 hour	0.0	4.1	2.8	4.6
2 hour	1.2	4.0	-0.4	2.8
4 hour	-3.4	0.4	-5.9	-1.4

Parameter and Timepoint	Placebo N=40	100 mg Sumatriptan N=39	LTN 200 mg N=39	LTN 200 mg + 100 mg Sumatriptan N=39
24 hour	-3.0	-2.9	-2.6	-2.8
Pulse (beats per minute)				
1 hour	-2.7	-2.4	-7.6	-5.9
2 hour	-3.5	-2.9	-9.9	-8.3
4 hour	5.0	5.0	-0.2	-0.1
24 hour	9.5	9.8	8.3	9.6

Data is taken from the 28/05/2019 response to an information requested dated 22/05/2019. Vitals reported were taken in the supine position.

Similar findings of an increase in SBP and DBP and decrease in pulse rate, with a similar time course, were observed in study LAHI.

A vital sign outlier analysis performed by the sponsor for study LAHU, and included in a 28/05/2019 response to an information requested dated 22/05/2019, showed similar rates in subjects who received lasmiditan 200 mg + sumatriptan 100 mg compared to subjects who received lasmiditan 200 mg.

In the same response, the sponsor performed an analysis of mean change in orthostatic vital signs for study LAHI. No evidence of orthostasis after study drug in the 200 mg lasmiditan + 100 mg sumatriptan arm was seen compared to 200 mg lasmiditan or 100 mg sumatriptan arms.

In the same response, the sponsor performed an orthostatic vital sign outlier analysis for study LAHI. The analysis showed a higher percentage of subjects who received lasmiditan 200 mg + sumatriptan 100 mg were orthostatic by DBP change (decrease of > 10 mmHg) as compared to subjects who received lasmiditan 200 mg (7.5% versus 0%). The overall difference in the number of subjects with orthostatic DBP changes between the two treatment arms was low (n=3).

In study LAHI, a higher incidence of TEAEs were reported in subjects who received 200 mg lasmiditan + 100 mg sumatriptan reported compared to subjects who received 200 mg lasmiditan (71.4% (30/42) versus 63.4% (26/41), respectively). A higher percentage of subjects who received 200 mg lasmiditan + 100 mg sumatriptan reported the TEAE of hypersomnia compared to subjects who received 200 mg lasmiditan (38.1% (16/42) versus 22.0% (9/41), respectively.

In study LAHI, ECGs were performed at baseline, 1, 1.5, 2, 2.5, 4, 8, and 24 hours post-dose. A higher percentage of subjects who received 200 mg lasmiditan + 100 mg sumatriptan reported the TEAE of first-degree AV block compared to subjects who received 200 mg lasmiditan (9.5%

(4/42) versus 4.9% (2/41), respectively). The PR interval in all cases was no greater than 208 msec and no greater than 13 msec above the subject's baseline. For a summary of cases of AV block occurring in Study LAHI, the reader is referred to the Cardiovascular Safety Section of this review.

No cases of AV block were reported in study LAHU where ECGs were performed at baseline and on Study Day 2 at 24 hours.

In conclusion, higher mean blood pressures were observed in the 200 mg lasmiditan + 100 mg sumatriptan group as compared to 200 mg lasmiditan group within 24 hours of dosing. The TEAE of hypersomnia was reported in a higher percentage of subjects who received 200 mg lasmiditan + 100 mg sumatriptan compared to subjects who received 200 mg lasmiditan. A higher percentage of cases of first-degree AV block were noted in study LAHI in the 200 mg lasmiditan + 100 mg sumatriptan arm compared to 200 mg lasmiditan arm; however, in these cases the PR interval after dosing was similar to the subject's own baseline value.

Topiramate

The sponsor conducted a drug-drug interaction study with topiramate and lasmiditan and did not find increased adverse events with the two drugs combined. Topiramate is indicated for prophylactic treatment of migraine and therefore could potentially be administered with lasmiditan. Study LAHT assessed the effects of coadministration of lasmiditan 200 mg with topiramate 50 mg and compared it to lasmiditan 200 mg and topiramate 50 mg in combination with placebo. Subjects received lasmiditan 200 mg or placebo on Study Day 1 followed by topiramate titrated up to 50 mg twice daily on Study Days 3 to 13 and then coadministration of lasmiditan 200 mg or placebo with topiramate 50 mg on Study Day 14. Vital signs were measure at baseline, 2, 4, 8, and 24 hours after dosing.

The mean difference from baseline for lasmiditan 200 mg + topiramate 50 mg was not meaningfully different for systolic blood pressure. Mean diastolic blood pressure and pulse rate values in subjects receiving lasmiditan 200 mg + topiramate 50 mg were not meaningfully different when compared to subjects receiving lasmiditan 200 mg.

Outlier analysis of vital signs in study LAHT showed that subjects receiving lasmiditan 200 mg + topiramate 50 mg had similar rates of outliers for SBP, DBP and pulse rate as compared to subjects receiving lasmiditan 200 mg.

Mean change in orthostatic vital signs for LAHT showed that subjects receiving lasmiditan 200 mg + topiramate 50 mg were orthostatic by mean decrease in diastolic blood pressure at 4 hours after dosing (12.3 mmHg); however, subjects taking topiramate (11.9 mmHg) and placebo (12.4 mmHg) had similar mean change in DBP at this time point.

An outlier analysis of orthostatic vital sign changes in LAHT showed that the incidence of orthostasis by pulse rate was higher in lasmiditan 200 mg + topiramate 50 mg treated subjects compared to lasmiditan 200 mg- treated subjects four hours after dosing (40% versus 25%). The absolute difference between the two treatment arms in the number of subjects who were orthostatic by pulse rate at that timepoint was small (n=3).

In study LAHT, the incidence of TEAEs reported in subjects taking lasmiditan 200 mg + topiramate 50 mg treatment arms was similar to the rate of TEAEs reported after a single dose of lasmiditan 200 mg alone.

In studies 301 and 302, 18 subjects used topiramate on a non-PRN basis. The rate of subjects reporting at least one TEAE in lasmiditan and non-PRN topiramate use was not greater than the rate of subjects reporting at least one TEAE and exposed to lasmiditan (35.9%).

In conclusion, subjects who received lasmiditan 200 mg in combination with topiramate had mean changes in orthostatic vital signs that were similar to placebo and topiramate. An outlier analysis of orthostatic vital signs in LAHT showed a higher incidence of orthostasis by pulse in 200 mg lasmiditan + topiramate compared to lasmiditan alone at four hours after dosing however the absolute difference in number of subjects affected between the two arms was small (n=3).

Propranolol

The sponsor conducted a drug-drug interaction study with propranolol and lasmiditan and found increased heart-rate lowering effects in the two drugs combined compared to each drug individually. Propranolol is indicated for prophylactic treatment of migraine and therefore could potentially be administered with lasmiditan. Study LAHD assessed the effects of coadministration of a single dose of lasmiditan 200 mg with propranolol 80 mg twice daily.

Subjects received lasmiditan 200 mg as a single dose on Study Days 1 and 9. Propranolol 80 mg was administered twice daily on Study Days 4 through 10. Vital signs measurements were performed predose and up to 12 hours after dosing.

The following two tables show the maximum mean change from baseline for blood pressure and pulse rate in study LAHD and the difference in mean pulse rate between treatment arms at the time of maximal mean decrease in pulse rate for lasmiditan 200 mg + propranolol (1.5 hours). Pulse rate decreased in lasmiditan 200 mg + propranolol treated subjects, with a maximum mean decrease of 19.3 bpm at 1.5 hours post dose. The maximum mean decrease in pulse rate for lasmiditan 200 mg and propranolol alone was 10.7 bpm and 14.2 bpm, respectively. The range of decrease in pulse rate from baseline in subjects treated with lasmiditan 200 mg + propranolol was between 6.6 bpm to 19.3 bpm.

Table 62. Maximum Mean Change from Baseline for Vital Signs in Study LAHD.

Vital Sign Parameters	Propranolol 80 mg twice daily	Lasmiditan 200 mg single dose	Lasmiditan 200 mg + propranolol
Systolic blood pressure (mmHg) (maximum mean change from baseline)	-11.9	+8.2	-11.1
Diastolic blood pressure (mmHg) (maximum mean change from baseline)	-12.7	-7.6	-12.5
Pulse Rate (bpm) (maximum mean change from baseline)	-14.2	-10.7	-19.3

Data is taken from the CSR of LAHD.

Table 63. Mean Decrease in Pulse Rate from Baseline at 1.5 Hours Post Dose.

Propranolol 80 mg twice daily	Lasmiditan 200 mg single dose	Lasmiditan 200 mg + propranolol
-13.7	-10.4	-19.3

Data is taken from the 19/06/2019 response to an information requested dated 18/06/2019.

Mean change in orthostatic vital signs for LAHD showed that subjects receiving lasmiditan 200 mg + propranolol 80 mg were not orthostatic by mean change in vital signs at 1 and 2 hours after dosing.

An outlier analysis of orthostatic vital sign changes in LAHD showed that subjects in the lasmiditan 200 mg + propranolol 80 mg arm had a lower incidence of orthostasis compared to subjects in the lasmiditan 200 mg arm.

In study LAHD, the incidence of subjects reporting TEAEs after taking lasmiditan 200 mg + propranolol 80 mg twice daily was similar to the incidence of subjects reporting TEAEs after a single dose of lasmiditan 200 mg (40.5% (17/42) versus 47.7% (21/44), respectively).

In studies 301 and 302, there were 33 subjects who had non-PRN use of propranolol. The rate of subjects reporting at least one TEAEs in lasmiditan and non-PRN propranolol use was 36.4% and was similar to the rate of subjects reporting at least one TEAE and exposed to lasmiditan (35.9%).

In conclusion, propranolol in combination with lasmiditan 200 mg 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 (10.4 bpm, 13.7 bpm, respectively).

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

At the time of the 120 Day Safety Update, two AEs belonging to the Neoplasm SOC were reported in lasmiditan-treated subjects in studies 201, 202, 301, and 302. None of the AEs were malignant (uterine leiomyoma, pituitary tumour benign). No AEs belonging to the Neoplasm SOC were reported in placebo-treated subjects.

In study 305, 20 AEs belonging to the Neoplasm SOC were reported: adenocarcinoma of colon; anogenital warts; basal cell carcinoma; benign breast neoplasm; benign neoplasm (n=2); cholesteatoma; haemangioma of skin; lipoma; malignant melanoma; melanocytic naevus; non-small cell lung cancer; seborrhoeic keratosis; skin papilloma; thyroid cancer recurrent; uterine leiomyoma (n=5). Two of the malignant AEs occurred in the lasmiditan 100 mg group and three of the malignant AEs occurred in the lasmiditan 200 mg group. All of the AEs occurred within eight months of the first dose of lasmiditan.

Reviewer comment: The clinical database is not adequate to evaluate human carcinogenicity (maximum exposure to lasmiditan was 1 year) and therefore, a conclusion about the carcinogenic potential of lasmiditan cannot be drawn.

8.8.2. Human Reproduction and Pregnancy

There are limited safety data on the use of lasmiditan in pregnant women or in women exposed via a male partner treated with lasmiditan. Pregnant and lactating women were excluded from entering the clinical studies. Subjects with reproductive potential were required to use a reliable method of birth control during the clinical studies.

As of the 120 Day Safety Update, there were 23 pregnancy cases across the clinical trials. Of the 23 cases, 22 cases involved maternal exposure and one case involved paternal exposure to lasmiditan.

The case of paternal exposure to lasmiditan reported conception occurring five weeks after the subject completed treatment. Further information on this case was not available as the subject was lost to follow up.

Of the 22 pregnancy cases with maternal exposure to lasmiditan, 9 cases involved lasmiditan administration 8 to 173 days prior to the last menstrual period or estimated date of conception. Of these nine cases, three reported the following pregnancy-related SAEs: spontaneous abortion, premature rupture of membranes, threatened abortion/spontaneous abortion. I reviewed the narratives and they were consistent with lasmiditan exposure occurring at least two weeks prior to the estimated dates of conception. It is unlikely that lasmiditan played a role

in these cases given the elimination half-life of lasmiditan.

Of the remaining 13 pregnancies where lasmiditan exposure occurred in close temporal proximity to pregnancy, exposure to lasmiditan occurred during the first trimester in all cases. The outcome of the 13 pregnancies was reported as follows: 5 normal; 1 premature birth; 3 spontaneous abortion; 1 elective termination; 3 awaiting follow up.

No congenital abnormalities were reported in any of the cases of pregnancy that resulted in birth. The following table summarizes the narratives of cases of spontaneous abortion and premature birth.

Table 64. Cases of Spontaneous Abortion and Premature Birth Occurring across the Clinical Trial Program.

(b) (6)	LTN 100 mg	Spontaneous Abortion	6.5 weeks
Concomitant medications: levonorgestrel IUD, trazodone, bupropion, buspirone, gabapentin, metformin, quetiapine, sitagliptin, insulin detemir Obstetric history: previous elective termination Past medical history: Bipolar, Diabetes mellitus type 2			
(b) (6)	LTN 100 mg	Spontaneous Abortion	~ 3.5 weeks
Concomitant medications: obetrol PRN Past medical history: Attention deficit disorder			
(b) (6)	LTN 200 mg	Spontaneous Abortion	7.5 weeks
Concomitant medications: norethisterone, valacyclovir hydrochloride Obstetric history: 3 pregnancies and caesarean section Past medical history: genital herpes, environmental allergies, anxiety			
(b) (6)	LTN 100 mg	Premature Birth	31 weeks
Outcome: Baby experienced intraventricular hemorrhage, neonatal. Concomitant medications: aspirin, escitalopram, aripiprazole, Adderall, bupropion, clonazepam, topiramate, metformin, exenatide, levothyroxine Obstetric history: premature births, abortions (2) Past medical history: Diabetes mellitus type 2, hypertension, depression, hypothyroidism, asthma			

The reviewer created this table using narratives provided by the Sponsor.

No lactating females were exposed to lasmiditan during the clinical trials.

Reviewer comment: There is limited information on the effects of lasmiditan during pregnancy. This issue can be addressed with a postmarketing Pregnancy Registry.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Lasmiditan is a new molecular entity. It is not approved in other regions of the world.

8.9.2. Expectations on Safety in the Postmarket Setting

Additional adverse reactions will likely be identified after a larger group of patients is exposed to lasmiditan, and this may include patients with ischemic heart disease in whom there is relatively little experience. PMRs to study the effects of lasmiditan during pregnancy and on pregnancy outcomes will help to address the lack of adequate information on the safety of lasmiditan in pregnancy.

8.9.3. Additional Safety Issues from Other Disciplines

Please see other disciplines' review.

8.10. Integrated Assessment of Safety

Safety findings from NDA 211280 are summarized below.

Deaths. No deaths occurred in Phase 1, 2, or 3 studies.
SAE. The evaluation of SAEs did not identify any significant safety issues with lasmiditan. There was a low number of SAEs reported in the oral placebo-controlled Phase 2/3 trials and no increased rate of SAEs occurred in subjects who received lasmiditan compared to subjects who received placebo. The incidence of SAEs occurring in the open-label extension study was 3.1% with similar rates in the 100 mg and 200 mg dose group (3.0% versus 3.1%, respectively).
AE leading to drug or study discontinuations. There was one discontinuation due to an AE in the oral placebo-controlled trials. In the open-label extension study, 11.3% of subjects who received 100 mg of lasmiditan and 14.2% of subjects who received 200 mg of lasmiditan discontinued due to at least one AE. The most frequent AEs causing discontinuation belonged to the groupings dizziness/light-headedness, somnolence/sedation, asthenia/fatigue/malaise/weakness, paresthesias/hypoaesthesias, nausea/vomiting, and confusion/delirium/altered mental status/disorientation.
Significant AEs. Evaluation of severe AEs did not identify a new safety signal.
Most common AE. The SOC with the greatest percentage of treatment emergent AEs in the oral placebo-controlled and the open-label extension study was the Nervous System Disorders SOC. In the Phase 3 placebo-controlled studies, treatment emergent AEs with at least 2% risk (rounded) and at least 2% greater than placebo in any lasmiditan group belonged to the following groupings: dizziness/balance disorder (9% ,16%, 18%, and 3% on lasmiditan 50 mg, 100 mg, and 200 mg, and placebo, respectively), somnolence/fatigue/sedation (8% ,10%, 11%,

and 3% on lasmiditan 50 mg, 100 mg, and 200 mg, and placebo, respectively), asthenia/fatigue/malaise/weakness (4% , 7%, 8%, and 1% on lasmiditan 50 mg, 100 mg, and 200 mg, and placebo, respectively), paresthesias/hypoaesthesias, and nausea/vomiting (2% ,6%, 8%, and 2% on lasmiditan 50 mg, 100 mg, and 200 mg, and placebo, respectively).
Vital sign, laboratory and ECG evaluations in the oral Phase 2/3 studies did not identify a signal however these assessments did not occur at the time of lasmiditan administration. Vital signs in clinical pharmacology studies showed increases in blood pressure and decreases in pulse within one hour of dosing. Laboratory and ECG evaluations in clinical pharmacology studies did not identify a signal.
Pre-specified AE of interest

- Cardiovascular Safety – The number of SAEs with potential cardiovascular etiology occurring in subjects who received lasmiditan was low in the oral placebo-controlled trials (n=1). The rate of SAEs with potential cardiovascular etiology in the open-label extension study was similar between the 100 mg and 200 mg dose groups (0.7% versus 0.6%, respectively). The incidence of subjects experiencing at least one TEAE with potential cardiovascular etiology in the oral placebo-controlled trials for lasmiditan 50 mg, 100 mg, and 200 mg, and placebo dose groups was 1.5%, 2.1%, 2.6%, and 0.6%, respectively. The incidence of subjects experiencing at least one TEAE with potential cardiovascular etiology in the open-label extension study for lasmiditan 100 mg and 200 mg dose groups was 1.8% and 2.5%, respectively. In clinical pharmacology studies, increases in blood pressure and decreases in pulse were observed to occur within one hour of dosing.
- Hepatic Safety – There was no signal of hepatotoxicity identified. Cases of hepatic laboratory abnormalities were missing diagnostic evaluations to rule out alternate causes for hepatic laboratory abnormalities or had multiple confounding factors.
- Hypersensitivity Reactions: In the Phase 3 placebo-controlled trials, 0.2% of subjects who received lasmiditan compared to 0% of subjects who received placebo experienced hypersensitivity reactions (narrow SMQ) and including rash and angioedema. Most of the cases were mild to moderate in severity but some lead to discontinuation.
- Suicidality. There was no evidence of an increased risk of suicidality with lasmiditan.
- Abuse Potential: Treatment-emergent adverse events related to abuse potential in the Phase 3 oral placebo-controlled studies occurred in 28.5% of subjects who received lasmiditan compared to 7.6% of subjects who received placebo.
- Pulse Rate Lowering: 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 or propranolol alone. The mean maximal decrease in pulse rate for lasmiditan and propranolol alone was 10.7 bpm and 14.2 bpm, respectively.
- Driving Impairment. In a double-blinded, randomized, placebo-controlled simulated driving study, subjects given lasmiditan were observed to have an SDLP difference from placebo of >4.4 centimeters which is the difference from placebo that has been previously identified to occur in subjects with a blood alcohol concentration of 0.05%. In a second randomized,

placebo-controlled simulated driving study designed to assess the duration of effect of lasmiditan on SDLP, difference in mean SDLP scores for lasmiditan 100 mg and 200 mg were not greater than the pre-specified inferiority margin of 4.4 centimeters at 8, 12, and 24 hours after dosing. Subjects lacked insight into when they might be impaired to drive based on a Self-Perceived Safety to Drive question.

- Serotonin Syndrome: Two cases met criteria for Serotonin Syndrome with one case occurring in the setting of triptan use. In both cases, the majority of symptoms had resolved within six hours without treatment.

9. Advisory Committee Meeting and Other External Consultations

There was no FDA AC meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

I recommend that Hypersensitivity Reactions be added as a Warnings and Precautions statement to the label. I recommend that the label indicate that some subjects experience impaired driving up to 8 hours after dosing. I recommend that Serotonin Syndrome be added as a Warnings and Precautions statement to the label.

10.2. Nonprescription Drug Labeling

Not Applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Not Applicable.

12. Postmarketing Requirements and Commitments

This product will be used in women of childbearing potential. I recommend a postmarketing Pregnancy Registry and a Pregnancy Outcomes Study.

13. Appendices

13.1. References

13.2. Mean Chemistry and Hematology Laboratory Values for Study LAHE.

Table 65. Mean Chemistry and Hematology Laboratory Values for Study LAHE.

Cohort 1						
Laboratory Parameter	Lasmiditan 200 mg N=28			Placebo N=11-12		
	Baseline	Day 2	Day 6	Baseline	Day 2	Day 6
ALT	20.5	19	19.1	19.3	16.8	17.5
ALK PHOS	70.2	71	68.8	61.6	61.7	59
AST	18.8	16.1	15.7	20	15.6	16
BILI	8.1	7	7.3	7.7	7.7	8
Blood Urea Nitrogen	4.6	5.4	4.7	4.4	5.8	4.7
Calcium	2.4	2.4	2.4	2.4	2.4	2.4
Carbon Dioxide	23.3	22.1	23.8	23.7	21.5	24.2
Chloride	101.4	101.6	101.9	101.9	101.7	101.7
Creatinine	78.3	80.9	80	75.1	76.7	76.4
Glucose	5.1	4.9	4.8	5	4.9	4.8
Magnesium	0.9	0.9	0.9	0.9	0.8	0.8
Phosphate	1.1	1.2	1.2	1.1	1.2	1.2
Potassium	4.6	4.4	4.5	5.1	4.4	4.6
Sodium	138.4	139.1	138.2	139.2	138.8	138.7
Hemoglobin	8.3	8.6	8.3	8.7	8.9	8.6
Leukocytes	5.9	6	6.1	6	5.9	5.7
Platelets	260.2	262.9	264.4	264.8	263.5	253.4
Cohort 2						
Laboratory Value	Lasmiditan 400 mg N=14-15			Placebo N=14-15		
	Baseline	Day 2	Day 6	Baseline	Day 2	Day 6
ALT	21.5	20.8	22.1	20.7	18.8	18.9
ALK PHOS	70.9	69.9	70.1	67.8	65.9	64.5
AST	20.4	18	17.7	21	17.9	17.9
BILI	8.1	7.9	7.1	7.1	7.3	9

Cohort 1						
Laboratory Parameter	Lasmiditan 200 mg N=28			Placebo N=11-12		
	Baseline	Day 2	Day 6	Baseline	Day 2	Day 6
Calcium	2.4	2.4	2.4	2.4	2.4	2.4
Carbon Dioxide	26.5	24.9	26.3	26.9	25.2	27.3
Chloride	101.9	101.5	99.9	102.3	102.2	100.3
Creatinine	80.2	84.4	86.3	78.8	75.6	78.1
Glucose	5.1	4.9	4.7	5.1	4.8	4.7
Magnesium	0.9	0.8	0.8	0.9	0.8	0.8
Phosphate	1.2	1.2	1.4	1.2	1.2	1.2
Potassium	4.7	4.5	4.4	4.6	4.7	4.6
Sodium	138.6	138.6	137	138.9	139.2	138.1
Hemoglobin	8.6	8.9	8.8	8.5	8.7	8.6
Leukocytes	5.8	5.7	6	6.2	5.6	5.6
Platelets	280.1	275.6	271.9	257.2	265.4	253.8

The reviewer created this table from the LAHE dataset LB and EX.

13.3. Driving Assessments performed in Studies 106 and LAIF

Driving assessments performed in Studies 106 and LAIF included: Country Vigilance-Divided Attention (CVDA) Driving Scenario; self-perceived safety to drive; subjective level of sleepiness using the Karolinska Sleepiness Scale; CogScreen SDC; Visual Analog Scale to assess a subject's motivation and self-appraisal following driving assessments.

The CVDA Driving Scenario is a 60-minute simulated 2-lane highway driving test that has a divided attention task of responding to visual stimuli from the left and right directions. The test generates measures of accuracy and measures of response speed. Additionally, lane exceedance, speed-related measures, excessive speed in corners, and collisions are measured.

The Karolinska Sleepiness Scale is a self-reported scale used to assess situational sleepiness. Subjects were asked to perform this test within 30 minutes prior to the CVDA Driving Scenario.

The Self-Perceived Safety to Drive Question was a yes or no question that subjects answered prior to driving. Subjects were asked whether they felt safe to drive.

The CogScreen Symbol Digit Coding is a test designed to measure attention, visual scanning, working memory, and speed of information processing. The subject was asked to tap an associated digit for each symbol on a touchscreen with a stylus. The principal test score measured the number of correct responses within 120 seconds and was impacted by speed and

accuracy. Subjects were asked to perform the test within 30 minutes prior to the CVDA Driving Scenario.

The Visual Analogue Scale was used to assess a subject's motivation and self-appraisal. Immediately upon completion of the CVDA Driving Scenario, subjects were asked to self-assess their performance and motivation to perform their best during the driving scenario with the following questions: How well did you think you drove for the last 60 minutes? How motivated did you feel to drive at your best during the last 60 minutes of driving? Subjects recorded their response on a Visual Analog Scale indicating their performance (not satisfactory to satisfactory) and motivation (not motivated to motivated).

13.4. Results of Secondary Endpoints for Study LAIF

Table 66. Cogscreen Symbol Digit Coding - Mean Accuracy (%)

Time	Lasmiditan 100 mg	Lasmiditan 200 mg	Diphenhydramine 50 mg	Placebo
8 hours	99.6	99.6	99.3	99.4
12 hours	99.6	99.9	99.2	99.6
24 hours	99.5	99.5	99.3	99.5

Reviewer created table from Study LAIF dataset ADXC, PARAM = SDC-Accuracy, time = ATPT, treatment= TRTA.

Table 67. Cogscreen Symbol Digit Coding - Mean Number of Items Correct

Time post dose	Lasmiditan 100 mg	Lasmiditan 200 mg	Diphenhydramine 50 mg	Placebo
8 hours	70	70	69	70
12 hours	71	72	68	71
24 hours	71	71	68	71

Reviewer created table from Study LAIF dataset ADXC, PARAM = SDC-Number of Items Correct, time = ATPT, treatment= TRTA.

Table 68. Cogscreen Symbol Digit Coding - Mean Speed (sec)

Time	Lasmiditan 100 mg	Lasmiditan 200 mg	Diphenhydramine 50 mg	Placebo
8 hours	1.5	1.6	1.5	1.5
12 hours	1.5	1.5	1.5	1.5
24 hours	1.5	1.5	1.5	1.5

Reviewer created table from Study LAIF dataset ADXC, PARAM = SDC-Speed (sec), time = ATPT, treatment= TRTA.

Table 69. Cogscreen Symbol Digit Coding - Mean Standard Deviation of Reaction Time (sec)

Time	Lasmiditan 100 mg	Lasmiditan 200 mg	Diphenhydramine 50 mg	Placebo
8 hours	0.5	0.6	0.6	0.6
12 hours	0.5	0.5	0.6	0.5
24 hours	0.5	0.6	0.6	0.5

Reviewer created table from Study LAIF dataset ADXC, PARAM = SDC-Std Dev of Reaction Time (sec), time = ATPT, treatment= TRTA.

Table 70. Cogscreen Symbol Digit Coding - Mean Thruput (Number Correct/Minute)

Time	Lasmiditan 100 mg	Lasmiditan 200 mg	Diphenhydramine 50 mg	Placebo
8 hours	40	39	40	41
12 hours	41	41	40	41
24 hours	40	40	39	41

Reviewer created table from Study LAIF dataset ADXC, PARAM = SDC- Thruput (Number Correct/Minute), time = ATPT, treatment= TRTA.

Table 71. Additional Statistically Significant Secondary Endpoints in Study LAIF for Lasmiditan 100 mg, Lasmiditan 200 mg and Diphenhydramine 50 mg Compared to Placebo.

Secondary Endpoints	Time	Lasmiditan 100 mg	Lasmiditan 200 mg	Diphenhydramine 50 mg
Karolinska Sleepiness Scale	8 h	No difference	Worse	Worse
	12 h	No difference	No difference	Worse
	24 h	Better	No difference	No difference
Visual Analog Scale	8 h	No difference	No difference	Worse
	12 h	No difference	No difference	Worse
	24 h	No difference	No difference	Worse
Performance	8 h	No difference	No difference	No difference
	12 h	Worse	No difference	Worse
	24 h	No difference	No difference	Worse
Reaction Time Variability	8 h	No difference	No difference	No difference
	12 h	No difference	No difference	Worse
	24 h	No difference	Worse	Worse
Response Accuracy	8 h	No difference	No difference	No difference
	12 h	No difference	No difference	Worse
	24 h	No difference	No difference	No difference
Number of Lane Exceedances	8 h	No difference	Worse	Worse
	12 h	Worse	Worse[a]	Worse
	24 h	No difference	No difference	Worse
Maximum	8 h	No difference	No difference	Worse

Secondary Endpoints	Time	Lasmiditan 100 mg	Lasmiditan 200 mg	Diphenhydramine 50 mg
Lane Exceedance	12 h	No difference	No difference	Worse
	24 h	No difference	No difference	Worse
Lane Exceedance Duration	8 h	No difference	No difference	Worse
	12 h	No difference	No difference	Worse
	24 h	No difference	No difference	Worse
Speed Deviation	8 h	No difference	No difference	Worse
	12 h	No difference	Better	Worse
	24 h	No difference	No difference	Worse
Speedings	8 h	No difference	No difference	No difference
	12 h	No difference	No difference	No difference
	24 h	No difference	No difference	No difference
Average Speed	8 h	No difference	No difference	No difference
	12 h	No difference	No difference	No difference
	24 h	No difference	No difference	No difference
Excessive Speeding Around Corners	8 h	No difference	No difference	Worse
	12 h	No difference	No difference	No difference
	24 h	No difference	No difference	No difference
Collisions	8 h	No difference	No difference	Worse
	12 h	No difference	No difference	No difference
	24 h	No difference	No difference	Worse
Divided Attention: Correct Responses	8 h	No difference	No difference	Worse
	12 h	No difference	No difference	No difference
	24 h	No difference	No difference	Worse
Divided Attention: Errors of Omission	8 h	No difference	No difference	Worse
	12 h	No difference	No difference	Worse
	24 h	No difference	No difference	Worse
Divided Attention: Reaction Time	8 h	No difference	No difference	Worse
	12 h	No difference	No difference	Worse
	24 h	No difference	No difference	No difference
Divided Attention: Reaction Time Variability	8 h	No difference	No difference	No difference
	12 h	No difference	No difference	Worse
	24 h	No difference	No difference	No difference
Divided Attention:	8 h	No difference	No difference	No difference
	12 h	No difference	No difference	No difference

Secondary Endpoints	Time	Lasmiditan 100 mg	Lasmiditan 200 mg	Diphenhydramine 50 mg
Errors of Commission	24 h	No difference	No difference	No difference

Reviewer created this table from report of Study LAIF. [a]Not statistically significant.

13.5. Financial Disclosure

The reader is referred to the review of clinical efficacy by Dr. Viveca Livezey for financial disclosures.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NATALIE M BRANAGAN
10/10/2019 01:05:46 PM

SALLY U YASUDA
10/10/2019 02:22:48 PM

CLINICAL REVIEW

Application Type	NDA
Application Number	211280
Priority or Standard	Standard
Submit Date(s)	10-11-2018
Received Date(s)	10-12-2018
PDUFA Goal Date	10-11-2019
Division/Office	Division of Neurology Products/Office of New Drugs
Reviewer Name(s)	Viveca Livezey, MD
Review Completion Date	10-9-2019
Established/Proper Name	Lasmiditan
(Proposed) Trade Name	REYVOW
Applicant	Eli Lilly
Dosage Form(s)	50 mg, 100 mg tablet
Applicant Proposed Dosing Regimen(s)	50 mg, 100 mg or 200 mg; Take one tablet at the onset of migraine. (b) (4) (b) (4) .
Reviewer Proposed Dosing Regimen(s)	50 mg, 100 mg or 200 mg; Take one tablet at the onset of migraine.
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Acute treatment of migraine with and without aura in adults

Table of Contents

Table of Tables

Table of Figures

Glossary

5-HT	5-hydroxytryptamine
AC	advisory committee
AE	adverse event
AHS	American Headache Society
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CYP	Cytochrome P450
DMC	data monitoring committee
ECG	electrocardiogram
eDiary	electronic diary
EU	European Union
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
ICH	International Council for Harmonization
ICHD	International Classification for Headache Disorders
IHS	International Headache Society
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
mITT	modified intent to treat
NAI	No Action Indication
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OUS	Outside the United States
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	Standardized MedDRA Queries
SOC	standard of care
TEAE	treatment emergent adverse event
UK	United Kingdom
U.S.	United States
VAI	Voluntary Action Indicated

1. Executive Summary

1.1. Product Introduction

Lasmiditan (REYVOW) is an oral, first in class, drug that the applicant states acts selectively on the 5-hydroxytryptamine (5-HT) 1F serotonin receptor. Lasmiditan is a new molecular entity (NME) that is intended to be prescribed for the acute treatment of migraine.

The applicant has proposed marketing tablets in 50 milligrams (mg) and 100 mg strengths with doses of 50 mg, 100 mg, or 200 mg to be taken orally at the onset of an acute migraine attack. (b) (4) (b) (4) The maximum dose proposed by the applicant is 200 mg in a 24-hour period.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant provides substantial evidence of the effectiveness of lasmiditan for the acute treatment of migraine to support approval. The applicant provided data from two adequate and well-controlled studies that demonstrated that lasmiditan leads to increased rates of pain freedom and most bothersome symptom (MBS) freedom at 2 hours (the primary and key secondary endpoints, respectively) after treatment of a single migraine attack. These effects are both statistically significant and clinically meaningful across all treatment groups compared to placebo in both studies. There was a dose response for pain freedom at 2 hours, and less of a dose response effect for MBS freedom at 2 hours. Based on my analysis of the results of the controlled clinical trials, I recommend that lasmiditan be approved for the acute treatment of migraine in adults at doses of 50 mg, 100 mg, and 200 mg. The appropriateness of lasmiditan in an individual patient will need to be assessed, taking into account alternative acute migraine treatment options, and considering the risk profile discussed in Dr. Natalie Branagan's safety review of this application. Please refer to her review for conclusions regarding the safety data provided in this application.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Lasmiditan (REYVOW) is a new molecular entity that is proposed to be a selective $5HT_{1F}$ serotonin receptor agonist that is being developed for the acute treatment of migraine with and without aura in adults. Efficacy was demonstrated in two adequate and well-controlled clinical trials conducted in migraine patents.

Migraine is a very common, chronic, and often debilitating disease characterized by recurrent attacks of head pain with associated symptoms of nausea, vomiting, photophobia, and/or phonophobia. The attacks are typically of moderate to severe intensity, and can impact patients' quality of life. There are several FDA-approved drugs for the acute treatment of migraine. Some of the drug classes used to treat acute migraine include triptans, ergotamines, and nonsteroidal anti-inflammatory medications. The most widely used drugs, the triptans, act on a different class of serotonin receptors which can lead to vasoconstriction, and thus limit the use in some at-risk populations. There have not been any novel classes of drugs approved for the indication of acute treatment of migraine in many years.

The efficacy results of two adequate and well-controlled studies, both in patients with migraine with and without aura, demonstrated a benefit of lasmiditan for this indication. Both studies used the same primary and key secondary endpoints (pain freedom at 2 hours and most bothersome symptom (photophobia, phonophobia, or nausea) freedom at 2 hours, respectively), which are endpoints accepted by the Division for acute migraine trials. The applicant had to meet both endpoints (treated as co-primary), in each study, in order to demonstrate efficacy for a given dose. Both studies examined the effect of lasmiditan on the treatment of a single migraine attack.

A total of three doses of lasmiditan were tested (50 mg, 100 mg, and 200 mg) and each dose demonstrated efficacy on the primary and key secondary endpoints. Lasmiditan treatment resulted in pain freedom 2 hours after dosing in approximately 28-38% of patients, in a dose-dependent manner, compared to pain freedom of approximately 15-20% of patients at that timepoint in the placebo group. Lasmiditan treatment also resulted in resolution of the most bothersome symptom (MBS) 2 hours after dosing in approximately 40-48% of patients (with less of a dose effect), compared to resolution of the MBS in 30-33% of patients at that timepoint who took placebo. While these findings were statistically significant across all groups when compared to placebo, the effect appears to be modest and benefit for an individual patient will need to be weighed against risks of lasmiditan. Subgroup analyses (e.g., race, gender, age) did not reveal clinically significant differences in response to treatment.

Although there was no benefit to a second dose for rescue therapy (for a migraine that had not resolved with the first dose by 2 hours) in either

trial, both trials demonstrated a trend towards benefit to a second dose for recurrence of a migraine (one that had resolved by 2 hours but then recurred). However, this trend is confounded by selection bias, and other confounders (such as missing data and patients taking another rescue medication in addition to the study drug) making the results uninterpretable. Therefore, the efficacy results do not support the effectiveness of a second dose for either rescue or recurrence of migraine.

There were several safety issues identified, that are highlighted in Dr. Natalie Branagan's safety review, that informed her overall risk assessment of lasmiditan. These safety concerns, in combination with the uninterpretable efficacy results for the use of a second dose of lasmiditan for rescue or recurrence of migraine, are the basis for my recommendation to not include language in the label regarding the use of a second dose of lasmiditan for rescue or recurrence of migraine.

The efficacy of lasmiditan compared to placebo for the treatment of the first migraine attack has been established by the pivotal clinical trials conducted by the applicant. The appropriateness of lasmiditan for the treatment of acute migraine in any individual patient will need to be weighed carefully, taking into consideration the safety profile discussed in Dr. Branagan's review, as well as the alternative available treatment options.

