CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211280Orig1s000

NON-CLINICAL REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 211280
Submission date: 10/11/2018
Drug: lasmiditan
Applicant: Eli Lilly and Company
Indication: Acute treatment of migraine with or without aura

Reviewing Division: Division of Neurology Products

Discussion:
The pharmacology/toxicology reviewer and supervisor conducted a thorough review of the nonclinical information submitted and concluded that lasmiditan could be approved from the pharmacology/toxicology perspective.

Serotonin (5-HT)1F receptor agonist is an appropriate Established Pharmacologic Class for lasmiditan.

Maternal death, abortion, dose-related increases in post implantation loss, delayed skeletal ossification, and dose-related decreases in maternal body weight gain and food consumption were observed in a rabbit embryofetal developmental study at maternally toxic doses. The exposure at the NOAEL for these effects was similar to human exposure at the maximum human dose.

A 26-week study in transgenic RasH2 mice and a 2-year study in Sprague-Dawley rats were conducted. The executive carcinogenicity assessment committee concluded that the studies were adequate and that there were no drug-related neoplasms in either study.

Conclusions: I agree that this NDA can be approved from a pharm/tox perspective.

Comments on labeling were provided separately.

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/s/

PAUL C BROWN
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MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: October 9, 2019

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 211-280 (Reyvow, lasmiditan, COL-144, LY573144)

NDA 211-280 was submitted by Eli Lilly and Company on October 11, 2018, to support marketing approval of lasmiditan for the acute treatment of migraine with or without aura in adults. Clinical development of lasmiditan was conducted by Eli Lilly under IND 103420.

The sponsor conducted a standard battery of nonclinical studies to support clinical development and an NDA for lasmiditan administered by the oral route. In addition, the sponsor conducted nonclinical studies to address concerns regarding the potential for lasmiditan to cause coronary artery vasoconstriction. Nonclinical studies of lasmiditan were reviewed by Dr. Thompson under the IND (Pharmacology/Toxicology IND Review and Evaluation, D. Charles Thompson, Ph.D., dated August 18, 2011, May 18, 2012, and September 30, 2015) and by Dr. Nesti under the NDA (Pharmacology/Toxicology NDA Review and Evaluation, NDA 211280, Edmund Nesti, Ph.D., October 9, 2019). Based on the reviews, Dr. Nesti concludes the nonclinical data are adequate to support approval of the NDA.

Pharmacology

Theories regarding the pathophysiology of migraine continue to evolve (e.g., Puledda F et al. J Neurol 264:2031-2039, 2017); therefore, the precise mechanism underlying the therapeutic effects of lasmiditan in the acute treatment of migraine is unknown. The sponsor's studies indicate that lasmiditan is a high affinity serotonin (5HT) 1F receptor agonist (Ki of 2.22 nM).

PK/ADME/TK

The PK/ADME of lasmiditan was assessed in the animal species used for the pivotal nonclinical studies (mouse, rat, rabbit, and dog). In humans, the major circulating metabolites are M8 and[S,R]-M18, which account for 47.5 and 10.5% of drug-related material in circulation. Both metabolites were produced in mouse, rat, rabbit, and dog. At the highest doses tested in the appropriate nonclinical studies, plasma exposures (AUC) were similar to or greater than those in humans at the maximum recommended human dose (200 mg/day; plasma AUCs for M8 and [S,R]-M18 were 7651 and 1700 ng*hr/mL, respectively).

Toxicology

According to the sponsor, lasmiditan was initially developed for intravenous (IV) administration; therefore, some nonclinical studies (e.g., safety pharmacology, embryofetal development studies in rat and rabbit) were conducted by the IV route. Only the pivotal oral studies will be discussed in this memo.

General Toxicology: the oral toxicity of lasmiditan was tested in Sprague-Dawley rat (4-week + 2-week recovery, 13-week + 4-week recovery, and 26-week + 8-week recovery) and Beagle dog (2-week, 4-week + 2-week recovery, 13-week + 4-week recovery, and 39-week + 8-week recovery).

In rat, lasmiditan was administered at doses up to 100 (4-week study) or 200 (13- and 26-week studies) mg/kg/day. Renal findings characterized by study pathologists as consistent with chronic nephropathy were observed in the 13- and 26-week studies. In addition, death (200 mg/kg/day), myoclonic jerks/convulsions (100 and 200 mg/kg/day), cardiomyopathy (100 and 200 mg/kg/day), neuronal inclusions (characterized as minimal to slight in severity) consistent with lipofuscin deposits in large motor neurons of the brain stem and spinal cord (100 and 200 mg/kg/day) were observed in the 26-week study. The no-adverse-effect-level (NOAEL) was 50 mg/kg/day, which was associated with plasma lasmiditan exposure (AUC of 18404 ng*hr/mL) ~9 times that in humans at the maximum recommended human dose (MRHD) of 200 mg/day (2100 ng*hr/mL).

Intraneuronal cytoplasmic inclusions (minimal to slight in severity) in brain and spinal cord were also observed in the 2-year carcinogenicity study in Sprague-Dawley rat, at doses of 25 and 75 mg/kg/day. (No CNS clinical signs were observed.) At the NOAEL (low dose of 10 mg/kg/day), plasma lasmiditan exposure (AUC of 3860-4100 ng*hr/mL) was approximately 2 times that in humans at the MRHD. Although the effect-dose decreased with increased duration of dosing, the severity of the finding did not.

In dog, lasmiditan was administered at doses up to 60 (4-week study), 50 (13-week study), and 50/40 mg/kg/day (39-week study). In the 39-week study, the high dose was reduced to 40 mg/kg/day because of intolerability. The primary findings were CNS signs (tremors, ataxia, myoclonic jerks, and/or hypoactivity) and reduced (or absence) body weight gain at the highest doses tested. In addition, prolongation of QT_c and QRS duration were observed at 50 mg/kg/day in the 39-week study. The NOAEL was 30 mg/kg/day, which was associated with plasma lasmiditan exposure (AUC of 15368 ng*hr/mL) ~7 times that in humans at the MRHD.

Reproductive and Developmental Toxicology

A standard battery of reproductive and developmental toxicology studies was conducted for lasmiditan (fertility and early embryonic development in male and female Sprague-Dawley rat; embryofetal development in Sprague-Dawley rat and New Zealand White rabbit; pre- and postnatal development in Sprague-Dawley rat).

Fertility: Oral administration of lasmiditan to male (0, 100, 175, or 200 mg/kg/day) and female (0, 100, 150, or 200 mg/kg/day) rats prior to and during mating and continuing in females to

Gestation Day (GD) 7 resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (54590 and 70017 ng*hr/mL in males and females, respectively) at the highest dose tested (200 mg/kg/day) were approximately 26-33 times that in humans (2100 ng*hr/mL) at the maximum recommended human dose (MRHD) of 200 mg/day.

Embryofetal development: Oral administration of lasmiditan (0, 100, 175, or 250 mg/kg/day) to pregnant rats throughout organogenesis resulted in increases in skeletal variations at the mid and high doses and reduced fetal body weight at the high dose. The high dose was associated with maternal toxicity. At the no-effect dose (100 mg/kg/day) for adverse effects on embryofetal development in rats, plasma exposure (22122 ng*hr/mL) was approximately 10 times that in humans at the MRHD.

Oral administration of lasmiditan (0, 50, 75, or 115 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in malformations (skeletal and visceral), increases in skeletal variations and embryofetal mortality, and decreased fetal body weight were observed at the highest dose tested, which was associated with maternal toxicity. Plasma exposure (1512 ng*hr/mL) at the no-effect dose (75 mg/kg/day) for adverse effects on embryofetal development in rabbits was less than that in humans at the MRHD.

Pre- and postnatal development: Oral administration of lasmiditan (0, 100, 150, or 225 mg/kg/day) to rats throughout pregnancy and lactation resulted in increases in stillbirth and neonatal mortality at the highest dose tested, which was associated with maternal toxicity. Plasma exposure (34065 ng*hr/mL; sponsor's estimate based on data from the embryofetal development study in rat) at the no-effect dose (150 mg/kg/day) for adverse effects on pre- and postnatal development was approximately 16 times that in humans at the MRHD.

Oral administration of [^{14}C]lasmiditan to lactating rats resulted in excretion of radioactivity in milk, with approximately 3-fold higher exposure (AUC) in milk compared to plasma.

Genetic Toxicology
Lasmiditan was negative in adequately designed and conducted in vitro (bacterial reverse mutation, chromosomal aberration in mammalian cells) and in vivo (mouse bone marrow micronucleus) assays.

Carcinogenicity
The carcinogenic potential of orally-administered lasmiditan was tested in a 26-week study in Tg.rasH2 mice (0, 20, 50, or 150 mg/kg/day in males; 0, 25, 80, or 250 mg/kg/day in females) and in a 2-year study in rats (0, 10, 25, or 75 mg/kg/day). Both studies were adequately conducted, and no drug-related neoplasms were identified in either species (see Executive CAC minutes, dated June 20, 2019). In rat, plasma lasmiditan exposures (AUC) at the highest dose tested were 29800 and 32400 ng*hr/mL in males and females, respectively, at Week 26, which are approximately 15 times that (2100 ng*hr/mL) at the maximum recommended human dose of 200 mg/day.

Conclusions and Recommendations

The nonclinical studies conducted by the sponsor are adequate to support approval of lasmiditan for the acute treatment of migraine, with appropriate labeling and a post-marketing requirement for a juvenile animal toxicology study to support clinical development of lasmiditan in the pediatric population under PREA.

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/s/

LOIS M FREED
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	211280
Supporting document/s:	1
Applicant's letter date:	October 10, 2018
CDER stamp date:	October 11, 2018
Product:	REYVOW (COL-144, LY573144, lasmiditan)
Indication:	Acute treatment of migraine with or without aura in adults
Applicant:	Eli Lilly and Company
Review Division:	Division of Neurology Products
Reviewer:	Edmund Nesti, PhD
Supervisor:	Lois M. Freed, PhD
Acting Division Director:	Eric Bastings, MD
Project Manager:	Emilios Papanastasiou, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 211280 are owned by Eli Lilly and Company or are data for which Eli Lilly and Company has obtained a written right of reference.
Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application are for descriptive purposes only and are not relied upon for approval of NDA 211280.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Lasmiditan is an orally administered serotonin 5-HT_{1F} receptor agonist intended for the acute treatment of migraine with or without aura in adults. The proposed maximum recommended human dose is 200 mg/day.

1.2 Brief Discussion of Nonclinical Findings

In 5-HT_{1F} *in vitro* binding and functional assays, lasmiditan had low nanomolar affinity and agonist activity. In rodent efficacy models, lasmiditan inhibited trigeminovascular protein extravasation (neuroinflammatory response), induction of c-fos, dural-evoked nociception transmission, α-CGRP release, and vasodilation.

In off target *in vitro* binding assays to ~50 ion channels and receptors and functional assays with exogenously expressed GABA isoforms, lasmiditan and its major human metabolites, M8 and M18, showed no binding or activity. In addition to the standard battery of secondary pharmacology studies, a recommended vasoactivity assessment found no lasmiditan-induced constriction of the rabbit saphenous vein, dog coronary or carotid artery, guinea pig atria and ileum, human internal mammary artery, or human proximal or distal coronary artery.

IV distribution studies in rat showed that the highest concentrations of lasmiditan were in the bladder, brain (pituitary gland, pineal gland), and cerebrospinal fluid. In pregnant rats, lasmiditan concentrations were measurable in all fetal tissues. Lasmiditan was primarily excreted in the urine. In the plasma, approximately 55% of lasmiditan was protein bound in rat, dog, and human. The major metabolites in humans were M8 and M18. These metabolites were adequately assessed in the nonclinical studies.

In hERG assays, IC_{50}s for lasmiditan (~3.0 µM) and metabolites M8 and M18 (>30 µM) exceeded 4-fold the plasma C_{max} in humans following oral administration of 200 mg. ECG, respiratory, and vasoactivity assessments were negative. A single dose (IV) CNS safety pharmacology study in mice showed lasmiditan increased convulsive threshold and decreased sensorimotor reactivity.

An adequate battery of genetic, carcinogenicity, general, and reproductive and developmental toxicology studies were conducted. Lasmiditan was negative in OECD compliant Ames, *in vitro* chromosome aberration, and mouse bone marrow micronucleus assays. Lasmiditan was not carcinogenic in 2-year rat or 6-month Tg rasH2 mouse studies.

All pivotal *in vivo* nonclinical studies were conducted using oral administration. In the 39-week toxicology study in dog, there were lasmiditan-related tremors and hypoactivity. The safety margin was 8-fold compared to the maximum human dose based on AUC at the NOAEL of 30 mg/kg. In the 26-week rat study, there was lasmiditan-related death, convulsions, cardiomyopathy and hypertrophy, and chronic progressive nephropathy (CPN). The safety margin based on AUC at the NOAEL of 50 mg/kg was 9-fold relative to that at the maximum human dose.

In the fertility and early embryonic development study in rat, there were 2 deaths, decreases in body weight, hypoactivity, ataxia, and labored respiration. The safety margin based on AUC at the NOAEL of 200 mg/kg was 27-fold relative to that at the maximum human dose. In the pivotal embryofetal development study in rat, there were

lasmiditan-related decreases in fetal and maternal body weight and delayed skeletal ossification. The safety margin based on AUC at the NOAEL of 175 mg/kg was 31-fold relative to that at the maximum human dose. In the pivotal embryofetal development study in rabbit, there was maternal death, abortion, dose-related increases in post implantation loss, delayed skeletal ossification, and dose-related decreases in maternal body weight gain and food consumption. There was no safety margin based on AUC at the NOAEL of 50 mg/kg relative to that at the maximum human dose.

Lasmiditan was found to be excreted in the milk of lactating rats after oral administration. In the pre-and postnatal development study in rat, in F_0 animals, there was maternal death, stillborn pups, increased gestation period, and underdeveloped mammary glands. In the F_1 animals, there were postnatal death, decreases in body weight (during lactation), fewer implantation sites, and fewer delivered pups. On a mg/m^2 basis, there was no safety margin at the NOAEL of 150 mg/kg, relative to that at the maximum human dose, for the F_0 or F_1 generations.

1.3 Recommendations

1.3.1 Approvability

The nonclinical NDA package supports approval of lasmiditan.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

8.1 Pregnancy

Risk Summary

(b) (4) In animal studies, adverse effects on development (increased incidences of fetal abnormalities, increased embryofetal and offspring mortality, decreased fetal body weights) occurred at maternal exposures (b) (4) or greater than those observed clinically (b) (4) (b) (4).

Data

(b) (4)

12.1 Mechanism of Action

(b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

2.1 Drug

CAS Registry Number: 439239-92-6

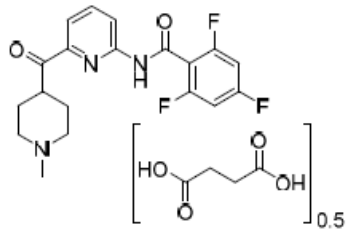
Generic Name: lasmiditan hemisuccinate

Code Name: LY573144

Chemical Name:
IUPAC: 2,4,6-trifluoro-N-(6-(1-methylpiperidine-4-carbonyl)pyridine-2-yl)benzamide hemisuccinate
CAS: Butanedioic acid, compd. with 2,4,6-trifluoro-*N*-[6-[(1-methyl-4-piperidinyl)carbonyl]-2-pyridinyl]benzamide (1:2)

Molecular Formula/Molecular Weight: $C_{19}H_{18}F_3N_3O_2 \cdot 0.5[C_4H_6O_4]/436.41$ g mol^{-1}

Structure or Biochemical Description



Sponsor's figure

Pharmacologic Class
Serotonin (5-HT) 1F receptor agonist.

2.2 Relevant INDs, NDAs, BLAs, and DMFs

IND 103420

2.3 Drug Formulation

Table 3.2.P.1-1 Unit Formula for Lasmiditan 50 mg and 100 mg Tablets

Component	Quantity (mg/tablet) 50 mg	100 mg	Function	Reference to Standards
Core Tablet			(b) (4)	
Lasmiditan Hemisuccinate[a]	57.824	115.65	Active Ingredient	In house, refer to Section 3.2.S.4.1
Lasmiditan Free Base (LY573144)	*50*	*100*		
Microcrystalline Cellulose[a] Cellulose, Microcrystalline	(b) (4)			USP-NF, JP Ph.Eur.
Pregelatinized Starch Starch, Pregelatinised				USP-NF, JPE Ph.Eur.
Croscarmellose Sodium				USP-NF, Ph.Eur., JP
Sodium Lauryl Sulfate Sodium Laurilsulfate				USP-NF, JP Ph.Eur.
(b) (4)				
Magnesium Stearate	(b) (4)			USP-NF, Ph.Eur., JP
Core Tablet Weight:				
Film Coating				
(b) (4)				In house[d]
				In house[d]
				USP-NF, JP Ph.Eur.
Total Tablet Weight:	120.8	241.5		
(b) (4)				

Sponsor's table

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Lasmiditan is indicated for the acute treatment of migraine with or without aura in adults. Recommended dosing: should not to exceed 200 mg in a 24-hour period.

2.7 Regulatory Background

May Proceed Letter (September 12, 2011); End of Phase 2 meeting minutes (December 21, 2011); Type C, (October 1, 2015); Agreed Initial Pediatric Study Plan (January 4, 2018); Filing meeting (November 26, 2018).

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology

- 5-HT_{1F} *in vitro* binding and functional assays with lasmiditan.
- Rodent efficacy studies with lasmiditan assessed inhibition of trigeminovascular protein extravasation (neuroinflammatory response), induction of c-Foc, dural-evoked nociception transmission, CGRP release (*ex vivo*), and vasodilation after activation.

Secondary Pharmacology

- Off target binding and functional assays with lasmiditan and its metabolites (M3, M7, M8, (S,S)-M18, and (S,R)-M18).

Safety Pharmacology

- Lasmiditan and its metabolites were assessed in hERG, ECG (dog), respiratory (rat), CNS (mice and dog), vasoactivity (*ex vivo*: rabbit saphenous vein, dog coronary or carotid artery, guinea pig atria and ileum, human internal mammary artery, or human proximal or distal coronary artery), and renal toxicity (rat) assays.

Pharmacokinetics.

- Liquid chromatography with tandem mass spectrometric (LC-MS/MS) detection method validation studies for lasmiditan and its major metabolites in mouse, rat, rabbit, dog, and human plasma.
- Single and repeat dose (oral and IV) absorption studies conducted in mouse, rat, rabbit, and dog.
- Distribution studies of lasmiditan in the brain, body, plasma, placenta, and lactate conducted in rat.
- Metabolism studies of lasmiditan (oral and IV) in rat assessing the plasma, urine, feces, bile, and blood; and *in vitro* assessing rat S9.
- Excretion studies following IV or Oral administration of [^{14}C]lasmiditan to rat or dog, evaluating the plasma, urine, feces, bile, and blood.

General toxicology
- 5-day to 13-week daily oral administration studies in mouse.
- 4-day to 2-week daily IV administration studies in mouse.
- 4-day to 26-week daily oral administration studies in rat.
- 2-week daily IV administration study in dog.
- 2- to 39-week daily oral administration studies in dog.

Genetic toxicology
- *In vitro* Ames and chromosome aberration assays.
- *In vivo* micronucleus assay in rat.

Carcinogenicity
- 26-week study in Tg.rasH2 mouse.
- 104-week study in rat.

Reproductive and Development toxicology
- Fertility and early embryonic development oral administration study in rat.
- Pilot embryo-fetal development IV and oral administration studies in rat and rabbit.
- Embryo-fetal development IV and oral administration studies in rat and rabbit.
- Pre and postnatal development oral administration study in rat.

Special toxicology studies
- Bovine corneal opacity and permeability assay.
- *In vitro* Balb/c 3T3 neutral red uptake phototoxicity assay.
- 4-week renal toxicity study in rat.
- Hemolytic potential assay in rat, dog, and human blood.

3.2 Studies Not Reviewed

Drug Dependence Studies

3.3 Previous Reviews Referenced

IND 103420, D. Charles Thompson, Ph.D., August 18, 2011.
IND 103420, D. Charles Thompson, Ph.D., May 18, 2012.
IND 103420, D. Charles Thompson, Ph.D., September 30, 2015.