For an integrated assessment of the benefit-risk of lasmiditan, based on the combined efficacy and safety reviews, please refer to the Joint Supervisory Review.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Migraine is a very common, chronic neurological disease in which patients have a broad spectrum of disease, with varying frequency and severity of migraine. • Migraine is characterized by recurrent attacks of headache that are typically moderate to severe in intensity. Attacks tend to be unilateral headaches associated with other symptoms, such as	Migraine leads to significant pain, disability, decreased productivity, and diminished quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	nausea, vomiting, phonophobia, or photophobia. • Typical migraines can be exacerbated by even minor physical activity, and may last anywhere from 4 hours to 72 hours. • Some patients may experience an aura 30 minutes to an hour prior to the onset of their headache, and other patients may experience a general prodrome a day or two prior to the onset of the headache. • Migraine can be very disabling and contribute to loss of productivity and diminished quality of life. • Migraine can occur on an episodic or chronic basis. • Migraine is more frequent in females than in males. In one United States population-based study, the one-year prevalence of migraine was 18% in females and 7% in males and 12% overall (Lipton, Stewart, et al. 2001). • Migraine prevalence peaks in the 4th decade of life for both males and females (Lipton, Bigal, et al. 2007).	
Current Treatment Options	• There are many FDA-approved treatments for acute migraine, as well as other products that are used off-label. • Currently used acute migraine treatments include: o Triptans, including oral, oral disintegrating, nasal spray, subcutaneous formulations – however, these treatments are contraindicated in patients with cardiovascular or cerebrovascular disease o Specific non-steroidal anti-inflammatories (NSAIDs), used alone or in combination with a triptan o Dihydroergotamine (nasal spray, subcutaneous or intramuscular) – contraindicated in patients with	Additional medications are still needed for patients with acute migraine, especially in patients with contraindications (such as cardiovascular disease) to currently approved acute migraine medications. Another oral medication for acute migraine treatment with a new mechanism of action, and potentially less cardiovascular or gastrointestinal risk, would be desirable for clinicians to offer to some patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cardiovascular disease • Non-specific therapies (not FDA approved but used off-label), including non-specific NSAIDs and acetaminophen.	
Benefit	• The data demonstrate there is a benefit in terms of pain freedom and resolution of most bothersome symptom (nausea, photophobia or phonophobia) with the first dose of lasmiditan, in the acute treatment of migraine, when compared to placebo. • Efficacy on pain freedom and MBS freedom at 2 hours was demonstrated at doses of 50 mg, 100 mg and 200 mg. The therapeutic gain (the percentage effect of active drug minus percentage effect of placebo) for pain freedom at 2 hours, of lasmiditan compared to placebo, ranges from 7% for the 50 mg dose, to 10-13% for the 100 mg dose, and ~18% for the 200 mg dose. There is a dose-response seen for the primary endpoint of pain freedom at 2 hours. • The therapeutic gain of lasmiditan compared to placebo for MBS freedom at 2 hours ranges from 8% to 16%. • The benefit on pain freedom is sustained for up to 48 hours in some patients. • There is no benefit to a second dose of lasmiditan if a migraine has not resolved with the first dose (rescue), and there is a slight trend to benefit of a second dose of lasmiditan for a recurrent migraine (if a migraine recurs after two hours). However, due to shortcomings of second dose data for both rescue and recurrence, including the exploratory nature of endpoints, selection bias and confounding due to ~10% of patients also taking rescue medications other than	The efficacy of lasmiditan for the acute treatment of a migraine attack in patients with migraine with and without aura has been established, as lasmiditan leads to a modest improvement in headache pain freedom and associated most bothersome symptom freedom at higher rates than placebo. The doses of lasmiditan for approval should be 50 mg, 100 mg, and 200 mg. A second dose of lasmiditan should not be administered for rescue (if a headache is not resolved after the first dose) or recurrence of migraine (if a headache resolves and then recurs after 2 hours).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	study drug, interpretability of second dose data is limited.	
Risk and Risk Management	• Please refer to the Safety Review by Dr. Natalie Branagan for an assessment of the risks and risk management plan for this drug.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		Sec 6.1 Study endpoints
		☒	Patient reported outcome (PRO)	Sec 6.1 Study endpoints
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The proposed indication for lasmiditan is for the acute treatment of migraine with and without aura in adults. Migraine is estimated to affect 1 billion people worldwide, and is estimated to

cause 45 million years of life lived with disability. The 1-year prevalence of migraine is 12%, and it is the third most prevalent illness in the world (Lipton, Bigal, et al. 2007). In women, the lifetime prevalence is 33%, and in men, the lifetime prevalence is 13%. Migraine is most prevalent between the ages of 25 and 55 years, and the prevalence rises through early adult life, before decreasing after age 55 years (Dodick 2018).

Diagnostic criteria for migraine with and without aura [International Classification for Headache Disorders (ICHD-3)] have been refined by the International Headache Society (IHS) and are widely used for clinical practice and research purposes. By this definition, a migraine is a recurrent headache disorder manifesting in recurrent attacks of head pain. Under the ICHD-3, migraine attacks must fulfill the following criteria: last 4-72 hours, have two of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity, and must have associated symptoms of either nausea and/or vomiting, or photophobia and/or phonophobia.

Previous theories suggested that migraine was predominantly a vascular phenomenon, however, more recent theories have demonstrated that it is primarily neuronal dysfunction in the trigeminovascular system, and that neurotransmission both centrally (in the trigeminal nucleus caudalis, mesencephalic grey, and thalamus) and peripherally, are involved in migraine genesis. Messenger molecules, such as nitric oxide, 5-hydroxytryptamine (5-HT), and calcitonin-gene related peptide (CGRP) are also implicated in migraine phenomenon, and therapies targeting these molecules have been developed and some have been approved (such as the CGRP antagonists for preventive treatment of migraine).

Patients with migraine typically experience recurring bouts of moderate to severe head pain that can cause significant morbidity, interruption of activities (including lost time at work and school), and decreased quality of life. Many patients take medications for acute treatment of migraine, including FDA-approved drugs (e.g., triptans and dihydroergotamine, non-steroidal anti-inflammatories (NSAIDs)), unapproved drugs (opiates), and over the counter drugs, including NSAIDs, acetaminophen, or drug combinations such as caffeine/acetaminophen/aspirin preparations. Patients may also use behavioral techniques, or certain approved devices, for the treatment of acute migraine (Dodick 2018). Patients with episodic and chronic migraine often also take medications on a daily or regular basis for the preventive treatment of migraine, in addition to these acute therapies.

2.2. Analysis of Current Treatment Options

Table 1: Summary of Treatment Armamentarium for Acute Treatment of Migraine

Product (s) Name	Year of Approval	Route	Important Safety and Tolerability Issues	Other Comments (for example, subgroups addressed)
FDA Approved Treatments				
ERGOTS				
Dihydroergotamine (DHE) Nasal Spray 2 mg	1997	Nasal spray	CYP3A4 inhibitor interaction; contraindicated with cardiovascular disease; fibrotic complications	
DHE 1 mg injection	1946	Sub-cutaneous	CYP3A4 inhibitor interaction; contraindicated with cardiovascular disease; fibrotic complications	
TRIPTANS				
Almotriptan 12.5 mg	2001	Tablet	Contraindicated in patients with coronary artery disease, coronary artery vasospasm, conduction pathway disorders, cerebrovascular disease, hemiplegic or basilar migraine, peripheral vascular disease, ischemic bowel disease or uncontrolled hypertension; Warnings/precautions in patients with history of myocardial ischemia, arrhythmias, cerebral hemorrhage, subarachnoid hemorrhage or stroke	Indicated for patients age 12 to 17 years old
Eletriptan 20, 40 mg	2002	Tablet		Interacts with CYP3A4 inhibitors
Frovatriptan 2.5 mg	2001	Tablet		
Naratriptan 1, 2.5 mg	1998	Tablet		
Rizatriptan 5, 10 mg	1998	Tablet		Indicated for patients age 6 to 17 years old
Sumatriptan Oral 25, 50, 100mg	1992	Tablet		
Sumatriptan Nasal Spray 10, 20 mg		Nasal Spray		
Sumatriptan Nasal Powder 22 mg	2016	Nasal Powder		
Sumatriptan SC 4, 6 mg	2009	Sub-cutaneous		
Zolmitriptan NS 2.5, 5 mg	2015	Nasal Spray		Indicated for patients 12 years of age or older
Zolmitriptan Oral 2.5, 5 mg	1997	Tablet		
Sumatriptan/naproxen 85/500 mg	2008	Tablet		Indicated for patients 12 years and older; Cardiovascular risk, increased risk of bleeding due to naproxen component
NSAIDS				
Diclofenac (Cambia) 50 mg	2009	Oral (Packet)	Cardiovascular risk for thrombotic events, myocardial infarction and stroke; gastrointestinal	

			adverse events, especially in elderly	
Devices				
GammaCore device	2017	Device		
Cerena device	2013	Device	Contraindicated in patients with magnetic metals in head, neck or upper body, or pacemakers, or other implanted devices	
Cefaly ACUTE device	2017	Device	Contraindicated with recent trauma to skull/face or with skin conditions/rashes	
Other treatments (including nonprescription treatments and those recommended by the American Headache Society (AHS) Evidence Assessment (Marmura, Silberstein, et al. 2015))				
Acetaminophen	n/a	Tablet	Liver toxicity	
Aspirin	n/a	Tablet	Gastrointestinal toxicity, bleeding complications	
Opioids (butorphanol, codeine, meperidine, methadone, tramadol)	n/a	Tablet	Dependence, overuse, constipation	
NSAIDs (ibuprofen, ketorolac, naproxen)	2000 (Advil Migraine)	Tablet, capsule	Gastrointestinal toxicity, bleeding complications	Advil Migraine is indicated for the treatment of migraine.
Antiepileptics (valproate)	n/a	Tablet	Drug interactions	
Acetaminophen/aspirin /caffeine	1998 (Excedrin Migraine)	Tablet	Overuse, see effects for individual categories	Excedrin Migraine is indicated for the temporary relief of mild to moderate pain associated with migraine headache.
Antiemetics (Chlorpromazine, droperidol, metoclopramide, prochlorperazine)	n/a	Tablet	Dopamine blockade, movement disorders	

*I created this table using the Drugs@FDA website, and reviewing the approvals, labels, and dates for drugs indicated for the acute treatment of migraine, and utilizing the American Headache Society review article by Marmura, Silberstein, et al. 2015.

Reviewer comments: This list should be used to understand the context in which acute treatments for migraine exist, and where there still may be needs for patients.

The current treatment options do provide physicians treating migraine with therapies that are often quite effective in treating acute migraines, with efficacy and side-effect profiles differing substantially between patients (Dodick 2018). Some treatment options are limited to patients

without cardiovascular disease. Therefore, additional options for the treatment of acute migraine for patients with cardiovascular disease would be a beneficial addition to clinicians treating patients with migraine. Some medications also carry the risk of adverse events, such as gastrointestinal upset, or have a risk of habituation, addiction, tolerance, withdrawal syndromes, or medication-overuse headache. (Marmura, Silberstein, et al. 2015) Given varying efficacy and side-effects from patient to patient, safe and efficacious drugs that could be used in this population would help augment the armamentarium available to clinicians treating patients with migraine.

3. Regulatory Background

3.1. United States (U.S.) Regulatory Actions and Marketing History

Lasmiditan is a New Molecular Entity (NME), and is not currently marketed in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The investigational new drug application (NDA) 103420 was opened for lasmiditan (also known as COL-144 or LY573144) in **July 2011** by the applicant at that time, CoLucid. A "Study May Proceed" letter was issued on September 2011 for a food effect study in health volunteers. The applicant had previously conducted several studies, including bioavailability, pharmacokinetic, and initial tolerability studies, outside the United States (OUS).

In **December 2011**, an End of Phase 2 (EOP2) meeting was held. Multiple issues were discussed including dosing, the high incidence of dose-related neurologic adverse events (AE) (including vertigo, dizziness, fatigue, somnolence) seen in the Phase 1 and 2 studies and a possible driving effect. Additionally, the applicant was given feedback regarding the need to study drug effects in elderly patients and to evaluate cardiovascular (including QT interval) effects. Of note, the applicant stated that the mechanism of action of lasmiditan may allow the use in patients who have cardiovascular contraindications to triptans. The Division stated that patients with pre-existing cardiovascular disease should be included in studies to further investigate if this drug may be safe in this population, but that the assay sensitivity would likely be low to make this determination based on the low risk of cardiac events that would likely be seen in the context of a clinical trial. The applicant was advised to use a study design that examined the effect of lasmiditan for the treatment of a single migraine attack (not multiple attacks), using pain freedom at 2 hours, along with freedom from associated symptoms (nausea, photophobia and/or phonophobia) as the preferred co-primary endpoint. The applicant was also advised that a composite endpoint on associated symptoms was inadequate as a co-primary endpoint.

In **February 2014**, a meeting was held to discuss the novel proposed co-primary outcome of proportion of patients with pain freedom at 2 hours and Most Bothersome Symptom (MBS) freedom at 2 hours, a recommendation first suggested by the Agency. The Division stated that patients should prospectively identify MBS prior to randomization to avoid bias. Please refer to Section 6 for more details on this endpoint.

In **April 2014**, the Special Protocol Assessment (SPA) for the Study 301/LAHJ was agreed upon. The Division agreed to allow the proportion of patients who are pain-free at 2 hours as the primary endpoint and the MBS as a key secondary endpoint. However, the Division stated that the study would need to meet both endpoints to demonstrate efficacy. It was agreed that the second dose of study drug would be an exploratory endpoint, since true re-randomization (with patients coming in to be re-randomized after first dose) for the second dose was not occurring. The Division also noted that patients with cardiovascular disease were excluded from Study 301, and conveyed concerns regarding this exclusion.

The Division gave the applicant feedback on the SPA, which included information regarding how to handle patients with none/mild pain severity at onset. In **March 2015**, the applicant sent an amendment to the SPA, which included 21 changes. The applicant interpreted one of the Division's comments to mean that patients with none/mild severity pain at migraine onset should be included in the primary analysis population. However, this was not the intention of the Division's initial feedback, and this is discussed in the context of the analysis of the primary and key secondary endpoints below. The applicant also incorporated other feedback, including modifying eligibility criteria, to not exclude certain cardiovascular conditions, and adding a stratification for use of concomitant medications to treat migraine.

In **July 2015**, a Type C meeting was held to discuss the Division's position on including patients with vascular risk factors and conditions described in the triptan class label. It was again reiterated that the applicant should include patients with cardiovascular disease to examine the risk of lasmiditan in this population.

There was initial disagreement with the SPA for the applicant's second pivotal proposed study (302/LAHK) because of concern about the applicant not "prospectively identifying the most bothersome migraine associated symptom in addition to pain." In **February 2016,** the applicant sent a SPA request resubmission, clarifying that the MBS would be identified prospectively, and time stamped, so it could not be recorded in retrospect. This was considered acceptable by the Division, and a letter was subsequently sent to the applicant regarding a SPA agreement for Study 302.

In **January 2017**, the applicant changed from CoLucid to Lilly.

In **June 2017**, a letter was sent to the applicant regarding the abuse potential study and

recommendations regarding how to perform this study.

In **October 2017**, the Division met with the applicant to discuss their clinical development plan. There was discussion regarding the need for a food-effect study on the formulation that was to be marketed, and the applicant clarified that the metabolism of lasmiditan was not mediated by cytochrome P450 (CYP) enzymes, so they did not plan additional drug-drug interaction studies. There was also discussion on the benefit-risk for the second dose of lasmiditan, and the applicant clarified that the second dose was not re-randomized in between doses, but that randomization for the sequence of dosing occurred with the initial randomized dose. Regarding the exposure data, the Division stated that there must be an adequate number of patients at the highest frequency of administration (number of attacks treated per month) at the highest dose (200 mg). The Division advised the applicant to examine concomitant cardiovascular medication changes, blood pressure, and electrocardiogram changes, and to analyze safety in cohorts by age. They were also advised to characterize adverse reactions of vertigo, dizziness, fatigue, somnolence, and abuse related AEs. The applicant was also advised that if the nonclinical data supported a lack of potential vasoconstrictive effects and if there was no clinical data supporting a vasoconstrictive effect of lasmiditan, it may be possible to have labeling that did not restrict the product's use to patients without cardiac disease or cardiovascular risk factors.

In **August 2018**, the Division held a pre-NDA meeting with the applicant to discuss pharmacokinetics, the need for additional drug-drug interaction studies, issues regarding scheduling of the drug given the studies examining abuse potential, how safety pools should be generated, and clarification on comparisons for second dose for rescue/recurrence.

3.3. Foreign Regulatory Actions and Marketing History

Lasmiditan is not approved or marketed in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please refer to the reviews conducted by the Office of Scientific Investigations for details regarding clinical site inspections for this application. Two sites from each pivotal clinical trial were chosen for inspection.

I have briefly summarized the findings below.

For Study 301, Site 120, Dr. Harry Geisberg, was issued a Voluntary Action Indicated (VAI) letter due to findings including under-reporting of adverse events in two of 50 enrolled patients, enrollment of one patient without availability of complete screening labs, and late review of end-of-study labs with clinically significant results.

For Study 301, Site 131, Dr. William Kirby, was issued a Voluntary Action Indicated letter for an inspectional finding due to inadequate records. Specifically, copies of signed informed consent documents could not be located for two of 60 screened patients.

For Study 302, Sites 134 and 395 were inspected, and both sites received No Action Indicated (NAI) letters.

4.2. Product Quality

The drug product is available as oval 50 mg and 100 mg, debossed, aqueous film-coated, immediate-release tablets. The 50 mg tablet is light gray, and the 100 mg tablet is light purple. The active ingredient is lasmiditan hemisuccinate, (b) (4) microcrystalline cellulose, and (b) (4) (b) (4) pregelatinized starch. Please refer to the review by the Office of Product Quality, multidisciplinary review, for further details on product quality.

4.3. Nonclinical Pharmacology/Toxicology

The applicant asserts that lasmiditan is a selective 5-HT_{1F} receptor agonist without significant activity at 5-HT_{1B} and 5-HT_{1D} receptors. In nonclinical studies, lasmiditan did not constrict ex-vivo rabbit saphenous veins, ex-vivo human coronary arteries, ex-vivo human internal mammary arteries, in-vivo dog coronary arteries, or in-vivo dog carotid arteries.

For further details, please refer to the review by Dr. Edmund Nesti, nonclinical reviewer.

4.4. Clinical Pharmacology

The clinical pharmacokinetics of lasmiditan demonstrate that following oral administration, lasmiditan has a median peak plasma concentration of approximately 1.8 hours. The elimination half-life is approximately 5.7 hours.

Please refer to the review by Dr. Priya Brundson, clinical pharmacology reviewer, for further details of the clinical pharmacology of this drug.

4.5. Devices and Companion Diagnostic Issues

Not applicable.

4.6. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The studies submitted to this application to support the efficacy and safety of lasmiditan in the acute treatment of migraine are described in Table 2 below.

Table 2: Clinical Studies To Support Efficacy/Safety of Lasmiditan

Trial/ National Clinical Trial (NCT) No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients randomized and treated	Study Population	No. of Centers and Countries
201/LAHM	Dose-finding, pharmacokinetic study	Intravenous lasmiditan 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 45 mg, 60 mg	Primary endpoint of pain relief (from moderate to severe to mild or none) at 2 hours after study drug infusion	Treat first migraine attack	130; 42 in placebo and 88 in active	Adults with migraine with or without aura, baseline 1-8 migraines per month.	3 sites in the European Union (EU)
202/ LAHO NCT00883051	Dose-finding, randomized, double-blind, placebo-controlled trial	Oral lasmiditan 50 mg, 100 mg, 200 mg, 400 mg, or placebo to take at onset of migraine	Primary endpoint of headache response at 2 hours	Treat first migraine attack	512; 378 analyzed for efficacy	Adults with migraine with or without aura, baseline 1-8 migraines per month.	43 sites in EU
301/ LAHJ NCT02439320 - SAMURAI	Randomized, double-blind, placebo-controlled trial	Oral lasmiditan 100 mg, 200 mg, or placebo to take at onset of moderate-severe migraine; Second dose for rescue/recurrence	Primary endpoint of headache pain free at 2 hours and key secondary endpoint of Most Bothersome Symptom (MBS) free at 2 hours	Screening visit, up to 8 weeks to treat first migraine attack, and follow-up within 1 week of treating attack	2231; 1545 analyzed for efficacy and 1856 analyzed for safety	Adults with migraine with or without aura, with baseline 3-8 migraines per month.	99 sites – all in U.S.
302/ LAHK NCT02605174 - SPARTAN	Randomized, double-blind, placebo-controlled trial	Oral 50 mg, 100 mg, 200 mg, or placebo to take at onset of moderate-severe migraine; Second dose for rescue/recurrence	Primary endpoint of headache pain free at 2 hours and key secondary endpoint of MBS free at 2 hours	Screening visit, up to 8 weeks to treat first migraine attack, and follow-up within 1 week of treating attack	3005; 2156 analyzed for efficacy, 2583 analyzed for safety	Adults with migraine with or without aura, with baseline 3-8 migraines per month.	125 sites, U.S., United Kingdom (UK) - 12 sites, Germany - 16 sites
305/ LAHL NCT02565186 - GLADIATOR	Prospective, randomized, open-label study	Oral lasmiditan 100 mg or 200 mg	Primary endpoint of safety and tolerability of long-term lasmiditan for acute treatment of migraine; long-term efficacy of headache response	Treat all migraine attacks, up to 12 months	2116 patients randomized	Adults with migraine who completed Study 301/LAHJ or 302/LAHK.	199 sites, U.S. - 186 sites, Germany - 4 sites, UK - 9 sites

5.2. Review Strategy

This review focuses on the efficacy data of lasmiditan for the acute treatment of migraine. For efficacy, I will review the data from the two large pivotal studies, Studies 301 and 302, and will present the data from each study individually (Section 6.1 and Section 6.2), noting key differences in the 302 trial, and then integrating the study results to assess overall efficacy (Section 7). I will also include a brief discussion (Section 6.3) of Study 305. Since Study 305 was an open-label study, only an overview is included since the open-label nature does not lead to interpretable results regarding efficacy. Of note, studies 201 and 202 were dose-finding studies, and are briefly mentioned in the Rationale for Dose Selection (Section 6.1.1) of this review.

The clinical review is divided into this review of clinical efficacy and a separate review of clinical safety (by Dr. Natalie Branagan), and relies on data from several clinical studies, including one dose-finding study (202), two pivotal phase 3 studies (301 and 302 - both randomized and placebo-controlled), and an open-label safety study (305). All patients in Studies 202, 301, 302, and 305 had a diagnosis of migraine with or without aura, and were instructed to treat acute migraine attacks. The applicant also submitted data from 19 phase 1 clinical pharmacology studies in various populations, including healthy patients, elderly patients, recreational drug users, patients with renal or hepatic impairment, or migraine patients. The interpretation of these studies will be described in the reviews by other disciplines, including the Clinical Pharmacology review.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 301/LAHJ: A Study of Two Doses of Lasmiditan (100 mg and 200 mg) Compared to Placebo in the Acute Treatment of Migraine: A randomized, double-blind, placebo-controlled parallel group study (SAMURAI)

6.1.1. Study Design

Overview and Objective

Study 301/LAHJ (hereafter referred to as Study 301) evaluated the efficacy and safety of multiple doses of lasmiditan compared to placebo on headache pain freedom and most bothersome symptom (MBS) freedom at 2 hours for treatment of a single migraine attack.

Trial Design

Study 301 was a phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-

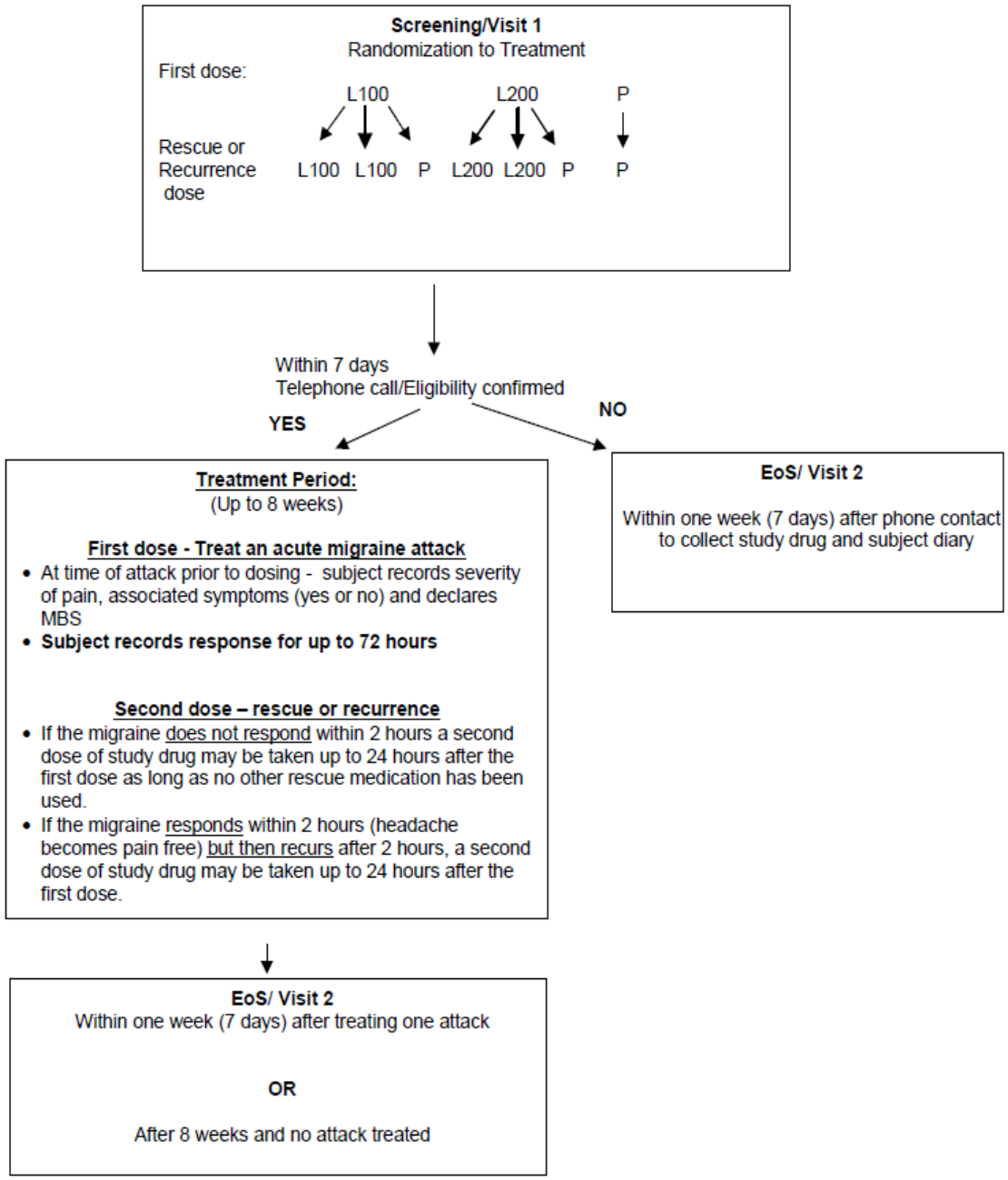
group study to evaluate the safety and efficacy of lasmiditan for the treatment of a single migraine attack. The study was conducted under a SPA (See Section 3.2 - Summary of Presubmission/Submission Regulatory Activity). This was a three-arm study, assessing lasmiditan at doses of 100 mg and 200 mg, versus placebo. Patients were enrolled if they met eligibility criteria, including age ≥ 18 years of age, met International Classification for Headache Disorders (ICHD)-II criteria for diagnosis of migraine with or without aura, had a history of 3-8 migraine attacks per month (< 15 headache days), and a Migraine Disability Assessment (MIDAS) score ≥ 11.

Study 301 specifically excluded patients with coronary artery disease (CAD), clinically significant arrhythmia, or uncontrolled hypertension. However, the study did intentionally enroll patients with cardiovascular risk factors (including age > 40, hypertension, diabetes mellitus, and hyperlipidemia).

This study was conducted entirely in the U.S., with 2231 patients enrolled at 98 sites.

Patients had a screening visit and were randomized to receive study drug or placebo, with a telephone contact within 7 days to confirm eligibility (after reviewing laboratory results). Patients then had up to 8 weeks to treat a migraine attack of at least moderate severity, and then were asked to return for an end of study visit within 7 days of treating the single migraine attack. For the same treated migraine attack, patients also had an option of taking a second dose (determined at initial randomization with first dose) for either rescue (migraine had not resolved after 2 hours) or recurrence (migraine had resolved but recurred), 2 to 24 hours after initial dose.

Figure 1: Study 301 - Study Design



Source: NDA 211280: \\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\protocol-col-mig-301-v2-3.pdf

Reviewer comment: The applicant's study design aligns with what is recommended in the Migraine: Developing Drugs for Acute Treatment Guidance to Industry published in February 2018 (https://www.fda.gov/media/89829/download), with regards to endpoints, study population, and general design of treating one migraine attack in a study evaluating an acute treatment for migraine.

Basic Study Design

Screening Phase/Randomization (1 week)
Double-blind treatment phase (up to 8 weeks)
End of study follow up visit (1 week after treating an acute migraine with study drug)

Diagnostic Criteria
The applicant utilized the ICHD-2 (2004) and required that patients met the criteria for migraine with or without aura (see below) to be eligible for the study.

Diagnostic criteria for migraine without aura:
A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours [when untreated in adults]
C. Headache has at least two of the following characteristics:
    1.unilateral location
    2.pulsating quality
    3.moderate or severe pain intensity
    4.aggravation by or causing avoidance of routine physical activity
D. During the headache, at least one of the following [is present]:
    1.Nausea and/or vomiting
    2.Photophobia and phonophobia
E. Not attributable to another disorder

Diagnostic criteria for migraine with aura:
A. At least two attacks fulfilling criterion B
B. Migraine aura fulfilling criteria (described below)
C. Not attributed to another disorder

Key Inclusion Criteria
- Patients with migraine with or without aura, fulfilling the ICHD diagnostic criteria
- History of disabling migraine for at least 1 year
- MIDAS score ≥ 11
- Migraine onset before the age of 50 years
- History of 3-8 migraines per month (< 15 headache days per month)
- Adults, age 18 years and older

Key Exclusion Criteria

- Any medical condition or clinical laboratory test which made the subject unsuitable for the study
- Pregnant or breast-feeding women
- Women of childbearing potential not using or not willing to use highly effective contraception
- Known coronary artery disease, clinically significant arrhythmia or uncontrolled hypertension
- History or evidence of hemorrhagic stroke, epilepsy or any other condition placing the subject at increased risk of seizures
- History of recurrent dizziness and/or vertigo, including BPPV, Meniere's disease, vestibular migraine, and other vestibular disorders
- History of diabetes mellitus with complications
- History within three years or current evidence of abuse of any drug, prescription or illicit or alcohol
- History of orthostatic hypotension with syncope
- Significant renal or hepatic impairment
- Known Hepatitis B or C or HIV infection
- History, within past 12 months, of chronic migraine or other forms of primary/secondary chronic headaches (e.g. hemicranias continua, medication overuse headache) with headache frequency > 15 days per month
- Use of more than 3 doses per month of either opiates or barbiturates
- Initiation of or a change in concomitant medication to reduce the frequency of migraine episodes within 3 months of screening/visit 1

Reviewer comment: The applicant specifically wanted to include patients with cardiovascular risk factors to avoid including language in the triptan label against use in patients with many types of cardiovascular disease. Study 301 specifically excluded patients with cardiovascular disease (initially defined as ischemic heart disease, coronary artery disease (CAD), other moderate to severe heart problems, cranial blood vessel disease (stroke, transient ischemic attack), high grade peripheral vascular disease, or ischemic colitis). However, they subsequently submitted an amendment to the protocol (from V2.2 to the final V2.3) that only excluded patients with known CAD, clinically significant arrhythmia, or uncontrolled hypertension. The applicant did include patients with cardiovascular risk factors, though. The amendment took place prior to study initiation.

Rationale for Dose Selection

The applicant conducted two Phase 2 dose-finding studies: Studies 201/LAHM and 202/LAHO. Study 201 investigated intravenous doses of 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 45 mg,

and 60 mg, and using pharmacokinetic data, identified a concentration value of 20.8 ng/mL corresponding to 50% of the maximal effect of lasmiditan. This was compared to a model describing lasmiditan concentrations after oral dosing, and it was determined that doses of 50 mg, 100 mg and 200 mg would exceed the maximal effect in at least half of patients, in a dose-dependent manner.

The applicant then conducted Study 202, examining oral doses of 50 mg, 100 mg, 200 mg, and 400 mg of lasmiditan in adults with migraine. There was a dose-response for efficacy demonstrated in Study 202. There was also dose-related increase in adverse events. Based on this study, doses of 100 mg and 200 mg were selected for Study 301. However, FDA did give the applicant feedback during the EOP2 meeting that they should consider evaluating the 50 mg dose, as well.

Study Treatments

Lasmiditan dosing consisted of two tablets for the treatment of a single attack and two tablets for rescue or recurrent treatment. Patients were randomly assigned to one of 3 treatment sequences, in a 1:1:1 ratio, for the first dose of lasmiditan (placebo, 100 mg, or 200 mg). At the same time as the initial randomization for the first dose, patients then were assigned to either the same dose of lasmiditan as the first dose (2 in 3 chance), or placebo (1 in 3 chance) for their second dose (to be used for rescue or recurrence).

Assignment to Treatment

Patients were assigned a unique seven-digit patient number at screening. Patients were screened at visit 1 and if eligible, were randomized and discharged home with study drug to treat a single migraine attack and a second dose for rescue or recurrence. A telephone confirmation occurred within 7 days if the patient was still eligible. If a patient was not randomized, they were considered a screen failure. If the patient was randomized but then deemed ineligible at the telephone confirmation, the patient would be considered a randomization failure. Randomization occurred through a central randomization process by Interactive Response Technology (IRT) during screening/visit 1.

Reviewer comment: Patients and the study team were blinded to what drug the patient would be receiving for the second dose. The second dose data is helpful, however, to evaluate the safety of repeated dosing from 2 to 24 hours after first dose. Please see Dr. Branagan's safety review for details on the safety of a second dose.

Blinding

The study was a double-blind placebo-controlled trial. Patients, site personnel and applicant personnel were all blinded to the treatment assignment. Both lasmiditan and matching placebo

tablets were provided in double-blinded treatment packs.

Dose Modification/Discontinuation

There was no dose modification allowed, as patients were instructed to only take the randomized doses. Patients could discontinue from the study at any time for any reason.

Procedures and Schedule

The schedule of trial procedures and assessments for Study 301 is summarized in Table 3.

Table 3: Study 301 - Schedule of Assessments

Assessment	**Visit 1** Screening and Baseline	**Telephone Contact** Within 7 days after Visit 1	**Treatment** Treatment of an attack within 8 weeks	**EoS/Visit 2** Within 7 days after treatment **OR** After 8 weeks and no attack treated[1]
Obtain informed consent/HIPAA	X			
Document migraine characteristics per IHS criteria	X			
Review inclusion / exclusion criteria	X			
Complete MIDAS	X			
Review migraine history including prior treatment	X			
Review medical history and concomitant medication	X			
Review resource utilization (visits to specialists, emergency rooms, etc)	X			X
Physical examination and vital signs (heart rate, blood pressure)	X			X
Weight and height	X			
12-lead ECG	X			X
Clinical laboratory[2]	X			X
Columbia Suicide Severity Rating Scale	X			X
Randomization	X			
Dispense study drug, study diary, and provide detailed instructions	X			
Confirm eligibility[3]		X		X
Migraine attack (electronic diary) documentation by subject			X	
Documentation of rescue/recurrence medication			X	
Documentation of adverse events and concomitant medication	X	X	X	X
Collect unused/empty study drug pack.				X[1]

Source: NDA 211280: \\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\protocol-col-mig-301-v2-3.pdf
[1] Subjects that did not treat a migraine for any reason during the 8 weeks attended an End of Study (EoS) visit to return unused study drug and the electronic diary (eDiary). No other assessments were required.
[2] Clinical laboratory tests included hematology, biochemistry, lipid profile, urinalysis, and pregnancy test for women of childbearing potential.
[3] The confirmation of eligibility was made by telephone contact with final eligibility based on laboratory results. If a patient was not eligible, he/she had to return for a follow up visit to return unused study drug and the e-Diary.
Abbreviations: IHS=International Headache Society; MIDAS=Migraine Disability Assessment Score; ECG=electrocardiogram.

Concomitant Medications

Study 301 allowed for stable doses (for at least 3 months before screening) of concomitant medications for the preventive treatment of migraine. Patients were not allowed to change doses or initiate new preventive treatment of migraine medications during the study. Randomization was stratified by use/non-use of concomitant medications. Concomitant medications (including devices) for migraine or pain were recorded for 3 months prior to study enrollment and other medications were recorded for 1 month prior to enrollment.

Of note, opioids, barbiturates, triptans, and ergots were not allowed within 24 hours of study drug administration. Additionally, the number of opioids or barbiturates was restricted to a maximum of 3 doses per month, and patients were excluded if they had medication overuse headache (with headache frequency > 15 headache days per month). However, in the next 24 hours (after taking study drug), patients were not prohibited from using any rescue medication.

Reviewer comments: In Study 301, 25.8% of patients used concomitant medications for preventive treatment of migraines. Opioids, barbiturates, triptans, and ergots were not allowed and are typically used in patients for acute migraine treatment. I recommend including this information in the label when discussing the clinical trial results, so prescribers will know that lasmiditan was not given with other commonly used acute migraine medications. The applicant did perform one clinical study evaluating one triptan and lasmiditan (see Dr. Branagan's review for details), but there is no data on the effect of other commonly used acute migraine medications with lasmiditan.

Treatment Compliance

Patients were given study drug prior to discharge at screening/visit 1. They were asked to record the time and date of each dose in the electronic diary (eDiary). They were asked to return all unused study drug to the clinic at the end of study/visit 2.

Reviewer comments: There were some concerns with the electronic diary data, in that these were initially not provided by the applicant to FDA. Also, some patients did not prospectively identify their Most Bothersome Symptom, as was required per protocol. During earlier

regulatory interactions, we had emphasized that the MBS must be identified prospectively to avoid recall bias. It was subsequently determined that a number of patients had defined this retrospectively. Dr. Jinnan Liu, FDA statistician, performed several sensitivity analyses and determined the results were still positive when these patients (who did not identify the MBS prospectively) were excluded. Please see the section below on sensitivity analyses of the MBS endpoint.

Patient completion, discontinuation or withdrawal

Patient disposition was based on the first dose. Patients were able to withdraw or discontinue from the study for any reason at any point. Patients who discontinued between scheduled visits were asked to schedule an early termination visit within 14 days of discontinuing treatment.

Migraine Disability Assessment Test (MIDAS)

The applicant used the Migraine Disability Assessment Test (MIDAS) to identify patients who had a score of at least 11 to enrich the population for patients who had migraine associated with at least moderate disability. Briefly, this is a 5-question test that asks patients how many days in the last 3 months a headache resulted in one of the following: patient missed work/school, decreased productivity at work/school, inability to do household work, decreased productivity with household work, missed family/social/leisure activities. The total number of days are then tabulated with a score of 0-5 indicating little or no disability, 6-10 indicating mild disability, 11-20 indicating moderate disability, and > 20 indicating severe disability.

This questionnaire was only administered at screening to determine eligibility, and not repeated or followed during the study.

Patient Global Impression of Change (PGIC)

The Patient Global Impression of Change is a non-migraine specific 7-point scale in which a patient is asked to describe the change (if any) in activity, limitations, symptoms, emotions, and overall quality of life related to their condition since the beginning care at the clinic for the complaint (of migraine). The scale ranges from “very much better” to “very much worse,” and was only administered once, 2 hours after taking study drug.

Study Endpoints

Primary Endpoint and Key Secondary Endpoint

The primary efficacy endpoint was the proportion of patients who were headache pain free at 2 hours following the initial dose. Pain freedom was defined in the original Statistical Analysis Plan (SAP) as a reduction in severity of migraine pain from moderate to severe at baseline to no

pain at 2 hours. While this was changed by the applicant (to include patients with mild migraine intensity at baseline) prior to submission of the NDA, we subsequently agreed that the original definition would be used for the efficacy analysis population. Migraine pain freedom was assessed using a 4-point scale (with 0-none, 1=mild, 2=moderate, 3=severe) and recorded in an eDiary. Patients were only instructed to use study drug and treat a migraine attack when the migraine pain was moderate or severe.

The key secondary efficacy endpoint was the proportion of patients who were MBS free at 2 hours following the initial dose. The MBS was defined as either nausea, phonophobia, or photophobia that had to be identified by the patient prior to treatment, in the eDiary, by answering if they were experiencing nausea, phonophobia, or photophobia (yes/no), and which symptom was the most bothersome. Patients then had to report resolution (or not) of MBS after taking study drug at various time points, including the 2-hour time point for efficacy.

Reviewer comments: During the multiple interactions the applicant had with FDA, it was conveyed that though the endpoints above were primary and key secondary (not co-primary), the applicant would have to demonstrate statistical significance on both endpoints to have a successful study.