4 Pharmacology

4.1 Primary Pharmacology

In *in vitro* binding assays, lasmiditan had low nanomolar affinity to the mouse, rat, rabbit, dog, and human 5-HT_{1F} receptors. Lasmiditan had at least a 250-fold higher affinity for the human 5-HT_{1F} receptor compared to other human receptor subtypes (5-$HT_{1A, 2A, 1B, 2B, 2C, 1D, 1E, 6, and 7}$). In cellular assays, lasmiditan showed functional agonist activity at the 5-HT_{1F} receptor, with EC_{50} values in the low nanomolar range; there was no activity (up to 10 µM) at other 5-HT receptor subtypes (1A, 1B, and 1E).

In rodent efficacy models, lasmiditan was assessed for inhibition of trigeminovascular protein extravasation (neuroinflammatory response), induction of c-fos, dural-evoked nociception transmission, CGRP release (*ex vivo*), and vasodilation. In the protein extravasation model, rats (4 M/group) were administered oral doses of lasmiditan (up to 10 mg/kg) 1 hour prior to electrical stimulation of the trigeminal nerve. The ID_{50} for inhibition of extravasation was $2x10^{-4}$ µg/kg at 1 hour post stimulation. In the c-fos expression model, rats (6-8 M/group) were given oral doses of lasmiditan (up to 100 µg/kg) 1 hour prior to stimulation. There were dose-dependent decreases (up to 50%, 1.5 hours post stimulation) in c-fos staining in second order nociceptive neurons located in the cervical, spinal substantia gelatinosa, and the brainstem nucleus caudalis. In the assessment of dural-evoked trigeminovascular nociception, IV administration of 5 mg/kg lasmiditan (90 minutes prior to stimulation) to rats (5-10 M/group) produced a maximum decreased in the neuronal responses of approximately 40% (at 90 min). In the *ex vivo* assessment of CGRP release from the mouse trigeminovascular system, pretreatment with lasmiditan or sumatriptan (up to 30 µM, 10 minutes prior to stimulation) resulted in both attenuating CGRP release (~55%) after KCl challenge. In an assessment of vasodilatory response, rats were dosed with IV lasmiditan or sumatriptan (up to 10 mg/kg) pre or post administration of IV capsaicin, periarterial electrical stimulation, or administered α-CGRP. Both sumatriptan and lasmiditan inhibited dural artery vasodilation in response to IV capsaicin and periarterial electrical stimulation by approximately (70%). Neither sumatriptan nor lasmiditan inhibited α-CGRP induced vasodilation. With no stimulation, sumatriptan dose-dependently increased mean arterial pressure and dural artery diameter, while lasmiditan did not.

4.2 Secondary Pharmacology

Using radiolabeled receptor binding assays, approximately 50 ion channels and receptors were assessed for affinity to lasmiditan and its metabolites. Lasmiditan did not demonstrate affinity for the other ion channels or receptors, when tested at concentrations <10µM. The M7 metabolite was found to have inhibitory activity (68%) at the $GABA_A$ receptor at 10 µM in a radioligand counter screening study.

In functional assays measuring current from different exogenously expressed $GABA_A$ isoforms (α1/β3/γ2, α2/β3/γ2, α3/β3/γ2, α4/β3/γ2, and α5/β3/γ2) in HEK293 cells, there were no agonist, antagonist, or positive allosteric modulation (PAM) activities associated with lasmiditan or its major metabolites (M3 and M7) at concentrations up to 100 µM.

4.3 Safety Pharmacology

Lasmiditan and its metabolites, M7, M8, (S,S)-M18, and (S,R)-M18, were tested in the hERG assay in HEK cells. The IC_{50} (~3.0 µM, or 1170 ng/mL) for hERG inhibition was 4-fold higher than the human $C_{max, u}$ (299 ng/mL) for lasmiditan following a single oral 200 mg dose. IC_{50}s for M7, M8, (S,S)-M18, and (S,R)-M18 were greater than 30 µM.

In the *in vivo* single dose (0, 0.6, 2, or 6 mg/kg, 20-minute IV infusion) cardiovascular study in dogs (8/dose, 2 M and 6 F), inotropic state, systemic arterial pressures, heart rate, and electrocardiograms were recorded. There were no drug-related findings. ECG assessments in 2-, 4-, 13-, and 39-week oral and IV toxicology studies also showed no drug related findings.

In a single dose (0, 0.1, 1, 4, or 12 mg/kg, IV) study in mice (~10 M/group), which evaluated behavioral and CNS endpoints (Irwin,1968), the following observations were made: decrease in activity at the HD, which correlated with decreased core body temperature; increase in the convulsive threshold in the electroshock and pentylenetetrazol administration tests at the HD; a reduction in the number of writhes after intraperitoneal injection of acetic acid at the HD; increase in response times in the sensorimotor reactivity to an auditory stimulus test in all lasmiditan groups.

In a 2-week dog study (3/sex/group; 2, 6, or 15 mg/kg, IV), a neurological evaluation showed no drug-related findings.

In single dose respiratory and renal system studies in rats (8/group) IV doses of 0, 1, 4, or 12 mg/kg were assessed. There were no drug-related findings.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 103420*, D. Charles Thompson, Ph.D.,* August 18, 2011*)*

In *ex vivo* studies, lasmiditan (up to 100 µM) did not induce constriction of the rabbit saphenous vein, dog coronary or carotid artery, guinea pig atria and ileum, human internal mammary artery, or human proximal or distal coronary artery.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Liquid chromatography with tandem mass spectrometric (LC-MS/MS) detection methods were validated for lasmiditan and its major metabolites in mouse, rat, rabbit, dog, and human plasma.

Single and repeat dose PK/TK studies were conducted in mouse, rat, rabbit, and dog. When CD-1 mice (~4/group) were administered a single oral dose of 200 mg/kg, T_{max} occurred at 30 minutes, and $t_{1/2}$ ranged between 5 to 7 hours for lasmiditan and major metabolites M3 and M7. In repeat oral dose studies (see table below), C_{max} and $AUC_{0\text{-}24\ h}$ were similar between sexes for lasmiditan and its metabolites. C_{max} generally increased less then dose proportionally for lasmiditan and metabolites M3, M7, and M8. $AUC_{0\text{-}24\ h}$ increased approximately dose proportionally for lasmiditan and metabolite M18. Repeat dosing did not result in accumulation of lasmiditan or its metabolites.

Repeat oral dose studies in mouse

Study type	Duration	Strain	Dose mg/kg
Tox-TK	2-day	CD-1	Up to 250
Tox-TK	12-day	CD-1	Up to 200
Tox-TK	4-week	WT Ras H2	Up to 250
Carcinogenicity	26-week	Ras H2	Up to 150(M)/250(F)

In SD rats administered a single oral dose of up to 100 mg/kg or an IV dose of 6 mg/kg, the $t_{1/2}$ for lasmiditan and radioactivity was 2 to 3 hours and 27 to 32 hours, respectively. For oral dosing, bioavailability was approximately 60%. In repeat dose IV studies in Fischer rats (4, 12, or 40 mg/kg daily for 2 weeks) and pregnant SD rats (5, 15, or 75 mg/kg during GD 6 through 17), C_{max} increased dose proportionally and less than dose proportionally, respectively. $AUC_{0\text{-}24\ h}$ increased dose proportionally for both SD and Fischer rats.

In repeat dose oral studies in rat (up to 100 mg/kg for 4 weeks; up to 200 mg/kg for 13 and 26 weeks; up to 75 mg/kg in a 2-year carcinogenicity study; and up to 250 mg/kg on GD 6 through 17 in an embryofetal development study), exposure (C_{max} and $AUC_{0\text{-}24\ h}$) values were similar between sexes for lasmiditan and its metabolites (M3, M7, M8, (S,S)-M18, and (S,R)-M18). C_{max} generally increased less then dose proportionally and $AUC_{0\text{-}24\ h}$ increased approximately dose proportionally. After repeat dosing, exposures for lasmiditan and its metabolites was approximately unchanged.

Distribution studies (with [^{14}C]lasmiditan) in rat show that lasmiditan crosses the blood brain barrier, with brain to plasma ratios of approximately 3 over a 24-hour period after IV dosing. The highest concentrations of [^{14}C]lasmiditan were found in the urinary bladder and uveal tract of the eye. In distribution studies in the CNS, the highest concentrations of lasmiditan were found in the pituitary gland, pineal gland, and cerebrospinal fluid. In pregnant rats, a whole-body autoradiograph found [^{14}C]lasmiditan radiation was measurable in all fetal tissues at 24 hours post dose.

In the plasma, approximately 55% of lasmiditan was protein bound in rat, dog, and human, and 90% in monkey.

After oral administration, recovery of [^{14}C]lasmiditan from rats and dogs was approximately 90 and 80%, respectively. ^{14}C was primarily excreted in the urine, with only 28% excreted in the feces. After oral dosing of lactating rats, [^{14}C]lasmiditan radiation was detected in the milk, resulting in a milk to plasma AUC ratio of ~3.

The most abundant metabolites of lasmiditan in plasma, after oral administration of lasmiditan were: M3 in mouse, rat, and dog; M8 in rabbit; M8 and M18 in human.

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: A Single-Dose Toxicity Study in Fischer 344 Rats Given LY573144 Hemisuccinate Intravenously

Study no.:	R036025
Study report location:	EDR
Conducting laboratory and location:	Eli Lilly and Company Indianapolis, IN, USA
Date of study initiation:	May 21, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot 02100258, purity 84.4%

Summary Description and Conclusions
Fischer 344 rats (5/sex/dose; 9-10 weeks old; 141-200 g) were administered a single intravenous (10 mL/kg via tail vein) dose of lasmiditan at dose levels of 0 (normal saline), 10, 30, or 100 mg/kg and then observed for morbidity/mortality over 14 days. All animals underwent necropsy. Two males dosed at 100 mg/kg died immediately following dosing and the remaining HD animals were not dosed and were removed from the study. No other treatment-related effects were reported.

(Taken from Pharmacology/Toxicology IND Review and Evaluation, IND 103420*, D. Charles Thompson, Ph.D.,* August 18, 2011*)*

Study title: A Dose-Escalating Toxicity Study in Beagle Dogs Given 573144 Hydrochloride (Compound 587815) by 20-Minute Infusion

Study no.:	B01-240
Study report location:	EDR
Conducting laboratory and location:	Not specified
Date of study initiation:	June 21 2001
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Lasmiditan, lot 01109687, purity not defined

Summary Description and Conclusions
Beagle dogs (1/sex/dose; 27-29 months old; 12-15 kg) were administered a single 20-minute IV infusion of lasmiditan (0.2 mL/kg/min in 0.9% NaCl) at dose levels of 5, 20, and 30 mg/kg (control group not included). Animals were monitored (mortality, body weight, food consumption, clinical signs, and TK) for up to 7 days post infusion and then returned to test facility stock. At 30 mg/kg, hypoactivity, abnormal gait, lateral recumbency, myoclonic movement of legs, head down, liquid feces, licking, emesis, and a low temperature were observed. At 20 mg/kg, head shaking, recumbency, abnormal gait, tremor, hypoactivity, hypersalivation, and emesis were observed. The NOAEL was the LD.

(Taken from Pharmacology/Toxicology IND Review and Evaluation, IND 103420*, D. Charles Thompson, Ph.D.,* August 18, 2011*)*

Study title: Escalating Dose Range-Finding Capsule Study with COL-144 in Dogs

Study no.:	7874-101
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Could not be located
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Lasmiditan, lot # and purity: not specified

Methods

Doses:	10, 30, 60, 90, or 120 mg/kg
Frequency of dosing:	Animals were given escalating doses for 5 days on Days 1, 2, 5, 6, and 7
Route of administration:	Oral
Dose volume:	N/A
Formulation/Vehicle:	Gelatin capsules
Species/Strain:	Dog/beagle
Number/Sex/Group:	2/sex/group
Age:	6 months old at initiation of dosing
Weight:	7.1 to 9.2 kg
Satellite groups:	None
Unique study design:	In each group, animals were dosed on Days 1, 2, 5, 6, and 7 at the following dose levels 10, 30, 60, 90, and 120 mg/kg, respectively.
Deviation from study protocol:	None affecting study validity

Summary Description and Conclusions

The following parameters were assessed: clinical signs, body weight, and clinical pathology. At ≥60 mg/kg/day, there were drug-related tremors. At ≥90 mg/kg, there were additional signs of ataxia, myoclonic jerking, and hypoactivity. One male and one female administered 120 mg/kg were sacrificed 1-hour post dose due to clonic convulsions. The MTD and NOAEL were 60 and 30 mg/kg, respectively.

6.2 Repeat-Dose Toxicity

Study title: Dose Range-Finding and Multiple-Dose Toxicity and Toxicokinetic Study with COL-144 in Mice

Study no.:	7874-112
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 24, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot 02100258, purity 99.7%

Methods

Doses:	Phase 1: 0, 10, 30, 50, 100, or 200 mg/kg Phase 2: 0, 30, 100, 200, or 300 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.25% methylcellulose in water.
Species/Strain:	Mice/Crl:CD1(ICR)
Number/Sex/Group:	Phase 1: 5 males/group; Phase 2: 10/sex/group; TK: 6/sex/group (C) and 36/sex/group (Dosing)
Age:	At dosing initiation (Phase 2): 7 weeks
Weight:	28.3 to 39.5 (M); 20.5 to 32.9 (F)
Satellite groups:	None
Unique study design:	Phase 1 MTD study + Phase 2 main study
Deviation from study protocol:	None affecting study validity

Summary Description and Conclusions

In the Phase 1 study, all animals survived, and there were no drug-related findings. In the Phase 2 study, at ≥300 mg/kg/day, all animals were terminated after a single dose due to drug-related convulsions, clonic convulsions, tremors, ataxia, hypoactivity, few or no feces, squinted eyes, rough haircoat, irregular respiration, and hunched posture. The NOAEL was 200 mg/kg/day. Plasma exposures in Phase 2, on Day 13: C_{max}: 8,543 ng/mL (M) and 5,427 ng/mL (F), $AUC_{0\text{-}24\ h}$: 55,199 ng*h/mL (M) and 45,666 ng/*h/mL (F).

Study title: 30-Day Oral Gavage Toxicokinetic Study with COL-144 in Mice

Study no.:	8225235
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 15, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot 77056-02, purity 101.5%

Methods

Doses:	100 or 200 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	10 mL/kg,
Formulation/Vehicle:	Methylcellulose 0.25% (w/v) in water.
Species/Strain:	Mouse/Crl:CD1(ICR)
Number/Sex/Group:	60/sex/group TK: 5/sex/group
Age:	At dosing initiation: 6-7 weeks
Weight:	26.8 to 38.7 g (M); 17.9 to 32.9 g (F)
Satellite groups:	TK
Unique study design:	None
Deviation from study protocol:	None affecting study validity

Summary Description and Conclusions

Animals were assessed for clinical observations, body weights, food consumption, and TK on Days 1 and ~30. No animals were necropsied. At 100 mg/kg, 2 males and 3 females found dead or moribund were replaced between Days 3 and 7. At 200 mg/kg, one male was found dead, with no cause identified, and a female was euthanized on Day 25 due to hunched appearance, swollen ventral thorax (left), and few feces. Based on mortality in both groups, a NOAEL could not be defined.

Exposure (C_{max} and $AUC_{0\text{-}24\ h}$) for lasmiditan and its metabolites increased from 100 to 200 mg/kg (see sponsor's tables below). Repeat dosing did not result in accumulation of lasmiditan or its metabolites.

COL-144

Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)
Day 1				
100	M	5066	0.5	41,845
	F	3582	0.5	30,306
200	M	9480	0.5	54,319
	F	6474	1	48,795
Day 30				
100	M	3812	1	34,457
	F	3834	1	28,093
200	M	6118	0.5	58,482
	F	5154	1	45,588

Day 30/Metabolites

Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	M/P Ratio
M3					
100	M	1136	1	6759	0.20
	F	1119	0.5	6956	0.25
200	M	2186	1	10,871	0.19
	F	1806	0.5	11,922	0.26
M7					
100	M	1565	0.5	14,920	0.43
	F	975	1	8573	0.30
200	M	2450	1	26,690	0.46
	F	1720	1	14,455	0.32
M8					
100	M	915	1	8845	0.26
	F	934	1	9482	0.34
200	M	1421	1	14,184	0.24
	F	1363	1	15,410	0.34
(S,S)-M18					
100	M	322	2	3427	0.10
	F	261	2	3268	0.12
200	M	517	2	5505	0.09
	F	391	1	4473	0.10
(S,R)-M18					
100	M	89	2	901	0.03
	F	138	2	1598	0.06
200	M	138	2	1436	0.02
	F	162	1	1973	0.04

Sponsor's tables

(Taken from Pharmacology/Toxicology IND Review and Evaluation, IND 103420*, D. Charles Thompson, Ph.D.,* May 18, 2012*)*

Study title: 13-Week Oral Gavage Preliminary Carcinogenicity Dose Range-Finding Study with COL-144 in Mice

Study no.:	7874-126
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 15, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot 77056-02, purity 101.2%

Methods

Doses:	0, 30, 100, or 200 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	10 mL/kg
Formulation/Vehicle:	Methylcellulose 0.25% (w/v) in water.
Species/Strain:	Mice/Crl:CD1(ICR)
Number/Sex/Group:	Main Study: 10/sex/group; TK: 36/sex/group
Age:	At dosing initiation: 7 weeks
Weight:	24.7 to 35.7 g (M); 20.5 to 32.9 g (F)
Satellite groups:	TK
Unique study design:	None
Deviation from study protocol:	None affecting study outcome

Summary Description and Conclusions

There was a total of 18 unscheduled deaths, 8 in the main study (1 C, 5 LD, and 2 HD) between Days 14 and 29, which the sponsor attributed to gavage error, and 10 in the TK study (2 C, 6 LD, and 2 HD) between Days 10 and 26, with no cause of death indicated. There were no drug-related clinical signs, body weight, food consumption, gross pathology, or histopathology findings. The NOAEL was the HD, corresponding to Week 13 C_{max} and $AUC_{0\text{-}24\ h}$ values of 7,130 ng/mL and 64,144 ng•hr/mL, respectively, in males, and 4,733 ng/mL and 46,905 ng•hr/mL, respectively, in females.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 103420, D. Charles Thompson, Ph.D., May 18, 2012)

Study title: A Toxicity and Companion Blood Level Study in Sprague-Dawley Rats Given Daily Infusion Doses of Compound 573144 Hydrochloride (587815) Over a 20-Minute Period for 4 Days

Study no.:	B01-266
Study report location:	EDR
Conducting laboratory and location:	Not specified
Date of study initiation:	July 9, 2001
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Lasmiditan, lot 01109687, purity not specified

Summary Description and Conclusions

Lasmiditan was administered by IV infusion (over 20 minutes) for 4 days at doses of 0, 10, 25, and 55 mg/kg (5 mL/kg, 3/F/group). One HD rat died following the fourth dose (Day 3). There were dose-related intermittent tremors, sternal recumbency, labored respiration, shaking, and/or decreased activity in MD and HD animals. The HD animals also exhibited sternal recumbency and labored respiration throughout the study. In the MD and HD groups, there were decreases in body weight of 3 to 4 g (Day 3), with no corresponding change in food consumption. In HD rats, there was a slight to moderate increase in reticulocyte count (187%) and mean corpuscular volume (12%). There were dose-related decreases in thymus weight of 7 and 36%, associated with minimal to slight thymic involution, at the MD and HD, respectively. The NOAEL was the LD (C_{max}=1140 ng/mL; $AUC_{0 \text{ to } 24 \text{ h}}$ =3300 ng*h/mL).

Table 1: Pharmacokinetic Parameters for 573144 Administered as the Hydrochloride Salt (587815), After Single Intravenous Administration

Dose (mg/kg)	Group	C_{max} (ng/mL)	C_{max}/D (ng/mL)	$t_{1/2}$ (h)	$AUC_{0\rightarrow 24}$ (h*ng/mL)	$AUC_{0\rightarrow\infty}$ (h*ng/mL)	AUC/D (h*ng/mL)
10	5	1140	114	3.2	3300	3310	331
25	6	4970	199	3.1	10100	10100	406
55	7	7310	133	3.6	27300	27500	500

Sponsor's table

Study title: A 2-Week Intravenous Infusion Toxicity Study of LY573144 Hemisuccinate (Compound 683974) in the Fischer 344 Rat

Study no.:	57493
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 06, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot 02100258, purity 86.4%

Key study findings: The NOAEL was the HD (C_{max} = 3,884 mg/mL; AUC = 14,036 ng*hr/mL)

Methods

Doses:	0, 4, 12, or 40 mg/kg
Frequency of dosing:	20 min daily
Route of administration:	IV
Dose volume:	0.2 mL/kg/min
Formulation/Vehicle:	0.9% Sodium Chloride for Injection
Species/Strain:	Rattus norvegicus, Fischer 344
Number/Sex/Group:	10/sex/control and 17/sex/LY573144
Age:	10 to 18 weeks
Weight:	M: 175 – 227 g; F: 118 – 164 g
Satellite groups:	TK
Unique study design:	None
Deviation from study protocol:	There were minor deviations that did not affect study validity

Observations and Results

Mortality

Observations were made twice daily.

There were no deaths during this study.

Clinical Signs

Detailed observations were made daily.

There were no drug-related findings.

Body Weights

Recordings were made weekly.

There were no drug-related findings.

Food Consumption

Recordings were made weekly.

There were no drug-related findings.

Ophthalmoscopy

Examinations were made prior to dosing and during Week 2.

There were no drug-related findings.

ECG

Not assessed.

Hematology

The following parameters were assessed: activated partial thromboplastin time, blood, cell morphology, erythrocyte indices (MCV, MCH, MCHC and RDW), hematocrit, hemoglobin, mean platelet volume, platelet count, prothrombin time, red blood cell count, reticulocyte count, and white blood cell count (total, absolute, and differential).

There were no drug-related findings.

Clinical Chemistry

The following parameters were assessed: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, cholesterol, creatinine, creatinine kinase, globulin (calculated), glucose, inorganic, phosphorus, potassium, sodium, total bicarbonate, total bilirubin, total protein, and triglycerides.

There were no drug-related findings.

Urinalysis

The following parameters were assessed: bilirubin, blood, color and appearance, creatinine, GGT, glucose, ketones, LDH, NAG, nitrite, pH, protein, specific gravity, urobilinogen, and volume.

There were no drug-related findings.

Gross Pathology and Organ Weights

There were no drug-related findings.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Signed pathology report: Yes

Histological Findings

There were no drug-related findings.

Special Evaluation

None

Toxicokinetics

C_{max} and $AUC_{0\text{-}24.33\ h}$ were similar between sexes and increased dose proportionally. Drug $t_{1/2}$ occurred between 2 and 7 hours post dose. There were no drug-related effects on P450 enzymes.

	Administered LY573144 Dose (mg/kg/day, n = 1/time point/sex/group)								
Parameter	4			12			40		
Sex	M	F	M + F	M	F	M + F	M	F	M + F
Day 1									
C_{max} (ng/mL)	349	280	315	931	857	894	4201	3080	3632
AUC (ng•hr/mL)	1004	1058	1031	3304	3262	3283	12666	14248	13457
$AUC_{0\text{-}\infty}$ (ng•hr/mL)	1051	1059	1049	3312	3269	3290	12697	14282	13490
Day 14									
C_{max} (ng/mL)	297	299	298	1147	1149	1148	4351	3417	3884
$AUC_{0\text{-}24.33\ hr}$ (ng•hr/mL)	945	1093	1019	3115	3734	3424	12291	15781	14036

Abbreviations: M = male; F = female; C_{max} = maximal plasma concentration observed; AUC = area under the concentration-time curve; $AUC_{0\text{-}\infty}$ = area under the concentration-time curve Time 0 to infinity; $AUC_{0\text{-}24.33}$ = area under the concentration-time curve Time 0 to 24.33 hours (tau).

Sponsor's table

Dosing Solution Analysis

Daily doses were within ±20 % of nominal.

Study title: A Repeat-Dose Study in Fischer 344 Rats Given Compound 573144 Hydrochloride (587815) Daily by Gavage for 4 Days

Study no.:	B01-135
Study report location:	EDR
Conducting laboratory and location:	Not specified
Date of study initiation:	April 23, 2001
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Lasmiditan, lot 01107852, purity not specified.

Summary Description and Conclusions

The toxicology and TK of lasmiditan hydrochloride was assessed at 0, 50, 150, or 300 mg/kg (3/males/group) over a 4-day period. There were two HD animals with convulsions, one died on Day 2. There were no hematology, clinical chemistry, organ weight, or histopathology findings. C_{max} and $AUC_{0\text{-}24\ h}$ increased less than dose proportionally. The MTD was 150 mg/kg.

Time (hr)	50 mg/kg	150 mg/kg	300 mg/kg
0.5	1210	2030	2010
1	1230	2440	4150
2	975	1230	2760
4	455	1040	2020
8	363	873	1450
24	20.5	409	749
AUC(0-24hr) (ng*hr/mL)	8149	19812	34810
AUC/Dose	163	132	116
Cmax (ng/mL)	1230	2440	4150
Cmax/Dose	25	16	14
Tmax (hr)	1	1	1

Sponsor's Table

Daily doses were within ±20 % of nominal values.

Study title: 5-Day Oral Gavage Toxicity and Toxicokinetic Study with COL-144 in Male SD Rats

Study no.:	7874-100
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Could not locate in study report
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Lasmiditan, lot # and purity not specified

Summary Description and Conclusions

Lasmiditan (0, 10, 30, 60, 100, 250, or 300 mg/kg, 3 males/group) was administered orally for 5 days. At doses ≥250 mg/kg, there was decreased body weight gain (60%, 250 mg/kg; 23%, 300 mg/kg) and lower food consumption. Clinical chemistry was assessed, and there were no drug-related findings. The NOAEL was 100 mg/kg.

TK was assessed at 30 mg/kg. T_{max} and $t_{1/2}$ were 1 and 3 hours, respectively. C_{max} was 934 ng/mL and $AUC_{0-\infty}$ was 9185 ng*h/mL.

Study title: A Repeat-Dose Study in Fischer 344 Rats Given Compound 573144 Hydrochloride (587815) Daily by Gavage for 14 Days

Study no.:	B01-217
Study report location:	EDR
Conducting laboratory and location:	Lilly Development Centre, Mont-Saint-Guibert, Belgium
Date of study initiation:	June 13, 2001
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Lasmiditan, lot # 01109687, purity not specified.

Summary Description and Conclusions

Lasmiditan (0, 30, 100, or 250 mg/kg, main study: 5/sex/group, TK: 7/sex/group) was assessed for mortality, clinical signs, body weight, clinical chemistry, histopathology, and TK. In MDF and HDF, mortality was observed in 1 and 2 animals, respectively. One of the HDF experience convulsions prior to death (Day 6). No cause of death was identified for the other HDF (Day 9) or MDF (Day 11). Histopathology findings consisted of medullary tubular degeneration of the kidney in all HDM, HDF, and MDM, which correlated with increased water consumption. In all HD animals, hepatocellular hypertrophy, foamy alveolar macrophages, epithelial vacuolation in the seminal vesicle, vacuolation and lymphoid depletion of the marginal zone in the spleen, cortical hypertrophy of the adrenals, decreased hematopoietic tissue in the bone marrow, and thymic involution were also observed (see sponsor's table below).

Histologic Changes in Rats Given Compound 573144

Final necropsy		Administered Dose (mg/kg/day)					
		30		100		250	
Sex		M	F	M	F	M	F
Lesions (incidence) / N° in group		**5**	**5**	**5**	**4**	**5**	**3**
Adrenal	(Cortical Hypertrophy)			--	--	5(MI-SL)	3(MI-SL)
Bone Marrow	(Decreased Hematopoietic Tissue)			--	--	2(MI-SL)	--
Kidney	(Medullary Tubular Degeneration)	--		5(MI)	--	5(SL)	3(MI-SL)
	(Mitosis)	--		2(MI)	--	5(SL-MO)	2(MI)
	(Protein Cast)	--		--	--	5(MI-SL)	1(MI)
Liver	(Hepatocellular Hypertrophy)			--	--	5(MI-SL)	3(MI-SL)
Lung	(Foamy Alveolar Macrophages)			--	--	5(MI)	3(MI-SL)
Seminal Vesicle	(Epithelial Vacuolation)			--		5(MI-SL)	
Spleen	(Marginal Zone Vacuolation)			--	--	5(MI)	3(SL)
	(Lymphoid Depletion)			--	--	5(MI-MO)	3(SL-MO)
Thymus	(Involution)			--	--	5(MI-SL)	3(SL)

Symbols: M = male; F = female; -- = No changes.
Severity grading scale: Minimal (MI); slight (SL); moderate (MO).

TK data showed that drug accumulated in the MD and HD (up to 2-fold) groups. The NOAEL, based on mortality, was the LD.

Table 13 Pharmacokinetic Parameters for 573144 Hydrochloride (587815) in Male and Female Fischer 344 Rats (n = 1), After Single and Multiple (14 Days) Oral Administration of 30, 100, or 250 mg/kg

Dose (mg/kg)	Day	Sex	T_{max} (hr)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	*$AUC_{0\text{-}24/28hr}$ (hr.ng/mL)	Calculated $AUC_{0\text{-}24}$ (hr.ng/mL)	C_{max}/D (ng/mL)	$AUC_{0\text{-}24}$/D (hr.ng/mL)
30	1	F	0.50	1200	5.4	7690	7690	40	256
30	1	M	0.50	1510	2.9	9760	9760	50	325
30	13	F	0.50	1420	3.9	9600	9023	47	301
30	13	M	0.50	1370	nc	8450	7964	46	265
100	1	F	1.00	2090	8.4	22600	22600	21	226
100	1	M	0.50	1690	nc	17400	17400	17	174
100	13	F	1.00	2810	5.6	28300	27471	28	275
100	13	M	1.00	2390	4.0	28400	27739	24	277
250	1	F	1.00	4650	7.7	40900	40900	19	164
250	1	M	1.00	5440	10.8	39300	39300	22	157
250	13	F	1.00	5170	10.9	80100	75355	21	301
250	13	M	1.00	4240	nc	77900	70033	17	280

nc: not calculable
* AUC was calculated to 28 hours for the Day 13 samples, as the 24-hour sample was taken at 28 hours postdose.

Sponsor's table

(Taken from Pharmacology/Toxicology IND Review and Evaluation, IND 103420*, D. Charles Thompson, Ph.D.,* August 18, 2011*)*

Study title: 4-Week Oral Gavage Toxicity and Toxicokinetic Study with COL-144 in Rats with a 2-Week Recovery Period

Study no.:	7874-108
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 4, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot 02100258, purity 101.2%.

Methods

Doses:	0, 10, 30, 50, or 100 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Methylcellulose 0.25% (w/v) in water
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	Main study: 10/sex/10 to 50 mg/kg, 15/sex/C & 100 mg/kg TK: 9/sex/10 to 100 mg/kg, 3/sex/C
Age:	At study initiation: 5 to 6 weeks old
Weight:	At study initiation: M: 251-348 g; F: 161 -229 g
Satellite groups:	TK
Unique study design:	N/A
Deviation from study protocol:	There were minor deviations which did not affect study validity

Summary Description and Conclusions

Animals were assessed for mortality, clinical signs, body weight, food consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, histopathology, and TK. The NOAEL was the HD, with C_{max} values of 1440 ng/mL (M) and 1867 ng/mL (F) and $AUC_{0\text{-}24\ h}$ values of 22,454 ng•hr/mL (M) and 23,808 ng•hr/mL (F).

(Taken from Pharmacology/Toxicology IND Review and Evaluation, IND 103420*, D. Charles Thompson, Ph.D.,* August 18, 2011*)*

Study title: 13-Week Oral Gavage Toxicity and Toxicokinetic Study with COL-144 in Rats with a 4-Week Recovery Period

Study no.:	7874-116
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 18, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot 77056-02, purity 101.2%

Methods

Doses:	0, 10, 30, 50, 100, or 200 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Methylcellulose 0.25% (w/v) in water
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	Main study: 10/sex/10 to 50 mg/kg,15/sex/0, 100, & 200 mg/kg TK: 9/sex/10 to 200 mg/kg, 3/sex/C
Age:	At study initiation: 6 to 7 weeks old
Weight:	At study initiation: M: 190-290 g F: 149-199
Satellite groups:	TK
Unique study design:	Animals were housed individually
Deviation from study protocol:	There were minor deviations which did not affect study validity

Summary Description and Conclusions

There were three unscheduled deaths. Two deaths in females (100 and 200 mg/kg) were attributed to dosing or blood sampling error. A third death (HDM) had evidence of an erosive inflammatory response in the GI tract. The sponsor did not believe this death was drug-related because no other HD animals had this finding. One HDM and 4 HDF were observed with swollen abdomen, which did not resolve during the recovery period. There were no drug-related findings on body weight, food consumption, or hematology parameters. At 100 and 200 mg/kg, there were increases urine volume and decreases urine specific gravity, suggesting drug-related effects on renal function. There were drug-related increases in heart (~15%-HD), liver (~15%-MD, ~50%-HD), adrenal (~27%-HDF), and kidney (up to~45%, dose related) weights, relative to brain and body weight. The increase in liver weight was correlated with histopathology findings of centrilobular hepatocyte vacuolation at ≥50 mg/kg. The increased kidney weight was correlated with kidney lesions consistent with chronic progressive nephropathy (CPN) in males ≥100 mg/kg and females at 200 mg/kg. The NOAEL was 50 and 100 mg/kg for males and females, respectively (Week 13: C_{max} was 1617 ng/mL in males and 2253 ng/mL in females and $AUC_{0\text{-}24\ h}$ was 18233 ng*h/mL in males and 32523 ng*h/mL in females).

TK parameters for lasmiditan and metalbillies M3, M7, M8, and M18 were evaluated; however, only data for lasmiditan and M8 were presented; levels of the other metabolites were generally below detection limits. Exposure (C_{max} and $AUC_{0\text{-}24\ h}$) was generally similar between sexes. Exposure for lasmiditan increased less then dose proportionally. Exposure for M8 increased dose proportionally up to 100 mg/kg and less then dose proportionally at HD on Day 1. During Week 13, exposure generally increased greater than dose proportionally. Lasmiditan and M8 accumulated after repeat dosing. The M8 to lasmiditan $AUC_{0\text{-}24\ h}$ ratios did not change with increased or repeated dosing.

(Taken from Pharmacology/Toxicology IND Review and Evaluation, (b) (4)*, D. Charles Thompson, Ph.D.,* May 18, 2012*)*

Study title: 26-Week Oral Gavage Toxicity and Toxicokinetics Study in Rats with an 8-Week Recovery

Study no.:	8202968
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 19, 2019
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, batch no. 77056-02, purity 101.9%

Key Study Findings

The NOAEL was 50 mg/kg (C_{max}: 1,619 ng/mL; $AUC_{0\text{-}24\ h}$: 18,404 ng*h/mL), based on death, CNS related clinical signs, CPN, and cardiomyopathy at higher doses.

Methods

Doses:	0, 10, 30, 50, 100, or 200 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	Methylcellulose 0.25% (w/v) in water
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	Main study: 10/sex/10 to 50 mg/kg,16/sex/0, 100, & 200 mg/kg TK: 9/sex/LD to HD, 3/sex/C
Age:	At study initiation: 6 to 7 weeks old
Weight:	At study initiation: M: 185-280 g; F: 139-222 g
Satellite groups:	TK
Unique study design:	Animals were housed individually
Deviation from study protocol:	There were minor deviations which did not affect study validity

Summary Description and Conclusions

There were 8 unscheduled deaths. In 3 males (1 at 50 mg/kg and 2 at 200 mg/kg) and 3 HDF, no cause of death was determined. One male (50 mg/kg) and one female (30 mg/kg) were sacrificed with findings consistent with gavage-related injury and a mammary carcinoma, respectively. Convulsions and/or myoclonic jerking were noted in one control female, one 100 mg/kg male, one HD male, and two HD females. The frequency of convulsions generally increased in HD animals. During the recovery period, convulsions persisted in the control female and the two HD females. In the HD males, there were decreases in body weight (11%) and body weight gain (16%), which resolved during the recovery period. In all HD animals, there were nonreversible clinical chemistry finds of higher urine protein-to-creatinine ratio, mildly higher UNAG-to-creatinine ratio (males), and lower urine specific gravity. These findings correlated with histopathology observations of lesions in kidney that were consistent with CPN and increased kidney weights in main study and recovery animals. Other drug-related histopathology findings included pigmentary inclusions in the cytoplasm of large motor neurons of the brain stem and spinal cord of HD main study and recovery animals. These inclusions were not associated with degenerative changes in affected neurons or surrounding nerve tissue or clinically observed functional effects, and they partially resolved during the recovery period. Degenerative cardiomyopathy and increased heart weight were observed with increased severity in HD males and increased incidence and severity in HD females. The cardiomyopathy did not resolve during the recovery period.

The increases in lasmiditan, M3, M7, (S,S)-M18 and (S,R)-M18 exposure (C_{max} and $AUC_{0\text{-}24\ h}$) were generally less than dose proportional. The increases in M8 C_{max} for males and females were generally less than dose proportional, while the increases in $AUC_{0\text{-}24\ h}$ were roughly dose proportional. Accumulation of lasmiditan, M3, M7, M8, (S,S)-M18 and (S,R)-M18 was observed after repeat dosing. Exposure values were similar between sexes for lasmiditan, M8, (S,R)-M18. Males generally had higher M3 and lower M7 and (S,S)-M18 exposure than females. The NOAEL was 50 mg/kg (see table below).

NOAEL Exposure (Male/Female)

Drug/metabolite	C_{max} ng/mL	$AUC_{0\text{-}24\ h}$ ng.h/mL
lasmiditan	1747/1490	17891/18917
M8	83 /83	1199 /1140
M3	992/830	7827/8013
M7	913/852	7793/10134
(S,S)-M18	384/817	5339/11641
(S,R)-M18	81/80	1088/1131

(Taken from Pharmacology/Toxicology IND Review and Evaluation, IND 103420*, D. Charles Thompson, Ph.D.,* May 18, 2012*)*

Study title: A 2-Week Intravenous Infusion Toxicity Study of LY573144 Hemisuccinate in the Beagle Dog

Study no.:	57494
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 2, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % potency:	Lasmiditan, Lot # 02100258, potency 86.4%

Methods

Doses:	2, 6, or 15 mg/kg
Frequency of dosing:	Daily
Route of administration:	20-minute IV
Dose volume:	3.3 mL/kg
Formulation/Vehicle:	0.9% Sodium Chloride for Injection, U.S.P.
Species/Strain:	Beagle dog
Number/Sex/Group:	3/sex/group
Age:	At study initiation: ~7 months old
Weight:	At study initiation: M: 7.8-9.8 kg; F: 5.5-8.0 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	There were minor deviations which did not affect study validity

Observations and Results

Mortality

Examinations were made twice daily.

There were no animal deaths or morbidity.

Clinical Signs

Detailed examinations were made weekly.

At the HD, there were observations of excessive licking, vomitus (foamy/liquid/mucoid-white/yellow/brown; partly digested food), or retching.

Body Weights

Recordings were made weekly.

There were no drug related findings.

Food Consumption

Recordings were made daily.

There were no drug-related findings.

Ophthalmoscopy

Examinations were made once prior to dosing and during Week 2.

There were no drug-related findings.

ECG and Body Temperature

Examinations were made once prior to dosing, on Day 2, and during Week 2.

There were no drug related findings.

Hematology and Clinical Chemistry

A standard battery of parameters was assessed.

There were no drug-related findings.

Urinalysis

The following parameters were assessed: blood, color and appearance, creatinine, gamma glutamyl transferase GGT, glucose, ketones, LDH, microscopy of sediment, NAG, nitrite, pH, protein, specific gravity, urobilinogen, and volume.

There were no drug-related findings.

Gross Pathology and Organ Weights

There were no drug-related findings.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Signed Pathology Report: Yes

Histological Findings

There were no drug-related findings.

Special Evaluation

CNS

A neurological evaluation was conducted at baseline and during Week 2. The evaluation consisted of behavior, gait, head movements/symmetry, muscle tone, eye reactions/symmetry/position, corneal and pupillary light reflex, nasal septum, tongue and pharynx tests, and spinal nerves (muscle tone and patellar and flexor reflexes).