Statistical Analysis Plan (SAP)

The final statistical analysis plan for Study 301 was approved 22 August 2016, however the applicant states they made several changes to the plan, including changing the analyses of the primary efficacy measure, and other related measures described in the protocol. The agreed upon SAP (submitted with the SPA) stated that the analysis would be limited to headaches that were of moderate or severe intensity at the time of dosing. The initially agreed upon SAP also stated that the full analysis set for the primary endpoints would include patients that had taken one dose of study drug and had one post-dose assessment, however the applicant also limited this to patients who had taken study drug within 4 hours of migraine onset during a protocol change. Additionally, FDA had given the applicant feedback on how to assess patients with mild or no headache at baseline as non-responders, but the applicant interpreted this as the need to include patients with migraines of none/mild intensity (at the time of treatment for the primary endpoint analysis). The Division sent the applicant an Information Request to clarify that the population for the primary analysis was only patients who had a moderate/severe intensity migraine at onset, and not patients with none/mild intensity migraine at baseline. The applicant then modified the primary analysis population, such that it was in line with the original SAP.

Analysis Populations

Randomized: All randomized patients
Safety: All randomized patients who used at least 1 dose of study drug, whether or not they underwent any study assessments

Intent-to-treat: (ITT) All randomized patients who used at least 1 dose of study drug and had any post-dose pain severity or most bothersome symptom assessments
Modified Intent-to-treat (mITT): All ITT patients who treated a qualifying migraine attack (migraine attack within 4 hours of onset), have any post-dose assessments, and recorded severity at baseline
Corrected mITT: All ITT patients who treated a qualifying migraine attack (migraine attack within 4 hours of onset and moderate to severe intensity) and have any post-dose assessments
Per Protocol: All ITT patients will be considered per protocol if they dose a migraine attack and do not deviate from the protocol

The primary efficacy and key secondary analyses were performed on the mITT population; all other efficacy analyses were conducted in the ITT population, and this was pre-specified in the SAP. A qualifying migraine was defined as a migraine treated with study drug within 4 hours of onset. It was also pre-specified that patients who took rescue medication within the first two hours, or who did not record headache severity at 2 hours, would be assumed to have no response in the mITT and ITT analyses. It was pre-specified that patients who treated no (0) or a mild (1) qualifying migraine would be assumed to have no headache response for the mITT analysis.

Reviewer comment: FDA typically defines the mITT or efficacy analysis population as patients that are randomized, treat a qualifying migraine (one of moderate to severe intensity) and have at least one efficacy assessment. In general, we do not restrict this definition to only include patients in the mITT if patients treat a qualifying migraine within 4 hours. However, since the time restriction was agreed upon in the SPA, the 4-hour time frame will be allowed for the efficacy analysis population. To avoid confusion, I will refer to the population that is randomized, treat a qualifying migraine (of only moderate to severe intensity) and treat within 4 hours of migraine onset as the corrected mITT - to differentiate this population from the applicant's mITT (which included patients with none/mild intensity migraine at onset).

Sample Size Estimations

The applicant estimated the sample size based on the 2-hour headache pain free and most bothersome symptoms free response rate observed in their phase 2 studies. In their phase 2 study, Study 202, the applicant observed the following percentages for pain freedom: in the placebo group, 7.4%, 100 mg, 12.6% and 200 mg, 18.8%. Based on this, a sample size of 570 evaluable patients per arm provided a power of > 90% for both the 100 mg, and the 200 mg dose. Study 302 used the same estimates, but added another dose arm of 50 mg.

To estimate the sample size for the key secondary endpoint of proportion of patients who were MBS free at 2 hours, the applicant used a simulation of multiple scenarios, and estimated the power to be > 99% for MBS at sample sizes of 450 to 570 per arm for 100 mg dose and an

average power of 71% for the 200 mg dose.

Randomization and Stratification Factors

Study 301:
Patients were centrally randomized to one of 5 treatment sequences for both doses of study drug (placebo or lasmiditan), which included the following drug sequences:

Placebo/placebo
100 mg /placebo
100 mg/100 mg
200 mg/placebo
200 mg/200 mg

The second study drug was to be used for rescue or recurrence of migraine, if needed.

Patients were also stratified by use of current concomitant medications for preventive treatment of migraine.

Hypothesis Testing

The primary objective of the study was to evaluate the efficacy of lasmiditan at 100 mg and 200 mg, compared to placebo, on migraine headache pain at 2 hours and on the MBS.

Null Hypothesis

$P_T \leq P_P$

Alternative Hypothesis

$P_T > P_P$

Per the statistical analysis plan, P_T and P_P are the true proportion of patients who are pain free at 2 hours post dose for lasmiditan 200 mg (P_T) and placebo (P_P). Confirmatory hypothesis testing could be conducted on the true proportion of patients who were pain free at 2 hours post dose for the lasmiditan 100 mg patients, as well. The significance level of the test is 2.5%.

Pre-specified Methods of Handling Missing Data

The applicant stated in the SAP that the prespecified approach for handling missing data was to assume that patients with missing data are nonresponders.

Sensitivity Analyses

The applicant also performed additional sensitivity analyses of the primary and key secondary endpoints to handle patients with missing data. For the sensitivity analysis, the method was to impute missing data for subjects from the placebo arm under the assumption of the missing at random (MAR) mechanism, where these subjects were assumed to have unobserved values in line with similar placebo subjects with available data, taking into account their values observed prior to time points with missing data. For subjects in the lasmiditan arms, missing data would be imputed from the MAR-based imputation model that was estimated from the placebo subjects, assuming that the lasmiditan subjects with missing data would drift towards the mean response of the placebo arm.

Statistical Methodology for Adjusting for Multiplicity

The applicant utilized a gatekeeping procedure to prevent Type I error inflation for multiple comparisons for the primary and key secondary analyses. The treatment effect between lasmiditan 200 mg (the highest dose) and placebo was tested first for the primary endpoint (proportion of patients who are headache pain free) and for the key secondary endpoint of MBS free at 2 hours in their mITT population.

If the primary analysis was statistically significant (one sided p <.025) then the confirmatory hypotheses could be tested in sequential order which would include:

Proportion of patients who were headache pain free at 2 hours in lasmiditan 100 mg and placebo group.

Proportion of patients MBS free at 2 hours in lasmiditan 100 mg and placebo group.

These were the only two endpoints adjusted for multiplicity, and all other endpoints were prespecified as exploratory endpoints, per the SAP.

Reviewer comment: Please see the review by Dr. Jinnan Liu, statistical reviewer, for further details of the statistical analysis.

Protocol Amendments

There was one protocol amendment for Study 301 (with the final protocol dated 14 March 2015), which is summarized above in regulatory history.

As stated previously, an amendment to the SPA for Study 301, in March 2015, included 21 changes to the protocol, most minor, including address changes, but also changing the primary

analysis population to include patients with none/mild headache at baseline, and stratifying patients for use of concomitant medications to reduce the frequency of migraines. The amendment also removed the exclusion of certain cardiovascular co-morbidities in the inclusion criteria.

6.1.2. Study Results

Compliance with Good Clinical Practices

Lilly provided attestation that the study was conducted in accordance with the Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in compliance with Good Clinical Practices (GCP).

Financial Disclosures

Lilly provided certification that there were no financial agreements with the clinical investigators, defined in 21 CFR part 54.2, for Study 301, whereby the value of compensation to the investigator could be affected by the outcome of the study, and that no investigators were the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f). (Sources: \\cdsesub1\evsprod\nda211280\0001\m1\us\financial-301-lahj.pdf and \\cdsesub1\evsprod\nda211280\0001\m1\us\financial-302-lahk.pdf) The applicant included a supplemental site personnel listing for Form 3454 with all the Primary Investigators and there were no investigators with disclosable information for either study. Please see the financial disclosures at the end of this document.

Patient Disposition

Date of first patient randomized: 27 April 2015
Date of last patient randomized: 03 June 2016
Date of last patient completed: 12 August 2016

Table 4: Study 301 - Summary of Patient Disposition Based on First Dose - All Patients

Patient Disposition	301/Study Arm			
	Placebo	100 mg	200 mg	All Patients
Randomized, n (%)	742 (100.0%)	744 (100.0%)	745 (100.0%)	2231 (100.0%)
Confirmed Eligibility, n (%)	705 (95.0%)	710 (95.4%)	695 (93.3%)	2110 (94.6%)
Treated, n (%)	617 (83.2%)	630 (84.7%)	609 (81.7%)	1856 (83.2%)
Treated with 2nd Dose	401	289	238	928

	(54.0%)	(38.8%)	(31.9%)	(41.6%)
- Treated with 2nd Dose – For Rescue (Percentage of 2nd Dose)*	382 (95.3%)	254 (87.9%)	205 (86.1%)	841 (90.6%)
- Treated with 2nd Dose – For Recurrence (Percentage of 2nd Dose)*	19 (4.7%)	35 (12.1%)	33 (13.9%)	87 (9.4%)
Analysis Populations, n (%)	742	744	745	2231
ITT Population	554 (74.7%)	562 (75.5%)	555 (74.%)	1671 (74.9%)
Applicant mITT Population	524 (70.6%)	503 (67.6%)	518 (69.5%)	1545 (69.3%)
Corrected mITT Population[1]	515 (69.4%)	498 (66.9%)	503 (67.5%)	1516 (67.9%)
PP Population	465 (62.7%)	435 (58.5%)	464 (62.3%)	1364 (61.1%)
ITT-2nd dose Population				
Safety Population	617 (83.2%)	630 (84.7%)	609 (81.7%)	1856 (83.2%)
Completed Study, n (%)	643 (86.7%)	648 (87.1%)	631 (84.7%)	1922 (86.1%)
Treated	599 (93.2%)	613 (94.6%)	593 (94.0%)	1805 (93.9%)
Not Treated	44 (6.8%)	35 (5.4%)	38 (6.0%)	117 (6.1%)
- No Migraine*	21 (47.7%)	15 (42.9%)	14 (36.8%)	50 (42.7%)
- No Eligible Migraine*	16 (36.4%)	16 (45.7%)	19 (50.0%)	51 (43.6%)
- No Study Medication*	6 (13.6%)	4 (11.4%)	5 (13.2%)	15 (12.8%)
- Missing*	1 (2.3%)	0	0	1 (0.9%)
Discontinued Study	99 (13.3%)	96 (12.9%)	114 (15.3%)	309 (13.9%)
- Treated*	18 (18.2%)	17 (17.7%)	16 (14.0%)	51 (16.5%)
- Not Treated*	81 (81.8%)	79 (82.3%)	98 (86.0%)	258 (83.5%)

Source: NDA 211280 – Table of Clinical Study Report Table 10.1 and 11.1 (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf)

[1]The corrected mITT is the primary and key secondary analysis population of interest.
*=Indicates a percentage of those patients in the Patient Disposition category listed directly above the row (for example, in the category "Not treated," of 44 patients not treated who were randomized to the placebo arm, 21 (47.7%) were not treated due to "no migraine."

Summary of key disposition data:

Randomized: 2231
Confirmed Eligibility: 2110
Completed Study: 1922
Received 1 or more doses of IP (Safety set): 1856
Intent-to-treat set: 1671
Efficacy analysis set (applicant mITT): 1545 (includes mild, moderate and severe intensity)
Efficacy analysis set (corrected mITT): 1516 (moderate to severe intensity only, primary and key secondary population)

Of note, one patient enrolled and completed the study at two different study sites, receiving the study drug approximately 2 months apart.

Reviewer comment: There were 309 patients in this study who discontinued the study for various reasons, however only 51 of the discontinuations actually received study medication. If these patients had been included in the analysis population, it is unlikely that they would affect the interpretation of the efficacy or safety of the drug. The discontinuations seemed even across assigned treatment arms, as well, so do not raise cause for concern for validity of data based on disposition.

Protocol Violations/Deviations

Of 2231 randomized patients, there were 2110 with confirmed eligibility and 1856 that were treated. Of the randomized population, there were 481 (22.8%) major protocol deviations. The most common deviation was not treating a migraine of at least mild severity in 171 (8.1%) patients. Many patients also used an excluded rescue medication before the 2-hour timepoint (147 (7.0%)), or treated with study drug 4 hours after symptom onset (127 (6.0%)).

Reviewer comments: Excluding patients who treated a mild severity migraine or treated with study drug 4 hours after symptom onset are not issues the Division would consider protocol deviations. I do not believe these reasons for protocol deviations affect the integrity of the study, but they do decrease the total available analysis population.

Demographics

Table 5: Study 301 - Demographics of Analysis Population (Corrected mITT*)

Demographic Parameter	Study Arm		
	Placebo N=515 N (%)	**100 mg N=498 N (%)**	**200 mg N=503 N (%)**
Sex			
Male	74 (14.4%)	96 (19.3%)	79 (15.7%)
Female	441 (85.6%)	402 (80.7%)	424 (84.3%)
Age			
Mean years	42.0	42.1	41.3
Median (years)	42	42	41
Min, max (years)	18, 78	18, 74	18, 72
Age Group			
≥ 18 - < 30 years	101 (19.6%)	80 (16.1%)	97 (19.3%)
≥ 30 - < 50 years	264 (51.3%)	283 (56.8%)	277 (55.1%)
≥ 50 - < 65 years	130 (25.2%)	124 (24.9%)	113 (22.5%)
≥ 65 years	20 (3.9%)	11 (2.2%)	16 (3.2%)
Race			
White	414 (80.4%)	384 (77.1%)	382 (75.9%)
Black or African American	86 (16.7%)	87 (17.5%)	98 (19.5%)
Asian	2 (0.4%)	2 (0.4%)	2 (0.4%)
American Indian or Alaska Native	1 (0.2%)	4 (0.8%)	5 (1.0%)
Native Hawaiian or Other Pacific Islander	1 (0.2%)	1 (0.2%)	2 (0.4%)
Multiple	5 (1%)	10 (2.0%)	5 (1.0%)
Other	6 (1.2%)	10 (2.0%)	9 (1.8%)
Ethnicity			
Hispanic or Latino	73 (14.2%)	64 (12.9%)	61 (12.1%)
Not Hispanic or Latino	439 (85.2%)	431 (86.6%)	437 (96.9%)
Not reported or unknown	3 (0.6%)	3 (0.6%)	5 (1.0%)
Region			
United States	515 (100%)	498 (100%)	503 (100%)

*Note, this table is derived from the mITT population from the Study 301 ADSL dataset and I excluded patients with mild intensity at baseline, which excludes 9 patients in the placebo arm, 5 patients in the 100 mg arm and 15 patients in the 200 mg arm.

Reviewer comment:

The demographic characteristics are fairly balanced across all arms. There was a slightly higher percentage of males in the 100 mg arm of this study, and a lower percentage of males in the 30-50 age group, compared to other groups. Migraine is known to be more prevalent in females than males. Migraine prevalence is typically reported in the literature as a 3:1 ratio of females: males (Lipton, 2007). The ratio is higher in this study (about 5:1), but randomized controlled trials in migraine generally report a similar ratio, so this is reflective of the population that participates in migraine trials. A recent literature review that noted of 36 recent (since 2011) clinical trials studying migraine, 84.2% of participants were women and 82.9% were white (Robbins and Bernat 2017). *Thus the demographics of this study are consistent with what is reported in the literature.*

There is also a slightly lower percentage of those >65 years old in the placebo arm of this study. About 1/5 of the patients were black and there were only a few patients from other racial groups represented. This is not atypical for a clinical trial in migraine.

Also, not included in the table above are the following parameters conducted on the entire safety population (Source Table 11.2 of the 301_LAHJ 04 Body file \\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf):

- Average BMI (kg/m^2) of the population was 30.41 (Standard deviation of 7.918), similar across groups
- Current smokers were 13.5% of the total population, similar across groups
- Family history of coronary artery disease in 33.6%, similar across groups

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The applicant examined certain migraine specific disease characteristics, including the duration of migraine history, the average number of migraines per month (in the prior 3 months), the percentage of patients with migraine with and without aura, the use of preventive medication for migraine, the MIDAS (Migraine Disability Assessment Test) total score, the total number of headache days in the past 3 months, and the average headache pain in the past 3 months (on an 11-point scale). Results of these analyses in the applicant's mITT population (including patients with mild, moderate, or severe intensity migraine at baseline) are below.

Table 6: Study 301 - Migraine Specific Disease Characteristics (applicant mITT*)

Characteristic	Study Arm			
	Placebo N=524	100 mg N=503	200mg N=518	All patients N=1545
Duration of migraine history (years)				
Mean (SD)	19.2 (12.5)	19.3 (13.0)	18.6 (12.8)	19.1 (12.8)
Median	17.4	17.8	17,4	17.5
Min, Max	0, 73	0, 64	0, 59	0, 73
Average Migraines/Month in past 3 months				
Mean (SD)	5.2 (1.8)	5.1 (1.8)	5.1 (1.7)	5.1 (1.8)
Median	5.0	5.0	5.0	5.0
Min, Max	3, 16	1, 15	3, 10	1, 16
Experienced Migraine with and without Aura				
Yes - n (%)	157 (30.0%)	156 (31.0%)	160 (30.9%)	473 (30.6%)
No - n (%)	367 (70.0%)	347 (69.0%)	358 (69.1%)	1072 (69.4%)
Use of Medication to Reduce Migraines				
Yes - n (%)	133 (25.4%)	128 (25.4%)	133 (25.7%)	394 (25.5%)
No - n (%)	391 (74.6%)	375 (74.6%)	385 (74.3%)	1151 (74.5%)

*This table was adapted from the applicant provided table 14.1.3.3 from the 301 Clinical Study Report (source: \\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf). Of note, this is in the applicant's mITT and includes the patients with mild intensity migraine at baseline. When these analyses were repeated without these patients, the results were similar.

Table 7: Study 301 - Additional Migraine Characteristics (applicant mITT*)

	Placebo/ Placebo	100 mg/ Placebo	100 mg/ 100 mg	200 mg/ Placebo	200 mg/ 200 mg
MIDAS total score Mean (SD)	31.3 (21.5)	29.6 (21.4)	32.0 (20.4)	31.2 (20.1)	32.3 (21.2)
Days with Headache - Past 3 months Mean (SD)	17.5 (10.6)	17.3 (10.8)	18.3 (10.7)	17.8 (10.7)	18.5 (12.2)
Average Headache Pain – Past 3 months Mean (SD)	7.5 (1.6)	7.4 (1.6)	7.1 (1.7)	7.5 (1.7)	7.7 (1.6)

*This table above was adapted from Applicant Table 14.1.3.8.2 from the 301 Clinical Study Report (source: \\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf). However, the applicant conducted many of these analyses on the safety population or by dose (not dose sequence), so I re-analyzed these characteristics in the corrected mITT population (not presented here). The results were similar across all analyses populations.

Co-morbidities

This study included patients with cardiovascular risk factors, as defined by the American College of Cardiology/American Heart Association recommended variables. These included the following variables: age >40, current smoker, high total cholesterol (≥240 mg/dL), low HDL cholesterol (<40 mg/dL men, <50 mg/dL women), high blood pressure (SBP ≥ 140 mm Hg or history of hypertension), history of diabetes mellitus. The most common risk factor was age greater than 40 in both studies across all subgroups.

The applicant excluded patients with baseline cardiovascular disease (including known coronary artery disease (CAD), arrhythmia, uncontrolled hypertension) from the protocol of Study 301.

However, the applicant then retrospectively identified baseline cardiovascular disease if a patient's medical history or preexisting conditions included a cardiovascular disease-related Standardized MedDRA Queries (SMQs) that included the following: Narrow terms in Hypertension (SMQ 20000147), Narrow terms in Cardiac arrhythmias (includes sub-SMQs; SMQ 20000049), Narrow terms in Cardiac failure (SMQ 20000004), Narrow terms in Cardiomyopathy (SMQ 20000150), Narrow terms in Central nervous system vascular disorders (includes sub-SMQs) (SMQ 20000060), Narrow terms in Embolic and thrombotic events (includes sub-SMQs) (SMQ 20000081),), Narrow terms in Ischemic heart disease (includes sub-SMQs) (SMQ 20000043), Pulmonary hypertension (SMQ 20000130) and Torsade de pointes/QT prolongation (SMQ 20000001).

Table 8: Study 301 - Baseline Cardiovascular Co-morbidities (applicant mITT)

Characteristic	Study 301/arm		
	Placebo N=524	**100 mg N=503**	**200 mg N=518**
Baseline cardiovascular risk factor (age > 40, current smoker, high total cholesterol (≥240 mg/dL), low HDL cholesterol (<40 mg/dL men, <50 mg/dL women), high blood pressure (SBP ≥ 140 mm Hg or history of hypertension), history of diabetes mellitus)			
Present (n)	439	411	430
(%)	82.1%	81.7%	83.0%
Baseline cardiovascular disease (hypertension, arrhythmia, cardiac failure, cardiomyopathy, CNS vascular disorders, embolic and thrombotic events, ischemic heart disease, pulmonary hypertension and Torsade de pointes/QT prolongation)			

Present (n)	105	104	101
(%)	6.8%	6.7%	6.5%
Age > 40 as cardiovascular risk factor			
Yes (n)	285	273	257
(%)	54.3%	54.3%	49.6%
Current smoker as cardiovascular risk factor			
Present (n)	65	66	66
(%)	12.4%	13.1%	12.7%
SBP ≥ 140 mm Hg or history of hypertension as cardiovascular risk factor			
Present (n)	115	110	117
(%)	21.9%	21.8%	22.6%
High total cholesterol (≥240 mg/dL), low HDL cholesterol (<40 mg/dL men, <50 mg/dL women) as cardiovascular risk factor			
Present (n)	54	43	54
(%)	10.3%	8.5%	10.4%
Diabetes mellitus as cardiovascular risk factor			
Present (n)	28	26	34
(%)	5.3%	5.2%	6.6%

*Source: This table is derived from the Integrated Database (IDB) dataset for ADSL, examining TRT01A in Study 301 by each variable (CVRISKFL (from 301 ADSL), CVBSGPFL, AGEG40FL, SMOKERFL, SBPFL, BCHOLFL, DIABTFL) in the mITT population.

Reviewer comment: Generally, across groups, the risk factors for cardiovascular disease were balanced, with age > 40 being the most common risk factor in more than half of the patients across every dose group. This would be expected in this clinical trial of adults with migraine, since this is the average age of migraineurs. High cholesterol and high blood pressure were the next most common risk factors across both studies, and again may be expected in this mostly U.S. population. While this does provide some insight into co-morbidities present in this population, I do not believe these baseline risk factors necessarily preclude use of currently available acute migraine therapies (e.g. triptans or ergots). Therefore, I do not believe this demographic data reflects a population that does not have alternative acute migraine therapies.

Regarding a diagnosis of baseline cardiovascular disease, I noted above that any patient who had cardiovascular disease by the applicant's definition was included in this population. The patients who had these SMQs were all given a cardiovascular disease history "flag" for Study 301. Thus, though Study 301 specifically excluded patients with cardiovascular disease, on retrospective analysis using these SMQs, 21.0% of the randomized population (not table above is just applicant mITT and prevalence is 6-7% across groups) had what the applicant then retrospectively defined as baseline cardiovascular disease. The concern here is that these entities do not necessarily represent cardiovascular disease that would preclude use of certain

medications, like triptans. For example, "hypertension" without any modifiers is included in the baseline cardiovascular disease flag. Not all patients with hypertension (for example, those with controlled hypertension or a past medical history, but not currently active) would be considered as having cardiovascular disease that would prevent triptan use. It would be more accurate to only include patients from the contraindicated populations from the triptan labels to define baseline cardiovascular disease, since these are the patients who are need of alternative therapies. Establishing safety and efficacy in patients with specific cardiovascular diseases (e.g. ischemic heart disease, coronary artery vasospasm, stroke or transient ischemic attack, peripheral vascular disease, ischemic bowel disease and uncontrolled hypertension) is important and this dataset is limited in its ability to do this.

An analysis was conducted to see how many patients with hypertension drove the approximate 20% of randomized patients who reportedly had "baseline cardiovascular disease" that the applicant reports in the all randomized population. I conducted an analysis of the Medical History High Level Group Terms (MHHLGT) and found that in the 301 study, 384 patients had "vascular hypertensive disorders," 84 had cardiac arrhythmias, 9 had coronary artery disease, 4 had heart failure, and there were other terms that likely matched for the 468 patients with flags for cardiovascular disease. Overall in the applicant mITT, 6-7% of patients had cardiovascular disease at baseline.

Thus approximately 82% of the "baseline cardiovascular disease" in the Study 301 was driven solely by those patients with baseline hypertension (controlled or not). While this is technically a cardiovascular risk factor, triptans are not contraindicated in patients with hypertension, they are contraindicated in patients with <u>uncontrolled</u> hypertension only and in other specific cardiovascular diseases (e.g., ischemic heart disease, coronary artery vasospasm, stroke or transient ischemic attack, peripheral vascular disease, ischemic bowel disease, and uncontrolled hypertension). Therefore, I do not believe we can say that the demographics represent a population with baseline cardiovascular disease that precludes use of other acute migraine medications.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Of the 2231 randomized patients, 2110 had confirmed eligibility. Of those, 1856 had at least one dose of study drug (88% of confirmed eligibility) and this percentage reflects those who were compliant with taking study drug.

In the applicant's mITT population, 97% of patients had taken at least 1 prior concomitant medication for migraine treatment, with the most commonly reported medications being ibuprofen (33%), thomapyrin N (aspirin, caffeine and acetaminophen, similar to Excedrin) (29.5%), sumatriptan (27.1%), and paracetamol (14.5%). Table 6 demonstrates how many patients were taking concomitant medications for the preventive treatment of migraine.

In Study 301, in the applicant mITT population 112 patients used an early or excluded rescue medication. These patients were set to being evaluated as nonresponders in the primary and key secondary efficacy analyses for first dose.

Characteristics of Treated Migraines

The applicant examined certain characteristics of treated migraines based on the first dose, including time to dosing for migraine, baseline migraine severity, the MBS, including individual symptoms, and use of rescue medications.

Table 9: Study 301 - Characteristics of Treated Migraines Based on First Dose for Primary Analysis (applicant mITT)

Characteristic	**Study 301/arm**		
	L100 mg N=503	**L200 mg N=518**	**Placebo N=524**
Time to Dosing From Migraine Start (hours), n	503	518	524
Mean (SD)	1.03 (2.298)	1.10 (1.900)	1.04 (2.156)
Median	1.03	1.04	1.02
Time to Dosing From Mild/Moderate/Severe Pain (hours), n	503	518	524
Mean (SD)	1.03 (2.298)	1.10 (1.900)	1.04 (2.156)
Median	1.03	1.04	1.02
Baseline Migraine Severity, n (%)	503	518	524
Severe (3)	132 (26.2%)	148 (28.6%)	145 (27.7%)
Moderate (2)	366 (72.8%)	355 (68.5%)	370 (70.6%)
Mild (1)	5 (1.0%)	15 (2.9%)	9 (1.7%)
None (0)	0	0	0
Baseline Symptoms, n (%)	503	518	524
Nausea	210 (41.7%)	232 (44.8%)	221 (42.2%)
Phonophobia	303 (60.2%)	322 (62.2%)	327 (62.4%)
Photophobia	386 (76.7%)	391 (75.5%)	416 (79.4%)
None	34 (6.8%)	37 (7.1%)	36 (6.9%)
Baseline MBS, n (%)	469	481	488
Nausea	115 (22.9%)	118 (22.8%)	115 (21.9%)
Phonophobia	117 (23.3%)	96 (18.5%)	104 (19.8%)
Photophobia	237 (47.1%)	267 (51.5%)	269 (51.3%)

Accompanying Aura at First Dose, n (%)	503	518	524
Yes	9 (1.8%)	15 (2.9%)	15 (2.9%)
No	494 (98.2%)	503 (97.1%)	509 (97.1%)
Second Dose Taken Before 2-Hour Assessment, n (%)	503	518	524
Yes	4 (0.8%)	3 (0.6%)	1 (0.2%)
No	499 (99.2%)	515 (99.4%)	523 (99.8%)
Other Medications Taken to Treat Migraine, n (%)	503	518	524
No	382 (75.9%)	404 (78.0%)	353 (67.4%)
Yes, Before 2-Hour Assessment	45 (8.9%)	35 (6.8%)	32 (6.1%)
Yes, After 2-Hour Assessment	76 (15.1%)	79 (15.3%)	139 (26.5%)

Source: NDA 211280 Study 301 Clinical Study Report - Table 11.4: (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf)

The associated migraine symptoms at baseline were photophobia (ranging from 75-79%), phonophobia (60-62%), and nausea (42-45%), with rates similar across all treatment groups. Photophobia was identified as the MBS for the highest proportion of patients (47%, 52% and 51% in the lasmiditan 100 mg, 200 mg, and placebo groups, respectively).

Data Quality and Integrity

There were some concerns with data quality as the applicant did not provide electronic diary raw data with the submission. This could have resulted in incorrect dates and times being recorded for the primary analysis endpoint. The applicant was asked to submit the original electronic diary information for FDA review. They did also subsequently send the SAS code used to convert electronic diary data into interpretable data during a mid-cycle communication. This was reviewed as adequate.

Efficacy Results – Primary Endpoint

The primary endpoint of this study was pain freedom at 2 hours post dose. The applicant had originally defined their mITT population as all randomized patients who took at least one dose of study drug, recorded at least one post dose assessment, and treated a migraine within 4 hours, and also had *moderate or severe pain* at onset. The migraine pain freedom was rated on the IHS 4-point pain severity rating scale (0=no pain, 1=mild pain, 2=moderate pain, and 3=severe pain). Pain freedom was defined as reduction in pain severity from moderate or severe at baseline to none. I will call this the corrected mITT from now on, as the applicant received feedback from FDA that they misinterpreted and subsequently incorrectly revised their efficacy analysis population to include patients with mild intensity migraine at baseline (we will call this the applicant mITT). Through Information Requests (IRs), the applicant then

revised their analysis population to only include patients with moderate or severe intensity migraine at baseline, which was the original efficacy analysis population in the original SAP, and the preferred population for this analysis.

I have presented the analysis of the primary endpoint on the corrected mITT first, which is the agreed upon analysis population, and then presented the analysis on the applicant's mITT.

Table 10: Study 301 - Primary Efficacy Analysis (Corrected mITT*)

Pain freedom at 2 hours post dose (baseline moderate to severe)	Study 301/arm		
	Placebo N=515	100 mg N=498	200 mg N=503
N **%** **p-value****	79/515 **15.3%**	141/498 **28.3%** **p<.001**	160/503 **31.8%** **p<.001**

*Please note, this table is on the corrected mITT population, including patients with moderate/severe intensity migraine at baseline only.
**The p-values in this table are from analysis conducted by FDA statistical reviewer, Dr. Liu, using a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates.

Reviewer comment: The table above demonstrates that the trial met the primary efficacy endpoint of pain freedom at 2 hours in a statistically significantly higher proportion of patients in the lasmiditan treated group compared to placebo. The therapeutic gain (the percentage effect of active drug minus percentage effect of placebo) for pain freedom at 2 hours, of lasmiditan compared to placebo, ranges from 13% to 16.5%. While this is a modest effect, it is likely to be clinically meaningful to patients without other acute migraine treatment options.

We did examine how many patients in the applicant's mITT had mild intensity migraine at baseline and were included in their analysis population. In Study 301, the following number of patients had only mild intensity at baseline: 9 patients in placebo, 5 patients in 100 mg and 15 patients in 200 mg. We also analyzed the primary endpoint in the applicant's proposed efficacy population.

Table 11: Study 301 - Primary Efficacy Analysis (applicant mITT*)

Pain freedom at 2 hours post dose (mild, moderate or severe at baseline)	Study 301/arm		
	Placebo	100 mg	200 mg
N %	N=80/524 **15%**	N=142/503 **28.2%**	N=167/518 **32.2%**

p-value	(includes 9 patients with mild at baseline)	**<.001** (includes 5 patients with mild at baseline)	**<.001** (includes 15 patients with mild at baseline)

*Please note, this analysis was conducted on the applicant mITT, including patients with mild/moderate/severe intensity migraine at baseline.

Reviewer comment: The results of these analyses, including the patients who had a mild intensity migraine at baseline, are similar to what was found in the corrected mITT population. Adding in the few patients in each group who treated a mild intensity migraine at baseline did not affect the strength of the benefit seen with lasmiditan at all doses compared to placebo on pain freedom at 2 hours.

One other point to note is that there was one patient who enrolled and completed the study at two different study sites (Subject ID (b) (6) *). Removing either of this subject's efficacy responses did not change the outcome of the primary efficacy analysis.*

One other restriction on the analysis population was a time restriction. Patients had to have taken study drug within 4 hours of migraine onset. We would expect that most patients who experience a migraine of moderate to severe intensity would take study drug within several hours, however, the data demonstrate that many patients did not take study drug within 4 hours of headache onset. In Study 301, 126 patients did not take study medication within 4 hours, which resulted in an additional loss (in addition to a those that discontinued for various reasons, those who did not treat an attack, etc.) of approximately 7% of patients in the corrected mITT population. There are patients in the 'real world' who wait several hours after headache onset before taking drug, and thus inclusion of these patients would most resemble the clinical use of an acute treatment for migraine and therefore be the most clinically meaningful. Given these two concerns with the applicant's analysis population (the inclusion of patients with mild headache at baseline and the loss of patients who did not treat with study drug within 4 hours), we submitted an IR to the applicant regarding the FDA typical definition of mITT, which would include all randomized patients who had a migraine of moderate to severe intensity who took study drug and had one efficacy measurement. This resulted in 1640 patients in Study 301, and when we re-analyzed the efficacy data using this population (without a time restriction), results were similar across all groups and remained statistically significant (see below).

Table 12: Study 301 - Primary Efficacy Analysis (re-analyzed using moderate-severe intensity and no time restriction)

Pain freedom at 2 hours post dose (baseline moderate to severe)	Study 301/arm		
	Placebo N=544	100 mg N=556	200 mg N=540
N % p-value	82/544 **15.1%** 	162/556 **29.1%** **<.001**	169/540 **31.3%** **<.001**

Reviewer comment: The table above demonstrates that removing a time restriction for when study drug should be taken does not affect the robustness of the response, although the 100 mg and 200 mg arms have more similar percentages of responders, and thus the dose response is not as apparent as when patients take study drug within 4 hours.

All of the above tables on the primary efficacy endpoint demonstrate that there is a modest benefit with the first dose of lasmiditan (at all doses) compared to placebo in achieving migraine freedom at 2 hours that is statistically significant, clinically relevant, and persists across multiple analyzed populations, and sensitivity analyses. There appears to be a slight dose response seen, as well, with this study drug. This benefit exists in patients who treated a moderate to severe headache at baseline and persists even when excluding or including patients who treated a migraine within 4 hours of onset. It is difficult to make conclusions from any benefit in treating a migraine that is of mild intensity at onset given the small numbers in this group. It is clear from the multiple sensitivity analyses on the primary endpoint (including patients with mild intensity at baseline, removing limitation of 4-hour window, removing patients with duplicate data, etc.) that the data for the primary endpoint are robust since the effects persist across all analyses.

Rescue medication at < 2 hours

With regards to the primary endpoint, the applicant also recorded the number of patients who took a rescue medication (these patients were considered nonresponders). Of note, several rescue medications (including triptans and ergots) were not allowed. From my analysis, examining the PARAMCD RM2H (Rescue Medication Use Within 2 Hours), a total of 126 patients in the corrected mITT who were randomized took a rescue medication prior to 2 hours in Study 301. There were 35 patients in the placebo arm, 48 patients in the 100 mg arm, and 43 patients in the 200 mg arm who took a rescue medication prior to 2 hours after taking study drug. These patients were then considered nonresponders in the analysis for the primary endpoint of pain freedom at 2 hours.

Reviewer comments: The numbers are quite even across groups and the assignment of these patients as nonresponders for the efficacy analyses is appropriate.

Efficacy Results – Key Secondary and other relevant endpoints

The applicant had pre-specified that the Most Bothersome Symptom (MBS) would be the key secondary endpoint. The MBS was identified by the individual from the associated symptoms of nausea, phonophobia, or photophobia. Before dosing, patients were asked to report if they were experiencing nausea, phonophobia, and/or photophobia and if so, which was the most bothersome to them. This MBS was to be identified prior to dosing in order to avoid recall bias. The patients were then asked to report on resolution of these symptoms, including the MBS, 2 hours after treatment, and at other time points. Per the SAP, they would have to meet statistically on both the primary endpoint (pain freedom at 2 hours) and the key secondary endpoint (MBS freedom at 2 hours) to reject the null hypothesis.

Table 13: Study 301 - Key Secondary Endpoint Analysis (Corrected mITT)

Secondary endpoint of MBS freedom at 2 hours post dose	Study 301		
	Placebo	100 mg	200 mg
MBS Recorded at time of dosing	N=480	N=464	N=467
Total N	142/480	191/464	190/467
Percent responders	**29.6%**	**41.2%**	**40.7%**
Odds ratio (95% CI)		1.7 (1.3, 2.2)	1.6 (1.2, 2.1)
p-value		**<.001**	**<.001**

*Please note this population includes only those with moderate-severe intensity migraine at baseline. It excludes a higher number of patients than in the primary analysis population because it only includes patients who had a recorded MBS at the time of dosing. Several patients did not record MBS at time of dosing for unknown reasons and they are not included in this analysis.

**The p-values in this table are from the analysis conducted by FDA statistical reviewer, Dr. Liu, using a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates.

Reviewer comments: The trial met the key secondary endpoint of MBS freedom at 2 hours. There does not appear to be a stronger effect at higher doses (100 mg compared to 200 mg) as the percent responders is similar in both groups. These differences between lasmiditan-treated patients and placebo-treated patients are statistically significant and clinically meaningful.

Sensitivity analysis on key secondary endpoint

During the review, the applicant contacted FDA via an Information Amendment (Application 211280 - Sequence 0016 - MBS Sensitivity Analyses) on February 5, 2019, to inform the Division that there was an issue with data capture and with some patients not entering most bothersome symptom data prior to dosing. It had been discovered that the eDiary used in the studies allowed patients to enter their baseline MBS selection either before or after they had taken study medication. The applicant then performed sensitivity analyses for the key secondary endpoint of MBS freedom at 2 hours to determine the potential impact of this issue. In Study 301, of 1438 patients who reported MBS, 735 (51.1%) recorded this prospectively and 703 (48.9%) recorded this retrospectively. These numbers were similar across all treatment arms. Of those who recorded retrospectively, 38.1% of patients recorded the MBS in ≤ 5 minutes.

The applicant performed a sensitivity analysis on this key secondary endpoint only including patients who identified the MBS prospectively or retrospectively within 5 minutes of dosing and found that the results did not change, with all arms receiving study drug still demonstrating a statistically significant improvement in MBS freedom, compared to placebo, with p values of <.001 for the 100 mg and 200 mg study arms. When the applicant analyzed just those who collected their data prospectively, the findings remained similar to the entire corrected mITT data set, and this was confirmed by the statistical reviewer, Dr. Liu.

Table 14: Study 301 - Sensitivity Analysis on MBS Freedom at 2 Hours

Secondary endpoint of MBS freedom at 2 hours post dose	Study 301/arm		
	Placebo N=524	100 mg N=503	200 mg N=518
MBS Recorded **Prospectively**	N=243	N=248	N=244
Total Number of Responders	76/243	117/248	105/244
Percent responders	**31.3%**	**47.2%**	**43.0%**
Odds ratio (95% CI)		2.0 (1.4, 2.8)	1.7 (1.1, 2.4)
p-value		**<.001**	**<.001**

MBS Recorded **Prospectively or Retrospectively ≤ 5 minutes** Total Number of Responders	N=321 101/321	N=345 155/345	N=337 152/337
Percent responders	**31.5%**	**44.9%**	**45.1%**
Odds ratio (95% CI)		1.8 (1.3, 2.4)	1.8 (1.3, 2.5)
p-value		**<.001**	**<.001**

Reviewer comments: The issue of the eDiary not capturing this important information properly raised concerns about the validity of the data on this important endpoint. The sensitivity analysis did end up removing almost half of the patients who recorded an MBS, so it is difficult to interpret much from a post hoc analysis of a much smaller subset of patients. However, since most patients entered their data within 5 minutes post dose, this should be a short enough time that we would not see a treatment effect. Upon review of the data, both analyses did demonstrate a continued benefit in MBS freedom at both doses of lasmiditan compared to placebo, as demonstrated in the table above.