There were no drug-related findings.

Hepatic Microsomal Enzyme Induction

Total cytochrome P450 content was increased in females at 15 mg/kg.

Toxicokinetics

T_{max} was 0.08 hours and half-life for combined sexes was approximately 1.8 to 3.9 hours. C_{max} and AUC were higher in HDM then HDF.

	Administered LY573144 Dose (mg/kg/day, n = 3/sex/group)								
Parameter	2			6			15		
Sex	M	F	M + F	M	F	M + F	M	F	M + F
Day 1									
C_{max} (ng/mL)	395	385	390	1445	1108	1277	3015	2706	2860
± SEM	± 10	± 25	± 12	± 192	± 120	± 126	± 314	± 277	± 200
$AUC_{0-\infty}$ (ng•hr/mL)	729	868	799	3213	3474	3344	8619	6279	7449
± SEM	± 48	± 96	± 57	± 423	± 139	± 207	± 1091	± 216	± 722
Day 14									
C_{max} (ng/mL)	442	333	388	1110	1060	1085	3257	2337	2797
± SEM	± 47	± 31	± 35	± 271	± 48	± 124	± 167	± 104	± 224
$AUC_{0-24\ hr}$ (ng•hr/mL)	1009	957	983	3186	3519	3353	11634	7415	9525
± SEM	± 149	± 137	± 91	± 274	± 97	± 150	± 788	± 648	± 1048

Abbreviations: SEM = standard error of the mean; M = male; F = female; C_{max} = maximal plasma concentration observed; $AUC_{0-\infty}$ = area under the concentration-time curve Time 0 to infinity, AUC_{0-24} = area under the concentration-time curve Time 0 to 24 hours (tau).

Sponsor's Table

Dosing Solution Analysis

Mean drug concentrations were 98-99% of nominal.

Study title: A Repeat-Dose Study in Beagle Dogs Given 573144 Hydrochloride (Compound 587815) Daily by Oral Route for 2 Weeks

Study no.:	B01-218
Study report location:	EDR
Conducting laboratory and location:	Not specified
Date of study initiation:	June 13, 2001
GLP compliance:	No
QA statement:	No
Drug and lot #:	Lasmiditan and Lot # (587815)/01109687

Methods

Doses:	M: 0, 10, 50/60 mg/kg F: 0, 20, 80/90 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	0.6 mL/kg
Formulation/Vehicle:	10% acacia + 0.1% antifoam
Species/Strain:	Beagle dog
Number/Sex/Group:	1/sex for C, 1 M/ 10 mg/kg, 1 F/ 20 mg/kg, 1 M/50 (D 0) and 60 (D1 to 14) mg/kg, 1 F/80 (D 0) and 90 (D1 to 14) mg/kg
Age:	At study initiation: 11 months old
Weight:	At study initiation: 8-12 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None specified

Observations and Results

Mortality, clinical observations, body weight, food consumption, ECG, hematology, clinical chemistry, histopathology, and TK were assessed. On Day 0, no clinical signs were observed in the male given 50 mg/kg or in the female given 80 mg/kg; therefore, doses were increased to 60 and 90 mg/kg, respectively, from Day 1 to 14. In HDF, emesis, tremors, abnormal gait, loss of balance, lateral recumbency with rigid stance, and hypersalivation were observed. In HDM, emesis was observed.

	Administered Dose (mg 573144/kg/day)					
Parameter	0[a]		10	20	60	90
Sex	M	F	M	F	M	F
Emesis	-	-	-	-	some	repeatedly
Tremor	-	-	-	-	-	D1, 2, 3, 5, 7, 13
Abnormal gait	-	-	-	-	-	D1, 3
Loss of balance	-	-	-	-	-	D1
Recumbency	-	-	-	-	-	D1, 3, 5
Rigid stance	-	-	-	-	-	D5
Hypersalivation	-	-	-	-	-	D7 to 12

Symbols: M = male; F = female.
[a] Vehicle.

Sponsor's table

There were no ECG findings.

According to the sponsor, absolute and relative liver weights were increased at the HD (no data provided), which correlated with hepatocellular hypertrophy findings.

Histologic Changes in Dogs Given Compound 573144 Hydrochloride				
	Administered Dose (mg/kg/day)			
	10	20	60	90
Sex	M	F	M	F
Lesions (incidence) / N° in group	**1**	**1**	**1**	**1**
Liver (Hepatocellular Hypertrophy)	-	-	1(MI)	1(SL)

Symbols: M = male; F = female; - = No changes.
Severity grading scale: minimal (MI), slight (SL).

Sponsor's table

After a single dose, exposure (C_{max} and $AUC_{0\text{-}24\ h}$) increased dose proportionally in females (comparing 20 and 80 mg/kg) and greater than dose proportionally in males (comparing 10 and 50 mg/kg). At 10 and 20 mg/kg, exposure increased after repeat dosing.

Table 4 Pharmacokinetic Parameters for 587815 After Oral Administration in the Beagle Dog

Dose (mg/kg)	Day	Sex	Subject	T_{max} hr	C_{max} ng/mL	$t_{1/2}$ (hr)	$AUC_{0\rightarrow24}$ ng.hr/mL	C_{max}/D	$AUC_{0\rightarrow24}/D$
10	0	M	01B-0725	1.0	417	4.4	2400	42	240
10	14	M	01B-0725	2.0	503	4.2	3830	50	383
20	0	F	01B-0728	1.0	1670	4.8	7380	84	369
20	14	F	01B-0728	1.0	1290	4.1	8950	65	448
50	0	M	01B-0726	1.0	1910	4.0	20000	38	400
60	14	M	01B-0726	2.0	4410	4.6	34600	74	577
80	0	F	01B-0729	3.0	3610	5.3	25900	45	324
90	14	F	01B-0729	2.0	5720	4.6	39500	64	439

Sponsor's table

Study title: 4-Week Oral Capsule Toxicity and Toxicokinetic Study with COL-144 in Dogs with a 2-Week Recovery Period

Study no.:	7874-109
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not specified
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot # 02100258 and purity: 101.2%

Methods

Doses:	0, 5, 10, 20, or 60 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	N/A
Formulation/Vehicle:	Gelatin capsules
Species/Strain:	Dog/beagle
Number/Sex/Group:	3/sex/LD to mid-HD; 5/sex/C & HD
Age:	At dosing initiation: 6.4-7.4 months old
Weight:	6.9 to 10.9 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None affecting study outcome

Summary Description and Conclusions

Mortality, clinical signs, body weights, food consumption, ophthalmoscopy, ECG, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology, microsomal fraction analysis, and TK were assessed. At the HD, CNS signs consisted of tremors, ataxia, and myoclonic jerking. Non-CNS signs at the HD consisted of vomitus, decreased sensitivity to stimulus, excessive salivation, squinted eyes, thin appearance, cold to the touch, panting, dehydration, and pale skin. HD animals lost 10 to 14% of their body weight by Day 29 (M: -0.6 kg; F: -0.3 kg), which correlated with a decrease in food consumption. Compared to control, there was no difference in mean body weight, body weight gain, or food consumption during the recovery period. At the HD, mean liver/gallbladder weights were increased on Day 29, relative to controls (28-39% relative to body weight and 11-24% absolute in males and females, respectively). The increased liver weights were correlated with increases in hepatic cytochrome P450 content and activity, which correlated with minimal hepatocellular hypertrophy in 1/3 HD males.

Exposure (C_{max} and $AUC_{0\text{-}24\ h}$) was generally similar between sexes and generally increased greater than dose proportionally. Drug accumulation was minimal after repeat dosing.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 103420, D. Charles Thompson, Ph.D., August 18, 2011).

Study title: 13-Week Oral Capsule Toxicity and Toxicokinetic Study with COL-144 in Dogs with a 4-Week Recovery Period

Study no.:	7874-125
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 1, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot # 77056-02, and purity: 101.2%

Key Study Findings

The NOAEL was 20 mg/kg, based on based on CNS findings at higher doses.

Week 13 Toxicokinetic Parameters in Dog Plasma at NOAEL[a]

Analyte	Dose Group	COL-144 Dose Level (mg/kg/day)[a]	Interval	Sex	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng·hr/mL)
COL-144	4	20	Week 13	M	1522	2.67	12135
				F	1850	1.33	10696
M3	4	20	Week 13	M	1057	1.67	6976
				F	1577	1.33	6807
M7	4	20	Week 13	M	33.8	2.67	279
				F	48.0	2.33	320
M8	4	20	Week 13	M	261	4.00	3913
				F	213	2.67	2695
M18	4	20	Week 13	M	NR	NR	NR
				F	NR	NR	NR

F = Female; M = Male; NOAEL = No observed adverse effect level; NR = Not reported.

a The NOAEL for COL-144 in male and female dogs was 20 mg/kg/day.

Sponsor's Table

Methods

Doses:	0, 5, 10, 20, or 50 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	N/A
Formulation/Vehicle:	Gelatin capsules
Species/Strain:	Dog/beagle
Number/Sex/Group:	3/sex/LD to mid-HD; 5/sex/C & HD
Age:	At dosing initiation: 6.8-7.5 months old
Weight:	M: 8.1 to 10.5 kg; F: 6.3 to 8.9 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None affecting study outcome

Observations and Results

Mortality

Observations were made twice daily.

There were no animal deaths during the study.

Clinical Signs

Detailed observations were made daily in the main study and weekly during the recovery period.

Vomitus was observed at 20 and 50 mg/kg. Hunched posture, tremors, hypoactive, twitching, squinting eyes (females), and swollen conjunctivae (males) were only observed in HD animals.

Body Weights

Recordings were made weekly.

There were no drug-related findings.

Food Consumption

Recordings were made weekly.

There were no drug-related findings

Ophthalmoscopy

Examinations were conducted during predose, Week 13 of the main study, and Week 4 of the recovery period.

There were no drug-related findings.

ECG

Examinations were conducted during predose, Weeks 6 and 13 of the main study, and Week 4 of the recovery period.

There were no drug-related findings.

Hematology

There were no drug-related findings

Clinical Chemistry

There were no drug-related findings.

Urinalysis

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

There was a dose-dependent increase in liver relative to body weight (up to 45%), which partially resolved during the recovery period (up to 11%).

Histopathology

Adequate Battery: Yes

Peer Review: No

Signed pathology report: Yes

Histological Findings
Drug-related reduced glycogen was observed in the liver of 20 mg/kg males (1/3) and 50 mg/kg males (3/3). Cytoplasmic alteration, characterized by eosinophilic inclusions in hepatocytes, was observed in 50 mg/kg (2/3). These findings resolved during the recovery period.

Histopathology- Main Study

Sex	Male					Female				
Dose mg/kg	0	5	10	20	50	0	5	10	20	50
Animal number	3	3	3	3	3	3	3	3	3	3
Liver										
Perivascular neutrophilic Infiltrate,	0	0	0	0	0	0	0	0	0	1
Reduced glycogen	0	0	0	1	3	0	0	0	0	
Cytoplasmic alteration/inclusions, hepatocytes	0	0	0	0	2	0	0	0	0	0

Special Evaluation

None

Toxicokinetics

There were no sex differences in exposure (C_{max} and $AUC_{0\text{-}24\ h}$) for lasmiditan or its metabolites. Exposure for lasmiditan and M3 increased dose proportionally, for M7 increased less than dose proportionally, and for M8 increased generally greater than dose proportionally. After repeat dosing, lasmiditan, M3, and M8 accumulated; however, M7 did not. The metabolite-to-parent ratios were unchanged with the increasing repeat dosing.

Table 2. Summary of the Mean Toxicokinetic Parameters for COL-144 in Dog Plasma: Week 13

Dose Group	Dose Level (mg/kg/day)	Sex		C_{max} (ng/mL)	DN C_{max} (ng/mL)/(mg/kg/day)	T_{max} (hr)	$AUC_{0\text{-}t}$ (ng•hr/mL)	$AUC_{0\text{-}24}$ (ng•hr/mL)	DN $AUC_{0\text{-}24}$ (ng•hr/mL)/(mg/kg/day)	$t_{1/2}$ (hr)
2	5	M	Mean	387	77.4	1.67	2105	2105	421	4.26
			SD	92	NA	0.58	577	577	NA	0.13
			N	3	NA	3	3	3	NA	3
		F	Mean	386	77.2	1.33	1757	1757	351	3.95
			SD	39	NA	0.58	334	334	NA	0.19
			N	3	NA	3	3	3	NA	3
3	10	M	Mean	834	83.4	2.33	5777	5777	578	4.91
			SD	450	NA	1.53	4197	4197	NA	2.37
			N	3	NA	3	3	3	NA	3
		F	Mean	677	67.7	1.67	4255	4255	425	4.22
			SD	84	NA	0.58	991	991	NA	0.16
			N	3	NA	3	3	3	NA	3
4	20	M	Mean	1522	76.1	2.67	12135	12135	607	4.44
			SD	995	NA	1.15	7666	7666	NA	0.59
			N	3	NA	3	3	3	NA	3
		F	Mean	1850	92.5	1.33	10696	10696	535	4.40
			SD	478	NA	0.58	3117	3117	NA	0.45
			N	3	NA	3	3	3	NA	3
5	50	M	Mean	3906	78.1	1.60	24577	24577	492	4.89
			SD	538	NA	1.34	3464	3464	NA	1.02
			N	5	NA	5	5	5	NA	5
		F	Mean	4248	85.0	1.60	29594	29594	592	4.95
			SD	397	NA	0.55	3360	3360	NA	0.51
			N	5	NA	5	5	5	NA	5

DN Dose normalized.

Table 5. Summary of the Mean Toxicokinetic Parameters for M3 in Dog Plasma: Week 13

Dose Group	COL-144 Dose Level (mg/kg/day)	Sex		C_{max} (ng/mL)	DN C_{max} (ng/mL)/(mg/kg/day)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	AUC_{0-24} (ng•hr/mL)	DN AUC_{0-24} (ng•hr/mL)/(mg/kg/day)	$t_{1/2}$ (hr)	AUC_{0-24} M/P Ratios
2	5	M	Mean	486	97.1	1.67	1578	1578	316	4.50	0.712
			SD	454	NA	0.58	1039	1039	NA	0.47	0.288
			N	3	NA	3	3	3	NA	3	3
		F	Mean	392	78.3	1.00	1221	1221	244	3.33	0.717
			SD	97	NA	0	236	236	NA	0.16	0.209
			N	3	NA	3	3	3	NA	3	3
3	10	M	Mean	765	76.5	1.67	2985	2985	298	4.03	0.590
			SD	495	NA	0.58	1260	1260	NA	1.19	0.151
			N	3	NA	3	3	3	NA	3	3
		F	Mean	781	78.1	1.67	3049	3049	305	3.75	0.723
			SD	174	NA	0.58	759	759	NA	0.33	0.113
			N	3	NA	3	3	3	NA	3	3
4	20	M	Mean	1057	52.8	1.67	6976	6976	349	4.77	0.626
			SD	421	NA	0.58	3046	3046	NA	1.09	0.209
			N	3	NA	3	3	3	NA	3	3
		F	Mean	1577	78.8	1.33	6807	6807	340	4.74	0.670
			SD	35	NA	0.58	293	293	NA	0.60	0.174
			N	3	NA	3	3	3	NA	3	3
5	50	M	Mean	4352	87.0	1.20	17609	17609	352	5.26	0.714
			SD	1190	NA	0.45	3510	3510	NA	1.20	0.071
			N	5	NA	5	5	5	NA	5	5
		F	Mean	4296	85.9	1.60	19892	19892	398	5.69	0.678
			SD	1013	NA	0.55	3962	3962	NA	0.73	0.148
			N	5	NA	5	5	5	NA	5	5

DN Dose normalized.

Table 8. Summary of the Mean Toxicokinetic Parameters for M7 in Dog Plasma: Week 13

Dose Group	COL-144 Dose Level (mg/kg/day)	Sex		C_{max} (ng/mL)	DN C_{max} (ng/mL)/(mg/kg/day)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	AUC_{0-24} (ng•hr/mL)	DN AUC_{0-24} (ng•hr/mL)/(mg/kg/day)	$t_{1/2}$ (hr)	AUC_{0-24} M/P Ratios
2	5	M	Mean	9.49	1.90	2.67	54.1	65.4	13.1	5.42	0.0321
			SD	1.24	NA	1.15	2.2	5.8	NA	NA	0.0060
			N	3	NA	3	3	3	NA	2	3
		F	Mean	13.2	2.64	1.67	70.8	81.2	16.2	3.51	0.0466
			SD	1.6	NA	0.58	9.4	12.3	NA	0.55	0.0063
			N	3	NA	3	3	3	NA	3	3
3	10	M	Mean	18.6	1.86	3.00	125	138	13.8	7.17	0.0331
			SD	7.0	NA	1.73	12	16	NA	NA	0.0189
			N	3	NA	3	3	3	NA	2	3
		F	Mean	17.3	1.73	2.00	105	128	12.8	4.66	0.0302
			SD	1.0	NA	0	18	27	NA	1.38	0.0008
			N	3	NA	3	3	3	NA	3	3
4	20	M	Mean	33.8	1.69	2.67	267	279	13.9	5.31	0.0286
			SD	7.4	NA	1.15	46	28	NA	NA	0.0137
			N	3	NA	3	3	3	NA	2	3
		F	Mean	48.0	2.40	2.33	311	320	16.0	4.66	0.0290
			SD	27.4	NA	1.53	166	149	NA	NA	0.0091
			N	3	NA	3	3	3	NA	2	3
5	50	M	Mean	69.9	1.40	2.80	600	600	12.0	5.29	0.0247
			SD	32.1	NA	1.10	213	213	NA	1.43	0.0084
			N	5	NA	5	5	5	NA	5	5
		F	Mean	51.9	1.04	3.60	615	615	12.3	6.19	0.0207
			SD	12.0	NA	0.89	133	133	NA	1.42	0.0033
			N	5	NA	5	5	5	NA	5	5

DN Dose normalized.

Table 11. Summary of the Mean Toxicokinetic Parameters for M8 in Dog Plasma: Week 13

Dose Group	COL-144 Dose Level (mg/kg/day)	Sex		C_{max} (ng/mL)	DN C_{max} (ng/mL)/(mg/kg/day)	T_{max} (hr)	AUC_{0-t} (ng•hr/mL)	AUC_{0-24} (ng•hr/mL)	DN AUC_{0-24} (ng•hr/mL)/(mg/kg/day)	$t_{1/2}$ (hr)	AUC_{0-24} M/P Ratios
2	5	M	Mean	33.7	6.74	2.67	404	404	80.8	6.45	0.196
			SD	6.8	NA	1.15	71	71	NA	0.09	0.030
			N	3	NA	3	3	3	NA	3	3
		F	Mean	35.9	7.17	2.33	433	433	86.7	5.69	0.247
			SD	3.4	NA	1.53	86	86	NA	0.41	0.031
			N	3	NA	3	3	3	NA	3	3
3	10	M	Mean	109	10.9	6.67	1670	1670	167	4.18	0.261
			SD	67	NA	4.62	1555	1555	NA	NA	0.059
			N	3	NA	3	3	3	NA	2	3
		F	Mean	96.5	9.65	5.33	1282	1282	128	5.16	0.299
			SD	19.9	NA	2.31	353	353	NA	NA	0.015
			N	3	NA	3	3	3	NA	2	3
4	20	M	Mean	261	13.1	4.00	3913	3913	196	6.43	0.304
			SD	150	NA	0	3051	3051	NA	2.16	0.062
			N	3	NA	3	3	3	NA	3	3
		F	Mean	213	10.7	2.67	2695	2695	135	5.47	0.253
			SD	67	NA	1.15	846	846	NA	0.12	0.027
			N	3	NA	3	3	3	NA	3	3
5	50	M	Mean	467	9.35	2.80	6538	6538	131	6.91	0.262
			SD	123	NA	1.10	2280	2280	NA	1.68	0.066
			N	5	NA	5	5	5	NA	5	5
		F	Mean	574	11.5	4.00	8835	8835	177	7.54	0.300
			SD	59	NA	2.45	1321	1321	NA	1.66	0.037
			N	5	NA	5	5	5	NA	4	5

DN Dose normalized.

Sponsor's tables

Dosing Solution Analysis

Doses were within ±10 % of nominal.

Study title: 39-Week Oral Capsule Chronic Toxicity and Toxicokinetic Study with COL-144 in Dogs with an 8-Week Recovery Phase

Study no.:	8204494
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 12, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot # 77056-02, and purity: 101.5%

Key Study Findings

The NOAEL was 30 mg/kg, based on CNS related clinical signs at higher doses.

Week 39 Toxicokinetic Parameters in Dog Plasma at NOAEL

Analyte	Dose Group	COL-144 Dose Level (mg/kg/day)[a]	Interval	Sex	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-24} (ng·hr/mL)
COL-144	7	30	Week 39	M	2255	2.92	16361
				F	2382	1.50	14374
M3	7	30	Week 39	M	2011	2.17	8460
				F	2775	1.17	8936
M7	7	30	Week 39	M	26.6	4.00	285
				F	43.5	1.83	374
M8	7	30	Week 39	M	308	5.42	4698
				F	275	4.67	4069

Sponsor's table

Methods

Doses:	0, 5, 10, 20, 30, or 50/40 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	N/A
Formulation/Vehicle:	Gelatin capsules
Species/Strain:	Dog/beagle
Number/Sex/Group:	6/sex/5 to 30 mg/kg; 4/sex/C & 50/40 mg/kg
Age:	At dosing initiation: 6 to 7 months old
Weight:	M: 8.7 to 11.4 kg; F: 6.8 to 9.8 kg
Satellite groups:	None
Unique study design:	Two cohorts were studied.
Deviation from study protocol:	There were minor deviations which did not affect study validity

Observations and Results

Mortality

Observations were made twice daily.

There were drug-related animal deaths.

Clinical Signs

Detailed observations were made daily during the main study and weekly during the recovery period.

Tremors, hypoactivity, dehydrated appearance, hunched posture, excessive salivation, vomitus, no feces, and squinting were observed at the HD. Due to the severity of these clinical signs, dosing was suspended on Day 8. The HD was lowered to 40 mg/kg on Days 25 and 30, which reduced the severity of the clinical signs. All clinical signs resolved during the recovery period.

Body Weights

Recordings were made weekly.

At ≥20 mg/kg, there were decreases in body weight gain for males and females (up to 57 and 39%, respectively), which resolved during the recovery period.

Food Consumption

Recordings were made weekly.

At ≥20 mg/kg, there were drug-related decreases in food consumption, which resolved during the recovery period.

Ophthalmoscopy

Examinations were conducted during baseline, the final week of the main study, and final week of the recovery period.

There were no drug-related findings.

ECG

Examinations were conducted during baseline and Weeks 1, 13, 26, and 39 of the main study.

There were no drug-related findings.

Hematology

There were no drug-related findings.

Clinical Chemistry

There were no drug-related findings.

Urinalysis

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

There were increases in mean absolute and/or relative liver/gallbladder weights at ≥30 mg/kg (up to 28%) and mean absolute and/or relative thyroid/parathyroid weights at ≥20 mg/kg (up to 69%). Liver/gallbladder changes resolved during the recovery period, while thyroid/parathyroid changes partially resolved.

Adequate Battery: Yes

Peer Review: Yes

Signed pathology report: Yes

Histological Findings
There were findings of hepatocyte cytoplasmic alteration (≥10 mg/kg); hepatocyte intracytoplasmic body formation (≥20 mg/kg); increased submucosal pigment in the gallbladder (≥5 mg/kg), and increased pigment within follicular epithelial cells of the thyroid (≥20 mg/kg). During the recovery period, pigment in the gallbladder and thyroid persisted, while the liver changes resolved.

Text Table 2
Incidence and Severity of Test Article-Related Microscopic Findings - Dosing Phase Sacrifice, Cohorts 1 and 2

Sex	Males						Females					
Dose Level (mg/kg/day)	0[a,b]	5[a]	10[a]	20[a]	30[b]	50/40[a]	0[a,b]	5[a]	10[a]	20[a]	30[b]	50/40[a]
Liver												
Alteration, Cytoplasmic, Hepatocyte												
Minimal	0	0	2	3	2	3	0	0	2	2	3	3
Intracytoplasmic Body, Hepatocyte												
Minimal	0	0	0	0	1	1	0	0	0	1	0	1
Gallbladder												
Pigment, Submucosa, Increased												
Minimal	0	2	1	2	3	2	0	0	2	2	1	2
Thyroid												
Pigment, Epithelium, Increased												
Minimal	0	0	0	1	4	4	0	0	0	0	2	4

a Cohort 1.
B Cohort 2.

Sponsor's table

Special Evaluation

None

Toxicokinetics

There were no sex differences in plasma exposure (C_{max} and $AUC_{0\text{-}24\ h}$) for lasmiditan or its metabolites (M3, M7, and M8). Exposure for lasmiditan and M3 increased approximately dose proportionally, for M7 increased less than dose proportionally, and for M8 increased generally greater than dose proportionally. After repeat dosing lasmiditan, M3, and M8 accumulated, but M7 did not. Metabolite-to-parent ratios were unchanged with increasing dose and repeat dosing.

Table 5
Summary of the Mean Toxicokinetic Parameters for COL-144 in Dog Plasma: Week 39

Group	COL-144 Dose Level (mg/kg/day)	Sex		C_{max} (ng/mL)	DN C_{max} [(ng/mL)/(mg/kg/day)]	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	DN AUC_{0-24} [(ng•hr/mL)/(mg/kg/day)]	$t_{1/2}$ (hr)
2	5	M	Mean	303	60.7	1.50	2168	434	4.52
			SD	148	29.6	0.58	1693	339	0.88
			N	4	4	4	4	4	4
		F	Mean	318	63.7	1.25	1606	321	3.72
			SD	101	20.3	0.50	588	118	1.28
			N	4	4	4	4	4	4
3	10	M	Mean	611	61.1	1.50	4351	435	5.12
			SD	183	18.3	0.58	1294	129	1.08
			N	4	4	4	4	4	4
		F	Mean	605	60.5	1.50	3802	380	4.66
			SD	132	13.2	0.58	1358	136	0.38
			N	4	4	4	4	4	4
4	20	M	Mean	1228	61.4	1.75	8257	413	5.50
			SD	184	9.2	0.50	2615	131	2.38
			N	4	4	4	4	4	4
		F	Mean	1420	71.0	1.50	8576	429	4.00
			SD	279	14.0	0.58	1990	99	0.47
			N	4	4	4	4	4	4
7	30	M	Mean	2255	75.2	2.92	16361	545	4.86
			SD	625	20.8	2.76	2452	82	0.31
			N	6	6	6	6	6	5
		F	Mean	2382	79.4	1.50	14374	479	4.85
			SD	540	18.0	0.55	4758	159	0.96
			N	6	6	6	6	6	6
5	40	M	Mean	3350	83.8	1.33	21624	541	5.29
			SD	568	14.2	0.52	2407	60	0.54
			N	6	6	6	6	6	6
		F	Mean	2201	55.0	1.40	17257	431	5.21
			SD	1062	26.5	0.55	7897	197	0.61
			N	5	5	5	5	5	5

Table 11
Summary of the Mean Toxicokinetic Parameters for M3 in Dog Plasma: Week 39

Group	COL-144 Dose Level (mg/kg/day)	Sex		C_{max} (ng/mL)	DN C_{max} [(ng/mL)/(mg/kg/day)]	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	DN AUC_{0-24} [(ng•hr/mL)/(mg/kg/day)]	$t_{1/2}$ (hr)	M/P Ratio AUC_{0-24}
2	5	M	Mean	394	78.8	0.875	1520	304	4.35	0.941
			SD	130	25.9	0.250	716	143	2.20	0.579
			N	4	4	4	4	4	4	4
		F	Mean	371	74.2	1.25	1342	268	3.66	0.851
			SD	149	29.7	0.50	460	92	1.33	0.110
			N	4	4	4	4	4	4	4
3	10	M	Mean	804	80.4	0.875	3010	301	6.29	0.751
			SD	253	25.3	0.250	1031	103	1.82	0.322
			N	4	4	4	4	4	4	4
		F	Mean	1034	103	1.25	3465	346	4.89	0.950
			SD	372	37	0.50	1218	122	1.20	0.270
			N	4	4	4	4	4	4	4
4	20	M	Mean	1380	69.0	1.50	5992	300	6.01	0.715
			SD	388	19.4	0.58	2369	118	2.81	0.055
			N	4	4	4	4	4	4	4
		F	Mean	1278	63.9	1.50	5190	259	4.30	0.629
			SD	170	8.5	0.58	1024	51	0.72	0.191
			N	4	4	4	4	4	4	4
7	30	M	Mean	2011	67.0	2.17	8460	282	5.19	0.528
			SD	1596	53.2	1.47	2552	85	0.51	0.183
			N	6	6	6	6	6	6	6
		F	Mean	2775	92.5	1.17	8936	298	5.45	0.647
			SD	965	32.2	0.41	2627	88	1.56	0.162
			N	6	6	6	6	6	6	6
5	40	M	Mean	3783	94.6	1.33	14059	351	6.51	0.648
			SD	449	11.2	0.52	2736	68	1.07	0.090
			N	6	6	6	6	6	6	6
		F	Mean	2804	70.1	1.20	11847	296	5.18	0.766
			SD	1451	36.3	0.45	5657	141	0.97	0.270
			N	5	5	5	5	5	5	5

Table 17
Summary of the Mean Toxicokinetic Parameters for M7 in Dog Plasma: Week 39

Group	COL-144 Dose Level (mg/kg/day)	Sex		C_{max} (ng/mL)	DN C_{max} [(ng/mL)/(mg/kg/day)]	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	DN AUC_{0-24} [(ng•hr/mL)/(mg/kg/day)]	$t_{1/2}$ (hr)	M/P Ratio AUC_{0-24}
2	5	M	Mean	9.47	1.89	1.75	39.9	7.97	NA	0.0260
			SD	3.18	0.64	0.50	12.0	2.40	NA	0.0161
			N	4	4	4	4	4	0	4
		F	Mean	10.1	2.02	1.75	47.0	9.40	NA	0.0312
			SD	2.4	0.48	0.50	14.1	2.81	NA	0.0110
			N	4	4	4	4	4	0	4
3	10	M	Mean	12.7	1.27	2.50	89.2	8.92	NA	0.0213
			SD	4.3	0.43	1.00	34.7	3.47	NA	0.0079
			N	4	4	4	4	4	0	4
		F	Mean	20.3	2.03	1.50	145	14.5	4.80	0.0459
			SD	10.2	1.02	0.58	78	7.8	NA	0.0426
			N	4	4	4	4	4	2	4
4	20	M	Mean	30.0	1.50	2.50	199	9.94	5.26	0.0266
			SD	14.4	0.72	1.00	68	3.39	NA	0.0124
			N	4	4	4	4	4	2	4
		F	Mean	29.8	1.49	2.00	213	10.6	4.52	0.0250
			SD	22.1	1.11	0	101	5.0	NA	0.0116
			N	4	4	4	4	4	2	4
7	30	M	Mean	26.6	0.888	4.00	285	9.52	NA	0.0173
			SD	11.2	0.375	2.19	92	3.06	NA	0.0047
			N	6	6	6	6	6	0	6
		F	Mean	43.5	1.45	1.83	374	12.5	5.63	0.0257
			SD	15.7	0.52	0.41	166	5.5	1.97	0.0046
			N	6	6	6	6	6	4	6
5	40	M	Mean	47.5	1.19	3.00	479	12.0	6.36	0.0222
			SD	17.8	0.45	1.10	120	3.0	NA	0.0053
			N	6	6	6	6	6	2	6
		F	Mean	29.3	0.732	3.20	361	9.02	NA	0.0253
			SD	5.9	0.148	1.10	137	3.44	NA	0.0125
			N	5	5	5	5	5	0	5

NA Not applicable; NC Not calculated.

Summary of the Mean Toxicokinetic Parameters for M8 in Dog Plasma: Week 39

Group	COL-144 Dose Level (mg/kg/day)	Sex		C_{max} (ng/mL)	DN C_{max} [(ng/mL)/(mg/kg/day)]	T_{max} (hr)	AUC_{0-24} (ng•hr/mL)	DN AUC_{0-24} [(ng•hr/mL)/(mg/kg/day)]	$t_{1/2}$ (hr)	M/P Ratio AUC_{0-24}
2	5	M	Mean	40.2	8.04	3.75	566	113	NA	0.233
			SD	33.0	6.61	3.10	600	120	NA	0.062
			N	4	4	4	4	4	0	4
		F	Mean	28.0	5.60	3.00	369	73.8	6.82	0.220
			SD	9.7	1.93	1.15	197	39.5	NA	0.050
			N	4	4	4	4	4	2	4
3	10	M	Mean	74.2	7.42	2.50	1106	111	7.56	0.254
			SD	14.3	1.43	1.00	332	33	1.30	0.025
			N	4	4	4	4	4	3	4
		F	Mean	75.9	7.59	2.75	1069	107	6.41	0.277
			SD	27.1	2.71	1.50	425	42	0.27	0.055
			N	4	4	4	4	4	3	4
4	20	M	Mean	174	8.69	3.50	2727	136	5.71	0.307
			SD	100	4.98	1.00	2047	102	0.58	0.127
			N	4	4	4	4	4	3	4
		F	Mean	166	8.28	5.00	2112	106	4.76	0.247
			SD	35	1.76	3.46	493	25	NA	0.017
			N	4	4	4	4	4	2	4
7	30	M	Mean	308	10.3	5.42	4698	157	6.41	0.285
			SD	42	1.4	3.11	1096	37	1.44	0.050
			N	6	6	6	6	6	3	6
		F	Mean	275	9.18	4.67	4069	136	6.92	0.285
			SD	64	2.15	2.73	1309	44	NA	0.027
			N	6	6	6	6	6	2	6
5	40	M	Mean	404	10.1	3.33	5982	150	7.03	0.278
			SD	35	0.9	1.03	877	22	0.75	0.046
			N	6	6	6	6	6	6	6
		F	Mean	376	9.40	2.80	6378	159	8.21	0.339
			SD	200	5.00	1.10	3649	91	1.60	0.098
			N	5	5	5	5	5	5	5

Sponsor's tables

Dosing Solution Analysis

Daily doses were within ±10% of nominal.

7 Genetic Toxicology

Lasmiditan was non-mutagenic in an Ames assay and equivocal in an *in vitro* chromosomal aberration assay. Lasmiditan was negative in a bone marrow micronucleus assay in ICR mice (IV); however, the study was not adequate because systemic exposure to all major human metabolites was not demonstrated.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 103420, D. Charles Thompson, Ph.D., August 18, 2011)

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Lasmiditan: *In Vivo* Mouse Bone Marrow Micronucleus Assay

Study no: 963116

Study report location: EDR

Conducting laboratory and location: (b) (4)

Date of study initiation: December 1, 2016

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity:

Drug	Dose	% Purity
Lasmiditan hemisuccinate	2P2499C812	99.5%
Positive control (Cyclophosphamide monohydrate)	MKBS0021V	-

Methods

Doses in definitive study:

Drug	Dose mg/kg
Vehicle (methylcellulose, water, hydrochloric acid)	0
Lasmiditan hemisuccinate	62.5, 125, 250
Positive control (cyclophosphamide monohydrate)	80

Frequency of dosing: Two consecutive days
Route of administration: Oral gavage
Dose volume: 10 mL/kg
Formulation/Vehicle: 0.9% Sodium Chloride for Injection (USP)
Species/Strain: Mice/Hsd:ICR (CD-1)
Number/Sex/Group: Main: 3/sex/positive control; 6/sex/vehicle, LD, MD; 8/sex/HD.
TK: 3/sex for vehicle; 9/sex for LD and MD; 12/sex for HD
Satellite groups: None
Basis of dose selection: Dose range-finding study in (Wild Type) RasH2 Mice (8302173).
Negative control: 0.25% (w/v) methylcellulose inwater
Positive control: Cyclophosphamide monohydrate

Study Validity

This study was conducted according to OECD and ICH S2(R1), June 2012 guidances, except dosing was based on a range finding study in a different strain of mice.

Results

Lasmiditan was negative in the mouse bone marrow micronucleus assay. Lasmiditan and its metabolites (M3, M7, M8, (S,R)-M18, and (S,S)-M18) were detectable in plasma at all dose levels.

8 Carcinogenicity

Study title: 4-Week Oral Gavage Dose Range-Finding Toxicity and Toxicokinetic Study With COL-144 in 001178-W (Wild Type) RasH2 Mice

Study no.: 8302173
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: April 2, 2015

GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, batch 77056-02; purity 86.9%

Methods

Doses:	Phase 1: 0, 200, 450, or 900 mg/kg Phase 2: 0, 200, 250, or 300 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	10 mL/kg
Formulation/Vehicle:	Methylcellulose 0.25% (w/v, aqueous)
Species/Strain:	Mouse/wild type [001178-W, CByB6F1-Tg(HRAS)2Jic]
Number/Sex/Group:	Phase 1: Main Study: 10/sex/group TK: 6/sex/control, 36/sex/lasmiditan Phase 2: Main Study: 8/sex/control, 10/sex/lasmiditan TK: 18/sex/group (MD & HD)
Age:	At dosing initiation, Phase 1: 9-10 weeks; Phase 2: 11-12 weeks
Weight:	Phase 1: 17-34 g; Phase 2: 19-32 g
Satellite groups:	TK
Unique study design:	Females were group-housed (≤3/cage) and males were individually housed.
Deviation from study protocol:	There were minor deviations that did not affect study validity.

Summary Description and Conclusions

In Phase 1, acute toxicity was observed at the MD and HD, which resulted in the sacrifice of all HD animals. Clinical signs at the MD and HD consisted of hypoactivity, ataxia, low carriage, lateral recumbency, and cold to touch. Additional signs at the HD consisted of increased reactivity to stimulus, irregular/labored respiration, hypoactivity, myoclonic jerking, body tremors, clonic convulsions, hunched posture, barrel rolling, and sternal recumbency. At the HD, there were histopathology findings consisting of minimal to slight lymphocyte necrosis in the thymus, minimal to slight degeneration/necrosis of hepatocytes in the liver, minimal to slight necrosis of surface epithelium in the cecum, and minimal necrosis of colon surface epithelium.

In Phase 2, the HD was terminated because of acute toxicity. All MD animals survived to necropsy. At the MD, males had a 40% decrease in body weight gain, compared to controls. The NOAEL was 250 mg/kg in females and 200 mg/kg in males (Day 28 C_{max}: 5250 ng/mL (M) and 5940 ng/mL (F); Day 28 $AUC_{0\text{-}24\ h}$: 48500 ng·h/mL (M) and 65250 ng·h/mL (F).

C_{max} for lasmiditan and M7 increased less than dose proportionally. C_{max} and $AUC_{0\text{-}24h}$ for M3 and M8 increased approximately dose proportionally, while

(S,R)-M18 and (S,S)-M18 increased less than dose proportionally on Day 1 and dose proportionally on Day 28. C_{max} and AUC_{0-24h} for lasmiditan, M3, M7, M8, (S,R)-M18, and (S,S)-M18 were generally similar between sexes and did not accumulate with repeat dosing.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 103420*, D. Charles Thompson, Ph.D.,* September 30, 2015*)*

Study title: 26-Week Oral Gavage Carcinogenicity and Toxicokinetic Study With Lasmiditan In Transgenic (rasH2 hemizygous) and 001178-W (Wild Type) RasH2 Mice

Study no.: 8302174
Study report location: EDR
Conducting laboratory and location: (b) (4)
Date of study initiation: October 5, 2015
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity:

Drug	Lot #	Purity
Lasmiditan	2P2499C801	99.72%
	2P2499C812	99.96%
N-methyl-N-nitrosourea (positive control)	2EB0101	-

Methods

Doses:	Male: 0, 20, 50, or 150 mg/kg Female: 0, 25, 80, or 250 mg/kg Positive control: 75 mg/kg N-methyl-N-nitrosourea (MNU)
Frequency of dosing:	Daily; positive control: Day 1 only
Dose volume:	10 mL/kg (lasmiditan and positive control)
Route of administration:	Oral gavage; positive control: IP
Formulation/Vehicle:	0.25% [w/v] methylcellulose in water
Basis of dose selection:	ExeCAC recommended, based on mortality (males) and severe clinical signs (females)
Species/Strain:	Mice/([transgenic] rasH2 [001178-T{hemizygous}, CByB6F1-Tg{HRAS}2Jic]; rasH2 [001178-W{wild type}, CByB6F1-Tg{HRAS}2Jic]
Number/Sex/Group:	Main (transgenic): 25/sex/group TK (WT): 6/sex/C group; 36/sex/drug group Positive control (transgenic): 10/sex/group
Age:	At initiation: 8 weeks of age
Animal housing:	Females: up to 3 per cage Male: individually
Paradigm for dietary restriction:	*ad libitum*
Dual control employed:	No
Interim sacrifice:	None
Satellite groups:	TK
Deviation from study protocol:	There were minor deviations that did not affect study validity.