Dose Response and Other Secondary Endpoints

A dose response relationship appeared to be evident across groups in the primary efficacy analysis that was statistically significant as demonstrated from the tables above.

The applicant also analyzed several other secondary endpoints in an exploratory manner (not controlling for multiplicity) after the first dose of study drug. These included the following measures:

- Pain relief at 2 hours
- Time course of pain freedom
- Time course of freedom from MBS
- Time course of pain relief
- Associated symptoms of migraine at 2 hours
- Interference in daily activity due to migraine (disability captured on the eDiary) at 2 hours
- Patient Global Impression of Change (PGIC) at 2 hours
- Incidence of rescue or recurrence medication use

I have discussed the results of these exploratory measures briefly below.

<u>Pain relief at 2 hours</u>

Pain relief was defined as reduction in pain severity from moderate or severe at baseline to

mild or none, or a reduction in pain severity from mild to none at 2 hours following the first dose.

Table 15: Study 301 - Pain Relief at 2 Hours Following First Dose (mITT)

	Study 301/arm		
	Placebo N=515	100 mg N=498	200 mg N=503
Pain relief*, %	40.0%	54.0%	55.3%
Difference from placebo, %		14.0%	15.3%

Source: NDA 211280 - Integrated Summary of Efficacy (ISE) – adapted by Dr. Liu from applicant's ISE Table ISE.7.8 to only include corrected mITT population. (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5353-rep-analys-data-more-one-stud\ise\ise47-integrated-sum-of-efficacy.pdf)

*The analysis of pain relief was descriptive and not controlled for Type 1 error.

Reviewer comments: The table above demonstrates that all active treatment groups experienced a higher proportion of patients with pain relief at 2 hours compared to placebo. I did not include p values because these results were not controlled for multiplicity and were planned as an exploratory analysis in the SAP.

It is important to note that this analysis of pain relief at 2 hours provided by the applicant does not offer any new information regarding a new domain of migraine treatment, given that the prior tables demonstrate the drug's effect on pain freedom at 2 hours. Pain freedom, compared to pain relief, would be a higher bar to reach, and be more clinically meaningful since it would mean the headache has resolved, not just lessened in intensity. The goal of treatment in migraine is pain freedom, not just relief, since even a mild headache can contribute to significant morbidity. (b) (4) (b) (4) *. However it is important to note that trial designs for some other migraine treatments had different primary endpoints (for example, pain relief at 2 hours) and it is difficult to draw comparisons across trials (Ferrari, Goadsby, et al. 2002).*

Sustained Pain Freedom

The applicant examined sustained pain freedom in the ITT population. Sustained pain freedom was defined as experiencing headache pain freedom at 2 hours post first dose, at the assessment time (24 hours and 48 hours), and having not used any medications after the first dose.

Table 16: Study 301 - Sustained Pain Freedom at 24 and 48 hours (ITT)

Endpoint	Study 301/arm		
	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%**
Odds ratio versus placebo		2.1	2.8
p-value		**<.001**	**<.001**
Sustained pain free, 48 h, n	42	84	91
At 48 hours, % responders	**7.6%**	**14.9%**	**16.4%**
Odds ratio versus placebo		2.1	2.4
p-value		**<.001**	**<.001**

Source: NDA 211280 - Integrated Summary of Efficacy – adapted from applicant's ISE Table ISE.7.10 (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5353-rep-analys-data-more-one-stud\ise\ise47-integrated-sum-of-efficacy.pdf)

Reviewer comments:
This table demonstrates that there is a sustained effect in some patients with a most notable dose response seen at the 200-mg dose compared to placebo Many patients who experienced pain freedom at 2 hours without taking another medication at 24 hours had persistence of this effect (without a need for rescue medication) at 48 hours. There is one patient who reported pain freedom at 48 hours, but did not report pain freedom at 24 hours. Durability of an effect for an acute migraine medication is important as it allows return to activities. It is important to note that sustained response was measured only by those who did not take a rescue/recurrent medication within the specified time period. Measurements of pain intensity were not calculated at the 24- or 48-hour time period, so patients could have had a return of the same migraine or a new migraine and not treated the migraine with pharmacological therapy and therefore results would be difficult to interpret.

Time Course to Pain Freedom

The applicant also examined individual time points to pain freedom to determine when patients achieved the response of pain freedom or MBS freedom.

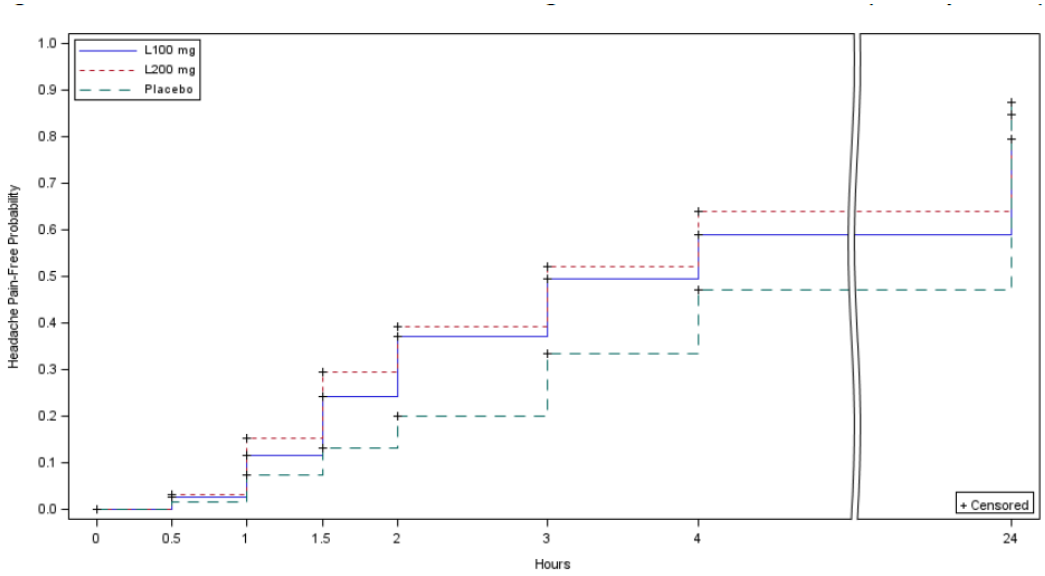
Table 17: Study 301 - Time to Headache Pain Freedom (applicant mITT)

Headache pain-freedom - Mild, moderate or severe at time of dosing	Study 301/Arm		
	Placebo N=524	100 mg N=503	200 mg N=518
0.5 hours post-dose Odds ratio P value vs placebo	7 (1.3%)	8 (1.6%) 1.2 (0.4, 3.3) 0.734	12 (2.3%) 1.8 (0.7, 4.5) 0.243
1 hour post-dose Odds ratio P value vs placebo	35 (6.7%)	44 (8.7%) 1.3 (0.8, 2.1) 0.215	74 (14.3%) 2.3 (1.5, 3.6) <0.001
1.5 hours post-dose Odds ratio P value vs placebo	53 (10.1%)	99 (19.7%) 2.2 (1.5, 3.1) <0.001	129 (24.9%) 3.0 (2.1, 4.2) <0.001
2 hours post-dose Odds ratio P value vs placebo	80 (15.3%)	142 (28.2%) 2.2 (1.6, 3.0) <0.001	167 (32.2%) 2.6 (2.0, 3.6) <0.001
3 hours post-dose	106 (20.2%)	190 (37.8%)	190 (37.8%)
4 hours post-dose	125 (23.9%)	188 (37.4%)	231 (44.6%)

Source: NDA 211280 - Integrated Summary of Efficacy – adapted from applicant's ISE Table ISE.7.11 (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5353-rep-analys-data-more-one-stud\ise\ise47-integrated-sum-of-efficacy.pdf)

Reviewer comments: The proportion of patients with headache freedom increased with time from administration of study drug. By 4 hours a greater proportion of patients had achieved headache freedom in the active treatment groups compared to placebo, but this is exploratory, and does not incorporate how many patients took a rescue medication after the 2-hour mark, so odds ratios and p values were not included. However, this table does demonstrate that more people achieved a response with more time, which seems to correspond with the pharmacokinetics of lasmiditan, which has a t_{max} of 1.8 hours and a half-life of about 5.7 hours, as well. The applicant did analyze the percentage of patients who were in the ITT-2nd dose population and while there was again a trend of higher proportion of patients with pain relief as time progressed, the trends were also seen at similar percentages in the placebo group. Since the 2nd dose population does not include the entire randomized population and just a subset of data, and therefore may be uninterpretable, the result of this analysis is not provided.

Figure 2: Study 301 - Time to Headache Pain Freedom Through 24 Hours Post First Dose (ITT)



Source: NDA 211280: Clinical Study Report Figure 11.1 (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf)
L100 = lasmiditan 100 mg, L200 = lasmiditan 200 mg

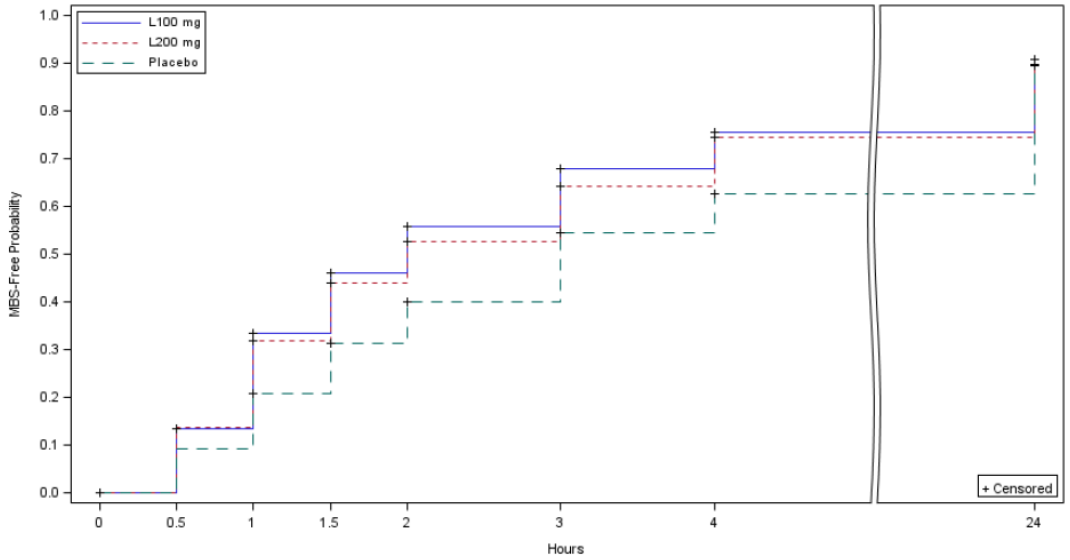
Reviewer comments: (b) (4) *, any data past the 2 hour timepoint does not take into account the number of patients who may have taken either study drug or their own rescue medication for rescue or recurrence of their migraine, so the graph above can be misleading.* (b) (4)

(b) (4)

Time Course to MBS Freedom

The time course to MBS freedom showed a similar pattern as the table/figure above for pain freedom with the highest proportion of patients achieving MBS freedom at 2 hours compared to earlier time point. The time points after 2 hours do not take into account the number of patients who took a rescue medication or study drug for rescue or recurrence of their migraine.

Figure 3: Study 301 - Time to MBS Freedom Through 24 Hours Post-dose (ITT)



Source: NDA 211280: Clinical Study Report Figure 11.3 (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf)
L100 = lasmiditan 100 mg, L200 = lasmiditan 200 mg

Reviewer comments: The proportion of patients with MBS freedom increased with time from administration of study drug. There is not a great separation of the curves for the two different arms of lasmiditan. (b) (4) (b) (4).

Time Course of Pain Relief

The time course of pain relief was examined by the applicant with similar results to the tables/figure above for pain freedom and MBS freedom. Given that this does not convey new information (as pain freedom is a more clinically meaningful outcome measure than pain relief), the results of this analysis are not provided in this review.

Associated symptoms of migraine at 2 hours

The applicant examined the presence of specific migraine symptoms at various time points. Nausea, photophobia or phonophobia had to be identified as the MBS prior to study drug administration. As stated above, photophobia was the most common identified MBS and also had the most improvement after treatment compared to those in the placebo group.

Table 18: Study 301 - Summary of MBS Freedom By Chosen Symptom (ITT)

MBS reported	Study 301/arm		
	Placebo N=554	Lasmiditan 100 mg N=562	Lasmiditan 200 mg N=555
Nausea reported as MBS (total n)	120	128	128
Nausea freedom, 2 hours post dose	41 (34.2%)	50 (39.1%)	61 (47.7%)
p-value	-	0.49	0.03
Phonophobia reported as MBS (total n)	115	130	105
Phonophobia freedom, 2 hours post dose	39 (33.9%)	57 (43.8%)	40 (38.1%)
p-value	-	0.11	0.53
Photophobia reported as MBS (total n)	282	264	283
Photophobia freedom, 2 hours post dose	72 (25.5%)	108 (38.2%)	112 (42.4%)
p-value	-	**<.001**	**<.001**

Source: NDA 211280: Clinical Study Report Table 14.2.3.3 (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf)

Reviewer comments: There was a trend to improvement in associated symptoms for all named symptoms, but the only symptom that showed a statistically significant proportion of patients with symptom freedom was photophobia. Photophobia was also identified as the most common MBS in all arms of the study, and this likely drove the results of the key secondary endpoint of MBS freedom. While the other groups did not demonstrate a statistical significance, there was a strong trend in improvement in symptoms compared to placebo. This is a subgroup analysis and it is possible the numbers were too small (since the study was not powered by these subgroups) to show a statistically significant difference for other chosen symptoms of nausea or phonophobia. However, this could also be interpreted that patients with self-identified photophobia as the MBS are more likely to have a response to lasmiditan treatment.

Interference in daily activity due to migraine

The applicant examined interference in daily activity (or what they called "time course of disability") due to migraine as an exploratory endpoint. Patients were asked to grade the degree of interference (on a 4-point scale with 0=not at all, 1=mild interference, 2=marked interference, and 3=completely, needs bed rest) of the migraine on normal activities. They were asked to record these assessments in the eDiary at the same time points post-dose (0.5 hours, 1 hours, 1.5 hours, 2 hours, 3 hours, 4 hours, 24 hours, and 48 hours) they were grading headache severity and other measures.

At 2 hours post-dose, 21.5% in placebo, 32.2% of patients in lasmiditan 100 mg and 32.4% of patients in lasmiditan 200 mg had scores of 0 (or no interference) while 13.4% of placebo, 11.4% of lasmiditan 100 mg, and 13.5% of lasmiditan 200 mg had scores of 3 (completely interferes, needed bed rest).

Reviewer comments: While patient-reported outcomes are important in assessing the benefit of a drug, this measure is not a validated one, and was only an exploratory endpoint. (b) (4) (b) (4) .

Patient Global Impression of Change (PGIC)

The applicant did present data on the PGIC for Study 301, which is a non-migraine specific scale in which a patient is asked to describe the change (if any) in activity, limitations, symptoms, emotions, and overall quality of life related to their condition since the beginning care at the clinic for the complaint (of migraine). This was measured at 2 hours post dose.

Table 19: Study 301 - Patient Global Impression of Change Scores

Patient Global Impression of Change - 2 hours post dose, n (%)	Study 301/arm		
	Placebo N=554	Lasmiditan 100 mg N=562	Lasmiditan 200 mg N=555
Very much better	34 (6.1%)	54 (9.6%)	57 (10.3%)
Much better	87 (15.7%)	155 (27.6%)	153 (27.6%)
A little better	159 (28.7%	83 (14.8%)	143 (25.8%)
No change	146 (26.4%)	16 (2.8%)	60 (10.8%)
A little worse	28 (5.1%)	8 (1.4)	31 (5.6%)
Much worse	14 (2.5%)	8 (1.4%)	13 (2.3%)
Very much worse	3 (0.5%)	8 (1.4%)	5 (0.9%)
Missing	83 (15.0%)	85 (15.1%)	93 (16.8%)

Source: NDA 211280 CSR Study 301 - Applicant Table 14.2.3.11. (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf)

Reviewer comments: The patients who received lasmiditan reported they were "very much better" (~10%) to "much better" (~28%) in a higher proportion than patients in the placebo group ("very much better," ~6%, and "much better," ~15%, respectively). Approximately 25-28% of patients in all arms reported they were "a little better." There was a higher proportion of patients with "no change" in the placebo group (26.4%) compared to those who received lasmiditan (10.8-14.8%). These data suggest that more patients who took lasmiditan had a positive effect on the impression of change, compared to placebo.

Use of Rescue or Recurrence Medication

The applicant examined the use of rescue or recurrence medication after the first dose of study drug. A subject was defined as having used rescue medication if at least 1 medication was documented in the rescue medication log in the diary, and if the patient recorded a mild, moderate, or severe headache at baseline and did not become pain-free at 2 hours post first dose. The medication could be the study drug or other rescue medication and the results are in the table below. This was measured at 2 hours for study drug medication use and at ≤ 2 hours for all rescue medication use, because some patients may have taken another medication prior to the 2 hour timepoint. A subject was defined as having used study drug recurrence medication if the patient recorded a mild, moderate, or severe headache at baseline and became pain free at 2 hours post first dose and then the headache recurred. Patients who took study drug for a recurrence medication were categorized by the time they reported taking study drug as their second dose. If the medication they took for recurrence was study drug or another rescue medication, they were categorized by the first time they reported taking their second dose, and the results are also in the table below.

Table 20: Study 301 - Incidence of Rescue or Recurrence Medication Use (ITT)

Medication Used	Study 301/arm		
	Placebo N=554	Lasmiditan 100 mg N=562	Lasmiditan 200 mg N=555
Study Drug Rescue Medication* used, 2 hours post-dose, N (%)	255 (46.0%)	147 (26.2%)	115 (20.7%)
Study Drug Recurrence Medication Used, 2-24 hours post-dose, N (%)	12 (2.2%)	22 (3.9%)	18 (3.2%)
All Rescue Medication, ** ≤ 2 Hours post-dose, N (%)	259 (46.8%)	156 (27.8%)	121 (21.8%)
All Recurrence Medication, *** ≤ 24 Hours post-dose, N (%)	11 (2.0%)	19 (3.4%)	17 (3.1%)

Source: NDA 211280 CSR Study 301 - Applicant Table 14.2.3.9. (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\301-lahj\study-col-mig-301.pdf)
*Study Medication was the study drug (randomized dose of lasmiditan or placebo);
**All rescue medications included a few patients who took rescue medication before the 2 hour timepoint.
***All Recurrence Medication could include study drug and/or the patient's own rescue medications, however there were a few patients, in each group, who took some other medication between 0-2 hours and they were excluded from this table, because by definition of recurrence, they should not have taken medications at < 2 hours.

Reviewer comments: The table demonstrates that more patients in the placebo group took a medication for rescue than in the lasmiditan treated groups. I did not present p-values since this data was not controlled for multiple comparisons. For recurrence of migraine, the number of subjects who took medication for recurrence were small, so it is difficult to draw conclusions. It does appear that numerically, more patients in the active lasmiditan groups took a medication for recurrence than in the placebo groups.

Second Dose

Patients had the option to take a second dose of study drug for rescue or recurrence 2 to 24 hours after the initial dose.

The applicant randomized all patients to a set sequence of drug or placebo for both the first and second dose. Patients were thus initially randomized to receive the following two tablets in sequence: placebo/placebo, lasmiditan 100 mg/lasmiditan 100mg, lasmiditan 100 mg/placebo, lasmiditan 200mg/lasmiditan 200mg or lasmiditan 200mg/placebo. They could take study drug for the second dose, but also had the option of taking another rescue medication (such as an NSAID or acetaminophen) for the second dose. Therefore, there was a loss of patients from those who were initially randomized to a more selected population of those who failed treatment with the first dose, and those who chose to take study drug (and not another rescue therapy).

Only one dose of drug (that could be repeated one time for rescue or recurrence) was allowed for each patient in Study 301. If patients took a second dose because they were not pain free at 2 hours, it was considered a rescue dose and analyzed as such. If patients took a second dose because they were pain free at 2 hours and then pain recurred, then this would be considered a second dose for recurrence and analyzed as such.

Of note, patients could take a rescue medication (other than study drug, if not a triptan, barbiturate, or opiate) for rescue or recurrence after 2 hours. However the population that was analyzed for the second dose was the "ITT-2nd dose population," defined as "all randomized subjects who were considered ITT after the first dose and use a second dose of study drug and have any post-dose headache severity or symptom assessments." Thus the dataset flag used to identify patients for these analyses identified patients in the intent-to-treat population without specifically excluding patients who might have reported using another rescue medication.

Through an IR with the applicant it was determined that in Study 301, of the 734 patients who took a second dose of medication, 47 (6.4%) took another medication (not study drug) prior to the second dose, and 19 (2.6%) took another medication within 2 hours of the second dose. Thus, 9.0% of patients took a second dose with a medication that was not study drug.

There were also many patients whose data was not available (because they either were not in the first dose ITT or did not have a post second dose pain or MBS assessment), so they were not included in the analyses below of second dose. The applicant also acknowledged, in the End-of-Phase 3 meeting, that the study was not powered to demonstrate a benefit of the second dose.

Second Dose for Rescue

The applicant examined the effect of a second dose of a pre-determined randomized dose of study drug (either placebo or the same dose as the first one) in the treatment of migraine that did not resolve at the 2-hour time point. The effect of a second dose of study drug was pre-specified in the SAP to be examined in the ITT population.

Table 21: Study 301 - Second Dose for Rescue

Endpoint	Study 301 – Treatment (first dose/second dose) for Rescue				
	Placebo/ Placebo	100 mg/ Placebo	100 mg/ 100 mg	200 mg/ Placebo	200 mg/ 200 mg
Pain free, n (%)	**54/319 (17%)**	**8/62 (13%)**	**40/138 (29%)**	**12/52 (23%)**	**29/109 (27%)**
Odds ratio vs LTN/Placebo (95% CI)	-	-	2.8 (1.2, 6.3)	-	1.2 (0.6, 2.6)
Odds ratio vs Placebo/Placebo		0.7 (0.3, 1.6)	2.0 (1.3, 3.2)	1.47 (0.7, 3.0)	1.8 (1.1, 3.0)
MBS free, n (%)	**78/279 (28%)**	**10/51 (20%)**	**48/119 (40%)**	**16/44 (36%)**	**32/95 (34%)**
Odds ratio vs LTN/Placebo (95% CI)	-	-	2.8 (1.3, 6.1)	-	0.9 (0.4, 1.9)
Odds ratio vs Placebo/Placebo	-	0.6 (0.3, 1.3)	1.7 (1.1, 2.7)	1.3 (0.8, 2.2)	1.5 (0.8, 2.9)

Source: NDA 211280: Regulatory Response to Midcycle Communication (\\cdsesub1\evsprod\nda211280\0022\m1\us\response.pdf)
LTN=lasmiditan

Reviewer comments: The analysis for the second dose as rescue treatment was a randomized sample, but not controlled for multiplicity. In addition, though the applicant did randomize patients to the second dose (at the initial randomization), the data represents a biased sample since the patients do not represent an independent sample (patients had already received one dose of either placebo or active study drug). Thus, there is both selection bias (given that not every patient took a second dose of study drug, as some took another rescue medication) and a bias from having already taken study drug and being aware of any effects (or the absence of an effect) associated with either placebo or lasmiditan. Last, many patients who took a second dose of study drug also took a dose of another rescue medication which confounds the results presented above. Please see my interpretation of this in reviewer comments below the next table.

The above table does demonstrate that there is no benefit for the second dose for rescue if the second dose is 200 mg of lasmiditan for either the primary or key secondary endpoint, and perhaps a trend to some benefit for the second dose, if it was 100 mg. This is not in keeping with a perceived dose response seen with the primary and key secondary endpoint. It is difficult to glean much from this data since the numbers are small, and it was a biased sample as stated previously.

Second dose for Recurrence

The applicant examined the effect of a second dose of either lasmiditan or placebo (determined at the initial randomization) for recurrence of migraine. Second dose for recurrence was defined as patients who achieved headache pain freedom 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. Patients had to have a post-dose headache severity or symptom assessment, and had to have had a first dose to be included in this ITT-2nd dose population.

There were very few patients in Study 301 who took a second dose of study drug for a recurrence of a resolved migraine, as demonstrated in the table below.

Table 22: Study 301 - Second Dose for Recurrence

Endpoint	Study 301 – Treatment (first dose/second dose) for Recurrence				
	Placebo/ Placebo	100 mg/ Placebo	100 mg/ 100 mg	200 mg/ Placebo	200 mg/ 200 mg
Pain free, n (%)	**3/10 (30%)**	**2/6 (33%)**	**6/15 (40%)**	**2/7 (29%)**	**7/11 (67%)**

Odds ratio vs LTN/Placebo (95% CI)	-	-	1.3 (0.2, 9.7)	-	4.4 (0.6, 34.0)
Odds ratio vs Placebo/Placebo	-	1.2 (0.1, 10.2)	1.6 (0.3, 8.5)	0.9 (0.1, 7.8)	4.1 (0.7, 25.4)
MBS free, n (%)	**4/7 (57%)**	**1/4 (25%)**	**8/14 (57%)**	**3/7 (43%)**	**8/9 (89%)**
Odds ratio vs LTN/Placebo (95% CI)	-	-	4.0 (0.3, 48.7)	-	10.7 (0.8, 138.2)
Odds ratio vs Placebo/Placebo	-	0.3 (0.02, 3.8)	1.0 (0.2, 6.3)	0.6 (0.1, 4.7)	6.0 (0.5, 77.8)

Source: NDA 211280: Regulatory Response to Midcycle Communication (\\cdsesub1\evsprod\nda211280\0022\m1\us\response.pdf)
LTN=lasmiditan

Reviewer comments: The analysis for the second dose as recurrence includes a very small number of patients. It can be inferred that not many patients who took study drug who had relief required a second dose for a recurrent migraine, which is favorable for the study drug having a positive benefit. There also is a trend towards benefit of lasmiditan compared to placebo, for the second dose for recurrence. (b) (4) (b) (4) (b) (4) *. While this may be suggested by the data above, there are several limitations. As stated above, this is a biased sample since it is a self-selected group that did not take another rescue medication. Second, all the patients are aware of effects (or lack of effects) since patients have already had one dose of lasmiditan or placebo, and this may have influenced their decision to take a second dose. Third, the applicant stated that about 10% of patients in Study 301 took another rescue medication (not study drug) in addition to the study drug, which confounds any effect of study drug. Furthermore, though there is a trend to benefit of lasmiditan for a second dose, the number of patients who actually took a second dose for recurrence is extremely small (< 15 patients per arm). Thus, this exploratory analysis is not powered to draw conclusions, but is rather hypothesis generating.*

Subgroup Analyses Conducted on the Individual Trial

The applicant conducted analyses on pre-specified subgroups on their original mITT population in Study 301 (including the patients with mild intensity at baseline). Their analysis demonstrated several key findings:

1) By age:
    a. In those < 65, lasmiditan was effective compared to placebo at all doses.
    b. In those ≥ 65, lasmiditan did not appear to be more effective than placebo in

those in the 200 mg arm only. Of note, there were only 11 patients in the 100 mg arm, 16 in the 200 mg arm, and 20 in the placebo arm, so it is difficult to draw conclusions based on limited data.

2) By sex:
    a. In females, lasmiditan was effective compared to placebo at all doses.
    b. In males, lasmiditan did not appear effective compared to placebo in the 200 mg arm only. The placebo group had 14.3% with pain freedom at 2 hours, compared to 31.3% in the 100 mg arm, and 23.5% in the 200 mg arm. Of note, the p value was 0.004 in the 100 mg arm and the p-value was 0.056 in the 200 mg arm (compared to placebo) so it did approach significance.
3) By race:
    a. When analyzed separately, in Caucasians and African Americans, lasmiditan was effective compared to placebo at all doses. Numbers of patients in the "Other" category were small, but in the 100 mg arm 29.6% (p-value of 0.062 compared to placebo (6.7%) and in the 200 mg arm 32.0% (p-value of 0.058 compared to placebo).
4) By weight:
    a. Of note, the median weight was 178 pounds (80.9 kg). The applicant picked 90 kg to examine the effects in those less than 90 kg and those greater than or equal to 90 kg.
    b. Lasmiditan was effective at all doses compared to placebo regardless of weight. See table below.

Table 23: Study 301 - Primary Endpoint by Weight

Endpoint	Study 301/arm		
Pain freedom at 2 hours	Placebo	100mg	200mg
Weight < 90 kg	58/344 **16.8%**	92/324 **28.4%**	96/312 **30.8%**
Weight ≥ 90 Kg	21/171 **12.3%**	49/174 **28.2%**	64/191 **33.5%**

Reviewer comments: I examined the primary endpoint by weight in the above table, using the mean weight of 90 kg as the cutoff weight. The effect of lasmiditan persisted whether the weight was < 90 kg or ≥ 90 kg, so the sex differences do not appear to be explained by weight

differences. The lack of an effect of lasmiditan compared to placebo in patients age ≥ 65 is likely due to the small numbers of patients in this subgroup. As stated previously, age did not have a clinically relevant effect on lasmiditan exposure, based on a population PK analysis (see clinical pharmacology review by Dr. Brundson).

I examined the primary endpoint by sex in the corrected mITT population (excluding those with mild intensity migraine at baseline) with the following results:

Table 24: Study 301 - Primary Efficacy Analysis by Subpopulation of Gender (Corrected mITT*)

Pain freedom at 2 hours post dose	Study 301/arm		
	Placebo N=515	100 mg N=498	200 mg N=503
Female			
N	68/441	111/402	142/424
%	**15.4%**	**27.6%**	**33.4%**
Male			
N	11/74	30/96	18/79
%	**14.9%**	**31.3%**	**22.8%**

*I analyzed AVALC by STUDYID, TRT01A and SEX for this analysis in a dataset which only included the mITT population with moderate to severe intensity migraine at baseline.

Reviewer comments: This analysis demonstrates that the benefit of 100 mg exists for males, but that this appears to be lost at the higher dose of 200 mg. When compared to the applicant's mITT, there is no clinically significant change in these percentages. It is possible the numbers were quite small in males compared to females in this post hoc analysis, and this analysis may not have been powered to demonstrate a benefit for males at the 200 mg dose or the effect seen at the 100 mg dose is by chance alone. Therefore, I do not believe we should draw conclusions about a differential effect of lasmiditan by sex, based on this data.

Dr. Liu, statistical reviewer, analyzed the treatment effect across clinically meaningful subgroups, including age, gender, and race and determined that the trend in treatment success was similar across all subgroups. Please see her review for further details of this analysis.

6.2. Study 302/LAHK: A Study of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to Placebo in the Acute Treatment of Migraine: A randomized, double-blind, placebo-controlled parallel group study (SPARTAN)

6.2.1. Study Design

Overview and Objective

Study 302/LAHK had a similar design to Study 301, in that it evaluated the efficacy and safety of lasmiditan compared to placebo on headache pain freedom and most bothersome symptom (MBS) freedom at 2 hours for treatment of a single migraine attack.

Trial Design

Study 302, like Study 301, was a phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel-arm study designed to evaluate the efficacy of lasmiditan for the treatment of a single migraine attack. One major difference is that Study 302 was a four-arm study, investigating lasmiditan at doses of 50 mg (not studied in Study 301), 100 mg, and 200 mg, versus placebo. Patients were randomized at confirmation of eligibility to receive two doses of study drug (the second blinded dose, for rescue or recurrence, was determined at the initial randomization just as in Study 301). Patients were enrolled if they met eligibility criteria, including age ≥ 18 years, met International Classification for Headache Disorders (ICHD)-II criteria for diagnosis of migraine with or without aura, had a history of 3-8 migraine attacks per month (< 15 headache days), and a Migraine Disability Assessment (MIDAS) score ≥ 11.

Of note, Study 301 specifically excluded patients with coronary artery disease (CAD), clinically significant arrhythmia, or uncontrolled hypertension, but 302 specifically included patients with these disorders. Both studies intentionally enrolled patients with cardiovascular risk factors (including age > 40, hypertension, diabetes mellitus, and hyperlipidemia).

Another major difference is that while Study 301 was conducted entirely in the U.S., Study 302 was conducted in the U.S. and Europe, including the United Kingdom and Germany. There were 2504 patients enrolled at 97 sites in the U.S., 191 patients at 12 sites in the United Kingdom and 310 patients at 16 sites in Germany. Therefore, 16.7% of patients were from OUS in Study 302.

In Study 302, patients had a screening visit and were randomized to receive study drug or placebo, with a telephone contact within 7 days to confirm eligibility (after confirming laboratory results). Patients then had up to 8 weeks to treat a migraine attack of at least moderate severity, and then were asked to return for an end of study visit within 7 days of treating the single migraine attack. Patients also had an option of taking a second dose (determined at initial randomization with first dose) for either rescue (migraine had not resolved after 2 hours) or recurrence (migraine had resolved at 2 hours, but recurred) 2 to 24 hours after initial dose. The schematic (Figure 1) for Study 301 is similar to that for this study, with the exception of an additional lasmiditan 50 mg study arm, so it is not included again here.

The details of the trial design and conduct, including the assignment to treatment, blinding, dose modification, Schedule of Assessments (Table 3), concomitant medications, treatment compliance, and measurements were all the same as Study 301, except where noted above.

Dose Rationale

As stated previously, at the end of phase 2 (EOP2) meeting, the Division suggested that the applicant add a 50 mg dose arm to their second pivotal efficacy trial, since preliminary data suggested this dose may also be effective. The applicant conducted Study 302 with 50 mg, 100 mg, and 200 mg doses of lasmiditan. Please see section for dose rationale of Study 301 for details of the dose selection for the pivotal trials.

Dosing and Randomization

Patients were centrally randomized to one of 7 treatment sequences, for both doses of study drug (placebo or lasmiditan), at the time of randomization, which included the following drug sequences:

Placebo/placebo
50 mg/placebo
50 mg/50 mg
100 mg /placebo
100 mg/100 mg
200 mg/placebo
200 mg/200mg

The second study drug in the sequence, which was determined at the initial randomization, was to be used for rescue or recurrence of migraine, if needed.

Study Endpoints

The primary efficacy endpoint for this study was the same as Study 301 – the proportion of patients who were headache pain free at 2 hours following the initial dose. Pain freedom was defined as a reduction in severity of migraine pain from moderate to severe at baseline to no pain at 2 hours. Migraine pain freedom was assessed using a 4-point scale (with 0-none, 1=mild, 2=moderate, 3=severe) and recorded in an eDiary. Patients were only instructed to treat when the migraine pain was moderate or severe.

The key secondary efficacy endpoint was the proportion of patients who were MBS free at 2 hours following the initial dose. The MBS was defined as either nausea, phonophobia, or photophobia, that had to be identified by the patient prior to treatment in the eDiary, by answering if they were experiencing nausea, phonophobia, or photophobia (yes/no), and which symptom was the most bothersome. Patients then had to report resolution (or not) of MBS after taking study drug at various time points, including the 2-hour time point for efficacy.

Statistical Analysis Plan

The final statistical analysis plan for Study 302 was approved 18 July 2017, however, the

applicant states they made several changes to the plan including the analyses of the primary efficacy measure and other related measures described in the protocol. This included adding in patients with none/mild intensity of migraine pain at baseline (due to misunderstanding Division feedback for Study 301). After an IR during the NDA review, the analysis population was later revised to remove patients with none/mild pain intensity at baseline, so the analysis population would only include patients with moderate/severe pain intensity at baseline (and in line with the original agreed SAP).

Planned Covariates and Planned Subgroup Analyses

Study 302 planned to include treatment group and background use of medications to prevent migraine as covariates.

Hypothesis Testing
The primary objective was to evaluate the efficacy of lasmiditan at 50 mg, 100 mg and 200 mg, compared to placebo, on migraine headache pain at 2 hours and on the MBS.

Null Hypothesis
$P_T \leq P_P$

Alternative Hypothesis
$P_T > P_P$

Per the statistical analysis plan, P_T and P_P are the true proportion of patients who are pain free at 2 hours post dose for lasmiditan 200 mg (P_T) and placebo (P_P). Confirmatory hypothesis testing could be conducted on the true proportion of patients who were pain free at 2 hours post dose for the lasmiditan 100 mg and lasmiditan 50 mg patients, as well. The significance level of the test was 2.5%.

Pre-specified Methods of Handling Missing Data

The applicant stated in the SAP that the prespecified approach for handling missing data was to assume that patients with missing data are nonresponders. The applicant also performed a sensitivity analysis to exclude patients with missing data.

Statistical Methodology for Adjusting for Multiplicity

The applicant used the gatekeeping procedure to prevent Type I error inflation for multiple comparisons with the primary efficacy endpoint tested first. If the primary analysis was statistically significant (with a one side $p < 0.025$), the following confirmatory hypotheses would be testing sequentially:

1) Treatment comparison, between lasmiditan 200 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.
2) Treatment comparison, between lasmiditan 100 mg and placebo, as measured by subjects who are headache pain-free at 2 hours post-dose.
3) Treatment comparison, between lasmiditan 100 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.
4) Treatment comparison, between lasmiditan 50 mg and placebo, as measured by subjects who are headache pain-free at 2 hours post-dose.
5) Treatment comparison, between lasmiditan 50 mg and placebo, as measured by subjects who are MBS-free at 2 hours post-dose.

Protocol Amendments

There were no protocol amendments for Study 302 (with the final protocol dated 30 November 2015). However, this protocol was revised several times before implementation during the Special Protocol Assessment submissions, but because this was done prior to Institutional Review Board (IRB) approval at any site, these iterations were not considered amendments by the applicant.

6.2.2. Study Results

Compliance with Good Clinical Practices

As with Study 301, Lilly provided attestation that the study was conducted in accordance with the Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in compliance with Good Clinical Practices (GCP).

Financial Disclosures

Lilly provided certification that there were no financial agreements with the clinical investigators defined in 21 CFR part 54.2 for Study 301 whereby the value of compensation to the investigator could be affected by the outcome of the study and that no investigators were the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f). (Sources: \\cdsesub1\evsprod\nda211280\0001\m1\us\financial-301-lahj.pdf and \\cdsesub1\evsprod\nda211280\0001\m1\us\financial-302-lahk.pdf) The applicant included a supplemental site personnel listing for Form 3454 with all the Primary Investigators (PI) and no one had disclosable information for either study. Please see the financial disclosures at the end of this document.