Observations and Results

Mortality

Observations were made twice daily.

The survival rates were ≥92% in all groups.

In the positive control group, unscheduled mortality occurred in 5 of 10 males and 8 of 10 females.

Clinical Signs

Detailed observations were made weekly.

On Day 1, at the HD, low carriage was observed in both sexes. There were no other drug-related clinical signs and no masses.

In the positive control group, there were observations of hunched posture, irregular and/or labored respiration, hypoactivity, swollen midline abdomen, and/or thin appearance. Masses were observed in 6 of 10 males and 10 of 10 females. They

generally consisted of wart-like lesions on the scrotum, vagina, and/or perineal areas. Two females had a firm stationary mass on the abdomen.

Body Weights

Recordings were made weekly.

Mean body weights and overall body weight gain were higher in HDM and lower in HDF, compared to controls.

Summary of mean body weight, Week 27

Male			
0 mg/kg	**20 mg/kg**	**50 mg/kg**	**150 mg/kg**
28.7 g	29.7 g	28.4 g	30.4 g
Female			
0 mg/kg	**25 mg/kg**	**80 mg/kg**	**250 mg/kg**
22.1 g	22.1 g	21.5 g	21.0 g

Sex	Male			Female		
Lasmiditan Dose (mg/kg/day)	20	50	150	25	80	250
Percent Difference in Mean Body Weight from Vehicle Control						
Day 183	+3.5	-1.0	+5.9	+0.5	-2.7	-5.0
Percent Difference in Mean Overall Weight Change from Vehicle Control						
Day 1 to 183	+19.4	-1.6	+27.4*	+8.1	-5.4	-24.3

+/- = Increased/Decreased.

* = Statistically significant at $P \leq 0.05$

Sponsor's table

In the positive control animals, weight gain was approximately 53 and 19% higher in males and females, respectively, compared to vehicle controls.

Food Consumption

Recording were made weekly.

There were no lasmiditan-related findings.

In the positive control, there were notable increases in food consumption.

Gross Pathology

There were no lasmiditan-related findings.

Histopathology

Complete battery of tissues: Yes

Peer Review: Yes

Signed pathologist report: Yes

Neoplastic

Based on the sponsor's analysis, in HDF, there was an increased incidence of bronchiolo-alveolar carcinoma (BAC = 12%) and an increased incidence of bronchiolo-alveolar carcinoma and adenoma (BAC and BAA = 16%) combined, compared to controls (see sponsor's table). The combined BAC and BAA finding in HDF was increased compared to historical control data from the same lab (see sponsor's table).

Based on the FDA statistical analysis, lasmiditan was not carcinogenic.

	Lasmiditan							
Sex	Males				Females			
Dose Level (mg/kg/day)	0	20	50	150	0	25	80	250
Number Examined	25	25	25	25	25	25	25	25
Lung								
M-Bronchiolo-alveolar carcinoma	0	0	1	1	0	0	1	3
B-Bronchiolo-alveolar adenoma	2	2	1	0	0	1	0	1
Combined incidence	2	2	2	1	0	1	1	4

B = Benign; M = Malignant.

Table 4.1. Incidence and Range of Selected Lung Findings in rasH2 Hemizygous Mouse[a]

Sex	Male		Female	
	Incidence (%)	Range (%)	Incidence (%)	Range (%)
Lung				
B-Adenoma, bronchiolo-alveolar (BAA)	56/924 (6.1)	0.0-16.0	29/925 (3.1)	0.0-12.0
M-Carcinoma, bronchiolo-alveolar (BAC)	15/924 (1.6)	0.0-12.5	8/925 (0.9)	0.0-8.0
Combined BAA and BAC	69/924 (7.5)	0.0-16.0	37/925 (4.0)	0.0-12.0
Hyperplasia, bronchiolo-alveolar[b]	16/924 (1.7)	0.0-12.0	20/925 (2.2)	0.0-8.0

[a] Data from 28 studies, 26 weeks in duration conducted (b) (4) from January 2011-December 2018.

[b] Includes synonyms: Hyperplasia, epithelium, Alv, Hyperplasia, epithelium, alveolus, and Hyperplasia, epithelium, bronchus/bronchiolus.

Note: Historical control data for this table were not reviewed by QA and are not GLP compliant.

Non-Neoplastic

Lasmiditan-related findings consisted of increased vacuolation of hepatocytes (MD and HD of both sexes) and an increase in vacuolated macrophages in the spleen of HDM and MDF and HDF.

	Lasmiditan							
Sex	Males				Females			
Dose Level (mg/kg/day)	0	20	50	150	0	25	80	250
Number Examined	25	25	25	25	25	25	25	25
Liver								
Vacuolation, hepatocyte, decreased								
Minimal	5	3	0	1	1	1	2	5
Slight	2	5	2	3	0	1	1	1
Moderate	2	1	9	7	0	1	9	10
Marked	1	1	8	9	0	1	0	3
Spleen								
Infiltrate, macrophage, vacuolated								
Minimal	2	1	3	9	9	8	14	2
Slight	0	0	0	0	4	1	7	19
Moderate	0	0	0	0	0	0	0	3

Sponsor's table

Toxicokinetics

On Day 1 and Week 26, plasma C_{max} and $AUC_{0\text{-}24\ h}$ for lasmiditan and its metabolites (M3; M7; M8; (S,R)-M18; and (S,S)-M18) increased approximately dose proportionally between the LD and MD and less than dose proportionally between the MD and HD. Generally, lasmiditan and its metabolites did not accumulate after repeat dosing. The abundance of the metabolites, based on exposure (C_{max} and $AUC_{0\text{-}24\ h}$), starting with the most abundant, was: M7, M8, M3, (S,S)-M18, and (S,R)-M18.

			Lasmiditan	Lasmiditan		M3		M7		M8		(S,R)-M18		(S,S)-M18	
Interval	Dose Group	Sex	Dose Level (mg/kg/day)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24}$ (ng·hr/mL)
Day 1	2	M	20	1170	5760	194	632	385	2220	145	653	28.2	144	108	691
		F	25	1470	6860	443	1350	393	1990	302	1460	46.0	285	91.6	606
	3	M	50	3150	16,100	302	1520	843	5600	377	1790	51.1	400	196	1520
		F	80	4030	24,000	756	4000	744	5480	727	4880	132	845	197	1520
	4	M	150	8580	48,300	1000	4340	2050	14,900	860	5210	138	942	415	4220
		F	250	11,200	64,500	2500	10,300	1270	13,000	1840	14,000	263	2340	306	3650
Week 26	2	M	20	1310	7100	243	1560	585	3190	267	1630	42.0	233	152	938
		F	25	1830	7940	566	1460	375	1980	448	2030	54.0	421	112	835
	3	M	50	3480	17,200	529	2510	1350	8360	531	3110	74.9	442	297	2040
		F	80	3760	25,600	824	4130	799	7150	1010	7310	92.4	1160	203	2560
	4	M	150	6470	32,400	940	5540	2640	17,200	1030	6960	118	777	525	3760
		F	250	7540	62,200	1970	10,800	2230	20,100	1990	21,700	228	2300	662	6880

F = Female; M = Male.

Sponsor's table

Dosing Solution Analysis

The mean concentration of lasmiditan formulations was ±10% of nominal. The mean concentration of MNU formulations was ±15% of nominal.

Study title: 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Lasmiditan in Rats

Study no.: 8302172
Study report location: EDR
Conducting laboratory and location: (b) (4)

Date of study initiation: February 24, 2015
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity:

Drug	Lot #	Purity
Lasmiditan	77056-02	86.9%
	2P2499C801	86.4%
	94974-2	87.1%
	94975-2	87.3%
	94976-2	86.9%
	2P2499C812	86.5%

Methods

Doses: 0, 10, 25, and 75 mg/kg
Frequency of dosing: Daily; positive control: Day 1 only
Dose volume: 10 mL/kg (lasmiditan and positive control)
Route of administration: Oral gavage; positive control: IP
Formulation/Vehicle: 0.25% [w/v] methylcellulose in water, pH 4.0 ± 0.05
Basis of dose selection: ExeCAC recommended, based on mortality in males and females.
Species/Strain: Rat/Crl:CD(SD)
Number/Sex/Group: Main: 60/sex/group
TK: 6/sex/C group, 12/sex/drug group
Age: At initiation: 6 to 7 weeks of age
Animal housing: Females: up to 3 per cage
Male: individually
Paradigm for dietary restriction: *ad libitum*
Dual control employed: None
Interim sacrifice: None
Satellite groups: TK
Deviation from study protocol: There were minor deviations that did not affect study validity.

Observations and Results

Mortality

Observations were made twice daily.

There was increased mortality in MDF, HDF, and HDM. For males, the sponsor's trend test for increased mortality was statistically significant compared to controls. No drug-related cause of death was identified in either sex. Dosing of HDM was discontinued on Day 591 (84 weeks), when the number of surviving males reached 21. All surviving HDM were sacrificed during Week 93, when only 15 remained, compared to 29 CM.

Figure 7.5: Adjusted Survival - Males

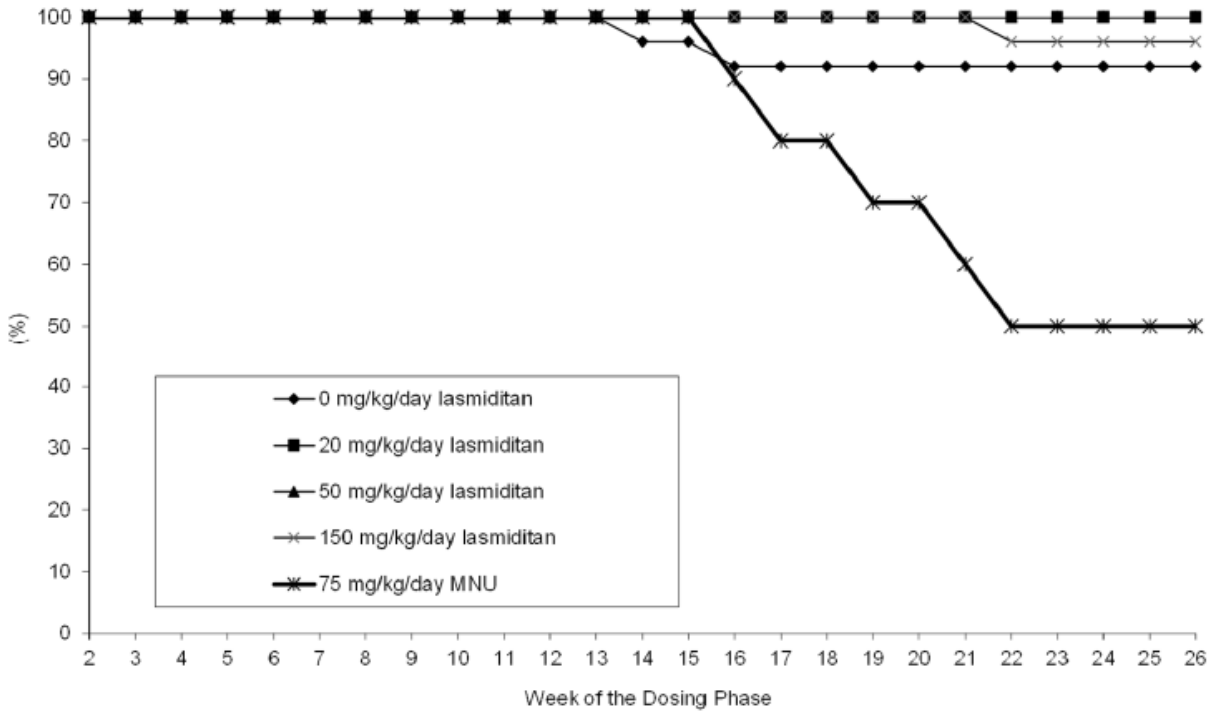


Table 5.1: Results of Statistical Analyses of Survival Data - Males

		Unadjusted Survival Incidence Rate			
Group	Trend	1	2	3	4
Dose Level(mg/kg/day)	(1,2,3,4)	0	10	25	75^
Group Size		60	60	60	60
Terminal Sacrifice		20	15	15	15
Deaths		40	45	45	45
Log-Rank P-value (v1)	0.0028**	N/A	0.1603	0.1894	0.0019**
Wilcoxon P-value (v1)	0.0026**	N/A	0.0864	0.1200	0.0011**

^ Dosing suspended from Day 591
* = Significant at 5% level; ** = Significant at 1% level;

Sponsor's figure and table

For MDF and HDF, dosing was discontinued on Day 589 (84 weeks), when the number of surviving females reached 20 or 21 rats, respectively. All surviving MDF and HDF were sacrificed during Week 92, when only 15 females/group remained, compared to 23 CF.

Figure 7.6: Adjusted Survival - Females

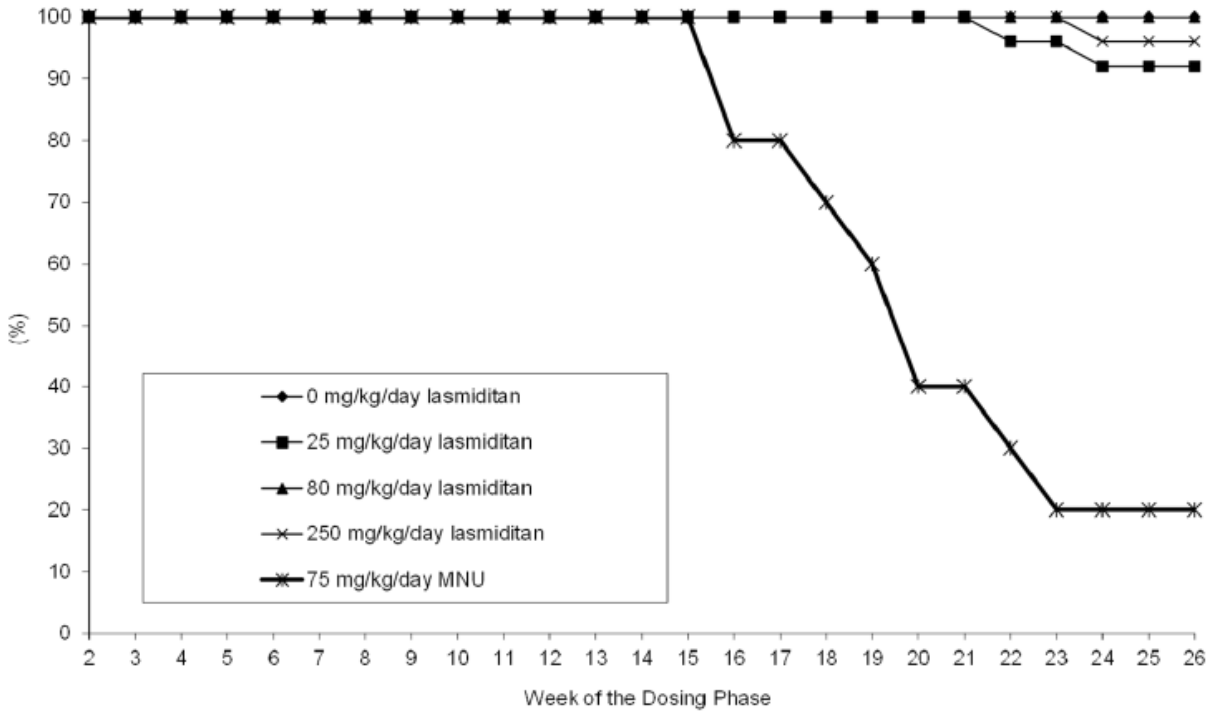


Table 5.2: Results of Statistical Analyses of Survival Data - Females

		Unadjusted Survival Incidence Rate			
Group	Trend	1	2	3	4
Dose Level(mg/kg/day)	(1,2,3,4)	0	10	25^	75^
Group Size		60	60	60	60
Terminal Sacrifice		18	20	14	15
Deaths		42	40	46	45
Log-Rank P-value (v1)	0.0809	N/A	0.6470	0.1327	0.1303
Wilcoxon P-value (v1)	0.0772	N/A	0.5958	0.1888	0.1572

^ Dosing suspended from Day 589

Sponsor's figure and table

Clinical Signs/Mass Palpations

Detailed observations were made weekly.

There were no drug-related findings.

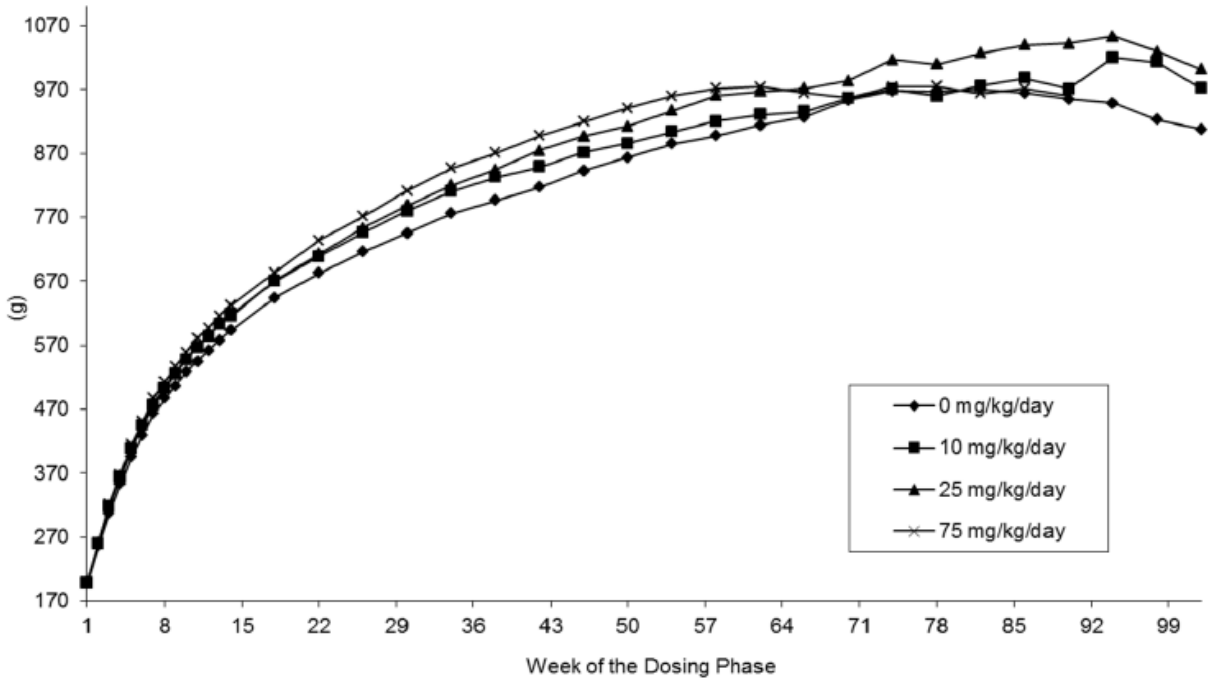
Body Weights

Recordings were made weekly.

From Week 2 through Week 66, there were dose-related increases (up to 10%) in mean body weight of males, compared to controls. After Week 66, HDM were similar to

controls; however, LDM and MDM remained higher and final body weights were approximately 9 and 15%, respectively, higher than controls.