Patient Disposition

Date of first patient randomized: 19 May 2016
Date of last patient randomized: 17 April 2017
Date of last patient completed: 29 June 2017

Table 25: Study 302 - Summary of Patient Disposition Based on First Dose – All Patients

Patient Disposition	Study Arm				
	Placebo N=751	50 mg N=750	100 mg N=754	200 mg N=750	All Patients N=3005
Randomized, n (%)	751 (100.0%)	750 (100.0%)	754 (100.0%)	750 (100.0%)	3005 (100.0%)
Confirmed Eligibility, n (%)	711 (94.7%)	716 (95.5%)	721 (95.6%)	721 (96.1%)	2869 (95.5%)
Treated, n (%)	645 (85.9%)	654 (87.2%)	634 (84.2%)	649 (86.5%)	2583 (86.0%)
Treated with 2nd Dose	361 (48.7%)	302 (40.3%)	260 (34.5%)	218 (29.1%)	1141 (38.0%)
- Treated with 2nd Dose – For Rescue*	287 (79.5%)	245 (81.1%)	187 (71.9%)	149 (68.3%)	868 (76.1%)
- Treated with 2nd Dose – For Recurrence*	10 (2.8%)	12 (4.3%)	11 4.2%)	10 (4.6%)	44 (3.9%)
Analysis Populations, n (%)	751	750	754	750	3005
ITT Population	576 (76.7%)	598 (79.7%)	571 (75.7%)	565 (75.3%)	2310 (76.9%)
Applicant mITT Population	540 (71.9%)	556 (74.1%)	532 (70.6%)	528 (70.4%)	2156 (71.7%)
Corrected mITT Population[1]	534 (71.1%)	544 (72.5%)	523 (69.4%)	521 (69.5%)	2122 (70.6%)
PP Population	506 (67.4%)	524 (69.9%)	488 (64.7%)	492 (65.6%)	2010 (66.9%)
ITT-2nd dose Population	297 (39.5%)	258 (34.4%)	198 (26.3%)	159 (21.2%)	912 (30.3%)
Safety Population	645 (85.9%)	654 (87.2%)	635 (84.2%)	649 (86.5%)	2583 (86.0%)
Completed Study, n (%)	659 (87.7%)	657 (87.6%)	640 (84.9%)	661 (88.1%)	2617 (87.1%)
Treated	628 (95.3%)	633 (96.3%)	606 (94.7%)	626 (94.7%)	2493 (95.3%)
Not Treated	31 (4.7%)	24 (3.7%)	34 (5.3%)	35 (5.3%)	124 (4.7%)
- No Migraine*	14 (45.2%)	9 (37.5%)	12 (35.3%)	21 (60.0%)	56 (45.2%)

- No Eligible Migraine*	11 (35.5%)	12 (50.0%)	17 (50.0%)	12 (34.3%)	52 (41.9%)
- No Study Medication*	6 (19.4%)	2 (8.3%)	2 (5.9%)	2 (5.7%)	12 (9.7%)
- Missing*	0	1 (4.2%)	3 (8.8%)	0	4 (3.2%)
Discontinued Study	89 (11.9%)	87 (11.6%)	112 (14.9%)	85 (11.3%)	373 (12.4%)
- Treated*	16 (18.0%)	18 (20.7%)	27 (24.1%)	20 (23.5%)	81 (21.7%)
- Not Treated*	73 (82.0%)	69 (79.3%)	85 (75.9%)	65 (76.5%)	292 (78.3%)
Reason for Discontinuation, n (%)	87	112	85	89	373
Adverse event	0	1 (0.9%)	4 (4.7%)	0	5 (1.3%)[b]
Lost to follow-up	27 (31.0%)	37 (33.0%)	30 (35.3%)	29 (32.6%)	123 (33.0%)
- Treated*	4 (4.6%)	13 (11.6%)	7 (8.2%)	9 (10.1%)	33 (8.8%)
- Not Treated*	23 (26.4%)	24 (21.4%)	23 (27.1%)	20 (22.5%)	90 (24.1%)
- Non-compliance with protocol*	14 (16.1%)	20 (17.9%)	14 (16.5%)	12 (13.5%)	60 (16.1%)
- Pregnancy*	1 (1.1%)	2 (1.8%)	0	0	3 (0.8%)
- Patient request*	15 (17.2%)	25 (22.3%)	10 (11.8%)	15 (16.9%)	65 (17.4%)
- Investigator request*	2 (2.3%)	0	0	3 (3.4%)	5 (1.3%)

Source: NDA 211280 –Study 302 Clinical Study Report - Table 10-1 and Table 10-2 (**\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\302-lahk\col-mig-302-04-csr-body.pdf)**

*= indicates a percentage of patients in Patient Disposition category listed directly above row (e.g., in category "Discontinued study," of 89 patients who discontinued the study, 16 (18.0%) of those in the placebo arm had been "treated" with study drug).

Summary of key disposition data:

Randomized: 3005
Confirmed Eligibility: 2869
Completed Study: 2617
Received 1 or more doses of IP (Safety set): 2583
Analysis set (ITT): 2310
Efficacy analysis set (Corrected mITT): 2122 (moderate to severe headaches only and treated in 4 hours)

In Study 302, of 3005 randomized patients, 2869 had confirmed eligibility and 2617 completed the study. There were 373 patients who discontinued the study, 89 in the placebo group and 284 in the treatment groups (even across groups). Reasons for discontinuation were the following: lost to follow-up (123), randomization failure (112), patient request (65), and non-compliance with protocol (60), pregnancy (3), investigator request (5), adverse event (5). Of note, of those who discontinued due to an adverse event, only one patient (302-606-2003) did take study drug (randomized to 200 mg for first dose, placebo for second dose), and

discontinued due to adverse event terms of dizziness, tiredness, and headache.

Reviewer comments: Study 302 had similar rate of discontinuations as that in Study 301. After a thorough review of the discontinuations by patient request, no concerning reasons for discontinuation were noted. Only one patient who was treated discontinued after an adverse event which was mild, and this patient was followed with resolution of the adverse event.

Protocol Violations/Deviations

Of 3005 randomized patients, 860 (30%) had major protocol deviations. The proportion of patients across groups was approximately 27-32% across each treatment group, including placebo. The most common protocol deviations leading to exclusion, in order of frequency, were the following: "did not treat a migraine of at least mild severity" in 563 (18.6%) of patients, "treated with study drug beyond 4 hours after the onset of migraine" in 158 (5.5%) of patients, and "used excluded rescue mediations or used rescue or recurrence medication before 2-hour time point" in 131 (4.6%) of patients.

Reviewer comments: While the applicant considered not treating a migraine of at least mild severity and treating beyond 4 hours after onset of migraine to be protocol deviations, the Division does not typically consider these to be major protocol deviations.

Demographics

Table 26: Study 302 - Demographics of Analysis Population (Corrected mITT*)

Demographic Parameter	Study 302 - Randomized Arm			
	Placebo N=534 N (%)	**50 mg N=544 N (%)**	**100 mg N=523 N (%)**	**200 mg N=520 N (%)**
Sex				
Male	80 (15.0%)	82 (15.1%)	75 (14.3%)	90 (17.3%)
Female	454 (85.0%)	462 (84.9%)	448 (85.7%)	431 (82.7%)
Age				
Mean (years)	42.8	42.8	43.5	41.7
Median (years)	42.5	42	44	42
Min, max (years)	18, 77	18, 77	18, 77	18, 79
Age Group				
≥ 18 - < 30 years	94 (17.7%)	99 (18.2%)	84 (16.1%)	93 (17.9%)
≥ 30 - < 50 years	272 (50.9%)	261 (48.0%)	260 (49.7%)	283 (54.3%)
≥ 50 - < 65 years	143 (26.8%)	154 (28.3%)	156 (29.8%)	125 (24.0%)
≥ 65 years	25 (4.7%)	30 (5.5%)	23 (4.4%)	20 (3.8%)
Race				
White	442 (82.8%)	443 (81.4%)	428 (81.8%)	432 (83.1%)

Black or African American	74 (13.9%)	80 (14.7%)	77 (14.7%)	71 (13.7%)
Asian	3 (0.6%)	5 (0.9%)	5 (1.0%)	7 (1.3%)
American Indian or Alaska Native	5 (0.9%)	3 (0.6%)	2 (0.4%)	0 (0%)
Native Hawaiian or Other Pacific Islander	2 (0.4%)	2 (0.4%)	0 (0%)	2 (0.4%)
Multiple	5 (0.9%)	7 (1.3%)	5 (1.0%)	4 (0.8%)
Other	3 (0.6%)	4 (0.7%)	6 (1.2%)	4 (0.8%)
Ethnicity				
Hispanic or Latino	105 (19.7%)	113 (20.8%)	111 (21.2%)	116 (22.3%)
Not Hispanic or Latino	426 (79.8%)	427 (78.5%)	407 (77.8%)	403 (77.4%)
Not reported or unknown	3 (0.6%)	4 (0.8%)	5 (1.0%)	1 (0.2%)
Region				
United States	444 (83.2%)	454 (83.5%)	446 (85.3%)	434 (83.3%)
Great Britain	37 (6.9%)	37 (6.8%)	29 (5.5%)	34 (6.5%)
Germany	53 (9.9%)	53 (9.7%)	48 (9.2%)	53 (10.2%)

*Note, this table is derived from the mITT population and I excluded patients with mild or none intensity at baseline, which thus excludes 6 patients in the placebo arm, 12 patients in the 50 mg arm, 9 patients in the 100 mg arm and 7 patients in the 200 mg arm.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The baseline characteristics of patients in this trial are in the tables below.

Table 27: Study 302 - Baseline Cardiovascular Co-morbidities (applicant mITT)

Characteristic	Study 302/arm			
	Placebo N=540	**50 mg N=556**	**100 mg N=532**	**200 mg N=528**
Baseline cardiovascular risk factor (age > 40, current smoker, high total cholesterol (≥240 mg/dL), low HDL cholesterol (<40 mg/dL men, <50 mg/dL women), high blood pressure (SBP ≥ 140 mm Hg or history of hypertension), history of diabetes mellitus)				
Present	432	420	425	430
n (%)	80.0%	75.5%	79.9%	81.4%
Baseline cardiovascular disease (hypertension, arrhythmia, cardiac failure, cardiomyopathy, CNS vascular disorders, embolic and thrombotic events, ischemic heart disease, pulmonary hypertension and Torsade de pointes/QT prolongation)				
Present	114	108	112	97
n (%)	21.1%	19.4%	21.1%	18.4%
Age > 40 as cardiovascular risk factor				
Yes	296	302	316	278

n (%)	54.8%	54.3%	59.4%	52.7%
Current smoker as cardiovascular risk factor				
Present	73	65	79	77
n (%)	13.5%	11.7%	14.8%	14.6%
SBP ≥ 140 mm Hg or history of hypertension as cardiovascular risk factor				
Present	115	111	121	100
n (%)	21.3%	20.0%	22.7%	18.9%
High total cholesterol (≥240 mg/dL), low HDL cholesterol (<40 mg/dL men, <50 mg/dL women) as cardiovascular risk factor				
Present	63	77	56	55
n (%)	11.7%	13.8%	10.5%	10.4%
Diabetes mellitus as cardiovascular risk factor				
Present	36	29	27	43
n (%)	6.7%	5.2%	5.1%	8.1%

*This table is derived from the Integrated Database (IDB) dataset for ADSL, examining TRT01A in Study 302 by each variable (CVRISKFL (from 302 ADSL), CVBSGPFL, AGEG40FL, SMOKERFL, SBPFL, BCHOLFL, DIABTFL) in the applicant's mITT population.

Reviewer comments: The cardiovascular risk factor distribution for Study 302 is similar to that for Study 301. The major difference is that there are a higher percentage of patients with baseline cardiovascular disease in Study 302 (approximately 18-21% across arms) compared to Study 301 (approximately 6-7% across arms).

Table 28: Study 302 - Migraine Specific Disease Characteristics (applicant mITT)

Characteristic	Study 302/arm				
	Placebo N=540	50 mg N=556	100mg N=532	200 mg N=528	All patients N=528
Duration of migraine history (years)					
Mean (SD)	17.8 (12.8)	18.6 (12.9)	19.3 (13.4)	17.7 (12.4)	18.4 (12.9)
Median	15.5	16.3	17	15.2	16.1
Min, Max	0, 55	0, 64	0, 62	0, 60	0, 64
Average migraines per month in past 3 months					
Mean (SD)	5.4 (2.4)	5.2 (2.0)	5.3 (1.8)	5.2 (1.9)	5.3 (2.0)
Median	5.0	5.0	5.0	5.0	5.0
Min, Max	3, 36	3, 18	3, 13	3, 36	3, 36
Experienced migraine with and without aura					
Yes - n (%)	203 (37.6%)	194 (34.9%)	206 (38.7%)	187 (35.4%)	790 (36.6%)
No - n (%)	335 (62.0%)	359 (64.6%)	326 (61.3%)	338 (64.0%)	1358 (63.0%)
Use of medication to reduce migraines					

Yes - n (%)	107 (19.8%)	106 (19.1%)	101 (19.0%)	94 (17.8%)	408 (18.9%)
No - n (%)	432 (80.0%)	450 (80.9%)	431 (81.0%)	433 (82.0%)	1746 (81.0%)

Table 29: Study 302 - Additional Migraine Characteristics (applicant mITT*)

Migraine characteristic	PBO/ PBO N=540	L50/ L50 N=366	L50/ PBO N=190	L100/ L100 N=359	L100/ PBO N=173	L200/ L200 N=352	L200/ PBO N=176
MIDAS total score Mean (SD)	32.2 (24.3)	32.7 (23.7)	32.2 (24.2)	31.5 (20.7)	29.5 (17.2)	32.7 (24.4)	31.5 (21.7)
Days with Headache - Past 3 months Mean (SD)	18 (10.9)	17.6 (11.0)	16.6 (9.6)	17.6 (8.9)	16.3 (8.7)	16.8 (9.6)	18.1 (10.9)
Average Headache Pain** – Past 3 months Mean (SD)	7.3 (1.7)	7.3 (1.7)	7.5 (1.6)	7.6 (1.6)	7.6 (1.6)	7.5 (1.6)	7.3 (1.5)

*This table above was adapted from Applicant Table 14.1.3.8.2 from the 302 Clinical Study Report (source: \\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\302-lahj\study-col-mig-302.pdf). Note, the applicant conducted this analysis by dose sequence.
**Average headache pain was measured on a scale of 0 to 10, where 0 is "no pain at all" and 10 is pain "as bad as it can be."
PBO=placebo, L50 = Lasmiditan 50 mg; L100=Lasmiditan 100 mg; L200=Lasmiditan 200mg

Reviewer comments: The results in the tables above are similar to that for Study 301, with patients experiencing a median of 5 migraines per month, and approximately 20% of patients taking a medication for the preventive treatment of migraine.

Table 30: Study 302 - Characteristics of Treated Migraines (applicant mITT*)

Characteristic	L50 mg N = 556	L100 mg N = 532	L200 mg N = 528	Placebo N = 540
Time to Dosing from Migraine Start (hours), n	556	532	528	540
Mean	1.14	1.24	1.23	1.19
SD	1.044	1.125	1.094	1.071
Median	0.95	1.01	1.01	1.00
Minimum	0.0	0.0	0.0	0.0
Maximum	3.9	4.0	4.0	4.0
Baseline Migraine Severity, n (%)	556	532	528	540
Severe (3)	152 (27.3%)	159 (29.9%)	147 (27.8%)	165 (30.6%)
Moderate (2)	392 (70.5%)	364 (68.4%)	374 (70.8%)	369 (68.3%)
Mild (1)	12 (2.2%)	9 (1.7%)	7 (1.3%)	5 (0.9%)
None (0)	0	0	0	1 (0.2%)
Baseline Symptoms, n (%)	556	532	528	540
Nausea	245 (44.1%)	235 (44.2%)	219 (41.5%)	249 (46.1%)
Phonophobia	330 (59.4%)	345 (64.8%)	326 (61.7%)	353 (65.4%)
Photophobia	427 (76.8%)	406 (76.3%)	397 (75.2%)	419 (77.6%)
None	44 (7.9%)	32 (6.0%)	45 (8.5%)	26 (4.8%)
Baseline MBS, n (%)	512	500	483	514
Nausea	127 (22.8%)	114 (21.4%)	104 (19.7%)	127 (23.5%)
Phonophobia	108 (19.4%)	110 (20.7%)	110 (20.8%)	119 (22.0%)
Photophobia	277 (49.8%)	276 (51.9%)	269 (50.9%)	268 (49.6%)
Accompanying Aura at First Dose, n (%)	556	532	528	540
Yes	15 (2.7%)	15 (2.8%)	7 (1.3%)	13 (2.4%)
No	541 (97.3%)	517 (97.2%)	521 (98.7%)	527 (97.6%)
Second Dose Taken Before 2-Hour Assessment, n (%)	556	532	528	540
Yes	1 (0.2%)	0	0	2 (0.4%)
No	555 (99.8%)	532 (100.0%)	528 (100.0%)	538 (99.6%)
Other Medications Taken to Treat Migraine, n (%)	556	532	528	540
No	416 (74.8%)	414 (77.8%)	408 (77.3%)	386 (71.5%)
Yes, Before 2-Hour Assessment	31 (5.6%)	41 (7.7%)	35 (6.6%)	26 (4.8%)
Yes, After 2-Hour Assessment	109 (19.6%)	77 (14.5%)	85 (16.1%)	128 (23.7%)

*Source: NDA 211280 302 Clinical Study Report Table 11-5 (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\302-lahj\study-col-mig-302.pdf)

L50=Lasmiditan 50 mg; L100=Lasmiditan 100 mg; L200=Lasmiditan 200 mg

Reviewer comments: The characteristics of treated migraines are similar to results for Study 301.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The rates for treatment compliance, concomitant medications and rescue medication use were similar to Study 301, and are not repeated here.

Data Quality and Integrity

The data quality was adequate, and the applicant conformed to GCP. There was an issue with how the eDiary captured data regarding the key secondary endpoint of MBS freedom and this is discussed below.

Efficacy Results – Primary Endpoint

The primary endpoint of this study was pain freedom at 2 hours post dose (similar to Study 301). With the NDA submission, the applicant defined their mITT population as all randomized patients who took at least one dose of study drug, recorded at least one post dose assessment and treated a migraine within 4 hours and had mild, moderate or severe pain at onset. However, per Information Requests and the mid-cycle meeting with the applicant, we determined that the corrected mITT (only including patients with moderate or severe intensity migraine at baseline) would be the analysis population for the primary and key secondary endpoints. These analyses are included below.

Table 31: Study 302 - Primary Efficacy Analysis (Corrected mITT*)

Primary Endpoint	Study 302/arm			
	Placebo N=534	50 mg N=544	100 mg N=523	200 mg N=521
Pain freedom at 2 hours post dose (baseline moderate to severe)	N=534	N=544	N=523	N=521
N	112/534	154/544	164/523	202/521
Percent	**20.9%**	**28.3%**	**31.4%**	**38.8%**
p-value**		**.006**	**<.001**	**<.001**

*This analysis only includes patients with moderate-severe intensity migraine at baseline and excludes the patients with mild-none headache at baseline. Thus this analysis excludes the following number of patients: in the placebo arm, there were 5 patients with mild intensity and 1 patient with "none" intensity, in the 50 mg arm, there were 12 patients with mild intensity, in the 100 mg arm, 9 patients with mild intensity and in the 200 mg arm, 7 patients with mild intensity.
**The p-values in this table are from the analysis conducted by FDA statistical reviewer, Dr. Liu, using a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates.

Reviewer comment: The therapeutic gain (the percentage effect of active drug minus percentage effect of placebo) ranges from ~7% for the 50 mg arm, to ~11% for the 100 mg arm, to ~18% for the 200 mg arm. There is evidence of a dose effect, and these results are statistically significant. Though these effects are modest, they are clinically meaningful to patients with limited options for treatment of acute migraines. Of note, we did analyze the primary endpoint using several different populations, including those with none/mild intensity at baseline (as the applicant had proposed) and not restricting to the 4-hour time window, and the efficacy results remained consistent with a treatment effect of lasmiditan compared to placebo across all study arms.

Study 302 Rescue Medication Users Prior to 2 Hours

A total of 44 patients were randomized and took a rescue medication within 2 hours in Study 302. There were 28 patients in the placebo arm, 32 patients in the 50-mg arm, 44 patients in the 100-mg arm and 40 patients in the 200-mg arm who took a rescue medication less than 2 hours after taking study drug. These patients were then considered nonresponders for the primary endpoint of pain freedom at 2 hours.

Efficacy Results – Secondary and other relevant endpoints

The applicant's key secondary endpoint for this study was MBS freedom at 2 hours in study drug compared to placebo.

Table 32: Study 302 - Key Secondary Endpoint Analysis (Corrected mITT)

Secondary endpoint MBS Recorded at time of dosing	Study 302/arm			
	Placebo	50 mg	100 mg	200 mg
MBS freedom at 2 hours post dose (baseline moderate to severe)	N=510	N=502	N=491	N=478
Total N	169/510	205/502	216/491	233/478
Percent responders	**33.2%**	**40.8%**	**44.0%**	**48.7%**
p-value		**0.014**	**<.001**	**<.001**

*Please note, this analysis includes fewer patients than in the efficacy analysis population for the primary endpoint because not all patients recorded MBS at time of dosing.
**The p-values in this table are from the analysis conducted by FDA statistical reviewer, Dr. Liu, using a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates.

Reviewer comments: These results indicate that there was a statistically significant and clinically meaningful improvement in a key associated symptom of migraine in patients who received lasmiditan compared to placebo.

Sensitivity Analysis for Key Secondary Endpoint

As with Study 301, during the review, the applicant contacted FDA via an Information Amendment (Application 211280 - Sequence 0016 - MBS Sensitivity Analyses) on February 5, 2019, to state there was an issue with data capture, and some patients did not enter symptom data prior to dosing. In Study 302, 55% of patients in the applicant's mITT population recorded MBS prospectively and 45% recorded it retrospectively, with 42.3% (of those who recorded it retrospectively) recording it within 5 minutes of dosing. The applicant performed a sensitivity analysis on this key secondary endpoint only including patients who identified the MBS prospectively or retrospectively within 5 minutes of dosing.

They found that the results did not change, with all arms receiving lasmiditan still demonstrating a statistically significant improvement in MBS freedom, compared to placebo. It is notable, though, that the p value for MBS freedom in the lasmiditan 50 mg arm was marginally significant (p=0.035 compared to the other arms, with p=.008 for 100 mg and p <.001 for 200 mg). When the applicant analyzed just those who collected their data prospectively, MBS freedom in the 50 mg arm had a p value of 0.269 and the 100 mg arm had a p value of 0.044.

Table 33: Study 302 - Sensitivity Analysis on MBS Freedom at 2 hours

Secondary endpoint of MBS freedom at 2 hours post dose	Study 302/arm			
	Placebo N=540	50 mg N=556	100 mg N=532	200 mg N=528
MBS Recorded **Prospectively** Total Number of Responders	N=290 112/290	N=276 114/276	N=264 122/264	N=274 147/274
Percent responders	**38.6%**	**41.3%**	**46.2%**	**53.6%**
Odds ratio (95% CI)		1.1 (0.8, 1.6)	1.2 (1.0, 1.9)	1.8 (1.3, 2.5)
p-value		**0.269**	**0.044**	**<.001**
MBS Recorded **Prospectively or Retrospectively ≤ 5 minutes**	N=385	N=377	N=358	N=367

Total Number of Responders	141/385	163/377	163/358	192/367
Percent responders	**36.6%**	**43.2%**	**45.5%**	**52.3%**
Odds ratio (95% CI)		1.3 (1.0, 1.8)	1.4 (1.1, 1.9)	1.9 (1.4, 2.5)
p-value		**0.035**	**0.008**	**<.001**

Reviewer comments: The issue of the eDiary not capturing this important information properly does raise concerns about the validity of the data on this important endpoint. The sensitivity analysis did end up removing almost half of the patients who recorded an MBS retrospectively, so it is difficult to interpret much from a post hoc analysis of a much smaller subset of patients. Given that the issue with not recording MBS prospectively is a concern for recall bias, examining the patients who identified MBS prospectively or within 5 minutes is a reasonable approach (since patients may be less likely to forget the symptom within a short time from taking study drug) and the results (table above) still appear to be valid for this endpoint in this patient population.

Other endpoints

The applicant also analyzed several other secondary endpoints in an exploratory manner (not controlling for multiplicity) after the first dose of study drug. These included the following measures:

- Pain relief at 2 hours
- Time course of pain freedom
- Time course of freedom from MBS
- Time course of pain relief
- Associated symptoms of migraine at 2 hours
- Interference in daily activity due to migraine (disability captured on the eDiary) at 2 hours
- Patient Global Impression of Change (PGIC) at 2 hours
- Incidence of rescue or recurrence medication use

Pain relief at 2 hours

Pain relief was defined as reduction in pain severity from moderate or severe at baseline to mild or none, or a reduction in pain severity from mild to none at 2 hours following the first dose.

Table 34: Study 302 - Pain Relief at 2 hours (mITT)

	Study 302/arm			
	Placebo N=534	50 mg N=544	100 mg N=523	200 mg N=521
Pain relief*, %	45.1%	55.9%	61.4%	61.0%
Difference from placebo, %		10.8%	16.3%	15.9%

Source: This analysis was conducted by Dr. Liu as part of her statistical review.
*The analysis of pain relief was descriptive and was not controlled for Type 1 error.

Reviewer comments: The table above demonstrates that all active treatment groups demonstrated a higher proportion of patients with pain relief at 2 hours compared to placebo. There is a slight dose response seen with higher doses (100 mg and 200 mg) compared to 50 mg. This is clinically relevant since patients will need to weigh the benefits of better response at higher doses with the risk of increased adverse events. Of note, this was an exploratory endpoint in this study and not controlled for multiplicity.

Time to Pain Freedom

The applicant examined pain freedom over time up to 2 hours following the first dose in the applicant's mITT, and pain relief up to 24 hours in the ITT population. The table for pain freedom at various time points is below and the graphical representation of time to pain freedom up to 24 hours follows.

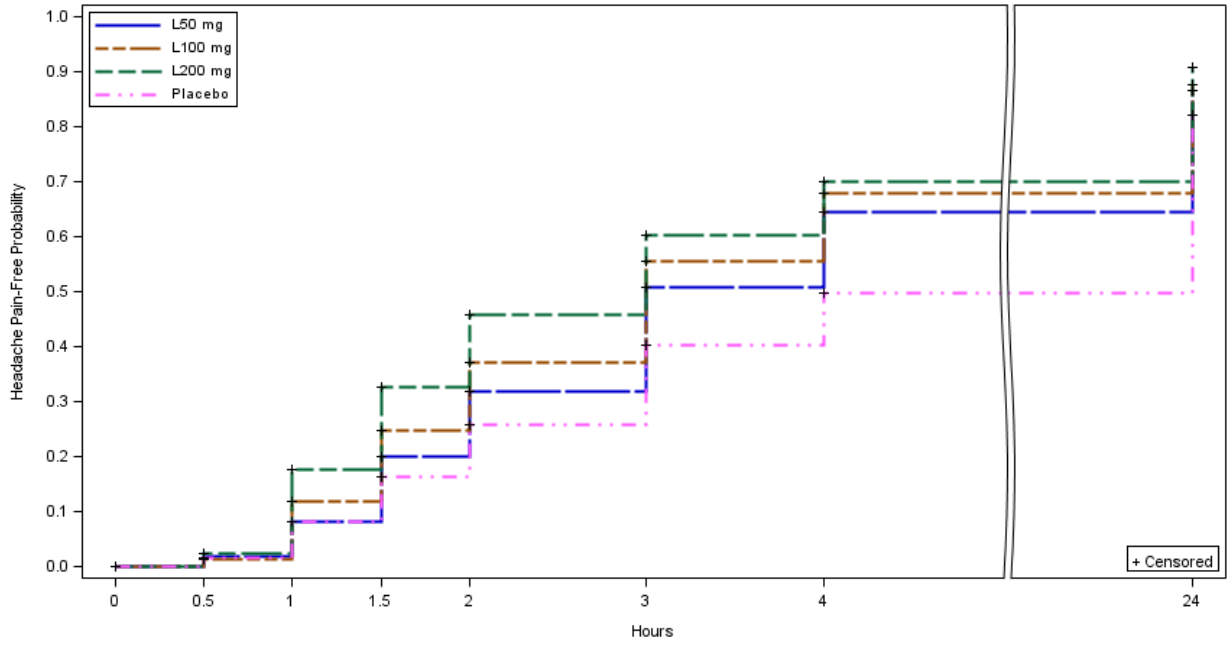
Table 35: Study 302 - Pain Freedom at Various Time Points (applicant mITT)

Endpoint of Headache pain-freedom (Mild, moderate or severe at time of dosing)	Study 302/arm			
	Placebo N=539	50 mg N=556	100 mg N=532	200 mg N=528
0.5 hours post-dose Odds ratio P value vs placebo	8 (1.5%)	11 (2.0%) 1.3 (0.5, 3.3) 0.536	8 (1.5%) 1.0 (0.4, 2.7) 0.983	13 (2.5%) 1.7 (0.7, 4.1) 0.257
1 hour post-dose Odds ratio p-value	39 (7.2%)	40 (7.2%) 1.0 (0.6, 1.6) 0.963	60 (11.3%) 1.6 (1.1, 2.5) 0.025	88 (16.7%) 2.6 (1.7, 3.8) <.001

1.5 hours post-dose Odds ratio p-value	74 (13.7%)	100 (18.0%) 1.4 (1.0, 1.9) 0.058	117 (22.0%) 1.8 (1.3, 2.4) <.001	151 (28.6%) 2.5 (1.8, 3.4) <.001)
2 hours post-dose Odds ratio p-value	115 (21.3%)	159 (28.6%) 1.5 (1.1, 1.9) 0.003	167 (31.4%) 1.7 1.3, 2.2) <.001	205 (38.8%) 2.3 (1.8, 3.1) <.001
3 hours post-dose	138 (25.6%)	201 (36.2%)	212 (39.8%)	239 (45.3%)
4 hours post-dose	153 (28.4%)	219 (39.4%)	223 (41.9%)	257 (48.7%)

Source: NDA 211280: Study 302 0 Clinical Study Report (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\302-lahk\col-mig-302-04-csr-body.pdf)

Figure 4: Study 302 - Time to Headache Pain Freedom Through 24 hours Post Dose (ITT)



Source: NDA 211280: Figure 11.1 of Clinical Study Report (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\302-lahk\col-mig-302-04-csr-body.pdf)

L50mg = lasmiditan 50 mg; L100 mg = lasmiditan 100 mg; L200 mg = lasmiditan 200 mg

Reviewer comments: The applicant used their ITT population for the analysis of pain freedom at 2 hours and up to 24 hours. The applicant did find that the Kaplan-Meier curves showed greater pain freedom for each of the lasmiditan doses relative to placebo, with higher doses of

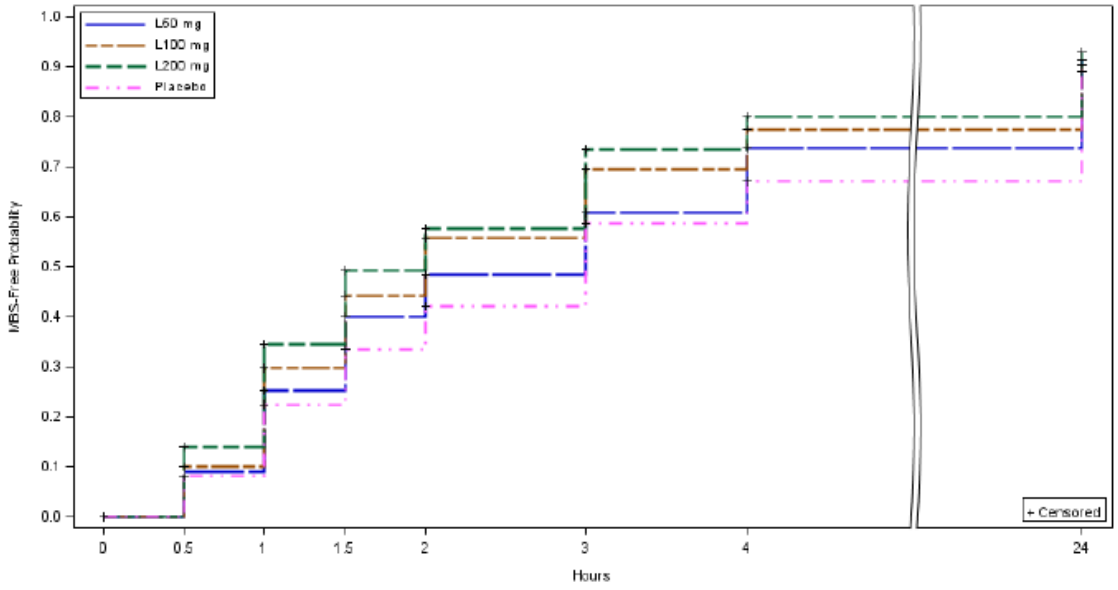
lasmiditan showing greater probability of pain freedom at each time point when compared to lower doses, especially after 1 hour. These results correspond with the pharmacokinetics of lasmiditan. (b) (4)

(b) (4)

Time to MBS Freedom

The applicant examined time to MBS freedom up to 24 hours.

Figure 5: Study 302 - Time to Most Bothersome Symptom Freedom Through 24 Hours Post-Dose (ITT)



Source: NDA 211280: Figure 11.3 of Clinical Study Report (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\302-lahk\col-mig-302-04-csr-body.pdf)

L50mg=Lasmiditan 50 mg; L100 mg = Lasmiditan 100 mg; L200 mg = Lasmiditan 200 mg

Reviewer comments: The applicant used their ITT population for the analysis of MBS freedom up to 24 hours and this figure represents that all treatment groups had a faster resolution of MBS compared to placebo at all time points after 1 hour. This figure could be included in the labeling, but I recommend only including time points up to 2 hours, and also ensuring that the graph includes only patients in the corrected mITT population (exclude patients with none/mild headache at baseline).

Sustained Response

The applicant examined sustained pain freedom in the ITT population. Pain freedom was defined as experiencing headache pain freedom at 2 hours post first dose and maintaining pain freedom at the assessment time (i.e. 24 hours and 48 hours), without using any rescue medications after the first dose. This was prespecified as an exploratory endpoint.

Table 36: Study 302 - Sustained pain freedom at 24 and 48 hours (ITT)

Exploratory endpoint	Study 302/arm			
	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%
Odds ratio versus placebo	-	1.3	1.4	1.9
p-value	-	.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%
Odds ratio versus placebo		1.3	1.3	1.8
p-value		.065	.058	<.001

Reviewer comments: This table demonstrates that there is a sustained effect of pain freedom in some patients, with a most notable dose response seen at the 200 mg dose compared to placebo in both studies. The 50 mg and 100 mg doses have a similar effect, which is less than that at the 200 mg dose. However, the differences between lasmiditan and placebo are small. Many patients who experienced pain freedom at 2 hours, without taking another medication at 24 hours, had persistence of this effect at 48 hours.

Associated symptoms of migraine at 2 hours

As with Study 301, the applicant examined the presence of specific migraine symptoms at 2 hours post dose. Nausea, photophobia, or phonophobia had to be identified as the MBS prior

to study drug administration. As stated above, photophobia was the most common identified MBS and had the most improvement after treatment compared to those in the placebo group.

Table 37: Study 302 - Summary of MBS freedom by Chosen Symptom (ITT)

	Study 302/arm			
MBS reported	Placebo N=576	Lasmiditan 50 mg N=598	Lasmiditan 100 mg N=571	Lasmiditan 200 mg N=565
Nausea reported as MBS (total n)	135	136	120	111
Nausea freedom, 2 hours post dose	55 (40.7%)	57 (41.9%)	58 (48.3%)	55 (49.5%)
p-value	-	0.89	0.25	0.17
Phonophobia reported as MBS (total n)	127	116	115	121
Phonophobia freedom, 2 hours post dose	48 (37.8%)	53 (45.7%)	59 (51.3%)	63 (52.1%)
p-value	-	0.20	0.04	0.03
Photophobia reported as MBS (total n)	287	298	300	287
Photophobia freedom, 2 hours post dose	82 (28.6%)	114 (38.3%)	118 (39.3%)	131 (45.6%)
p-value	-	0.02	0.01	<.001

Reviewer comments: As with Study 301, the symptom with the highest proportion of responders was photophobia. In this trial, though, phonophobia was also improved with lasmiditan compared to placebo for the higher dose groups (100 mg and 200 mg), but not the 50 mg dose. Again, photophobia likely drove the key secondary endpoint of MBS freedom being met in the previous analysis, since most patients identified photophobia as their most bothersome symptom.

Interference in daily activity due to migraine

The applicant examined interference in daily activity (or what they called "time course of disability") due to migraine as an exploratory endpoint. Patients were asked to grade the degree of interference (on a 4-point scale with 0=not at all, 1=mild interference, 2=marked

interference, and 3=completely, needs bed rest) of the migraine on normal activities. They were asked to record these assessments in the eDiary at the same time points post-dose (0.5 hours, 1 hours, 1.5 hours, 2 hours, 3 hours, 4 hours, 24 hours and 48 hours) they were grading headache severity and other measures.

At 2 hours post-dose, the following reported no interference of pain: 31.3% of patients in lasmiditan 50 mg, 33.8% in lasmiditan 100 mg, 37.0% in lasmiditan 200 mg, compared to 24.8% in the placebo group. At 2 hours post-dose, the following reported complete interference, needs bed rest: 12.7% in lasmiditan 50 mg, 9.1% in lasmiditan 100 mg, 10.1% of lasmiditan 200 mg, compared to 12.7% placebo.

Reviewer comments: Higher proportions of patients reported no interference of pain at 2 hours, compared to placebo. However, equal proportions of patients in all treatment arms and placebo still reported complete disability, and required bed rest. While patient-reported outcomes are important in assessing the benefit of a drug, this measure is not a validated one, and was only an exploratory endpoint. I would not recommend including this information in the label.

Patient Global Impression of Change (PGIC)

The applicant did present data on the PGIC with the following results: Of patient who reported they were "very much better": 11% in lasmiditan 50 mg, 13% in lasmiditan 100 mg, 14% in lasmiditan 200 mg and 8% in placebo. Of patients who reported there was "no change": 16.4% in lasmiditan 50 mg, 13.1% in lasmiditan 100 mg, 12.4% in lasmiditan 200 mg, and 26.4% in the placebo arm.

Use of Rescue or Recurrence Medication

The applicant examined the use of rescue or recurrence medication after the first dose of study drug in Study 302. Definitions of rescue and recurrence were the same as for Study 301.

Table 38: Study 302 - Incidence of Rescue Medication Use (ITT)

Medication Used	Study 302/arm			
	Placebo N=576	Lasmiditan 50 mg N=598	Lasmiditan 100 mg N=571	Lasmiditan 200 mg N=565
Study Drug Rescue Medication* used, 2 hours post-dose, N (%)	235 (40.8%)	191 (31.9%)	151 (26.4%)	107 (18.9%)
Study Drug Recurrence Medication used, 2-24 hours post-	10 (1.7%)	13 (2.2%)	11 (1.9%)	10 (1.8%)

dose, N (%)				
All Rescue Medication, ≤ 2 Hours Post-Dose, N (%)**	237 (41.1%)	197 (32.9%)	156 (27.3%)	109 (19.3%)
All Recurrence Medication, ≤ 24 Hours post-dose, N (%)***	10 (1.7%)	13 (2.2%)	11 (1.9%)	10 (1.8%)

Source: NDA 211280: Table 14.2.3.9 of Clinical Study Report (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5351-stud-rep-contr\302-lahk\col-mig-302-04-csr-body.pdf)

*Study Medication was the study drug (randomized dose of lasmiditan or placebo);
**All rescue medications included a few patients who took rescue medication before the 2 hour timepoint.
***All Recurrence Medication could include study drug and/or the patient's own rescue medications; however, no patients took their own rescue medication.

Reviewer comments: The table demonstrates that, numerically, more patients in the placebo group took a medication for rescue than in the lasmiditan treated groups. A dose-response is seen across groups, with patients randomized to higher doses of lasmiditan for their first dose, less likely to take a second dose for rescue. P values were not presented since this data was not controlled for multiple comparisons. Numbers of patients who took medication for recurrence were small, but included in table above for completeness.

Dose/Dose Response

Only one dose of drug was assessed for each patient in the study. A dose response relationship is evident across groups (Table 31), that was statistically significant.

Reviewer comments: In terms of clinical significance, there was clearly a dose response demonstrated with higher doses. This will have to be weighed against the adverse events that were also seen at a higher proportion with increasing dose (see Dr. Branagan's safety review). Based on these efficacy data, though we only have one trial examining the 50 mg dose, I do think we should approve the lower dose of 50 mg to allow patients flexibility in dosing, and to account for potential side effects that may occur at higher frequencies with higher doses.

Second Dose

The applicant randomized all patients to receive a combination of study drug or placebo for two doses (see dosing above), at the initial randomization, that would determine what they would receive for the second dose. The analyses on second dose were not controlled for multiplicity. Not all patients who took a second dose were analyzed below, as the applicant stated many patients did not provide efficacy data. In Study 302, 229 patients who took a second dose were

not included in this analysis for reasons such as not being in the first dose ITT population, and not recording a post second dose pain and MBS assessment. This does raise concern for interpretability of data presented below, as there is a risk for bias, as discussed in Study 301, and a high degree of missing data.

Additionally, the applicant responded to an FDA clarification request asking them to clarify if patients who were analyzed for the second dose had taken a rescue medication or not. The applicant clarified that the "ITT-2nd dose population," was defined as "all randomized subjects who were considered ITT after the first dose and use a second dose of study drug and have any post-dose headache severity or symptom assessments." Thus the dataset flag used to identify patients for these analyses identified patients in the intent-to-treat population, without specifically excluding patients who might have reported using another rescue medication.

It was determined that in Study 302, of the 912 patients who took a second dose of medication, 54 (5.9%) took another medication (not study drug), prior to the second dose, and 34 (3.7%) took another medication within 2 hours of the second dose. Thus, 9.3% of patients took another study medication (besides study drug) and this makes the data the applicant submitted below (on the effect of lasmiditan in a second dose) confounded by use of other medications.

Second dose for rescue

Table 39: Study 302 - Second Dose for Rescue

Endpoint	Study 302 – Treatment (first dose/second dose) for Rescue						
	Placebo/ Placebo	50 mg/ Placebo	50 mg/ 50 mg	100 mg/ Placebo	100 mg/ 100 mg	200 mg/ Placebo	200 mg/ 200 mg
Pain free, n (%)	**50/287 (17.4%)**	**18/79 (22.8%)**	**33/166 (19.9%)**	**23/63 (36.5%)**	**27/124 (21.8%)**	**15/51 (29.4%)**	**30/98 (30.6%)**
Odds ratio vs LTN/Placebo (95% CI)	-	-	0.8 (0.4, 1.6)	--	0.5 (0.3, 0.9)	-	1.1 (0.5, 2.2)
Odds ratio vs Placebo/Placebo	-	1.4 (0.8, 2.6)	1.2 (0.7, 1.9)	2.7 (1.5, 4.9)	1.3 (0.8, 2.2)	1.98 (1.0, 3.9)	2.1 (1.2, 3.5)
MBS free, n (%)	69/254 (27.2%)	23/69 (33.3%)	52/142 (36.6%)	26/58 (44.8%)	26/102 (25.5%)	18/46 (39.1%)	33/87 (37.9%)
Odds ratio vs LTN/Placebo (95% CI)	-	-	1.2 (0.6, 2.1)	-	0.4 (0.2, 0.8)	-	0.95 (0.5, 2.0)

Odds ratio vs Placebo/Placebo	-	1.3 (0.8, 2.4)	1.6 (1.0, 2.4)	2.2 (1.2, 3.9)	0.9 (0.5, 1.5)	1.7 (0.9, 3.3)	1.6 (0.98 2.7)

(Source: NDA 211280: Regulatory Response to Midcycle Communication \\cdsesub1\evsprod\nda211280\0022\m1\us\response.pdf)
LTN=lasmiditan

Second dose for Recurrence

As with Study 301, the applicant examined the effect of a second dose of study drug (either the same dose as the first dose or placebo) to treat a migraine that had resolved at the 2-hour time point and then returned. The results are below.

Table 40: Study 302 - Second Dose for Recurrence

Endpoint	Study 302 – Treatment (first dose/second dose) for Recurrence						
	Placebo/ Placebo	50 mg/ Placebo	50 mg/ 50 mg	100 mg/ Placebo	100 mg/ 100 mg	200 mg/ Placebo	200 mg/ 200 mg
Pain free, n (%)	**2/10 (20%)**	**2/4 (50%)**	**6/9 (67%)**	**0/3 (0%)**	**4/8 (50%)**	**2/5 (40%)**	**1/5 (20%)**
Odds ratio vs LTN/Placebo (95% CI)	-	-	2.0 (0.2, 22.1)	-	-	-	0.4 (0.0, 6.4)
Odds ratio vs Placebo/Placebo	-	4 (0.3, 48.7)	8 (1, 64)	0 (-,-)	4 (0.5, 32)	2.7 (0.3, 28.4)	1.0 (0.1, 14.6)
MBS free, n (%)	**5/9 (56%)**	**2/4 (50%)**	**5/6 (83%)**	**1/2 (50%)**	**6/8 (75%)**	**2/5 (40%)**	**2/4 (50%)**
Odds ratio vs LTN/Placebo (95% CI)	-	-	5 (0.3, 91.5)	-	3.0 (0.1, 73.6)	-	1.5 (0.1, 21.3)
Odds ratio vs Placebo/Placebo		0.8 (0.1, 8.5)	4.0 (0.3, 49.6)	0.8 (0.04, 17.2)	2.4 (0.3, 19.0)	0.5 (0.1, 4.9)	0.8 (0.1, 8.5)

Source: NDA 211280: Regulatory Response to Midcycle Communication (\\cdsesub1\evsprod\nda211280\0022\m1\us\response.pdf)
LTN=lasmiditan

Reviewer comment: The above tables for rescue and recurrence are similar to the data that was presented for Study 301. Pain freedom rates when taking lasmiditan and placebo for rescue for a migraine that has not resolved appear to be similar. There appears to be a trend to improvement in pain relief and MBS relief at 2 hours for treatment of a recurrent migraine (one that resolved at the 2-hour time point but then returned). Again, it is hard to interpret these results for many reasons. For one, many patients took another drug either before the study

drug, or after taking study drug and before the 2 hour timepoint, which confounds the efficacy of the effect of lasmiditan for a second dose. Additionally, there was a large amount of missing data, and this second dose is a much smaller dataset than the randomized set, so the population has changed. (b) (4) (b) (4).

Subgroup Analyses Conducted on the Individual Trial

The applicant conducted analyses on pre-specified subgroups on the applicant's mITT population in Study 302 (including the patients with mild intensity at baseline). The analysis (302_LAHK 04 Body Tables 14.2.1.1.9) demonstrated several key findings:

1) By age:
    a. In patients ages < 65 years old, lasmiditan was effective compared to placebo at all doses.
    b. In patients ages ≥ 65 years old, based on the results, it appears that lasmiditan was not more effective than placebo. However, there were a limited number of patients who were in the ≥ 65 years old, so it is difficult to adequately estimate an effect. The 2-hour pain freedom rates were the following: 12/26 (46.2%) in placebo, 15/31 (48.4% in 50 mg arm), 5/23 (21.7% in 100 mg arm), 10/20 (50.0% in 200 mg arm).
2) By sex:
    a. In females, lasmiditan was effective compared to placebo at all doses.
    b. In males, lasmiditan was not effective compared to placebo in the 50 mg arm and showed a trend to benefit in the 100mg and 200 mg arms. Table 25 below demonstrates the results of this analysis. Of note, the p value was not significant in any arm compared to placebo.
3) By race:
    a. In Caucasians, lasmiditan was effective compared to placebo at all doses. In African Americans, no dose of lasmiditan was more effective than placebo except there was trend to efficacy in the 200 mg arm. Numbers of patients in the "Other" category were small, but again there was no benefit to any specific dose compared to placebo.
4) By weight:
    a. Of note, the median weight was 178 pounds (80.9 kg). The applicant picked 90 kg to examine the effects in those less than 90 kg and those greater than or equal to 90 kg.
    b. Lasmiditan was effective at all doses compared to placebo regardless of weight, < 90 kg or ≥ 90 kg.

Table 41: Study 302 - Efficacy Analysis by Subpopulation of Sex (Corrected mITT*)

Pain freedom at 2 hours post dose	Study 302/arm			
	Placebo N=534	50 mg N=544	100 mg N=523	200 mg N=521
Female				
N	92/454	138/462	137/448	172/431
%	20.3%	29.9%	30.6%	39.9%
Male				
N	20/80	16/82	27/75	30/90
%	25.0%	19.5%	36.0%	33.3%

*I conducted these analyses on the mITT population that excluded patients with mild intensity migraine at baseline.

Reviewer comments: The results are similar to those seen in Study 301, in that there does not appear to be a significant benefit with lasmiditan compared to placebo in age ≥ 65 and in males. Of note, there were small numbers of patients age ≥ 65 years old (total 100 of 2156 or 4.6% of the applicant's mITT population) and small numbers of male patients (total 333 of 2156 or 15.4% of the applicant's mITT population) so the study may not have been powered to show any differences in these groups.

We examined if weight played a role in these findings, (see table below), but efficacy of lasmiditan at all doses was the same across weights (<90 kg or ≥ 90 kg), just as in Study 301.

Table 42: Study 302 - Analysis of Primary Endpoint By Weight (mITT)

Endpoint:	**Study 302/arm**			
Pain freedom at 2 hours	**Placebo**	**50 mg**	**100 mg**	**200 mg**
Weight < 90 kg	**78/367**	**115/384**	**121/370**	**142/357**
	21.2%	29.9%	32.7%	39.8%
Weight ≥ 90 kg	**34/167**	**39/160**	**43/153**	**60/164**
	20.4%	24.4%	28.1%	36.6%

Reviewer comments: There were no differences in response to lasmiditan by weight of <90 kg or ≥ 90 kg, so the sex differences are not explained by possible differences in weight.

The data suggests that the beneficial effect of lasmiditan is driven by women, and also by patients who are ages < 65, since these patient demographics comprise the majority of the patient population in these studies.

Dr. Liu, statistical reviewer, performed her own analysis of the treatment effect across clinically meaningful subgroups, including age, gender, race and country, and determined that the trend in treatment success was similar across all subgroups. Please see her review for further details.

6.3. Study 305/LAHL: An Open-label, Long-term, Safety Study of Lasmiditan (100 mg and 200 mg) in the Acute Treatment of Migraine (GLADIATOR)

Study 305 was an open-label study which enrolled patients who completed Studies 301 and 302. Patients were randomized to either 100 mg or 200 mg of lasmiditan for the duration of the 12-month study to treat more than 1 migraine attack.

A total of 2116 patients participated in the study, with 1014 randomized to receive lasmiditan 100 mg and 1102 randomized to receive lasmiditan 200 mg. The median length of participation was 270 days, with 1148 (54.3%) of patients discontinuing the study prior to the 12-month visit, with discontinuation rates similar in both the 100 mg (54.2%) and 200 mg (54.3%) groups. The most common reasons for discontinuation were: patient request (41.7%), adverse event (22.6%), lost to follow-up (18.9%).

Reviewer comment: Although the applicant included several efficacy measures in this safety study, due to the open-label nature of the study, these results are not interpretable. Please refer to Dr. Branagan's review for an overview of the safety analyses conducted from the data collected in this study.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The submission for NDA 211280 includes data from two studies in patients with episodic migraine with or without aura to evaluate lasmiditan as a potential acute treatment for migraine. The applicant was advised that they would need to demonstrate efficacy using two well-designed clinical trials. Studies 301 and 302, as described above in sections 6.1 and 6.2, respectively, were very similar in their design and conduct. Both studies evaluated the efficacy and safety of oral lasmiditan in the acute treatment of migraine attacks and were randomized, double-blind, placebo-controlled, studies. Both studies were conducted under SPAs.

<u>The key similarities between Study 301 and Study 302 are the following:</u>

- Inclusion criteria including:
    - patients ≥18 years old with a definition of migraine with or without aura, per the IHS criteria
    - at least a one-year history of migraine with onset prior to age 50
    - 3-8 migraine attacks per month with <15 headache days/month and a Migraine Disability Assessment Score of ≥11
    - Patients with cardiovascular risk factors allowed to enroll
- Many common exclusion criteria
- Study design the same - prospective randomized double-blind placebo-controlled trials of effect of study drug on a single migraine attack
- Same primary, key secondary and other exploratory endpoints
- Stratified by use of concomitant preventive medications to treat migraine
- Option to take second dose for either rescue or recurrence with no re-randomization for second dose

The key differences between Study 301 and 302 are the following:

- 301 was conducted only in the U.S., whereas 302 was conducted in the U.S., United Kingdom and Germany. In the combined 301 and 302 studies, 501 (9.5%) of 5237 enrolled patients were from OUS
- 302 had one additional arm of study drug at 50 mg, in addition to the 100 mg and 200 mg arms of Study 301
- 301 excluded patients with certain cardiovascular diseases (known CAD, clinically significant arrhythmia or uncontrolled hypertension), whereas 302 specifically allowed these patients to enter the study

7.1.1. Primary and Key Secondary Endpoints

Both studies had the same primary endpoint of pain freedom at 2 hours and were able to demonstrate a statistically significant improvement in pain freedom at 2 hours in the lasmiditan arms that increased with higher doses compared to placebo. The table below provides an overview of the primary and key secondary efficacy endpoints in Studies 301 and 302.

Table 43: Studies 301 and 302 - Primary and Key Secondary Efficacy Analyses Summary

Endpoint	Study 301/arm			Study 302/arm			
	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 N Percent p-value	79/515 **15.3%** 	141/498 **28.3%** **<.001**	160/503 **31.8%** **<.001**	112/5345 **20.9%** 	154/544 **28.3%** **0.006**	164/523 **31.4%** **<.001**	202/521 **38.8%** **<.001**
MBS freedom at 2 hours post dose N Percent p-value	N=480 142/480 **29.6%** 	N=464 191/464 **41.2%** **<.001**	N=467 190/467 **40.7%** **<.001**	N=510 169/510 **33.1%** 	N=502 205/502 **40.8%** **<.014**	N=491 216/491 **44.0%** **<.001**	N=478 233/478 **48.7%** **<.001**

Reviewer comments: In general, the primary efficacy data are consistent across both trials and there appears to be a consistent benefit to lasmiditan compared to placebo in treating a single acute migraine attack. There is also an apparent dose response across both trials for the primary endpoint, with a higher percentage of responders with regards to pain freedom at 2 hours in the lasmiditan-treated group. There does not seem to be any added benefit of the higher doses (except at the 200 mg dose) with regards to MBS freedom, but there is an improvement in MBS in the lasmiditan-treated groups compared to placebo in both studies (the dose-effect is also less apparent in Study 301 compared to Study 302).

*Both the primary endpoint and key secondary endpoints in these trials are typically treated as co-primary endpoints per the FDA guidance for acute migraine trials (Source: **https://www.fda.gov/media/89829/download**). This applicant's design, of keeping these as two individual endpoints that were controlled for multiplicity, is essentially the same statistically since both endpoints were met.*

It is important to note both of these studies were quite large (with over 2000 patients in Study 301 and over 3000 patients in Study 302). A large trial can demonstrate statistically significant differences; however, these differences may not always be clinically meaningful. The Number Needed to Treat (NNT) is helpful in understanding the clinical context of the treatment effect. The results of these studies demonstrate that the NNT to achieve pain freedom is 6 patients in the lasmiditan 200 mg arms of both studies. This is clinically meaningful. At the 100 mg dose, Study 301 had an NNT of 8 and Study 302 had an NNT of 10 - which are quite similar, and also clinically meaningful. Though the NNT is 14 for the 50 mg arm, it may offer an option for

patients who experience adverse effects at the higher doses. The similarity of the NNT across the studies for the 100 mg and 200 mg arms also raises confidence in these findings.

In summary, the difference in treatment effect on the endpoints of pain freedom and MBS freedom between lasmiditan and placebo-treated patients is statistically significant, and likely clinically meaningful to patients with migraine with and without aura. However, benefits will need to be weighed, in the individual patient, against the risk profile (as detailed in Dr. Branagan's safety review) and alternative treatment options.

7.1.2. Secondary and Other Endpoints

Second dose efficacy

As summarized above in Sections 6.1.2 and 6.2.2, there did not seem to be any benefit to a second dose of lasmiditan for rescue of a migraine that was not resolved at 2 hours. While the numbers in each group were small, this was also an exploratory endpoint and so the study was not powered to demonstrate an effect. Given that the number of patients who took a second dose for rescue and recurrence was significantly less than that of the randomized and mITT population (due to missing data), this also represents a different population than the efficacy analysis population. The applicant also stated that about 10% of the patients in both studies took a rescue medication before taking a second dose of study drug, or within 2 hours after taking a second dose of study drug.

While the analyses for second dose for recurrence demonstrated a trend to benefit for second dose for recurrence (as summarized above), the data are difficult to interpret due to the reasons stated above for second dose. Given the extremely small numbers in this group, and the fact that these data are confounded by patients who took another rescue medication, the data do not support a second dose of lasmiditan for either rescue or recurrence. Furthermore, in light of the safety concerns due to unknown effects of a second dose on driving(b) (4) (b) (4) (b) (4). Please refer to the reviews of Dr. Branagan (safety reviewer) and Dr. Brundson (clinical pharmacology reviewer) for further discussion of the safety issues surrounding allowing a second dose for rescue or recurrence.

7.1.3. Subpopulations

The applicant examined the effects of subpopulations of both studies 301 and 302 (separately and pooled) by evaluating the proportion of patients that were pain free and MBS free at 2 hours compared to placebo after the first dose for the following variables:

Sex, race, ethnicity, weight (< 90 kg or ≥ 90 kg), use of migraine preventive treatment, triptan use within 3 months of screening, history of aura, presence of cardiovascular risk

factors (and number of these) at baseline, and time of first dose relative to onset (within 4 hours of onset or after 4 hours of onset).

The following table is copied directly from the applicant's Integrated Summary of Effectiveness (ISE) (Table ISE.9.1) and is on the applicant's mITT population (which includes patients with mild intensity at baseline).

Table 44: Studies 301 and 302 - Summary of Subgroup Analyses of Proportions of Patients Pain Free at 2 hours (applicant mITT)

Variable n (%)	Subgroup	Patients Pain Free 2 Hours Postdose, %					P-value[a]
		N	PBO	LTN 50 mg	LTN 100 mg	LTN 200 mg	
Sex	Female	3109	164/905 (18.1)	143/473 (30.2)	251/862 (29.1)	320/869 (36.8)	
	Male	591	31/158 (19.6)	16/83 (19.3)	58/173 (33.5)	52/177 (29.4)	.035
Race	Caucasian	2958	145/862 (16.8)	121/452 (26.8)	242/821 (29.5)	290/823 (35.2)	
	Non-Caucasian	741	50/201 (24.9)	38/104 (36.5)	67/214 (31.3)	81/222 (36.5)	.326
Ethnicity	Hispanic	654	51/182 (28.0)	42/115 (36.5)	63/178 (35.4)	74/179 (41.3)	
	Non-Hispanic	3021	143/875 (16.3)	116/437 (26.5)	246/849 (29.0)	295/860 (34.3)	.393
Weight	<90 kg	2488	138/717 (19.2)	119/392 (30.4)	214/700 (30.6)	243/679 (35.8)	
	≥90 kg	1206	57/344 (16.6)	40/163 (24.5)	95/334 (28.4)	128/365 (35.1)	.712
Used topiramate or propranolol	Yes	340	13/107 (12.1)	10/48 (20.8)	25/93 (26.9)	24/92 (26.1)	
	No	3360	182/956 (19.0)	149/508 (29.3)	284/942 (30.1)	348/954 (36.5)	.710
Used triptans within 3 months of screening	Yes	1376	59/430 (13.7)	40/191 (20.9)	100/383 (26.1)	128/372 (34.4)	
	No	2324	136/633 (21.5)	119/365 (32.6)	209/652 (32.1)	244/674 (36.2)	.051
History of aura	Yes	1436	73/420 (17.4)	57/222 (25.7)	125/398 (31.4)	134/396 (33.8)	
	No	2239	120/636 (18.9)	101/331 (30.5)	182/632 (28.8)	235/640 (36.7)	.426
CVRFs	0 or 1	2204	118/640 (18.4)	95/343 (27.7)	166/605 (27.4)	211/616 (34.3)	
	2 or more	1496	77/423 (18.2)	64/213 (30.0)	143/430 (33.3)	161/430 (37.4)	.637
Timing of first dose relative to onset	≤4 hours after onset	3704	195/1064 (18.3)	159/557 (28.5)	309/1036 (29.8)	373/1047 (35.6)	
	>4 hours after onset	276	11/65 (16.9)	10/41 (24.4)	28/97 (28.9)	23/73 (31.5)	.945

Source: NDA 211280 Integrated Summary of Efficacy (\\cdsesub1\evsprod\nda211280\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\migraine\5353-rep-analys-data-more-one-stud\ise\ise47-integrated-sum-of-efficacy.pdf) Please note, this is the

applicant's mITT population, and not the corrected mITT.
ITT=intent-to-treat; LTN=lasmiditan; n=number of patients per subgroup; N=total number of patients per group; PBO=placebo.
[a] The p-value for treatment-by-subgroup interaction, based on logistic regression model: study, subgroup, treatment, treatment-by-subgroup.

Reviewer comments: From the table above, there does not appear to be any difference in benefit of lasmiditan in any of these subgroups except in males compared to females, where there is a treatment-by-sex interaction. This seems to occur predominantly in the 50 mg dose group, as numerically there is a higher proportion of responders in the lasmiditan 100 mg (33.5%) and 200 mg (29.4%) arms, compared to placebo (19.6%). As was discussed in each individual study above, it is not clear why there would be a difference in treatment effect due to sex. This did not seem to be driven by weight differences. There were fewer men in both studies than women, so it is possible the study was not powered to show a benefit in men. It is important to note there were no sex differences based on pharmacokinetics either, and the reader is referred to the review by Dr. Brundson, from clinical pharmacology, for details regarding this analysis.

Subgroup of Patients With Cardiovascular Risk Factors

The following table was created by Dr. Branagan as part of her safety review and is copied below to better understand the population with cardiovascular disease.

Table 45: Cardiovascular Disease by SMQ Term with Prevalence ≥ 1% for Studies 301 and 302

SMQ Term	Studies 301 and 302 (N=4439)	% of Total Population Enrolled in Studies 301 and 302
Hypertension	758	17.1
Cardiac arrhythmias	104	2.3
Embolic and thrombotic events	84	1.9
Ischemic heart disease	51	1.1
Embolic and thrombotic events, arterial	47	1.1
Tachyarrhythmias	46	1.0
Other ischemic heart disease	45	1.0
Bradyarrhythmias	44	1.0
Total number of patients with baseline cardiovascular disease*	**904**	**20.4**

Source: This table was created by Dr. Branagan, safety reviewer, using data from the applicant's submission ISS Appendix Table ISS.APP.18.2. and IDB ADSL dataset, study ID=301 and 302, SAFFL=Y, CVBSGPFL=Y. *Patient could be represented by more than 1 cardiovascular disease SMQ.

Reviewer comments: Patients with hypertension accounted for the highest percentage of patients with cardiovascular disease. Patients with contraindications for triptan use (e.g. ischemic heart disease, coronary artery vasospasm, stroke or transient ischemic attack, peripheral vascular disease, ischemic bowel disease and uncontrolled hypertension) only comprise 146 patients (or ~3%) of the 4439 patients in the safety population. Since the study was not powered to draw conclusions from this subpopulation, efficacy data are not presented here.

Regarding patients with "cardiovascular risk factors," the table above would indicate that up to 30% of patients in some arms of the study had cardiovascular risk factors. Cardiovascular risk factors included age >40, current smoker, high total cholesterol (≥240 mg/dL), low HDL cholesterol (<40 mg/dL men, <50 mg/dL women), high blood pressure (SBP ≥ 140 mm Hg or history of hypertension) and history of diabetes mellitus. However, the most common risk factor was age > 40 years old in both studies across all subgroups in both studies. Other drugs to treat migraine (for example, triptans) are not contraindicated in patients ages > 40 years old, so it is difficult to draw conclusions about a benefit in patients that are unable to take triptans.

Regarding patients with "cardiovascular disease," hypertension represented >80% of the cardiovascular disease that the applicant reported was present in ~20% of the patients across both studies. However, this was not necessarily "uncontrolled" and hypertension alone is not a contraindication for acute migraine therapies, like triptans. Therefore, the population examined in this study does not provide evidence that lasmiditan is necessarily safe in patients who have cardiovascular risk factors or cardiovascular disease.

7.1.4. Dose and Dose-Response

Table 46: Studies 301 and 302 - Analysis of Primary Endpoint to Evaluate Dose and Dose Response (Corrected mITT)

Pain freedom at 2 hours post dose	Study 301/arm			Study 302/arm			
	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
N	79/515	141/498	160/503	112/534	154/544	164/523	202/521
Percent	**15.3%**	**28.3%**	**31.8%**	**20.9%**	**28.3%**	**31.3%**	**38.8%**
p-value		<.001	<.001		0.003	<.001	<.001
NNT		NNT=8	NNT=6		NNT=14	NNT=10	NNT=6

NNT=Number needed to treat

Reviewer comments: The table above demonstrates the lasmiditan is effective compared to placebo at all doses tested in Studies 301 and 302. There is a dose response with increasing doses of lasmiditan, although the effect is less evident in the 50 mg arm. Dr. Branagan's safety review demonstrated that adverse events increase with increasing dose, so I believe the results support approval of the 50 mg dose to give some patients the flexibility of a lower dose, to either decrease the risk of adverse effects, or to use as an alternative to a higher dose.

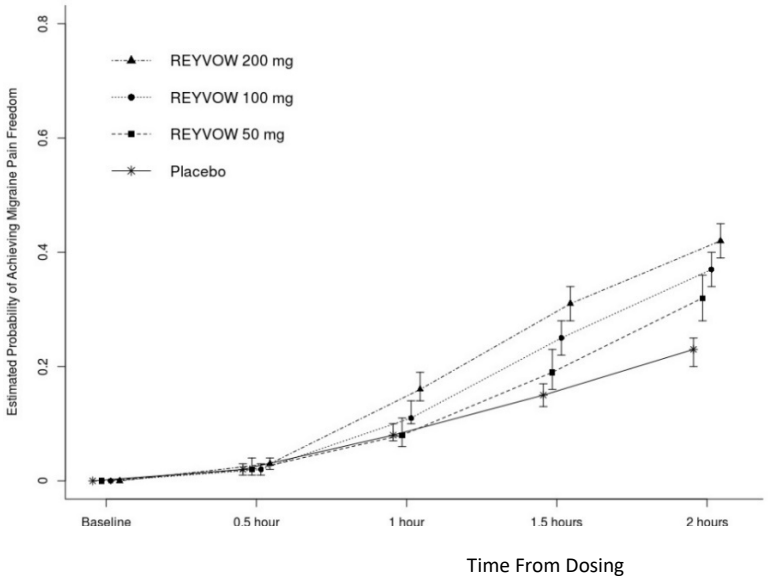
The comparisons to placebo at all doses show the results to be statistically significant. The number needed to treat (NNT) ranges from 6 at the high doses to 14 at the low dose. These results are clinically meaningful to patients who are need of alternative treatment options for acute migraine treatment, however these benefits will need to be weighed against the risks of lasmiditan as discussed in Dr. Branagan's safety review.

The table above demonstrates the primary efficacy analysis was also independently reproduced in both studies, and thus strengthens the confidence in the efficacy findings.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

In terms of efficacy, the onset of action of lasmiditan and the effect on pain freedom appears to increase with increased time as per Kaplan Meier graphs provided by the applicant.

Figure 6: Studies 301 and 302 - Estimated Probability of Achieving Migraine Pain Freedom at 2 Hours in Pooled Studies

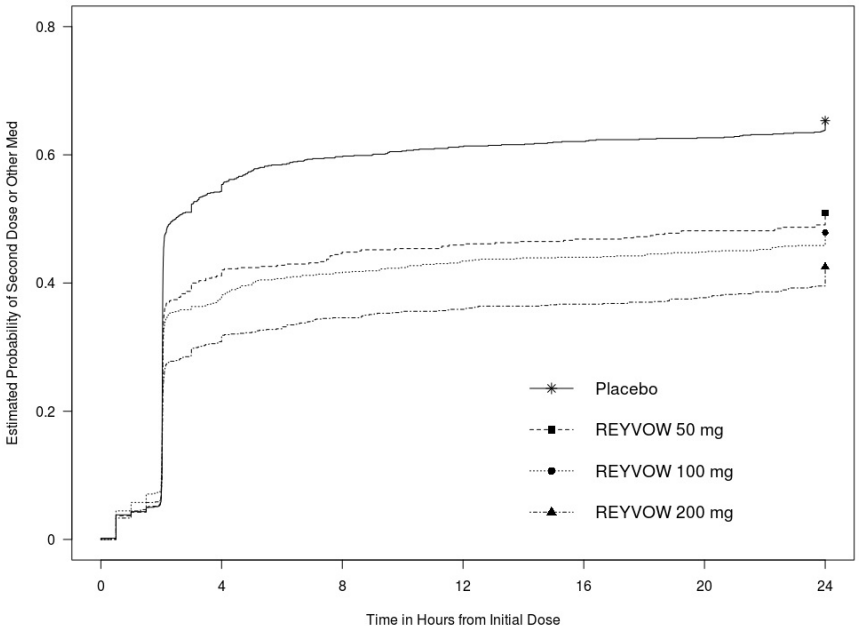


Source: NDA 211280 – Applicant's proposed Prescribing Information Figure 1.
(\\cdsesub1\evsprod\nda211280\0001\m1\us\proposed-uspi.docx)
Note: REYVOW is the proposed tradename for lasmiditan.

Reviewer comment: While these were not prespecified analyses, they do provide insight into the trajectory of when an effect can be expected which appears to be consistent with the known t_{max} of the drug of 1.8 hours. However, the interpretation of this graph is limited at any time point after 2 hours since rescue medications could be used after 2 hours.

In terms of sustainability of the effect, patients who took lasmiditan as their first dose in Studies 301 and 302 were less likely to take a second dose of study drug or rescue medication compared to those who were randomized to the placebo arm, as evidenced in the figure below.

Figure 7: Studies 301 and 302 - Estimated Probability of Taking a Second Dose or Other Medication Over the 24 Hours Following the Initial Dose of Study Treatment



Source: NDA 211280 – (b) (4)
(\\cdsesub1\evsprod\nda211280\0001\m1\us (b) (4)
Note: REYVOW is the proposed tradename for lasmiditan.

Reviewer comment: While these results demonstrate that less patients who took lasmiditan took a second dose of study drug, compared to those who were initially randomized to take placebo, it is an exploratory endpoint and was not controlled for multiplicity. Additionally, as stated previously, the evidence of a benefit of the second dose for any indication (rescue or recurrence) is limited. (b) (4)
(b) (4)

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The two adequate and well-controlled studies used to support approval of lasmiditan for the treatment of acute migraine examined the effects of lasmiditan on treatment of a single migraine attack. The long-term study (Study 305) provides some insight into the potential risks of this product in the population studied. Due to the open-label nature of this study, this data cannot be used to reliably support efficacy claims.

Given known safety risks of this drug (see Safety Review of Dr. Branagan for details), the benefit of the drug will have to be weighed against risks in individual patients.

7.2.2. Other Relevant Benefits

The applicant was able to demonstrate a benefit of lasmiditan compared to placebo on pain relief, the time course of freedom from pain, and most bothersome symptom freedom, and on pain freedom up to 48 hours after taking study drug. The applicant also demonstrated that patients randomized to lasmiditan for the first dose were less likely to take a second dose of medication for a migraine that did not resolve, compared to placebo.

7.3 Integrated Assessment of Effectiveness

This NDA submission provides substantial evidence of the effectiveness of lasmiditan to support approval of this product for the acute treatment of migraine in patients with migraine with and without aura. The applicant provided data from two adequate and well-controlled studies that demonstrated that lasmiditan leads to increased rates of pain freedom and most bothersome symptom (MBS) freedom at 2 hours (the primary and key secondary endpoints, respectively) after treatment of a single migraine attack compared to placebo. These effects were reproduced in both trials and demonstrate that the effects of lasmiditan are statistically significant, clinically meaningful, and reproducible across all treatment groups compared to placebo. The applicant also demonstrated a dose-response with the primary endpoint of pain freedom. While the lowest dose of 50 mg of lasmiditan did demonstrate the smallest response rates, there is likely a patient group that would benefit from being offered a lower dose, especially given the fact that there is an increase in adverse events at higher doses. Additionally, there were multiple secondary endpoints, including pain relief at 2 hours, sustained pain freedom at 24 and 48 hours and improvement in Patient Global Impression of Change (PGIC) that were also met, though these endpoints were not controlled for multiplicity and, in some cases, were confounded by the method of analysis. Patients randomized to lasmiditan for the first dose were less likely to take a second dose for a migraine that did not resolve (rescue), compared to placebo. In terms of second dose, the sponsor asserts that there is no benefit of a second dose when used as rescue, although they state there is a trend for the benefit of a second dose when used for recurrence. Based on the shortcomings of this analysis,

specifically the presence of selection bias and confounders, I think the efficacy data presented for a second dose are uninterpretable.

While cross-study comparisons are difficult to make (due to different study designs, patient populations and analysis methods), the overall benefit of lasmiditan (especially at higher doses) appears to be similar to other medications used to treat acute migraine (Ferrari, Goadsby, et al. 2002). The risk profile of this drug, compared to other acute migraine treatments, will need to be considered when determining if lasmiditan is appropriate for a given patient.

Based on my review of the pivotal studies presented above, from the perspective of therapeutic benefit, I recommend approval of a single dose (50 mg, 100 mg or 200 mg) of lasmiditan for the acute treatment of migraine with and without aura in adults.

8. Review of Safety

Please see the Review of Safety by Dr. Natalie Branagan.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee or external consultations were held.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The final label has been agreed upon.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

I do not recommend a REMS for lasmiditan.

12. Postmarketing Requirements (PMR) and Commitments

Pediatric PMRs and a pregnancy registry and database are required for NDA 211280.

1. Pediatric PMRs
    a) An open-label, pharmacokinetic (PK) and tolerability study of lasmiditan in pediatric migraine patients (≤ 40 kg).
    b) A randomized, double-blind, placebo-controlled, parallel-group study to assess the efficacy and safety of two doses of lasmiditan (high dose and low dose) versus placebo during a single migraine attack in pediatric patients, 6 to less than 18 years of age. This study must be designed to show superiority of lasmiditan over placebo.
    c) A long-term, open-label, safety study of lasmiditan in migraine patients, 6 to less than 18 years of age, for up to one year.
2. Pregnancy Registry
3. Pregnancy Database Study

13. Appendices

13.1. References

1. Dodick, D. Migraine. Seminar. Lancet 2018; 391:1315-1330.

2. Ferrari MD, Goadsby PJ, Roon KI and RB Lipton. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia. 2002; 22: 633-658.

3. Lipton R, Stewart W, Diamond S, Diamond M, and M Reed. Prevalence and Burden of Migraine in the United States: Data from the American Migraine Study II. Headache. 2001 Jul-Aug; 41(7):646-657.

4. Lipton R, Bigal M, Diamond M, Freitag F, Reed M, and W Stewart. Migraine Prevalence, Disease Burden, and the Need for Preventive Therapy. Neurology. 2007 Jan 30; 68(5):343-349.

5. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. Headache 2015; 55: 3–20.

6. Robbins, NM, Bernat JL. Minority Representation in Migraine Treatment Trials. Headache. 2017 Mar; 57 (3): 525-533.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 470		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: none Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in S Applicant of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant) *Contacted applicant and stated there were none.*
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Study 302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 477		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none Significant payments of other sorts: none Proprietary interest in the product tested held by investigator: none Significant equity interest held by investigator in S Applicant of covered study: none		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant) *Contacted applicant and stated there were none.*
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VIVECA B LIVEZEY
10/10/2019 10:26:13 AM

HEATHER D FITTER
10/10/2019 11:50:45 AM

Safety Team Leader Review

Date	October 10, 2019
From	Sally Usdin Yasuda
Subject	Safety Team Leader Review
NDA/BLA # Supplement#	NDA 211280
Applicant	Eli Lilly
Date of Submission	October 11, 2018
PDUFA Goal Date	October 11, 2019
Proprietary Name / Non-Proprietary Name	Reyvow/Lasmiditan
Dosage form(s) / Strength(s)	Tablet/50 mg, 100mg
Applicant Proposed Indication(s)/Population(s)	Acute treatment of migraine with or without aura in adults
Recommendation on Regulatory Action	There do not appear to be safety concerns that would preclude approval. If efficacy is demonstrated and the benefits of lasmiditan for acute treatment of migraine outweigh the risks, then I recommend that approval include appropriate labeling language addressing any adverse reactions of concern.
Recommended Indication(s)/Population(s) (if applicable)	

Benefit-Risk Integrated Assessment *(Risks only)*

Lasmiditan is proposed to be used for the acute treatment of migraines with or without aura in adults. This review evaluates the safety of lasmiditan. I believe that there are no safety concerns that prevent approval of lasmiditan from the clinical safety point of view. If efficacy is demonstrated and the benefits of lasmiditan outweigh the risks, then I recommend that approval be accompanied by labeling language including a medication guide to mitigate the risks.

This document reviews the risk profile of lasmiditan. Lasmiditan causes central nervous system effects including dizziness/balance disorder, somnolence/fatigue/sedation, and confusion/delirium/altered mental status/disorientation. Lasmiditan causes impaired ability to drive at 90 minutes after a single dose with lack of patient insight as to the impairment. The duration of the effect between 90 minutes and 8 hours is unknown. Lasmiditan is associated with palpitations and tachycardia. Lasmiditan also causes increases in blood pressure and decreases in pulse rate within one hour of dosing. Lasmiditan in combination with propranolol resulted in heart rate lowering greater than either drug alone. Lasmiditan is associated with hypersensitivity reactions including angioedema and with serotonin syndrome. I will provide an assessment of the risk and recommendations for labeling in an effort to mitigate the risk if efficacy is demonstrated and it is determined that the benefits outweigh the risk.

Risks:

CNS adverse events: Lasmiditan is associated with adverse reactions related to dizziness and balance disorder (up to 18%) and somnolence, fatigue and sedation (up to 11%) that occurred with frequency of more than 2% greater than placebo.

Driving Impairment: Dose-dependent impairment was seen in a simulated driving study 90 minutes after administration of lasmiditan. In a second driving study, the threshold for driving impairment was not reached at 8, 12, and 24 hours after lasmiditan administration. Subjects lacked insight into when they might be impaired to drive based on a Self-Perceived Safety to Drive question.

Abuse Potential: Treatment-emergent adverse events related to abuse potential in the Phase 3 oral placebo-controlled studies occurred in 28.5% of subjects who received lasmiditan compared to 7.6% of subjects who received placebo.

Pulse Rate Lowering: Propranolol in combination with lasmiditan 200 mg 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. Coadministering lasmiditan with other heart-rate lowering drugs may increase the risk of pulse rate lowering.

Hypersensitivity reactions in the Phase 3 oral placebo-controlled studies occurred in 0.2% of subjects who received lasmiditan compared to 0 subjects who received placebo.

Cardiovascular adverse events: Treatment emergent adverse events with potential cardiovascular etiology in the oral Phase 3 placebo-controlled studies occurred in 1.8% of subjects who received lasmiditan compared to 0.5% of subjects who received placebo. The most common events were palpitations and tachycardia. Lasmiditan also causes increases in blood pressure of approximately 2 to 3mm Hg within one hour of dosing after a single dose of lasmiditan compared to increases of approximately 1 mm Hg for placebo, with larger increases in patients over 65 years of age.

Potential for fetal harm: There is limited information on the effect of lasmiditan during pregnancy.
Appropriate labeling and a Medication Guide for patients may mitigate potentially serious outcomes of these adverse reactions.