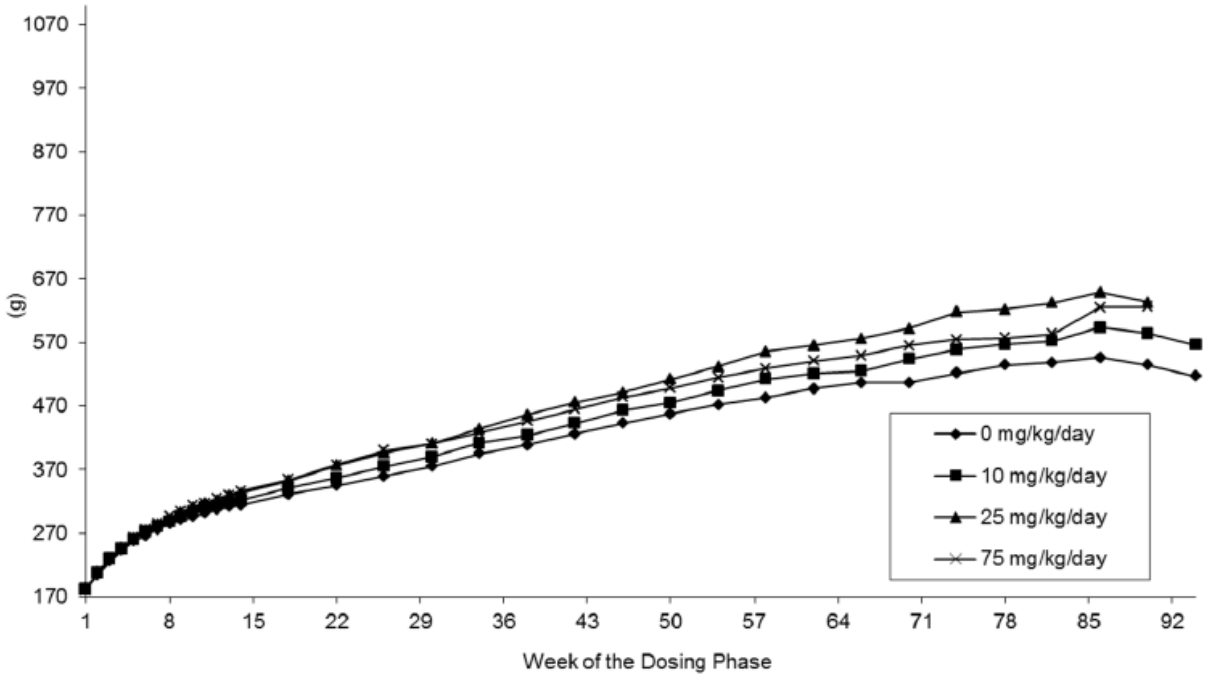
Figure 7.3: Mean Body Weight Data - Males



Sponsor's figure

From Week 6 on, there were drug-related increases (up to 19%) in mean body weight of MD females, compared to controls.

Figure 7.4: Mean Body Weight Data - Females



Sponsor's figure

Food Consumption

Recordings were made weekly.

Drug-related effects on food consumption were generally consistent with those on body weight.

Gross Pathology

There were no drug-related findings.

Histopathology

Complete battery of tissues: Yes
Peer Review: Yes
Singed pathologist report: Yes

Neoplastic
The sponsor excluded HDM from the statistical analysis because of an increase in mortality compared to the other groups.

In MDM, the incidence of pituitary B-Adenoma/M-Carcinoma, a common tumor type, was shown by the sponsor to be significantly higher, compared to control. In MDF, the incidence of skin/subcutis basal cell M-Carcinoma, a rare tumor, was significantly higher, compared to control.

Based on the FDA statistical analysis, lasmiditan was not carcinogenetic.

Males			0 mg/kg	10 mg	25	75	Trend
Tissue	Neoplasm	Total No. Examined	60	60	60	60	-
Pituitary	B-Adenoma/M-Carcinoma	Common	41	40	45	46	-
	Unadjusted P-value	-	N/A	N/A	0.0455*	N/A	0.0295
*Significant: P<0.05							

Females			0 mg/kg	10 mg	25	75	Trend
Tissue	Lesion	Total No. Examined	60	60	60	60	-
Skin/Subcutis	M-Carcinoma, basal cell	Rare	0	0	2	0	-
	Unadjusted P-value	-	N/A	N/A	0.0478*	N/A	0.4747
*Significant: P<0.05							

Non-neoplastic
Drug-related minimal to slight neuronal inclusions were observed in the brain and spinal cord of LDF, MDM, HDM, and HDF. In HDM, there was exacerbation of chronic progressive nephropathy in the kidneys, with secondary diffuse hyperplasia of the parathyroid gland.

Text Table 4.1: Incidence and Severity of Lasmiditan-Related Non-Neoplastic Microscopic Findings

	Lasmiditan							
Sex	Males				Females			
Dose Level (mg/kg)	0	10	25	75	0	10	25	75
Brain								
Number Examined	60	60	60	59	60	60	60	60
Inclusions, cytoplasm, neuron								
Minimal	0	0	1	29	0	0	0	19
Slight	0	0	0	14	0	0	0	12
Spinal cord								
Number Examined	59	60	60	60	59	60	59	60
Inclusions, cytoplasm, neuron								
Minimal	0	0	3	34	0	1	0	26
Slight	0	0	0	3	0	0	0	5
Kidney								
Number Examined	60	60	60	60	60	60	60	60
Nephropathy, chronic progressive								
Minimal	24	24	22	5	22	27	25	20
Slight	22	20	23	31	10	5	9	15
Moderate	4	3	7	19	0	2	0	1
Marked	1	2	0	3	0	0	0	1
Severe	0	0	0	1	0	0	0	0
Parathyroid								
Number Examined	56	58	57	57	59	59	57	58
Hyperplasia, diffuse								
Minimal	7	9	14	10	3	7	0	4
Slight	4	3	4	8	0	0	0	1
Moderate	0	0	0	1	0	0	0	0

Sponsor's table

Toxicokinetics

Plasma C_{max} and $AUC_{0\text{-}24\ h}$ were similar between sexes. C_{max} for lasmiditan, M3, and M7 increased less than dose proportionally, while $AUC_{0\text{-}24\ h}$ increased approximately dose-proportionally. C_{max} for M8 increased approximately dose-proportionally, while $AUC_{0\text{-}24\ h}$ increased greater than dose proportionally. C_{max} for (S,R)-M18 and (S,S)-M18 increased less than dose proportionally, while $AUC_{0\text{-}24\ h}$ increased approximately dose proportionally from the LD to the MD and greater than dose proportionally from the MD to the HD. Repeat dosing did not result in accumulation of lasmiditan or its metabolites. The abundance of the metabolites, based on exposure (C_{max} and $AUC_{0\text{-}24\ h}$), starting with the most abundant, was: M7, M8, M3, (S,S)-M18, and (S,R)-M18.

Summary of Lasmiditan C_{max} and AUC_{0-24} in Rat Plasma

Dose Interval	Dose Group	Lasmiditan Dose Level (mg/kg/day)	Sex	Lasmiditan C_{max} (ng/mL)	Lasmiditan AUC_{0-24} (ng·hr/mL)	M3 C_{max} (ng/mL)	M3 AUC_{0-24} (ng·hr/mL)	M7 C_{max} (ng/mL)	M7 AUC_{0-24} (ng·hr/mL)	M8 C_{max} (ng/mL)	M8 AUC_{0-24} (ng·hr/mL)	(S,R)-M18 C_{max} (ng/mL)	(S,R)-M18 AUC_{0-24} (ng·hr/mL)	(S,S)-M18 C_{max} (ng/mL)	(S,S)-M18 AUC_{0-24} (ng·hr/mL)
Week 3	2	10	M	324	2920	177	1450	134	1070	8.52	93.3	9.66	82.9	86.5	804
			F	419	3080	117	806	206	1710	10.8	71.8	7.55	77.8	122	1530
			MF	361	3000	147	1130	147	1390	9.28	82.6	8.61	80.4	104	1170
	3	25	M	691	7370	350	3320	194	1810	29.8	339	17.6	198	185	1670
			F	859	6390	230	1640	400	3870	21.6	223	20.8	228	329	3800
			MF	706	6880	287	2480	279	2840	25.1	281	19.2	213	257	2740
	4	75	M	1770	20700	944	9390	433	4870	98.4	1540	48.2	722	397	5920
			F	1700	23400	377	5530	853	11700	83.0	1280	57.0	927	974	14800
			MF	1730	22000	657	7460	567	8300	90.7	1410	52.6	825	655	10400
Week 13	2	10	M	484	4090	260	1790	258	1830	16.0	154	27.6	181	125	1290
			F	526	3640	280	1460	198	1750	14.7	102	14.9	145	137	1360
			MF	505	3870	270	1620	228	1790	15.4	128	20.1	163	129	1330
	3	25	M	945	9290	439	3500	286	3140	46.6	494	44.0	401	329	2750
			F	1040	8660	377	2890	521	4580	27.4	292	26.7	425	287	3940
			MF	961	8970	402	3190	400	3860	33.6	393	34.7	413	299	3340
	4	75	M	2000	30800	840	10900	601	10300	150	2530	88.7	1550	672	10900
			F	2140	25300	794	8420	864	12200	97.8	1490	88.2	1400	1060	15200
			MF	1830	28000	764	9660	713	11200	124	2010	88.5	1480	806	13000
Week 26	2	10	M	575	3860	227	1700	283	1870	18.5	185	31.7	242	139	1320
			F	541	4100	262	1550	230	1980	13.9	134	12.5	114	123	1390
			MF	558	3980	229	1630	256	1920	16.2	159	19.4	178	131	1350
	3	25	M	1120	9540	545	3850	335	3270	46.7	541	46.2	521	281	2670
			F	1180	11500	371	3520	491	5510	30.5	407	28.1	394	299	4460
			MF	1150	10500	442	3680	394	4390	38.6	474	36.5	457	290	3570
	4	75	M	2430	29800	982	10900	821	10200	147	2420	99.8	1640	584	9570
			F	2570	32400	800	9780	988	14700	131	1850	89.2	1380	1000	14100
			MF	2500	31100	881	10400	789	12400	135	2130	91.7	1510	735	11800

Note: MF toxicokinetic parameters were calculated from the mean of the individual male and female concentration-time data and are not an average of the separate male and female parameter values.

Sponsor's table

Dosing Solution Analysis

The mean concentration of lasmiditan formulations were ±15% of nominal.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Oral Gavage Fertility, Early Embryonic Development to Implantation and Toxicokinetic Study with COL-144 in Rats

Study no.:	8200081
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 27, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, lot # 77056-02, purity: 101.9%

Key Study Findings

The NOAEL for fertility and early embryonic development was 200 mg/kg, based on death at 250 mg/kg.

Toxicokinetic Summary at NOAEL for Fertility and Early Embryonic Development of 200 mg/kg/day

Analyte	Cmax (ng/mL)	AUC (ng*h/mL
Females Day 14		
COL-144	4303	70017
M3	938	17431
M7	1587	22419
M8	230	4508
(S,R)-M18	87	1705
(S,S)- M18	1163	21505
Males Day 28		
COL-144	3357	54590
M3	1397	18566
M7	1430	18634
M8	282	4238
(S,R)-M18	129	2077
(S,S)- M18	843	12267

Sponsor's table

Methods

Doses:	M: 0, 100, 175 or 250/200 mg/kg F: 0, 100, 150, or 200 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	0.25% (w/v) methylcellulose in water.
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	Main study: 22/sex/group TK: 3/sex/C, 9/sex/lasmiditan
Satellite groups:	TK
Study design:	Lasmiditan was administered daily to male and female rats prior to mating and until termination (males) or GD 7. TK (prior to mating), general toxicity, gonadal function, mating behavior, implantation, and fertility of male and female rats were assessed.
Deviation from study protocol:	Minor deviations were reported that did not affect study validity.

Observations and Results

Mortality and Clinical Signs

Observations were made twice daily. Detailed observations were made daily.

In main animals, 2 males at 250 mg/kg were sacrificed moribund on dosing Day 14 with severe reductions in body weight and food consumption, as well as clinical signs of a thin appearance, hunched posture, hypoactivity, ataxia, labored respiration, rough, yellow, and red haircoat, and/or few or no feces. In TK animals, at 250 mg/kg, 1 male was sacrificed and 1 male was found dead; both animals showed the same signs as the main study animals prior to premature sacrifice.

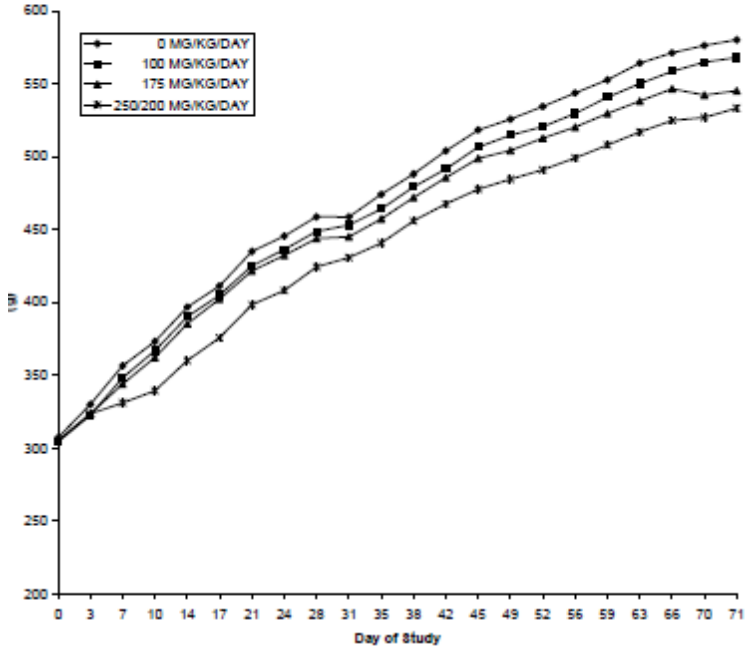
The high dose was lowered to 200 mg/kg/day for males beginning on Study Day 18 after a 3-day dosing holiday.

Body Weight

Recordings were made twice weekly.

In HDM, there were decreases in mean body weight (see sponsor's figure) and body weight gain throughout the study.

Figure 2
Mean Body Weights – Males



Mean Body Weight Changes in Males (g)

Day	0 mg/kg	100 mg/kg	175 mg/kg	250/200 mg/kg
0 to 71	272	263	240	227*

Statistically significant: *p≤0.05

Food Consumption

Recordings were made weekly.

During the first week, there were reductions in food consumption in MDM and HDM of 11 and 21%, respectively, and MDF and HDF of 10% and 18%, respectively, compared to control.

Estrous Cycle

During the premating phase, vaginal smears were assessed for main study animals.

There were no drug related findings.

Toxicokinetics

Exposures (C_{max} and $AUC_{0\text{-}24\ h}$) were similar between sexes. Plasma exposures of lasmiditan and metabolites M3 and M8 generally increased dose proportionally. Exposure of metabolites M7, (S,R)-M18 in females and (S,S)-M18 generally increased less than dose proportionally. Overall, the M/P ratio for all lasmiditan metabolites was independent of dose and sex.

Toxicokinetic Parameters for COL-144 and M3 in Rat Plasma

Day	Dose Group	COL-144 Dose Level (mg/kg/day)	Sex	COL-144 C_{max} (ng/mL)	COL-144 T_{max} (hr)	COL-144 AUC_{0-24} (ng·hr/mL)	M3 C_{max} (ng/mL)	M3 T_{max} (hr)	M3 AUC_{0-24} (ng·hr/mL)	M3 M:P Ratio AUC_{0-24}
14	6	100	F	2230	1.00	29491	594	0.500	6555	0.222
	7	150	F	2697	1.00	34065	684	1.00	7962	0.234
	8	200	F	4303	0.500	70017	938	1.00	17431	0.249
28	6	100	M	2273	2.00	27525	759	1.00	9679	0.352
	7	175	M	3033	4.00	42699	1447	4.00	15556	0.364
	8	200	M	3357	2.00	54590	1397	2.00	18566	0.340

NC Not calculated.

Toxicokinetic Parameters for M7 and M8 in Rat Plasma

Day	Dose Group	COL-144 Dose Level (mg/kg/day)	Sex	M7 C_{max} (ng/mL)	M7 T_{max} (hr)	M7 AUC_{0-24} (ng·hr/mL)	M7 M:P Ratio AUC_{0-24}	M8 C_{max} (ng/mL)	M8 T_{max} (hr)	M8 AUC_{0-24} (ng·hr/mL)	M8 M:P Ratio AUC_{0-24}
14	6	100	F	1047	1.00	14798	0.502	102	4.00	1637	0.0555
	7	150	F	1157	1.00	17141	0.503	188	8.00	2821	0.0828
	8	200	F	1587	1.00	24192	0.346	230	2.00	4508	0.0644
28	6	100	M	1103	2.00	10174	0.370	135	8.00	2097	0.0762
	7	175	M	1263	4.00	14199	0.333	238	4.00	3466	0.0812
	8	200	M	1430	2.00	18634	0.341	282	8.00	4138	0.0758

NC Not calculated.

Toxicokinetic Parameters for (S,R)-M18 and (S,S)-M18 in Rat Plasma after Administration of COL-144

Day	Dose Group	COL-144 Dose Level (mg/kg/day)	Sex	(S,R) C_{max} (ng/mL)	(S,R) T_{max} (hr)	(S,R) AUC_{0-24} (ng·hr/mL)	(S,R) M:P Ratio AUC_{0-24}	(S,S) C_{max} (ng/mL)	(S,S) T_{max} (hr)	(S,S) AUC_{0-24} (ng·hr/mL)	(S,S) M:P Ratio AUC_{0-24}
14	6	100	F	74.4	8.00	1264	0.0428	787	8.00	13778	0.467
	7	150	F	75.3	4.00	1228	0.0360	1056	4.00	17664	0.519
	8	200	F	87.1	8.00	1705	0.0243	1163	8.00	21505	0.307
28	6	100	M	82.6	2.00	1055	0.0383	593	2.00	7209	0.262
	7	175	M	134	4.00	1678	0.0393	947	4.00	10041	0.235
	8	200	M	129	4.00	2077	0.0380	843	8.00	12267	0.225

NC Not calculated.

Sponsor's tables

Dosing Solution Analysis

The mean results varied from 92 to 135% of nominal. Week 3 and 4 samples at the 15 mg/mL dose were not within ±10% of nominal.

Necropsy

Males were sacrificed after 10 weeks of dosing. Females were sacrificed on GD13. There were no drug-related findings in males.

Fertility Parameters

Reproductive indices (Male and female copulation and fertility indexes)

The male and female fertility indexes were reduced at the MD and HD (see sponsor's table), compared to control but were within historical controls (84 to 100%).

Text Table 1
Reproductive Indices

Males	0 mg/kg/day	100 mg/kg/day	175 mg/kg/day	200/250 mg/kg/day
Male Fertility Index[b] (-)	100	100	86	90
Female Fertility Index[d] (-)	100	100	86	86

Cesarean Section (pregnancy rate, abortions, corpora lutea, implantation sites, resorptions, early deliveries, and viable fetuses)

One HD dam had no viable fetuses at cesarean section. There was no effect on other parameters.

Male Organ Weights

There were no drug-related findings.

Sperm Motility and Total Sperm Counts.

Assessments were made at scheduled sacrifice.

There were no drug-related findings.

9.2 Embryofetal Development

Study title: A Dose Escalation Toxicity Study of LY573144 Hemisuccinate Administered by Intravenous Infusion in Pregnant Rats

Study no.:	98354
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 24, 2002
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	lasmiditan, Lot# 02100258, and purity 84.41%

Methods

Doses:	75 or 100 mg/kg
Frequency of dosing:	Daily (20-minute infusion)
Dose volume:	15 and 20 mL/kg/hour
Route of administration:	IV
Formulation/Vehicle:	0.9% Sodium Chloride Injection, U.S.P

Species/Strain:	Rat Sprague-Dawley CD
Number/Sex/Group:	3 F/group
Satellite groups:	None
Study design:	Dams were dosed from GD 6 to 9.
Deviation from study protocol:	Not specified

Observations and Results

Pregnant females were assessed for mortality and clinical signs. No animals died during the study. At both dose levels, there were observations of prostration, decreased activity, ptosis, and wet fur. At the HD, there were also convulsions and tremors.

Dosing formulations were ±5% of the nominal dose.