Paragraph #5: Analysis and Recommendation with Respect to Safety:
If lasmiditan is approved, I recommend labeling that includes Warnings for driving impairment, for CNS effects including dizziness and somnolence and for serotonin syndrome. I recommend a Medication Guide to describe these risks and symptoms of concern. I recommend enhanced pharmacovigilance postmarketing with periodic evaluation of malignancy, hypersensitivity, and serotonin syndrome and for cardiovascular events. I suggest a consideration of whether driving impairment should be evaluated after a second dose of lasmiditan. I recommend a pregnancy registry and a pregnancy outcomes study as postmarketing requirements.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Please refer to Dr. Livezey's review of clinical efficacy.	
Current Treatment Options	Please refer to Dr. Livezey's review of clinical efficacy.	
Benefit	Please refer Dr. Livezey's review of clinical efficacy.	
Risk and Risk Management	Safety Database The safety database for lasmiditan includes all patients from the Phase 2 placebo-controlled trial and the two Phase 3 placebo-controlled trials allowing treatment of a single migraine attack, and the open-label extension study as well as several Phase 1 studies that including driving impairment studies and that contribute to laboratory and vital signs data.	The safety database fulfills minimum ICH guidance. Current treatment options for acute migraine attacks have a safety profile that includes severe liver damage with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The safety database includes 4,878 subjects exposed to at least one dose of lasmiditan, including 361 subjects treating at least 2 migraines per month or at least 6 months, and 180 subjects treated over 12 months at the proposed doses. Safety Concerns • There were no deaths in the database. • The most common 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%), somnolence, fatigue and sedation (up to 11%), asthenia, fatigue, malaise, and weakness (up to 8%), paresthesia and hypoesthesia (up to 8%), and nausea and vomiting (up to 4%). • Overall, the database does not suggest cardiovascular or vascular risk. There was no imbalance in SAEs and AEs leading to discontinuation between lasmiditan vs placebo in placebo-controlled trials. Treatment emergent adverse events with potential cardiovascular etiology occurred in 1.8% of lasmiditan-treated patients vs 0.5% of placebo-treated patients, with a higher percentage of lasmiditan-treated patients reporting palpitations or increased heart rate/tachycardia that each occurred in 0.4% in lasmiditan-treated patients vs 0.1% in placebo-treated patients in the Phase 2/3 controlled trials. In Phase 1 studies, increases in blood pressure, and decreases in pulse were observed within 1 hour of dosing. 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. The thorough QT study showed no significant QT prolongation at supratherapeutic doses and no clinically meaningful effect on mean	acetaminophen; stomach bleeding, heart attack and stroke with non-steroidal anti-inflammatory medications; ischemic reactions such as cerebral hemorrhage, myocardial, peripheral vascular, and gastrointestinal ischemia with ergots and triptans; injection site reaction and constipation with calcitonin gene-related peptide antagonists. There were no significant safety findings that would preclude approval of lasmiditan. Adequate labeling, including a medication guide, and pharmacovigilance, will address most safety issues with lasmiditan. There was an imbalance between lasmiditan and placebo in AEs related to central nervous system (CNS) effects including events related to dizziness and somnolence. A Warning in the labeling could help mitigate risks in patients who have these adverse reactions. Lasmiditan results in impaired driving ability after a single dose. The impact of a second dose has not been evaluated. A Warning may help mitigate the risk. Whether to require a postmarketing trial evaluating the risk from a second dose should be considered.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	PR or QRS intervals. • Hypersensitivity reactions (including rash and angioedema) occurred in 0.3% of subjects who received lasmiditan compared to 0.1% of 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-blinded, randomized, placebo-controlled simulated driving study, in which subjects given a single dose of lasmiditan had a SDLP difference from placebo of >4.4 centimeters, a difference previously identified to occur in subjects with a blood alcohol concentration of 0.05%. In a second randomized, placebo-controlled simulated driving study designed to assess the duration of effect of a single dose lasmiditan on SDLP, impairment was not observed at 8, 12, or 24 hours after the dose. Subjects lacked insight into when they might be impaired to drive based on a Self-Perceived Safety to Drive question. The effect of a second dose of lasmiditan on driving impairment has not been evaluated. • Treatment-emergent adverse events related to abuse potential in Phase 3 placebo-controlled trials occurred in 28.5% of subjects who received lasmiditan compared to 7.6% of subjects who received placebo. Refer to the Controlled Substance Staff review of the human abuse liability study. • Two patients met criteria for serotonin syndrome after exposure to lasmiditan. Other uncertainties • Potential for fetal harm: 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. • Cardiovascular risk in patients with ischemic heart disease has not been characterized.	Potentially serious hypersensitivity reactions including angioedema have been reported. Labeling could alert patients and physicians to this risk. A Warning in the labeling regarding serotonin syndrome may help alert patients to the symptoms and mitigate this risk. I recommend including information about the increases in blood pressure and decreases in pulse rate in the labeling. I recommend describing the interaction with propranolol in section 7 of the labeling. Because the risk of adverse outcomes in pregnancy has not been characterized, and because lasmiditan will be used in women of childbearing potential, I recommend a pregnancy registry and a pregnancy outcomes study as postmarketing requirements. Because the risk of malignancy has not been characterized, I recommend enhanced pharmacovigilance for malignancy. Lasmiditan is, according to the sponsor, 440-fold selective for the $5HT_{1F}$ vs $5HT_{1B}$ receptor that is thought to be responsible for vasoconstriction. The limited number of patients with ischemic heart disease did not

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		allow for evaluation of lasmiditan safety in that population. The population studied had a low number of subjects with ischemic heart disease. I recommend enhanced pharmacovigilance to further assess the safety of lasmiditan with respect to myocardial infarction and stroke.

1. Background

This memorandum summarizes the primary concerns from the safety review of the lasmiditan NDA 211280 conducted by Dr. Natalie Branagan and provides my conclusions and recommendations regarding the safety findings and management of the risks.

- *The product information and the applicant's proposals*

Lasmiditan, according to the Sponsor, is a selective 5-HT_{1F} agonist that targets 5-HT_{1F} receptors on neurons in the central and peripheral trigeminal system, decreasing release of neuropeptides (such as CGRP) and inhibiting pain pathways. The Sponsor states that lasmiditan does not cause vasoconstriction in coronary arteries and that lasmiditan has more than 440-fold selectivity for the 5-HT_{1F} receptor vs the 5-HT_{1B} receptor that is thought to be responsible for vasoconstriction.

The proposed indication for lasmiditan is acute treatment of migraine with or without aura in adults. The proposed doses are 50 mg, 100 mg, or 200 mg given orally. The Sponsor proposes that (b) (4) (b) (4) the maximum dose should not exceed 200 mg in 24 hours.

The Sponsor included as safety topics of interest adverse cardiovascular safety given that migraine is an independent risk factor for cardiovascular disease, and because the triptans mediate vasoconstriction by an effect on 5-HT_{1B} receptors. The sponsor also included hepatic safety, injuries or accidents secondary to neurologic adverse events, suicidal ideation and behavior and non-suicidal self-injurious behavior, and hypersensitivity as safety topics of interest.

Lasmiditan is not approved for any other indication in the United States or outside of the United States.

- *Therapeutic context*

Migraine, often disabling, is characterized by recurrent episodes of headache attacks accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia. Dr. Branagan notes that migraine affects 18% of women, 6% of men, and 10% of children in the U.S. The Sponsor states that migraine is most common between 25 and 55 years old. Dr. Branagan provides a list of the 4 classes of drug products already approved for acute treatment of migraine in the United States, as well as their major adverse events.

- *Regulatory background and marketing history*

Please refer to reviews by Dr. Viveca Livezey and Dr. Branagan.

2. Product Quality

Please refer to the CMC review.

3. Nonclinical Pharmacology/Toxicology

Please refer to the nonclinical reviews.

4. Clinical Pharmacology

Please refer to the Clinical Pharmacology review. The following information regarding pharmacokinetics and pharmacodynamics is from of the Clinical Overview provided by the applicant and reflects the findings most relevant to safety.

- Median tmax was 1.8 hours following oral administration.
- Mean elimination half-life is 5.7 hours.
- No accumulation of lasmiditan was observed with repeated once daily dosing.
- Lasmiditan is metabolized by non-cytochrome P450 enzymes; 87% of the dose is recovered in urine with unchanged lasmiditan accounting for less than 3% of the administered dose.
- The major circulating metabolites are considered pharmacologically inactive.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

Please refer to Dr. Viveca Livezey's review of efficacy.

7. Safety

8.1 Safety Review Approach

The safety of lasmiditan was evaluated based on 3 randomized, placebo-controlled, double-blind studies of orally administered lasmiditan in the acute treatment of migraine as well as an ongoing open-label multiple attack study as shown in the table below Dr. Branagan notes that the following safety pools were agreed upon with the FDA[1].

Safety cohorts

Cohorts	Description	Studies	Lasmiditan-treated Population
Phase 3 pool	Oral-placebo controlled Phase 3 studies Doses of 100 mg and 200 mg in Study 301; doses of 50 mg, 100 mg, and 200 mg in Study 302	301 (LAHJ), 302 (LAHK)	**3177**

[1] Dr. Branagan included safety information from the intravenous formulation in Study 201 where relevant.

Phase 2/3 pool	Oral placebo-controlled Phase 2 and 3 studies (excluding the 400 mg dose from study 202) Doses of 50 mg, 100 mg, 200 mg, 400 mg in Study 202	301, 302, 202 (LAHO)	3412
All Lasmiditan Pool	All lasmiditan-treated patients from oral Phase 2 and Phase 3 studies Doses of 100 mg and 200 mg in 305 (LAHL, open label long-term extension with intermittent use of lasmiditan as first and second dose)	301, 302, 305, 202	4081

As of the 120 Day Safety Update, there were an additional 52 subjects added to the safety population of study 305 as per protocol amendments. The total number in the all lasmiditan pool as of the 120 Day Safety Update is 4128 according to Dr. Branagan.

Dr. Branagan analyzed vital signs and laboratory values from the Phase 1 studies as those measures were obtained at the time of dosing with lasmiditan in Phase 1 studies; they were not collected on the day of dosing in the pivotal clinical studies. She has also reviewed phase 1 studies related to driving, risk for abuse, ECG changes, and safety in special populations including elderly and renally and hepatically impaired subjects. Dr. Branagan also includes information, where applicable from a study of intravenous lasmiditan (Study 201).

In study 202, patients treated a single migraine attack within 4 hours of onset over a period of up to 8 weeks and could use rescue medication at least 2 hours after taking study medication. Triptans and ergot derivates were not to be used within 24 hours.

In studies 301 and 302, during the treatment period of up to 8 weeks, patients were asked to treat their next migraine attack within 4 hours of onset. Patients had the option to take a second dose 2 to 24 hours after the initial dose if no other rescue medication had been used. For the 2nd dose, patients were randomized to either the same dose of lasmiditan or to placebo. Triptans, ergots, opiates, and barbiturates were not allowed for rescue or recurrence within 24 hours of study drug administration.

In study 305, patients were to use lasmiditan as the first treatment for each new migraine attack within 4 hours of onset, for all migraine attacks for up to 12 months. Patients could also receive a second dose of the same strength as the randomized dose between 2 and 24 hours for rescue or migraine recurrence. Triptans, ergots, opiates, and barbiturates were not allowed for rescue or recurrence within 24 hours of study drug administration.

8.2 Review of the Safety Database

Adequacy of the drug exposure experience (i.e., the safety database)
The exposure to lasmiditan at relevant doses, as provided for in the original submission, included 4,831 total, 3570 in controlled trials, 350 treating at least 2 migraines per month for at least 6 months, and 156 for 12 months, meeting ICH criteria (1500 total, 300-600 for 6 months, 100 for 1 year) for drugs intended for long-term intermittent use. In Study 305 a median of 6 migraine attacks were treated (range 1-71). Only 16% of the Phase 3 clinical trials population were male although as Dr. Branagan notes migraine affects females to males in a 3:1 ratio. The mean age in those trials was 42 years. Four percent were 65 years of age or

older. Approximately 18% of patients were Black or African American and approximately 78% were White. The United States accounted for 90% of subjects.

The Sponsor studied lasmiditan in a population of patients with cardiovascular risk factors (defined as age > 40 years, elevated total cholesterol, low HDL cholesterol, elevated systolic blood pressure or baseline hypertension, diabetes mellitus, and current smoker status) and with cardiovascular disease. Dr. Branagan notes that in studies 301 and 302, 79% of patients had 1 cardiovascular risk factor, 41% had at least 2, and 15% had at least 3 cardiovascular risk factors, similar to the prevalence of cardiovascular risk factors as in the general US population with episodic migraine. She also notes the prevalence of cardiovascular disease overall was 20%, with the prevalence of hypertension of 17% in the population with other cardiovascular disease less than 2%. Only 1% had ischemic heart disease, and as Dr. Brangan notes, this limits the ability to interpret the safety of lasmiditan in patients with ischemic heart disease.

8.3 Adequacy of Applicant's Clinical Safety Assessments

Dr. Branagan notes that for studies 301 and 302 an event within 48 hours, of the first dose (which is beyond 5 half-lives) was included as a TEAE. Adverse events were recorded up to 7 days after the first dose. Dr. Branagan finds the coding of adverse events to be adequate. She notes that the vital signs obtained in studies 202, 301, 302 and 305 did not occur at the time the study drug was taken and do not reflect the effects of the drug on blood pressure and heart rate. In 301 and 302 for example, vital signs and laboratory values were obtained within 7 days of treatment. *I agree with Dr. Branagan that vital signs and laboratory values from Phase 1 studies are more likely to reflect changes due to study drug.*

8.4 Safety Results

There were no deaths in the lasmiditan safety database. Overall, in controlled trials there is no imbalance in serious adverse events (SAEs) and only 1 discontinuation due to adverse events (AEs). Treatment emergent adverse events (TEAEs) were more frequent in patients receiving lasmiditan compared to placebo, with evidence of a dose response in TEAEs.

In this section I first provide a general overview of the safety results regarding SAEs, discontinuations, and TEAEs. Next, I summarize laboratory values, and vital signs and electrocardiograms. Then I discuss Submission Specific Safety Issues incorporating information from SAEs, Discontinuations, TEAEs, and labs, as appropriate. That is followed by a summary of specific populations, pharmacodynamic drug interactions, and additional safety explorations. I finish with recommendations for labeling and for postmarketing evaluation.

Deaths

Dr. Branagan notes that no deaths occurred in patients taking the study drug in Phase 1, 2, or 3 trials.

SAEs and Discontinuations and TEAEs overall

Overall, SAES were few. In the controlled trials there was no imbalance overall in SAEs between lasmiditan and placebo, although the frequency of SAEs was greater with the 200 mg

lasmiditan dose. In the controlled trials each SAE occurred in only 1 patient and it is difficult to draw conclusions regarding the relatedness to lasmiditan. Discontinuations due to adverse events in the controlled trials occurred only in 1 patient in the lasmiditan-treated group. As Dr. Branagan notes, this is likely due to study design as subjects could take a minimum of 1 dose. Discontinuations due to adverse events in Study 305 occurred in 14% of patients, with evidence of a dose response. In the Phase 3 controlled trials, TEAEs occurred more frequently in lasmiditan treated groups than in placebo in general, and with evidence of a dose response. TEAEs occurred more frequently in Study 305 than in the controlled trials, and in Study 305 there was evidence of a dose response. Those results are shown in the table below.

Patients with SAEs, Discontinuations Due to Adverse Events, or TEAEs in Phase 3 Migraine Trials

	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)
TEAEs	176 (13.9)	167 (25.5)	459 (36.3)	513 (40.8)
	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)
TEAEs			447 (45.1)	542 (52.2)

[a] Withdrawal from treatment because of AEs
[b] Reflects the results as of the 120 Day Safety Update
Reflects the number of patients with at least 1 SAE or TEAE

Serious adverse events (SAEs)
As Dr. Branagan shows, SAEs were not frequent. In the controlled Phase 3 trials there was no imbalance overall between lasmiditan and placebo, although the frequency of SAEs was greater with the 200 mg lasmiditan dose as shown in the table above. In the combined Phase 2/3 controlled trials (with 3412 patients for all lasmiditan doses) 1 additional patient had an SAE in the 200 mg dose group. However, each SAE occurred in just 1 patient and it is difficult to conclude a dose-response relationship for SAEs. Only the Nervous system disorders SOC had more than 1 SAE, these were dizziness and presyncope that both occurred in the 200 mg dose in 2 different patients; these did not occur in the placebo group. In study 305 SAEs occurred in 3% of patients with no imbalance between doses. Dr. Branagan shows that the most frequent SAEs in Study 305 occurred in the SOCs of Infections and infestations (0.8%), Gastrointestinal disorders (0.4%), and

Injury, poisoning, and procedural complications (0.4%). In study 305, the only SAE in the Nervous system disorders SOC that occurred in at least 2 patients was seizure that occurred in 1 patient in each treatment group (0.1%).

Dr. Branagan has summarized 5 selected treatment emergent SAEs in the Phase 2/3 controlled studies as well as events that she considered to be potential cardiovascular SAEs in the database.

Dr. Branagan considers that lasmiditan may have played a role in the following events:

Dizziness (b) (6) in a 46-year-old female with no prior history of bradycardia, 30 minutes after taking lasmiditan 200 mg, bradycardia of 40 beats per minute (32 beats per minute lower than her baseline screening heart rate) was noted on hospitalization with an ECG showing sinus bradycardia. The following day, ECG showed sinus bradycardia at 52 beats per minute. *Given the onset after dosing, a role for lasmiditan cannot be ruled out. I agree with Dr. Branagan that given the elimination half-life of 5.7 hours, it is possible that lasmiditan could have contributed to the bradycardia still observed the following day.*

Hypertension (b) (6) in a 43 y.o. patient with a history of hypertension treated with nifedipine and reportedly compliant with taking nifedipine. The patient presented to the emergency room for a headache that reoccurred 12 hours after taking lasmiditan. She was hospitalized for 3 days reportedly for uncontrolled hypertension although blood pressure measurements were reportedly not available. She reportedly was treated with an increased dose of nifedipine and hospitalized until her blood pressure was stable. *The absence of blood pressure readings makes this event difficult to interpret. Assuming that uncontrolled hypertension occurred, the onset was within 5 half-lives of lasmiditan administration, although the event continued beyond five half-lives after administration. In addition, as Dr. Branagan notes, pain may have contributed to the blood pressure elevation.*

Hypotension/Dystonic Reaction (b) (6) in a 67 y.o. female was reported as hospitalization for orthostatic hypotension and dystonic jerky reaction that occurred 20 minutes after taking lasmiditan. The patient was reportedly stabilized after treatment with lorazepam and procyclidine. There was no information about blood pressure during the hospitalization. On page 15 of the summary of clinical safety the Sponsor states at the time of database lock, as per the clinical database, the SAE of hypotension was still reported as hypotension; however, in the safety database, the investigator updated the event term to the SAE of dystonia ("dystonic reaction "). According to the narrative in the ISS (page 141), the event of hypotension reportedly lasted 3 days and was treated with ibuprofen and omeprazole; it is not clear what the role of those drugs would be. Dr. Branagan notes that the patient experienced myoclonic twitching while hospitalized and an MRI showed "tiny focal hypersensitivities in the deep white matter". The exit interview from the study was notable for a positive Romberg test. *The absence of blood pressure readings makes this event difficult to interpret. Assuming that orthostatic hypotension occurred, the onset was shortly after administration of lasmiditan, but the duration exceeded 5 half-lives after lasmiditan administration. Whether a positive Romberg test was observed prior to this event is not reported. The relationship between lasmiditan and any of these findings is unknown.*

Presyncope (b) (6) was reported in a 53 year old female "immediately" after taking a 200 mg dose of lasmiditan. Symptoms included lightheadedness, syncopal feeling, sweaty palms, general weakness, dry mouth, slowed speech, impaired concentration and tiredness.

All symptoms except fatigue resolved after 8 hours with no treatment. She remained hospitalized for persistent fatigue for 1 day. *Blood pressure readings were not provided related to this adverse event. Although these symptoms occurred shortly after taking lasmiditan, it is not possible to determine whether they might be drug related or related to the migraine.*

I agree with Dr. Branagan that the following events in the controlled studies or Study 305, some of which have a potential cardiovascular etiology, are not likely related to lasmiditan in most cases because of the delay between the last dose of lasmiditan and the event, and in some cases likely related to a pre-existing condition:
Pituitary tumor (b) (6) was reported within 6 weeks after enrollment and after 2 doses of lasmiditan.
Atrial fibrillation/angina pectoris (b) (6) occurring 5 months after most recent dose of lasmiditan in a patient with risk factors including pre-existing mitral valve stenosis and hypertension
Bradycardia/sinus node dysfunction (b) (6) 12 hours after the last dose of lasmiditan requiring pacemaker implantation in a patient with bradycardia at screening visit and taking guanfacine that Dr. Branagan notes has been associated with worsening sinus node dysfunction.
Stress cardiomyopathy (b) (6) 9 days after most recent dose in a patient with risk factors (female, history of anxiety) and also taking verapamil that Dr. Branagan notes has been associated with left ventricular dysfunction.
Non-cardiac chest pain/Hypertension/Acute Kidney Injury/Sepsis/Syncope (b) (6) (b) (6) 15 days after the most recent dose of lasmiditan and 4 days after experiencing flu-like symptoms in a patient with uncontrolled hypertension at baseline, baseline renal insufficiency, and evidence of a urinary tract infection at the time of the event.
Noncardiac chest pain/Hypertension (b) (6), with blood pressure not reported, 19 days after the most recent dose of lasmiditan in a patient with a history of hypertension and anxiety.
Ischemic stroke (b) (6) that occurred 5 months after the last dose of lasmiditan in a patient with a past medical history of ischemic stroke, hypertension, diabetes mellitus, hyperlipidemia.
Transient Ischemic Attack (b) (6) 19 days after the last dose of lasmiditan in a patient with a history of hypertension, obesity, former tobacco use, and headache.
Hypertension (b) (6), blood pressure reading not reported, 32 days after the last dose of lasmiditan in a patient with a history of hypertension.
Fall (b) (6) resulting in hip fracture, with hospitalization for hip fracture 4 days after the last dose of lasmiditan in a patient with a past medical history of hypotension. The day of the fall was not reported.
Atrial flutter (b) (6) in a 51 year old patient with pre-existing hypertension who developed atrial fibrillation at the 4th study visit (Day 182; 73 days after most recent dose of lasmiditan) and was hospitalized for atrial fibrillation with atrial flutter on Day 366 (most recent dose on Day 358) after the most recent of 4 migraines treated with lasmiditan. I agree that lasmiditan was unlikely the cause of atrial fibrillation that began 73 days after a dose of lasmiditan.
Possible seizure (diagnosed as pseudoseizure) followed 4 days later by lethargy (b) (6) in a 34 y.o. female with history of obesity and tension headaches. The event occurred in Study 305, 41 days after the most recent dose of lasmiditan.
Seizure (b) (6) in a 50 y.o. man with history of cerebral palsy, depression, and anxiety. The event occurred in Study 305, 99 days after the last dose of lasmiditan.

Pulmonary embolism [redacted] (b) (6) in a 31 y.o. female with a past medical history of antithrombin III deficiency, history of recurrent pulmonary embolism, deep vein thrombosis, tobacco use, depression, anxiety, reflux who developed pulmonary embolism 9 days after the first dose of lasmiditan in study 305 and 5 days after her most recent dose. *I agree with Dr. Branagan that although a role for lasmiditan cannot be ruled out, the patient has contributing factors and a prior history of the event.*

Altered mental status [redacted] (b) (6) in a 46 y.o. female with history of alcohol use, hospitalized due to alcohol intoxication and mental status change, with alcohol withdrawal, hyperglycemia, and withdrawal syndrome from gamma hydroxybutyrate on the same day, 38 days after the most recent dose of lasmiditan.

Subdural hematoma [redacted] (b) (6) in a 77 y.o. female with history of hypertension hypothyroidism, chronic kidney disease, diabetes mellitus, depression, anxiety, and peripheral neuropathy with subdual hematoma after hitting her head after she slipped and fell; 4.5 months after most recent dose of lasmiditan.

Dr. Branagan notes a cerebellar haematoma [redacted] (b) (6) in a 34 year old healthy male volunteer 16 days after the last dose of lasmiditan. The patient had a history of intolerance to ciprofloxacin (muscle aches) and was a current alcohol drinker ("3 units" weekly) and former smoker. Eight days after the last dose of lasmiditan, the subject received alprazolam; the headache began 23 hours later. The headache was treated with 3 prn doses of ibuprofen over the next 7 days. He presented to the emergency room 16 days after the last dose of lasmiditan with increased headache and vomiting and was treated with a triptan and metoclopramide and was admitted to the hospital after MRI revealed hematoma in the right cerebellum with compression of the 4th ventricle. No source of bleeding was found. I note that ciprofloxacin has a warning for increased rate of aortic aneurysm and dissection within 2 months following use of fluoroquinolones; the timing of exposure to ciprofloxacin was not clearly documented. The event was reportedly not due to a fall or other accident. There do not appear to be precipitating factors but *given the time course of events it seems unlikely to be related to lasmiditan.*

Dr. Branagan also notes the following SAEs in Study 305:

Acute Kidney Injury [redacted] (b) (6) in a 56 y.o. female with a history of diabetes mellitus, hypertension, reflux disease, hypothyroidism, hypokalemia, hypomagnesemia, and elevated creatinine (1.3 mg/dL at baseline in Study 302), hospitalized for acute renal failure (creatinine 3.0, units not reported), metabolic acidosis and dehydration, 17 days after the most recent dose of lasmiditan. She as treated with intravenous fluids and four days later creatinine had decreased to 1.2 (units not provided). The event occurred 2 months after surgery for multinodular goiter with nausea, vomiting, and dehydration that had been ongoing since her surgery according to the narrative. Concomitant medications included hydrochlorothiazide, omeprazole, magnesium, and potassium. Although it is possible that this event could be related to drug-related insult 17 days prior, given, as Dr. Branagan notes, that this patient had risk factors for acute kidney injury and creatinine seemed to have resolved with intravenous fluids, *this may be more likely due to dehydration.*

Dr. Branagan identified 2 SAEs of intestinal obstruction and 2 SAEs of diverticulitis in Study 305. *Individually or in total these events do not appear to be strongly associated with lasmiditan given the time course and predisposing factors.*

Intestinal obstruction [redacted] (b) (6) and bilateral nonobstructing kidney stones in a 54 y.o. female with past history of oophorectomy, cholecystectomy, urinary bladder suspension,

esophagogastric fundoplasty, hospitalized for intestinal obstruction 7 days after the most recent dose of lasmiditan 200 mg and 17 days after the initial dose. *I agree with Dr. Branagan that a role for lasmiditan cannot be ruled out, although the patient has a risk factor of previous history of abdominal surgery.*

Small intestinal obstruction (b) (6) in a 45 y.o. female with a history of hysterectomy, hospitalized for small intestinal obstruction 2 months after her most recent dose of lasmiditan, and after having treated 7 prior attacks. Abdominal pain resolved after laparoscopic abdominal lysis of adhesions. *I agree that given the time course and her history of abdominal surgery, a role for lasmiditan is unlikely.*

Diverticulitis (b) (6) in a 43 y.o. female with a history of tubal ligation who had a diagnosis of diverticulosis 3 weeks after her first dose of lasmiditan. The most recent dose of lasmiditan was 41 days prior to being hospitalized for diverticulitis. *I agree that given the time course and the predisposing factor of diverticulosis, a role for lasmiditan in diverticulitis is unlikely.*

Diverticulitis (b) (6) in a 57 y.o. female with a history of dyspepsia who had taken 71 doses of lasmiditan in study 305, with the last known recorded dose 16 days prior to the event. Concomitant medications included celecoxib. I note that NSAIDs are associated with an increased risk of diverticulitis. *Although a role for lasmiditan cannot be ruled out, the time course of the event and concomitant medications are confounding factors.*

Discontinuations

Dr. Branagan shows that only 1 lasmiditan-treated patient in the controlled studies discontinued because of adverse events; the discontinuation was due to dizziness and fatigue. Approximately 13% of patients discontinued from Study 305 because of adverse events. The most frequent AEs resulting in discontinuation in Study 305 and with greater frequency in 200 mg vs 100 mg were dizziness and light-headedness; asthenia, fatigue, malaise, and weakness; paresthesia and hypoaesthesia; and nausea and vomiting that occurred in 2% to 4% of patients treated with 200 mg lasmiditan and approximately twice as much as in 100 mg lasmiditan.

Significant Adverse Events

Dr. Branagan notes approximately 35% of AEs were mild across controlled studies and in Study 305. She notes that in Study 202, 22-36% of AEs were severe in a dose-related fashion vs 18% for placebo. I note that similar findings were reported for Studies 301/302 (21% for lasmiditan vs 9% for placebo).

For lasmiditan, the preferred terms with the highest frequency in the Phase 3 controlled studies were dizziness, light headedness (1.4% in 200 mg with a dose-response), asthenia, fatigue, and malaise (approximately 0.5%) , nausea, vomiting (up to 0.5%), confusion, delirium, altered mental status, disorientation (up to 0.6%), somnolence, sedation (up to 0.4%), and balance disorder (up to 0.3%).

Treatment Emergent Adverse Events (TEAEs) and Adverse Reactions

Dr. Branagan used the ODE I strategy to evaluate TEAEs. The most commonly reported TEAEs across all trials were *dizziness/balance disorder/light-headedness*. In the controlled Studies 301 and 302 dizziness/balance disorder occurred in up to 18 % of patients with evidence of a dose response, vs 3% for placebo after a single dose. Similarly, the frequency of dizziness/light-headedness in Study 305 was 16% for the 100 mg dose and 21% for the 200

mg dose. In Study 202, the frequency of dizziness/balance disorder was 24% for the 50 mg dose, 28% for the 100 mg dose, and 44% for the 200 mg dose vs 1% for placebo, after a single dose. *Somnolence, fatigue and sedation* occurred with evidence of a dose response in up to 11% of patients in Studies 301/302, up to 31% in Study 202, and up to 15% of patients in Study 305.

The adverse events reported in at least 2% in any lasmiditan-treatment group and at least 2% greater than placebo in studies 301/302 are shown in the table below, extracted from Dr. Branagan' s review:

TEAEs after First Dose with an Incidence of At Least 2% and At Least 2% Greater than Placebo in Studies 301 and 302, Grouped.*

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%
Somnolence, 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%

Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 301 and 302, TRTEM1FL=Y. The denominator is the safety population for studies 301 and 302 (IDB ADSL dataset with ASETBFL=Y, TRT01A=Y). *The ODE-1 groupings were adjusted for preferred terms that primarily contributed to the groupings.

The ODE I query for confusion, delirium, altered mental status, and disorientation also includes somnolence and lethargy (although not included in the name of the grouping) and is driven by somnolence and lethargy. Please refer to Dr. Branagan's review for additional details about grouping of combined terms.

In Study 305, TEAEs after the first dose were similar in nature and frequency to those in 301 and 302. Those results are shown in the table below, as extracted from Dr. Branagan's review.

Table 1. TEAEs after First Dose of Lasmiditan with an Incidence of At Least 2% in Study 305, grouped.*

MedDRA AEs (preferred term), grouped	**100 mg N=963**	**200 mg N=1015**	**All N=1978**
Dizziness, light-headedness	16%	21%	19%

Somnolence, fatigue, sedation	12%	15%	14%
Confusion, delirium, altered mental status, disorientation, hallucinations	10%	12%	11%
Asthenia, fatigue, malaise, weakness	7%	10%	9%
Paresthesia, hypoesthesia	6%	8%	7%
Nausea, vomiting	5%	6%	6%
Infection, all	4%	4%	4%
Vertigo; vestibular dysfunction	1%	3%	2%
URI, cold, rhinitis, flu-like illness	2%	2%	2%

Reviewer created table from ISS IDB dataset ADAE (numerator) where STUDYID = 305, TRTEM4FL=Y. The denominator is the safety population for study 305 (IDB ADSL dataset with LAHLFL=Y, HLSAFFL=Y, TROL01A=Y). *The ODE-1 groupings were adjusted for preferred terms that primarily contributed to the groupings.

As noted by Dr. Branagan, somnolence and sedation from Study 305 (excluding fatigue from the grouping) occurred in 8%, 10%, and 9% of the lasmiditan 100 mg, 200 mg, and all-lasmiditan groups, respectively.

Dr. Branagan compared the mean number of TEAEs reported by patients after one dose of lasmiditan with the number reported after 2 doses of the same strength. She finds lower numbers of TEAEs and lower mean numbers of TEAEs in patients who took a second dose. *I agree with her that this could be a result of subjects experiencing a TEAE after one dose being less likely to take additional doses.*

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 Phase 2/3 studies. However, as previously noted, laboratory values were to have been drawn at baseline/screening and within 7 days after a dose in studies 301 and 302 and at months 1, 3, 6, 9, and end of study in 305, making it difficult to characterize any changes as being due to study drug. The laboratory evaluation primarily relies on results from Phase 1 studies. *I agree that there were no clinically meaningful changes to mean values for chemistry or hematology measurements after dosing with lasmiditan. One patient had an elevation of transaminases to >5X ULN; the case did not appear to be confounded, although there was insufficient information to rule out non-drug related causes.*

Dr. Branagan evaluated *hepatic related laboratory values and events*. The Sponsor identified Hepatic Safety as a Safety Topic of Interest, "selected based on standard drug registration topics"[2]. Dr. Branagan found no clinically meaningful differences for maximum post-dose values compared to baseline values for lasmiditan or placebo treated subjects for AST, ALT, Alk Phos or total bilirubin in the Phase 2/3 trials. She finds shifts of ALT or AST of 3X, 5X, or 10X ULN in 0.3% of patients or fewer (1 patient each in lasmiditan and placebo with ALT or AST > 10X ULN) and no excess in lasmiditan vs placebo in the controlled trials. Those

[2] Integrated summary of safety p. 532

shifts similarly occurred in fewer than 1% of patients when including results from Study 305, with 0.7% having ALT at least 3X ULN and 0.3% or fewer with other shifts. She finds only 1 patient with bilirubin greater than 2X ULN in the Phase 2/3 studies and no patients with values that met Hy's Law criteria (elevation of AST or ALT 3X or higher than ULN and total bilirubin greater than 2 X ULN without an elevation in alkaline phosphatase. Dr. Branagan found no SMQ terms related to hepatic safety with a frequency greater than 0.5% greater than placebo. Dr. Branagan reviewed the narratives of subjects with hepatic injury or abnormal hepatic enzymes and found confounding factors in most narratives including previous history of liver or gallbladder disease, baseline liver enzyme elevation, and concomitant medication use associated with hepatic injury. She identified subject (b) (6), a 46 y.o. female with normal liver laboratory values at baseline, and who took 9 doses of lasmiditan 200 mg through studies 302 and 305. Three weeks prior to the fourth study visit (and 2 days after the most recent dose) she developed tiredness that resolved in 2 weeks, followed by an increase in ALT to 53 U/L (approximately 1.3X ULN). After 2 additional doses over the next approximately 3 months, her ALT and AST continued to increase to approximately 6.3 and 3.6X ULN, respectively, with increased eosinophils approximately 3 months after the last dose. At the last study visit, ALT and AST were resolving. She had no report of symptoms including fever or rash. She had no previous history of liver disease, and no concomitant medications other than minoxidil which Dr. Branagan notes uncommonly is associated with transaminase elevations. She did not have viral hepatitis serologies performed at the time of the abnormal hepatic laboratory results. *Although the role of lasmiditan cannot be ruled out, there is insufficient information to determine the cause of the event.* Dr. Branagan also identified **Subject** (b) (6) (b) (6) with elevations in ALT (4.6 X ULN) and AST (3.1 X ULN) that began 5 days after a dose of alprazolam (rarely associated with aminotransferase elevations according to https://livertox.nlm.nih.gov/Alprazolam.htm), and 11, 14, and 17 days after the doses of lasmiditan, and were resolving 7 days later in an abuse liability study in recreational drug users. The subject was a recreational drug user who reported occasional use of cocaine (well known cause of acute liver injury when taken in overdose, according to livertox) and urine drug screen positive for benzodiazepine and marijuana metabolites at a follow-up visit. I agree with Dr. Branagan that a role for lasmiditan in this case cannot be established. *I agree with Dr. Branagan that a signal for hepatic injury is not identified in this database.*

Dr. Branagan shows the laboratory results from Phase 1 study LAHE in which nonelderly healthy volunteers were given lasmiditan 200 mg or 400 mg daily for 7 days, with lab values at baseline, Day 2 and Day 6 for each dose cohort (n=14-28) vs placebo (n=11-15). *I agree that there were no clinically meaningful changes to mean values for chemistry or hematology measurements after dosing with lasmiditan.* Dr. Branagan also notes that laboratory results on Days 1 and 2 from Phase 1 study LAHQ in nonelderly healthy volunteers given lasmiditan 50 mg, 100mg, and 200 mg and on Day 2 from Phase 1 Study LAHP (thorough QT study) in 56 nonelderly healthy volunteers given single oral doses of lasmiditan 100 mg and 400 mg did not show clinically significant changes from baseline values.

Vital Signs

Please refer to Dr. Branagan's review for details regarding vital signs findings. The findings are summarized below. As previously noted, measurements were not obtained at the time of lasmiditan dosing in the Phase 2/3 studies. The vital signs results rely on Phase 1 studies. *I*

agree with Dr. Branagan that lasmiditan appears to be associated with small increases in systolic and diastolic blood pressure and decreases in heart rate when compared with placebo. There do not appear to be important orthostatic changes in vital signs.

Study LAHE had vital sign measurements hourly for 8 hours and again at 12 hours after a single dose on Day 1. Dr. Branagan notes mean increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) that occurred at 1 hour but without evidence of dose response. The maximum mean change from baseline in systolic blood pressure 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 diastolic blood pressure 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 pulse of approximately 10 beats per minute for both doses of lasmiditan with maximum decreases at 2 to 3 hours after the dose (compared to a mean decrease of approximately 5-6 bpm for placebo). She reports similar findings with a similar time course in Study LAHU, a 24-hour ambulatory blood pressure monitoring study) and in Study LAIF, a study on simulated driving performance. Outlier analysis of bradycardia (pulse rate < 60 bpm) showed a higher percentage of subjects taking lasmiditan with bradycardia (79% for 200 mg lasmiditan, 93% for 400 mg lasmiditan) compared to placebo (67%) in Study LAHE, with evidence of a dose response. However, Dr. Branagan notes that more than 30% of subjects in the placebo and lasmiditan arms (60% in the lasmiditan 400 mg group) had heart rate of < 60 bpm at baseline, possibly due to the fact that the population studied was made up of healthy volunteers. This makes the evaluation of bradycardia difficult to interpret.

The applicant evaluated orthostatic blood pressure and pulse measurements after subjects had been laying down for 5 minutes and after they had been standing for 2 minutes in non-elderly healthy volunteer studies. Dr. Branagan considered evidence of orthostatic changes to be a decrease in SBP of greater than 20 mm Hg, a decrease in DPB of greater than 10 mm Hg, or an increase in pulse rate of greater than 20 bpm. She shows results for Study LAHE. Dr. Branagan does not show mean orthostatic changes in SBP or pulse. *I agree that the results are not suggestive of orthostatic changes.* She does not find evidence of orthostasis from other Phase 1 studies. Dr. Branagan provides outlier analysis of orthostatic changes in Study LAHE and finds outliers only in pulse rate greater than 20 bpm at 0.5 hours for the 400 mg dose (33%) vs lasmiditan 200 mg (25%) or placebo (25.9%). I agree that given the small number of subjects in the 400 mg arm (n=15), the significance of this finding is unclear

The applicant evaluated vital signs in 18 elderly (at least 65 y.o.) and 17 non-elderly (45 years of age or younger) healthy subjects in Study LAHA after a single 200 mg dose of lasmiditan. Dr. Branagan notes mean increases in SBP that were greater in elderly than nonelderly, as well as an increase in DBP and decrease in pulse rate in elderly slightly less than in non-elderly as shown in the table below, extracted from Dr. Branagan's review. Overall, differences from placebo had resolved by 3 to 6 hours after the dose.

Maximum Mean Vital Signs Change from Baseline in Study LAHA.

Time*	Parameter	Elderly Placebo N=18	Non-Elderly Lasmiditan 200 mg N=17	Elderly Lasmiditan 200 mg N=18
Systolic Blood pressure (mmHg)				
1 hour	Mean	-0.9	4.3	11.5
1.5 hour	Mean	2.4	1.8	14.5
Diastolic Blood Pressure (mmHg)				
1 hour	Mean	-1.7	5.4	3.8
Pulse (beats per minute)				
1.5 hour	Mean	-5.0	-8.0	-5.7

Data is taken from the 28/05/2019 response to an information requested dated 22/05/2019. Vitals were taken in the supine position. *Predose timepoints reflect actual SBP, DBP, and pulse rate measurements. Other timepoints reflect the change from predose values.

In Study LAIG ambulatory blood pressure was evaluated to confirm the results of LAHA in elderly with doses of 100 or 200 mg. Dr. Branagan notes changes in SBP and pulse rate that are consistent but smaller than those observed in LAHA with the largest mean increase from baseline for lasmiditan 200 mg was 7 mm Hg at 1 hr compared to the increase on placebo of 4 mm Hg at the same timepoint. The mean increase in diastolic blood pressure was approximately 3 mm Hg at 1 hours for either lasmiditan 200 mg or placebo. The maximum change in pulse rate was a decrease of approximately 6 bpm at 2 hours for lasmiditan 200 mg compared to placebo with a mean decrease of less than 1 bpm at the same timepoint. Dr. Branagan shows that elderly patients were more likely to have outlier values of SBP of > 140 mm Hg and > 160 mm Hg than non-elderly in whom these values were not observed. Dr. Branagan did not find mean orthostatic vital sign changes in elderly subjects. She did find outliers in orthostatic pulse Study LAHA in up to 17% of elderly patients at 0.5 and 2 hours (as well as at 24 hours) that were greater than observed in placebo.

Dr. Branagan also notes that decreases in heart rate were also observed in the through QT study in healthy volunteers, consistent with the changes observed in the Phase 1 studies described above.

Dr. Branagan notes that evaluations of temperature, body weight, respiratory rate, when collected in Phase 1 studies, did not contribute meaningfully to the assessment of safety.

Electrocardiograms (ECGs) and QT

Similar to other measurements, ECGs were not obtained at the time of lasmiditan administration in studies 202, 301, 302, or 305. I agree with Dr. Branagan that ECG results from those studies do not contribute meaningfully to characterizing the safety of lasmiditan. *ECG data from Phase 1 studies and from the thorough QT study do not show a clinically meaningful effect on mean PR or QRS intervals and the thorough QT study did not show significant QT prolongation.*

Dr. Branagan summarizes the conclusion of the QT-IRT regarding the results of the thorough QT study (LAHP). The largest upper bounds of the 2-sided 90% CI for the mean difference between lasmiditan (100 mg and 400 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines, in a study that demonstrated sensitivity with moxifloxacin. She notes the finding of "*no significant QTc prolongation effect of lasmiditan (100 mg and 400 mg) was detected in this TQT study*." She also notes that at the time of the review, the consult noted that that it was not known whether the concentrations covered in the study represented the expected highest clinical exposure scenario given that other factors such as food effect, renal/hepatic impairment or drug-drug interactions had yet to be reported. Dr. Branagan notes that a subsequent clinical pharmacology review has suggested that these factors do not contribute to exposure. The IRT also evaluated effects on other ECG parameters and reported that the largest upper limits of 90% CI for the PR mean differences between lasmiditan 100 mg and placebo, and between lasmiditan 400 mg and placebo were 2.0 ms and 5.2 ms, respectively, with similarly small changes in QRS where they reported that the largest upper limits of 90% CI for the QRS mean differences between lasmiditan 100 mg and placebo, and between lasmiditan 400 mg and placebo were 0.7 ms and 1.1 ms, respectively. *I agree with Dr. Branagan that lasmiditan did not have a clinically meaningful effect on mean PR or QRS intervals.*

Immunogenicity

Not applicable.

Submission Specific Safety Issues and Specific Safety Studies

Dr. Branagan considers the following in her review:

- Cardiovascular Risk
- Driving Impairment
- Suicidality and Depression
- Serotonin Syndrome
- Hypersensitivity
- Injuries, Accidents, and Impaired Mental Ability Caused by CNS Effects

Cardiovascular Risk

The Sponsor states that lasmiditan is a selective 5-HT_{1F} receptor agonist, and that "data from nonclinical studies indicate that, unlike sumatriptan, lasmiditan does not cause vasoconstriction in coronary arteries". The Sponsor notes that cardiovascular safety of lasmiditan was of interest given that migraine is an independent risk factor for cardiovascular disease. To address this, the Sponsor included patients with cardiovascular risk or disease in the clinical trial program. However, as I previously noted, Dr. Branagan reported that only 1% of patients in Studies 301/302 had ischemic heart disease, and I agree that this limits the interpretability of safety in patients with ischemic heart disease. Overall, vital signs from clinical pharmacology studies showed evidence of increases in systolic and diastolic blood pressure (maximum mean increase of 7.1 mm Hg and 4.3 mm Hg, respectively) within 1 hour of lasmiditan dosing along with decreases in pulse rate (maximum mean decrease of 10.1 beats

per minute). The most commonly reported cardiovascular TEAEs in the controlled studies were palpitations and heart rate increased/tachycardia, both occurring in 0.4% for lasmiditan vs 0.1% for placebo. The current database does not suggest an increased cardiovascular risk with lasmiditan.

The following section considers cardiovascular risk from the combined available findings.

As previously noted, there were no deaths in the database. Dr. Branagan notes that only 1 patient discontinued due to an AE in the controlled trials (b) (6), dizziness and fatigue; no information on vital signs at the time of the event). Dr. Branagan notes that as of the 120-day safety update, discontinuations in Study 305 due to a cardiovascular event occurred in 0.8% of lasmiditan patients (16/2030; 0.5% in the 100 mg group and 1.1% in the 200 mg group) due to a cardiovascular adverse event (compared to approximately 13% of lasmiditan patients (260/2030) discontinuing due to any adverse event.

AEs with a potential cardiovascular etiology were evaluated by the Sponsor using the following terms: abdominal pain (upper and lower) and terms in the SMQs of cardiac arrhythmias, cardiac failure, cardiomyopathy, CNS vascular disorders, embolic and thrombotic events, hypertension, ischemic heart disease, pulmonary hypertension, and torsade de pointe/QT prolongation.

Dr. Brangan shows that up to approximately 2% of patients treated with lasmiditan in Studies 202/301/302 combined had at least 1 TEAE with a potential cardiovascular etiology compared to approximately 0.6% of placebo patients. She reports similar findings for Study 305. The most commonly reported cardiovascular TEAEs in the controlled studies were palpitations and heart rate increased/tachycardia, both occurring in 0.4% for lasmiditan vs 0.1% for placebo. These were also the most commonly reported cardiovascular TEAEs in Study 305, occurring in 0.4% and 0.2%, respectively.

Dr. Branagan's review suggests a slightly higher incidence of TEAEs with potential cardiovascular etiology in patients with at least 1 cardiovascular risk factor compared to no risk factors in lasmiditan-treated subjects. The numbers are very small with frequencies of 1% or less. In addition, as previously noted, there were few patients with ischemic heart disease in the database. It is difficult to determine the role of pre-existing heart disease in the safety of lasmiditan.

I summarize the cases discussed by Dr. Branagan regarding cardiovascular or cerebrovascular events, and hypertension TEAEs.

SAEs potentially related to a cardiovascular etiology were previously discussed. In most cases the events appeared unlikely related to lasmiditan. *In general,* e*valuation of causal association for ECG changes is complicated by the fact that ECGs were intermittently recorded and therefore do not allow for documentation of when the event occurred in relation to dosing of lasmiditan.*

Dr. Branagan discusses the following additional narratives related to cardiovascular safety from phase 2/3 studies.

Palpitations [redacted] (b) (6) in a 26 y.o. female, also dizziness, 4 hours after lasmiditan and lasting for 50 minutes. *I agree that a role for lasmiditan cannot be ruled out.*

Change in baseline ECG [redacted] (b) (6) in a 56 y.o. female with no contributory medical history had screening ECG with QRS of 106 msec and QTcF of 407 msec; took 2 doses of lasmiditan 100 mg reportedly 2 weeks prior to study completion visit at which ECG showed right bundle branch block with left axis deviation, QRS of 154 msec (normal 80-100 msec), and QTcF of 461 msec. *Although Dr. Branagan believes the time course of events does not allow a role for lasmiditan to be ruled out, the finding 2 weeks after the dose seems difficult to attribute to lasmiditan given the short half-life.*

ECG QT prolonged [redacted] (b) (6) in a 57 y.o. female with history of hypothyroidism, hyperlipidemia, reflux disease, depression, and myocardial infarction who developed QT prolongation on ECG from QTcF of 395 msec and heart rate of 95 bpm at baseline to QTcF of 432 and heart rate of 112 bpm at follow-up visit 3 weeks later. *Dr. Branagan believes that a role for lasmiditan cannot be ruled out. I note that the event occurred 8 days after having taken 2 doses of lasmiditan and I believe it is difficult to attribute the event to lasmiditan given its short half-life.*

Dysarthria [redacted] (b) (6) in a 56 y.o. male with a history of hypertension, overweight who reported dysarthria on Study Day 7, the same day as lasmiditan administration (although timing in relation to the dose is unknown). This was included by Dr. Branagan as a CNS Vascular Event. The event was reported as resolved on the day of onset. On another occasion, the patient also had AEs of dizziness and lethargy 27 minutes after taking lasmiditan. *The mechanism for this event is not clear. I agree with Dr. Branagan that a role for lasmiditan in dysarthria cannot be determined and that lasmiditan likely contributed to the events of dizziness and lethargy.*

Cardiomyopathy/Elevated Blood Pressure [redacted] (b) (6) in a 44 y.o. female with a history of attention deficit hyperactivity disorder, overweight, left bundle branch block, asthma, and hypothyroidism who experienced elevated blood pressure on Day 151 and cardiomyopathy on Day 171. She had received 5 doses of lasmiditan within the 5 months prior to the onset of the AEs; the most recent dose was 13 days prior to the episode of hypertension and about 1 month prior to the finding of cardiomyopathy. The event of hypertension resolved after 2 days. Concomitant medications included amphetamine/dextroamphetamine. *I agree that a role for lasmiditan cannot be ruled out but as Dr. Branagan notes, amphetamine/dextroamphetamine has been associated with the development of cardiomyopathy. Given the short half-life of lasmiditan, the dosing 13 days prior to the episode of hypertension, and the resolution of hypertension within 2 days of the event, the elevated blood pressure does not seem likely related to lasmiditan.*

Dr. Branagan discusses the following additional narratives related to cardiovascular safety from the clinical pharmacology studies.

AV block in 4 subjects in study LAHI taking sumatriptan plus lasmiditan (and in 3 of the 4 also during lasmiditan alone, and in 2 of the 4 also during sumatriptan alone), within 8 hours of dosing. The PR intervals were no greater than 208 msec and no greater than 13 msec above the subject's baseline and resolved within hours to 3 weeks. Subject [redacted] (b) (6), highlighted by Dr. Branagan, was a 24 y.o. female who had AV block with sinus bradycardia 4

hours after dosing with lasmiditan plus sumatriptan that resolved after 4 hours, and another episode of sinus bradycardia with inverted T waves in V2, 8 hours after receiving lasmiditan plus placebo, in which the T wave resolved and bradycardia persisted at 24 hours post-dose. *I agree that a role for lasmiditan in AV block cannot be ruled out given the onset on the day of the dose and that it appeared to be reproducible in 3 of the subjects, although a persistent effect that resolved beyond 24 hours seems unlikely given the short half-life of lasmiditan. The significance or relatedness of T wave inversion in V2 is difficult to determine (T wave inversion is present in the background in approximately 1%-3%[3]) and persistence of bradycardia at almost 5 half-lives after administration make it difficult to attribute to lasmiditan.*

T wave inversion in lead III (b) (6) in a 27 y.o. female 1 hour after lasmiditan that resolved after 3 hours. She also had T wave inversion 24 hours after the dose with resolution 1.5 hours later. She also had T wave inversion 6 days later, 4 hours after a dose of lasmiditan plus sumatriptan that resolved 4 hours later. *I agree that the T wave inversion seems to be reproducible, although it also occurred 24 hours after a dose, a time that is almost 5 half-lives after the dose. T wave inversion in lead III may be a normal variant.[4] It is difficult to determine the role of lasmiditan in this event.*

Syncope (vasovagal syncope) (b) (6) in a 42 y.o. male with a history of bradycardia, dizziness, sleep apnea syndrome, rhinoplasty, anxiety, and hyperlipidemia experienced syncope 12 hours after taking lasmiditan 200 mg, and lasting for 8 minutes. Pre-dose the patient had a supine blood pressure of 139/84 mm H and at the stop time of the event, the patient had a sitting blood pressure of 91/59 mm Hg. He had decreased oral intake the day prior to the study. The narrative states that the subject recounted that he had recalled an upsetting memory just before the event. The narrative also states that patient admitted that he is "very poor" at staying hydrated and that he had fasted on the day of the event. He also had paresthesias 1 hour after dosing. *I agree that a role for lasmiditan in the episode of syncope cannot be ruled out, although it does not appear to be at the likely peak effect of the dose and had other contributing factors.*

Orthostatic hypotension (b) (6) in a 36 y.o. female with a history of migraine and overweight, who experienced the event 8 hours after taking lasmiditan, and that resolved after 5 minutes, although the CSR notes the subject was unable to stand for repeat orthostatic vital signs. *A role for lasmiditan cannot be ruled out, the peak effect might be expected to be at pharmacokinetic Tmax and resolution after 5 minutes does not seem consistent with the expected pharmacokinetics.*

Orthostatic hypotension (b) (6) 4 hours after the dose in a 61 y.o. male with past medical history of coronary artery disease, hypertension, hyperlipidemia, hyperphosphatemia, hypertensive retinopathy, hypertensive encephalopathy, hyperparathyroidism, chronic kidney disease on hemodialysis. Event resolved after 6 minutes. *I agree that a role for lasmiditan cannot be ruled out but as noted by Dr. Branagan the patient has predisposing factors including end stage renal disease and concomitant medications (glyceryl trinitrate, irbesartan, metoprolol).*

---

[3] Aro A et al. (Circulation. 2012;125:2572-2577.)
[4] Channer K, Morris F. BMJ 2002; 324:1023-1026.

Clinically significant changes in vital signs (b) (6) in a 59 y.o. man with history of hypertension, hepatitis C with moderate hepatic impairment, ascites, hepatosplenomegaly, and tremor, experienced increase in sitting heart rate to 115 bpm (49 bpm from baseline), 2 hours after dosing, with a decrease in blood pressure of 39/21 mm Hg compared to baseline. On Day 2, heart rate remained 14 bpm above his baseline value, and blood pressure had increase. *I agree that a role for lasmiditan in the elevated heart rate cannot be ruled out given the time course of the event.*
Feeling of Heart Racing/palpitations (b) (6) in a 24 y.o. man with a history of drug abuse, developed event 5 hours after a dose of lasmiditan, followed by postural orthostatic tachycardia. Palpitations resolved after 1.5 hours and orthostatic tachycardia resolved after 5 hours.[5] *I agree that a role for lasmiditan cannot be ruled out given the time course of the events.*

Please refer to the reviews of vital signs and ECGs in Dr. Branagan's review and elsewhere in this memo. Vital signs from clinical pharmacology studies showed evidence of increases in systolic and diastolic blood pressure within 1 hour of lasmiditan dosing along with decreases in pulse rate. Mean orthostatic changes did not appear to occur. The thorough QT study showed no significant QTc prolongation after lasmiditan at supratherapeutic doses and demonstrated no clinically meaningful effect on mean PR or QRS intervals.

I agree with Dr. Branagan that the current database does not support an increased cardiovascular risk with lasmiditan. As Dr. Branagan notes, there were few patients with ischemic heart disease in the database.

Suicidality and Depression

Dr. Branagan has evaluated the risks of suicidality and depressing using AE terms and using results of the C-SSRS. *I agree with Dr. Branagan that there does not appear to be an increased risk of depression or suicidality among patients treated with lasmiditan at to-be-marketed doses.*

In the Suicide and Self-Injury-Related SMQ, Dr. Branagan notes that in the controlled trials 1 lasmiditan patient reported an AE vs no subjects who received placebo. In the Phase 2/3 studies (All Lasmiditan Pool), 8 subjects (8/4081, 0.2%) reported at least 1 AE in this SMQ. She describes 1 patient ((b) (6) wo had a TEAE of suicidal ideation (along with anxiety, fatigue, depressed mood, and dizziness) 39 minutes after the most recent dose of lasmiditan and lasting for 4 hours; the patient was also taking valacyclovir that had common AEs including dizziness and depression. Other patients with TEAEs related to suicidal ideation generally had a history of anxiety and depression or had the event 5 days to more than 2 months after a dose of lasmiditan. *I agree with Dr. Branagan that because of the histories of depression and the delay in the event after the dose of lasmiditan it would be difficult to establish a role for lasmiditan in these events.*

[5] This patient also had visual hallucinations, paresthesia, dysphoria, and euphoric mood within 0.5 to 4.5 hours after dosing that resolved within 6 hours, for which a role for lasmiditan cannot be ruled out.

Two lasmiditan-exposed subjects (0.06%, (b) (6) and (b) (6)) in the Phase 3 controlled trials who both had a history of mental health disorders and 1 placebo patient (0.08%) answered affirmatively to C-SSRS questions to which they had a negative response at baseline, as noted by Dr. Branagan. It is not possible to determine the role of lasmiditan in those responses. In the All Lasmiditan Pool 20/4081 subjects (0.5%) had treatment emergent suicidal ideation based on the C-SSRS, 2 of whom developed suicidal behavior.

Dr. Branagan shows that TEAEs belonging to the SMQ of Depression (excluding suicide and self-injury) were reported in 0.6% of lasmiditan vs 0.1% of placebo treated patients in controlled trials, and in 1.6% of lasmiditan-treated patients in Study 305. I note that that according to a publication by Minen et al, a meta-analysis of 12 studies found that the incidence of depression in migraineurs is reportedly 8.6% to 47.9%.[6]

Hypersensitivity

A small imbalance in hypersensitivity reactions was observed for lasmiditan compared to placebo in the Phase 3 controlled trials (0.2% vs 0%). Reactions included rash, pruritus, swollen tongue, facial swelling, and photosensitivity. In some cases, the event occurred after administration of the first dose. *I agree with Dr. Branagan that a role for lasmiditan in these cases cannot be ruled out. Appropriate labeling may reduce the risks of potentially serious outcomes of hypersensitivity reactions.*

Dr. Branagan shows a small numerical imbalance in hypersensitivity reactions for lasmiditan compared to placebo in the controlled trials. In Studies 301 and 302 combined, 1.2% of patients who took lasmiditan 200 mg had an adverse event in the Hypersensitivity (Broad) SMQ compared to 0.8% of placebo patients, with evidence of a dose response for lasmiditan. Dr. Branagan shows similar findings for Study 202 but with no evidence of a dose response. Dr. Branagan notes that most of the TEAEs potentially related to hypersensitivity in the controlled studies and in Study 305 were mild or moderate in severity. None led to discontinuation in the controlled trials; 5 of the 29 TEAEs related to hypersensitivity in Study 305 led to discontinuation. She describes the cases, all in patients with a history of asthma, seasonal or food allergies, eczema, urticaria, or drug allergies. Reactions included rash, pruritus, swollen tongue, facial swelling, and photosensitivity. In some cases, the event occurred after administration of the first dose. It is possible that some of these events may be non-IgE-mediated hypersensitivity reactions.

Dr. Branagan also describes an event (b) (6) at first noted to be circulatory collapse, but later characterized by the investigator as “circulatory problems”, abnormal feeling, and paresthesia (“tingling at the body”). The patient reported that she felt being near to collapse. The event occurred on the day of the first dose and resolved after 1 hour. The patient was not assessed by a medical provider on the day of the event and did not have vital signs on the day of the event. *I agree with Dr. Branagan that the event appears to be characteristic of paresthesias or presyncope.*

Dr. Branagan notes that in the 120 Day Safety update, the sponsor reported 5 additional cases of hypersensitivity that included allergic rhinitis, asthma, dyspnea, edema, and photosensitivity

[6] Minen MT et al. J neurology, Neurosurgery, and Psychiatry 2016; 87:741-749.

reaction. She notes 5 patients with hypersensitivity events in the Phase 1 studies: skin reaction, contact dermatitis (3), eye swelling.

Serotonin Syndrome

Dr. Branagan and the Sponsor have identified 2 patients that meet Sternbach criteria for serotonin syndrome. Dr. Branagan notes that because lasmiditan acts on 5-HT receptors and could potentially cause effects seen with serotonin excess, serotonin syndrome was an area of special interest. Triptans have warnings in labeling regarding serotonin syndrome. Although 5-HT_{1A} and 5-HT_2 receptors have been implicated, the role of other 5-HT receptors in serotonin syndrome has not been well characterized. According to the literature, triptans are high affinity agonists at 5-HT_{1F} subtypes, as well as being agonists at 5-HT_{1B} and 5-HT_{1A} receptors.[7] The Sponsor notes that at least 7 serotonin receptor subtypes may be involved. Three different sets of criteria for serotonin syndrome have been published. Sternbach criteria[8], require recent addition or increase in the dose of a serotonergic agonist, absence of other etiologies, and at least 3 of the following: mental status change, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, or fever. The Hunter Serotonin Toxicity Criteria[9], developed based on cases of overdose of serotonergic drugs and considered by its authors to be more sensitive and specific than the Sternbach criteria, require the presence of one of the following features or groups of features: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia, temperature above 100.4° F (38° C), and ocular or inducible clonus. Radomski criteria[10] differentiate between major and minor symptoms; these criteria will not be further considered here because the cases identified in this submission do not meet the Radomski criteria. The literature suggests that approximately 60% of patients with serotonin syndrome present within 6 hours after initial use of medication, change in dosing, or overdose.[11] Severe cases of serotonin syndrome can result in death.

Dr. Branagan notes that 2 patients, identified by the Sponsor, meet the Sternbach criteria for serotonin syndrome. (b) (6) developed twitching muscles, tremor, and agitation that began within 1.5 hours after dosing with lasmiditan 100 mg, with twitching lasting for 10 minutes and tremor and agitation lasting for 1 hour. The patient treated 1 additional migraine in the study. The sponsor states in the ISS (p. 427) that it is not certain that muscle twitching is clinically equivalent to myoclonus. (b) (6) experienced mental status changes (perceptual distortion, agitation and derealization), tremor, incoordination (ataxia), nightmare, as well as muscle weakness of the jaw and eyes, and dizziness beginning within 25 minutes of dosing with lasmiditan 400 mg and resolved within 6 hours, except for agitation and nightmare which lasted 36 hours. The sponsor states in the ISS (p. 426) that it is not certain that ataxia is clinically equivalent to incoordination. The patient

[7] Evans RW et al. Headache 2010; 50:1089-1099.
[8] Sternbach H. Am J Psychiatry 1991; 148:705-713.
[9] Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. QJM 2003; 96:635-42.
[10] Radomski JW, Dursun SM, Reveley MA, Kutcher SP. Med Hypotheses 2000; 55:218-224.
[11] Boyer EW, Shannon M. N Engl J Med 2005; 352:1112-1120.

had a dose of frovatriptan 25 hours after the dose of lasmiditan. *I agree with Dr. Brangan and with the Sponsor that these two cases meet Sternbach criteria for serotonin syndrome.*

The sponsor states that in these cases the clinical information was limited and the clinical condition of the patient was not severe and signs and/or symptoms were self-limiting. *I note that the literature recognizes that mild cases can occur. The Hunter criteria were based on overdoses. In the present cases, the patients had only been exposed to a single dose of drug, and it is reasonable to consider that the cases may be mild.* The Sponsor states that in all cases, there were no known concomitant serotonergic agents, which decreases the likelihood that any of these events were serotonin syndrome. *Concomitant exposure with another serotonergic agent is not necessary.* The sponsor states that given the lack of specificity of the symptoms of serotonin syndrome, it can be difficult to distinguish mild serotonin syndrome from other clinical conditions, and that determination about the association of serotonin syndrome and lasmiditan should rely on the Hunter criteria. *The literature acknowledges the limitations of the published criteria, including the derivation of Hunter criteria from overdose conditions rather than therapeutic doses[4] such that minor cases could be missed if these criteria were used.*

These cases meet the Sternbach criteria for serotonin syndrome and a role for lasmiditan cannot be ruled out. These were relatively mild cases. However, given the potential seriousness of serotonin syndrome, the potential for drug interactions (such as with triptans that have Warnings for serotonin syndrome) that could potentiate the risk, and opportunity to mitigate serious outcomes if symptoms are recognized, I recommend considering labeling regarding serotonin syndrome.

Injuries, Accidents, and Impaired Mental Ability Caused by CNS Effects

- Injuries and Accidents
  Dr. Branagan reports on the Sponsor search regarding injuries and accidents related to an AE belonging to the Nervous system disorders SOC. In studies 301 and 302 Dr. Branagan shows 26% of lasmiditan subjects vs 7% of placebo subjects having at least 1 central nervous system (CNS) TEAE. However, AE events related to injury in patients with at least one CNS TEAE occurred in 0.3% in lasmiditan subjects (such as arthropod sting, laceration 9 days after dosing, sprained Achilles tendon 2 days after dosing) vs 0.5% in placebo subjects and did not appear to be related to a CNS TEAE.

  In Study 202 Dr. Branagan identified 3 subjects with dizziness on the day of dosing, with resolution on the same day. Subsequent injuries do not seem related (motor vehicle accident 4 days after dose, rib fracture, weakness, fatigue 4 days after dosing, brain concussion 10 days after dosing).

  In Study 305, a road traffic accident occurred 2 days after dosing in a patient with a CNS TEAE (b) (6). This is discussed in further detail below.

  In clinical pharmacology studies, Dr. Branagan reports that the sponsor found no AE related to Injury that occurred in the setting of a CNS TEAE.

- Impaired Mental Ability

  Dr. Branagan reports on the Sponsor search regarding TEAEs in Phase 2 and 3 studies with preferred terms in the Nervous system and Psychiatric disorders SOC that primarily reflect attentional, perceptual, or executive function impairments or changes in sensorium. Dr. Branagan notes that 21.2% of lasmiditan treated patients vs 5.1% of placebo patients that at least 1 TEAE in those categories for studies 301/302, and similar findings for studies 202/301/302 combined.

  In addition to *dizziness, somnolence, lethargy, and sedation* that occurred more frequently in lasmiditan than placebo, preferred terms included *cognitive disorder* and *mental impairment* that each occurred in 0.1% (n=3) of lasmiditan patients and none in placebo, as well as *confusional state* and *disorientation* that occurred in 0.2% of lasmiditan and 0.1% in placebo in the controlled studies.

  Dr. Branagan evaluated the database for road traffic accidents that could be related to the CNS effects of lasmiditan. Dr. Branagan notes that the protocols for 301 and 302 specified that subjects should be advised to not drive or operate machinery until 12 hours after treatment. In Study 305 subjects were advised not to drive or operate machinery until they knew how they would react to lasmiditan. There were no TEAEs of Road Traffic Accident, Impaired Ability to Use Machinery, or Accident in subjects who received study drug in the Studies 301/302. There were 5 AEs or TEAEs of Road Traffic Accident in the database as follows:
  (b) (6) with a road traffic accident 4 days after taking lasmiditan, with dizziness that started prior to the accident and moderate headache that started the day of the accident.
  (b) (6) with a road traffic accident 43 days after the most recent dose of lasmiditan.
  (b) (6) with a road traffic accident 50 days after the most recent dose of lasmiditan.
  (b) (6) with posttraumatic neck syndrome due to car accident 13 days after the most recent dose.
  (b) (6) with a road traffic accident 2 days after most recent dose; not know if patient was the driver; reported sciatica on the same day; concomitant medications were lithium and quetiapine.
  (b) (6) with a road traffic accident with unknown time in relation to any dose of lasmiditan.
  I agree with Dr. Branagan that in the first 5 accidents, a role for lasmiditan is unlikely given the timing after the dose of lasmiditan. In the last case, there is insufficient information to draw a conclusion regarding the role of lasmiditan.

  Driving Studies

In driving studies in healthy volunteers, a single dose of lasmiditan (50 mg, 100 mg, and 200 mg) impaired driving ability at 1.5 hours after the dose. Subjects lacked insight as to their impairment. In Study LAIF that evaluated impairment at 8, 12, and 24 hours after a dose of 100 mg or 200 mg lasmiditan, no mean impairment was observed. Although individual subjects showed changes in standard deviation of lateral position (SDLP), there did not appear to be differences in exposure that would explain impaired driving. The implications of a second dose on driving have not been evaluated.

Dr. Branagan has summarized the results of two driving studies (Study 106 and Study LAIF) conducted in healthy volunteers. In both studies the primary endpoint was standard deviation of lateral position (SDLP) in which the prespecified inferiority margin was 4.4 centimeters that, as Dr. Branagan notes, is consistent with a blood alcohol concentration of 0.05%. The conduct of the studies appears to be consistent with recommendations in the Guidance for Industry: Evaluating Drug Effects on the Ability to Operate a Motor Vehicle[12] with respect to a positive control, testing at a time when maximal levels of drug are achieved, considering the time course, and a crossover study with adequate washout between periods.

Study 106 evaluated lasmiditan doses of 50mg, 100 mg, and 200mg at 90 minutes after the dose compared with placebo and with alprazolam 1 mg as a positive control in a 5-period, randomized, crossover study. Dr. Branagan shows that the difference in least squared means for all doses tested compared to placebo was greater than 4.4 cm, indicating that lasmiditan is inferior to placebo. Dr. Branagan shows a dose-response relationship. The differences compared to placebo are similar for lasmiditan 200 mg and alprazolam 1 mg. The results are shown in the table below, from Dr. Branagan's review.

Difference in LS Means in SDLP (cm) compared to Placebo in Study 106.

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	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)

Data from the above table was taken from Table 11-3 of Study 106 report submitted by the sponsor. CI: confidence interval.

Lasmiditan was also inferior to placebo in secondary endpoints including measures of reaction time, sleepiness, and motivation and self-appraisal for driving. Dr. Branagan also notes that the most frequent TEAEs of somnolence, dizziness, fatigue, and lethargy observed in this study, consistent with those in the Phase 3 controlled studies, could be contributing to the driving impairment.

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 to

[12] https://www.fda.gov/media/90670/download

placebo and with diphenhydramine 50 mg as a positive control given 2 hours prior to each assessment. Dr. Branagan shows that at 8, 12, and 24 hours, noninferiority with placebo was demonstrated as shown in the table below. Dr. Eugenio Andraco-Carrera in an email communication of April 25, 2019, confirmed that this trial would be sensitive enough to detect a difference in SDLP of greater than 4.4 cm.

Table 2. Difference in LS Means in SDLP (cm) compared to Placebo in Study LAIF.

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)

Data from the above table was taken from Table LAIF.7.10 submitted by the sponsor. CI: confidence interval

Dr. Branagan shows that approximately 21-25%, 13-15%, and 9-13% of subjects had a difference from placebo in SDLP of greater than 4.4 cm at 8, 12, and 24 hours. However, Dr. Priya Brunson evaluated the exposure-response relationship in lasmiditan-treated subjects and did not find differences in exposure that would explain impaired driving. Most secondary measures related to speed and collision (mean average speed, mean excessive speeding around corners, mean speed deviation) did not show worse performance for lasmiditan compared to placebo, making changes observed in mean speeding count difficult to interpret. In addition, as Dr. Branagan shows from the Sponsor's 9/25/19 response to an information request, the variation in the lasmiditan treated arms had a distribution of SDLP scores that was more similar to placebo at 8, 12, and 24 hours than to the positive control arm.

Subjects given lasmiditan 200 mg in LAIF had a significant increase in sleepiness compared to placebo at 8 hours. TEAEs including somnolence, dizziness and insomnia had not resolved in 4 subjects by 8 hours after dosing.

Of note there is no information available about driving impairment between 90 minutes and 8 hours after the dose. *Therefore, I agree with Dr. Branagan suggesting that a warning be added to the label to indicate that patients should not drive for at least 8 hours after taking lasmiditan.*

Specific Populations

Dr. Branagan evaluated the incidence of common TEAEs of dizziness, fatigue, nausea, paresthesia, somnolence, and vomiting by the demographics of sex, age, ethnicity, and race.

Dr. Branagan finds the incidence of common TEAEs are similar in females and males treated with lasmiditan. She notes that dizziness occurred more frequently in patients at least 65 years old than in other age groups, and the incidence of paresthesias increased with increasing age for the age groups of less than 30 years old, at least 30 to less than 50 years old, and at least 50 years old.

With respect to ethnicity and race "Hispanic or Latino" patients had fewer TEAEs on lasmiditan than "not Hispanic or Latino" patients. The largest difference occurred in dizziness which Dr.

Branagan notes occurred in Hispanic/Latino 9.2% for lasmiditan (3.9% for placebo) vs 15.8% for lasmiditan (2.8% for placebo) in not Hispanic/Latino in Studies 301/302.

White patients, representing approximately 78% of the clinical trials population, generally had more frequent TEAEs of dizziness, fatigue, nausea, and paresthesias than did black or African American patients who represented approximately 18% of the population. The number of patients in the other racial groups was too small to allow for meaningful comparisons.

Dr. Branagan reviewed TEAEs in the hepatic impairment and renal impairment studies. The TEAEs seem consistent with those reported in the Phase 2/3 studies. Small numbers of patient make it difficult to draw conclusions in these studies.

Drug Interaction Studies

Dr. Branagan has reviewed pharmacodynamic drug interaction studies with sumatriptan, topiramate, and propranolol that could all be used to treat migraine and could potentially be administered with lasmiditan. Slight increases of approximately 3 mm Hg in systolic and diastolic blood pressure were observed with the combination of sumatriptan and lasmiditan compared to lasmiditan alone. Increases in TEAEs, particularly *hypersomnia* (38% for the combination vs 22% for lasmiditan alone) were also observed. When propranolol and lasmiditan were given together the decrease in *pulse rate* of 19. 3 bpm was greater than for either drug given alone. Coadministration of topiramate and lasmiditan did not appear to result in clinically meaningful differences compared to either drug alone. *I recommend describing the relevant pharmacodynamic drug interactions in the prescribing information.*

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Dr. Branagan reviewed the potential for human carcinogenicity or tumor development in the clinical database. She notes that 2 events in the Neoplasm SOC occurred in lasmiditan-treated patients in the Phase 2/3 controlled trials, and none in placebo. The majority (20) of AEs in the Neoplasm SOC occurred in study 305 and it is difficult to interpret these without a control group. The types of events are disparate and include skin and soft tissue (anogenital warts, basal cell carcinoma, lipoma, malignant melanoma, melanocytic naevus, seborrheic keratosis, skin papilloma), hemangioma of skin, adenocarcinoma of colon, benign breast neoplasm, recurrent thyroid cancer, non-small cell lung cancer, cholesteatoma, uterine leiomyoma (n=5), and benign neoplasm (n=2). Dr. Branagan notes that time to onset of these malignancies was < 8 months of exposure; this does not appear to suggest a drug related effect in those cases. *I agree with Branagan, that the duration the clinical trials with maximum exposure of 1 year does not allow for conclusions regarding carcinogenic potential of lasmiditan to be drawn.*

Human Reproduction and Pregnancy

Please refer to Dr. Branagan's review for details as summarized below. I agree with Dr. Branagan that the information is limited to assess the effects of lasmiditan on pregnancy. Given that lasmiditan will be used in women of childbearing potential, I agree with Dr.

Branagan's recommendation for a pregnancy registry and a pregnancy outcomes study as postmarketing requirements.

Pregnancies

Dr. Branagan identified 9 pregnancies in which maternal exposure to lasmiditan occurred 8 to 173 days prior to the last menstrual period or estimated date of conception. Three of those cases resulted in spontaneous abortion, premature rupture of membranes, or threatened abortion/spontaneous abortion, with the exposure to lasmiditan occurring at least 2 weeks prior to the estimated date of conception along with other concomitant medications, and I *agree with Dr. Branagan that given the short elimination half-life of lasmiditan it is unlikely that lasmiditan played a role in these outcomes*.

Dr. Branagan identified 13 additional pregnancies in which lasmiditan exposure during the first trimester. The outcomes were 5 normal, 1 premature birth, 3 spontaneous abortions, 1 elective termination, 3 awaiting follow-up. *The small number of pregnancies precludes a conclusion regarding effects of lasmiditan during pregnancy.*

Pediatrics and Assessment of Effects on Growth

Lasmiditan was not evaluated in the pediatric population in this development program.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Dr. Branagan notes that there were no cases of lasmiditan overdose across the clinical development program. Drug abuse potential and withdrawal will be reviewed in detail by the Controlled Substances Staff, to whom a consult was sent on October 18, 2018. Adverse event terms from the clinical trials database potentially related to abuse potential are summarized below.

Dr. Branagan has reviewed AE terms related to abuse potential based on a Sponsor-generated list that I agree appears to be consistent with terms suggested in the FDA Assessment of Abuse Potential of Drugs Guidance. Dr. Branagan reports an imbalance in TEAEs belonging to this list of terms that were reported in approximately 28% of lasmiditan exposed subjects in Studies 301 and 302 and approximately 8% of placebo-exposed subjects. This difference is driven by events of dizziness, paresthesias, and somnolence that do not necessarily imply abuse potential. However, groups of abuse related terms related to euphoria (euphoric mood, feeling abnormal, dizziness) and terms related to impaired attention, cognition, and mood (e.g. somnolence, disturbance in attention), for example, support the potential for abuse.

Concerns identified through U.S. or foreign postmarket experience

The sponsor states that lasmiditan is not approved in any region.

Potential safety issues that could cause concern when considering how the drug may be used in the postmarket setting

As Dr. Branagan notes additional adverse reactions will likely be identified after a larger group of patients is exposed to lasmiditan, and this may include patients with ischemic heart disease in whom there is relatively little experience.

8. Advisory Committee Meeting

An advisory committee meeting is not planned.

9. Pediatrics

This application did not evaluate use in pediatrics.

10. Other Relevant Regulatory Issues

Please refer to the clinical efficacy review.

11. Labeling

Prescribing Information
If lasmiditan is approved, I have the following general labeling recommendations:

Safety information in the WARNINGS AND PRECAUTIONS sections:

- I recommend WARNINGS and PRECAUTIONS for driving impairment and for sedation/CNS effects in general.
- I recommend language regarding serotonin syndrome in WARNINGS and PRECAUTIONS because recognizing the adverse reaction could mitigate a more serious outcome.
- I recommend including information regarding the potential for increased blood pressure in labeling because of the potential increased risk in patients with hypertension and overall adverse impact of even small increases in blood pressure.
- I recommend including language regarding hypersensitivity (including angioedema) in labeling.

Other Labeling
I believe that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risks. The Sponsor has proposed a medication guide.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)
I do not believe that a REMS is required for safe use of lasmiditan. Labeling can adequately explain the potential risk for impaired driving, hypersensitivity, serotonin syndrome, increased blood pressure, and other adverse reactions.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
I suggest a pregnancy registry and a pregnancy outcomes study as PMRs.

I recommend routine pharmacovigilance with periodic evaluation of malignancy, hypersensitivity, cardiovascular events, and serotonin syndrome.

Recommended Comments to the Applicant
None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SALLY U YASUDA
10/10/2019 04:07:59 PM