Study title: A Pilot Embryo-Fetal Development Study of LY573144 Hemisuccinate Administered by Intravenous Infusion in the CD Rat

Study no.:	98336
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 28, 2002
GLP compliance:	Yes
QA statement:	No
Drug, lot #, and % purity:	Lasmiditan, Lot# 02100258, and purity 84.41%

Key Study Findings

The NOAEL was 25 mg/kg, based on clinical signs and post implantations losses at higher doses.

Methods

Doses:	0, 10, 25, 55, or 75 mg/kg
Frequency of dosing:	Daily (20-minute infusion)
Dose volume:	15 mL/kg/hour
Route of administration:	IV
Formulation/Vehicle:	0.9% Sodium Chloride Injection, U.S.P.
Species/Strain:	Rat/Sprague-Dawley CD
Number/Sex/Group:	3/F/group
Satellite groups:	None
Study design:	Dams were dosed from GD 6 to 17
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Mortality and Clinical Signs

Animals were examined twice daily.

All animals survived to necropsy. Decreased activity was observed at 55 mg/kg. One dam at the 55 mg/kg and 1 dam at the HD were observed lying on their side.

Body Weight and Food Consumption

Recordings were made twice weekly.

There were decreases in mean body weight gain at the HD.

Mean body Weight Gain (g)

Day	0-3	3-6	6-9	9-12	12-15	15-18
Control	8.6	14.1	13.1	22.0	18.0	37.6
HD	0.9	15.4	12.0	18.7	13.9	27.0

There were no drug-related effects on food consumption.

Toxicokinetics

Not assessed.

Dosing Solution Analysis

Daily dosing formulations were within ±15% of nominal.

Necropsy

There were no drug-related findings.

Cesarean Section Data (corpora lutea, resorptions, implantation sites, sex ratio, dead fetuses, and pre and post implantation losses)

There were increases in early resorptions at0 ≥25 mg/kg.

Dose (mg/kg):	No. Dams with 1 or more resorptions	No. Dams with 2 or more resorptions
0	2/7 (28.6%)	0/7 (0.0%)
10	0/6 (0.0%)	0/6 (0.0%)
25	3/6 (50.0%)	1/6 (16.7%)
55	5/7 (71.4%)	3/7 (42.8%)
75	4/7 (57.1%}	4/7 (57.1%)

Offspring (Malformations, Variations, etc.)

There were lower group mean fetal weights at the HD (C = 3.69 g, HD = 3.31 g), which were below the historical control range (3.55 to 4.04 g).

Study title: An Embryo-Fetal Development Study of LY573144 Hemisuccinate (Compound 683974) Administered by Intravenous Infusion in the Rat and Companion Blood Level Study

Study no.:	98333
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 4, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, Lot# 02100258, and purity 84.41%

Key Study Findings

There was no NOAEL for dams, based on signs of decreased activity at all doses. The MD was the NOAEL for fetuses, based on findings of delayed skeletal ossification and decreased fetal weight at the HD ($AUC_{0\text{-}24\ h}$: 6431 ng*h/mL; C_{max}: 3541 ng/mL).

Methods

Doses:	0, 5,15, or 75 mg/kg
Frequency of dosing:	Daily (20-minute infusion)
Dose volume:	0.25 mL/kg/min
Route of administration:	IV
Formulation/Vehicle:	0.9% Sodium Chloride Injection, U.S.P.
Species/Strain:	Rat/Sprague-Dawley CD
Number/Sex/Group:	Main study 25/group; TK: 6/group
Satellite groups:	None
Study design:	Dams were dosed from GD 6 to 17 (main) and Days 6 to 12 (TK).
Deviation from study protocol:	There were minor deviations, with no impact on study validity

Mortality and Clinical Signs

Animals were examined twice daily.

All animals survived to necropsy.

There were dose-dependent observations of decreased activity, ptosis, prostration, clonus of jaws, and excessive licking; labored breathing (4/25) was observed at the HD.

Body Weight and Food Consumption

Recordings were made twice weekly.

There were decreases (~25%) in body weight gain at the HD between GD 6 and 18, compared to control. Food consumption was decreased (~6%) at the HD between GD 6 and 18.

Toxicokinetics

Plasma AUC for lasmiditan (Gestation Day 12) increased dose-proportionally.

Parameter Day 12 (following the seventh daily 20-minute infusion)	Daily Dose (mg/kg/day) 5	15	75
C_{max} (ng/mL)	623.61	3540.77	7994.48
$AUC_{0\text{-}24\ hrs}$ (ng•hr/mL)	1928.58	6431.05	31838.85
T_{max} (hours)	0.33	0.33	0.33
Half-life (hours)	2.56	2.56	2.76

Abbreviations: C_{max} = maximal plasma concentration observed; $AUC_{0\text{-}24\ hrs}$ = area under the concentration-time curve from time 0 to 24 hours; T_{max} = time to maximal plasma concentration observed.

Sponsor's table

Dosing Solution Analysis

Doses were within ±15% of nominal.

Necropsy

At the HD, there was thickening at the infusion site.

Cesarean Section Data (corpora lutea, resorptions, implantation sites, sex ratio, dead fetuses, and pre and post implantation losses)

At the HD, there was total resorption in 1 dam, and gravid uterus weights were decreased (22%). There were no other drug-related findings.

GROUP MEAN UTERUS WEIGHTS

0	5 mg/kg	15 mg/kg	75 mg/kg
83.8 g	82.9 g	84.7 g	**65.6 g**

Offspring (Fetal Weights, Malformations, Anomalies (External, Visceral, and Skeletal)

At the HD, fetal weights were decreased (15%), and there was a delay in skeletal ossification. There were no other drug-related findings.

FETAL FINDINGS

Dose	0	5 mg/kg	15 mg/kg	75 mg/kg
Group mean fetal weights (g)	3.78	3.81	3.84	**3.22**
Common skeletal variant: %/litter				
Thoracic centrum	31.5	28.5	21.7	33.0
Sternebrae 1 to 4	9.1	11.9	8.0	34.6
Sternebrae 5 and 6	93.6	92.3	93.5	98.6

Study title: A Pilot Embryo-Fetal Development Study of LY573144 Hemisuccinate Administered Intravenously to Female New Zealand White Rabbits and Companion Blood Level And Toxicokinetics of LY573144 in Gravid New Zealand White Rabbits Following a Single Intravenous Infusion of 5, 10, or 20 mg/kg LY573144 Hemisuccinate on Day 11 of Gestation

Study no.:	98330
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 23, 2002
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Lasmiditan, Lot# 02100258, and purity 84.41%

Methods

Doses:	0, 5, 10, 20, or 40 mg/kg
Frequency of dosing:	Daily (20-minute infusion)
Dose volume:	0.2 mL/kg/min
Route of administration:	IV
Formulation/Vehicle:	0.9% Sodium Chloride Injection, U.S.P.
Species/Strain:	New Zealand White rabbit
Number/Sex/Group:	Main study: 5/group
Satellite groups:	TK
Study design:	Dams were dosed from GD 7 to 19. Dams were evaluated for reproductive parameters, and fetuses were assessed for viability, weight, sex, and morphology on GD 29.
Deviation from study protocol:	There were minor deviations, with no impact on study validity

Observations and Results

HD animals were euthanized on the first day of dosing due to convulsions, decreased activity, labored breathing, decreased muscle tone, and lateral recumbency. At 20 mg/kg, there were observations of increased respiratory rate, decreased muscle tone and decreased activity during the dosing period. There were no drug-related findings on body weight, food consumption, or maternal reproductive parameters at doses ≤20 mg/kg. Drug half-life was 1 hour, and C_{max} and $AUC_{0\text{-}24\ h}$ increased approximately dose proportionally. The maternal and embryofetal MTD was 20 mg/kg (C_{max}: 7223 ng/mL; AUC $_{0\text{-}24\ h}$: 6057 ng*hr/mL).

Table 1: **Summary of Individual and Mean Toxicokinetic Parameters ± SEM for LY573144 in Gravid New Zealand White Rabbits Following the Initiation of the Fifth Daily 20-Minute Intravenous Infusion of 5, 10, or 20 mg/kg of LY573144 hemisuccinate on Day 11 of Gestation (n = 3 animals/group, Study (b) (4)98330)**

Toxicokinetic Parameter	Administered LY573144 Dose (mg/kg/day)											
Day 11 (fifth dose)	5				10				20			
Animal No.	2501	2502	2503	Mean	3501	3502	3503	Mean	4501	4502	4503	Mean
C_{max} (ng/mL)	1199	1658	1001	1286 ± 195	3418	5130	2394	3647 ± 798	7090	7853	6726	7223 ± 332
T_{max} (hours)	0.17	0.33	0.17	0.22 ± 0.06	0.33	0.33	0.17	0.28 ± 0.06	0.17	0.33	0.33	0.28 ± 0.06
$AUC_{0\text{-}24\ hrs}$ (ng*hr/mL)	973	1163	1165	1100 ± 64	2860	3385	2004	2749 ± 402	5378	6280	6512	6057 ± 346
Half-life (hours)	0.99	1.05	1.05	1.03 ± 0.02	1.05	1.16	0.96	1.05 ± 0.06	1.07	1.07	1.06	1.07 ± 0.00

Abbreviations: SEM = standard error of the mean; C_{max} = maximal plasma concentration observed; T_{max} = time of observed maximal plasma concentration; $AUC_{0\text{-}24\ hrs}$ = area under the plasma concentration-time curve from time 0 to 24 hours (tau).

Sponsor's Table

Study title: An Embryo-Fetal Development (Segment II) Study of LY573144 Hemisuccinate (Compound 683974) Administered Intravenously in the New Zealand White Rabbit

Study no.:	98331
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 4, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, Lot# 02100258, and purity 84.41%

Methods

Doses:	0, 5, 10, or 20 mg/kg
Frequency of dosing:	Daily (20-minute infusion)
Dose volume:	0.25 mL/kg/min
Route of administration:	IV
Formulation/Vehicle:	0.9% Sodium Chloride Injection, U.S.P
Species/Strain:	New Zealand White rabbit

Number/Sex/Group:	Main study 22/group
Satellite groups:	None
Study design:	Dams were dosed from GD 7 to 19. Dams were evaluated for reproductive parameters, and fetuses were assessed for viability, weight, sex, and morphology on GD 29.
Deviation from study protocol:	There were minor deviations, with no impact on study validity

Observations and Results

In the dams, mortality, clinical signs, body weight, and food consumption were assessed. At the MD and HD, decreased activity and respiratory rate, and/or tremors were observed. At the HD, there was a decrease in body weight gain (44%) and food consumption (20%).

Cesarean section (corpora lutea, implantation sites, sex ratio, live fetuses, dead fetuses, resorptions and the pre and post implantation losses), offspring (weights, malformations, anomalies, and skeletal variants), and necropsy data were assessed.

The maternal NOAEL was the MD, based on tremors and a decrease in body weight gain at the HD. The embryofetal NOAEL was at the HD.

Study title: Oral Gavage Dose Range-finding Developmental Toxicity and Toxicokinetic Study with COL-144 in Rats

Study no.:	7874-133
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 11, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, Lot# 77056-02, and purity 101.2%

Methods

Doses:	0, 5, 20, 50, or 100 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	0.25% (w/v) methylcellulose in water
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	Main: 6/group; TK: 3/C, 9/lasmiditan
Satellite groups:	TK
Study design:	Lasmiditan was administered from Gestation day 6 to 17.

Deviation from study protocol: There were minor deviations, with no impact on study validity.

Observations and Results

Mortality, clinical signs, body weight, food consumption, necropsy, TK, cesarean section (corpora lutea, implantation sites, sex ratio, live fetuses, dead fetuses, resorptions, and pre and post implantation losses), and offspring (weights, malformations, anomalies, and skeletal variants) were assessed. There were no drug-related findings.

Plasma exposure (C_{max} and $AUC_{0\text{-}24\ h}$) generally increased less than dose proportionally. No accumulation was observed after repeat dosing. The maternal and fetal NOAEL was the HD (GD 17: C_{max}: 1863 ng/mL; $AUC_{0\text{-}24\ h}$: 23099 ng•h/mL).

Study title: Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetic with COL-144 in Rats

Study no.:	8213912
Study report location:	EDR
Conducting laboratory and location:	CoLucid Pharmaceuticals, Inc. 2530 Meridian Parkway, Suite 300 Durham, North Carolina 27713
Date of study initiation:	August 7, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, Lot# 77056-02, and purity 101.9%

Key Study Findings

The NOAEL was the MD (see exposure in sponsor's table).

Toxicokinetic Summary at Embryo-Fetal Developmental NOAEL of 175 mg/kg/day on Gestation Day 17

Analyte	Cmax (ng/mL)	AUC (ng*h/mL)
COL-144	3827	64823
M3	777	11831
M7	694	11502
M8	325	6210
(S,S)-M18	1135	19456
(S,R)-M18	124	2069

Methods

Doses:	0, 100, 175, or 250 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	0.25% (w/v) methylcellulose in water
Species/Strain:	Rat/Sprague-Dawley CD
Number/Sex/Group:	Main study 25/group; TK: 3/C, 9/lasmiditan

Satellite groups:	None
Study design:	Lasmiditan was administered from Gestation Day 6 to 17. Animals were sacrificed and necropsied on Day 21.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Mortality and Clinical Signs

Observations were made twice daily.

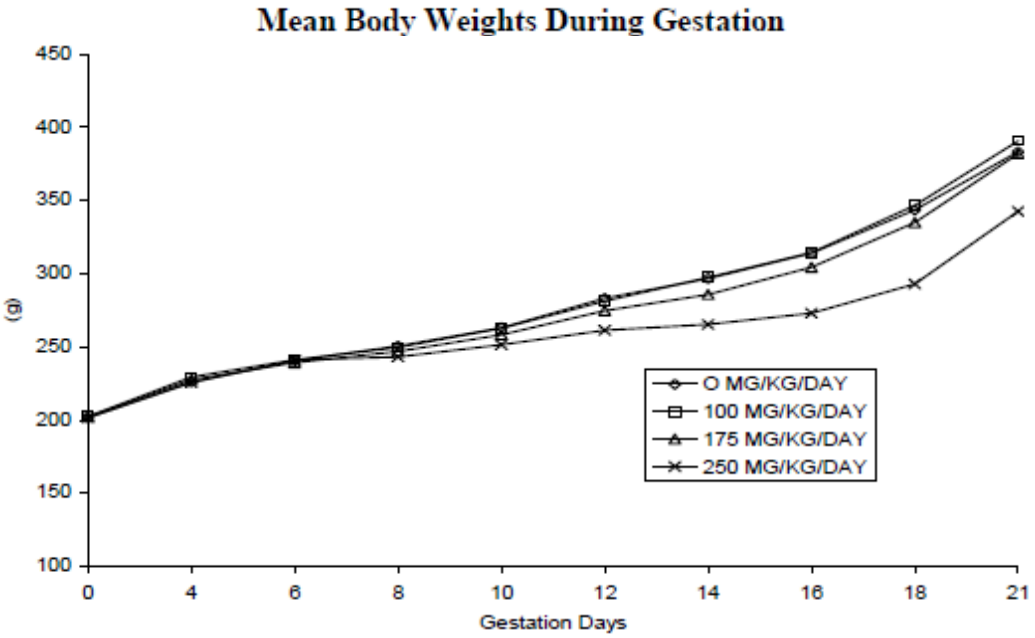
One MDF was sacrificed in moribund condition on GD 17. The cause of death was attributed to a mass in the kidney.

At the MD and HD, thin appearance, rough haircoat, and yellow haircoat in the perineal and ventral abdominal area were observed; the incidences increased with dose.

Body Weight and Food Consumption

Recordings were made twice weekly.

There were drug-related decreases in mean body weight and weight gain at the HD (GD 6 to 17), which partially recovered by GD 21.

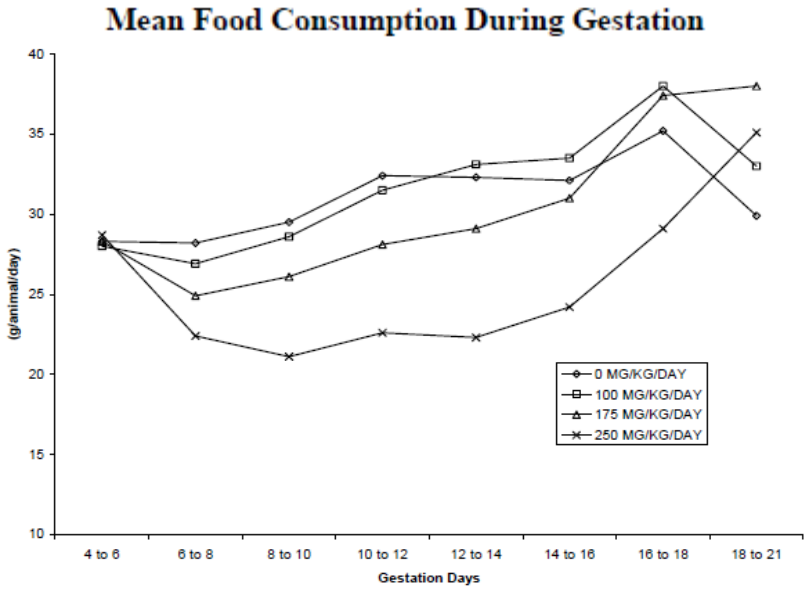


Mean Maternal Body Weight Changes During Gestation (g)

Days	0 mg/kg	100 mg/kg	175 mg/kg	250 mg/kg
6 to 18	103	105	96	52**
6 to 21	142	149	143	102**

** = P≤0.01

There was a dose-dependent reduction in mean food consumption at the MD and HD (GD 6 to 17), which resolved during the post dosing period (GD 18 to 21).



Sponsor's figure

Toxicokinetics

Plasma lasmiditan exposure (C_{max} and $AUC_{0\text{-}24\ h}$) generally increased less than dose proportionally on GD 6, and greater than dose proportionally on GD 17. Exposure was slightly higher on GD 17 than on GD 6. M3 and M8 exposure generally increased less than dose proportionally on GD 6 and dose proportionally on GD 17. M7, (S,S)-M18, and (S,R)-M18 exposure increased less than dose proportionally on GD 6 and GD 17. M3, M8, and (S,R)-M18 accumulated after repeat dosing, while M7 and (S,S)-M18 did not. Based on parent to metabolite (M/P) ratios of $AUC_{0\text{-}24\ h,}$ The M/P ratios were not dose-dependent.

Toxicokinetic Parameters for COL-144 and M3 in Plasma of Pregnant Rats

Interval	Dose Group	COL-144 Dose Level (mg/kg/day)	COL-144 C_{max} (ng/mL)	COL-144 T_{max} (hr)	COL-144 AUC_{0-24} (ng•hr/mL)	M3 C_{max} (ng/mL)	M3 T_{max} (hr)	M3 AUC_{0-24} (ng•hr/mL)	M3 M:P Ratio AUC_{0-24}
GD 6	6	100	1700	0.500	22112	359	0.500	3807	0.172
	7	175	1970	0.500	29743	403	0.500	5308	0.178
	8	250	2813	1.00	36787	451	1.00	6345	0.172
GD 17	6	100	1983	1.00	28968	319	8.00	5457	0.188
	7	175	3827	4.00	64823	777	4.00	11831	0.183
	8	250	6133	1.00	97930	893	2.00	18252	0.186

NA Not applicable.
Note: AUC_{0-24} is equivalent to AUC_{0-t}.

Toxicokinetic Parameters for M7 and M8 in Plasma of Pregnant Rats

Interval	Dose Group	COL-144 Dose Level (mg/kg/day)	M7 C_{max} (ng/mL)	M7 T_{max} (hr)	M7 AUC_{0-24} (ng•hr/mL)	M7 M:P Ratio AUC_{0-24}	M8 C_{max} (ng/mL)	M8 T_{max} (hr)	M8 AUC_{0-24} (ng•hr/mL)	M8 M:P Ratio AUC_{0-24}
GD 6	6	100	842	4.00	12241	0.554	71.3	8.00	1272	0.0575
	7	175	822	1.00	13290	0.447	73.4	4.00	1466	0.0493
	8	250	1283	1.00	16373	0.445	127	8.00	2301	0.0626
GD 17	6	100	562	4.00	7169	0.247	174	8.00	2536	0.0876
	7	175	694	8.00	11502	0.177	325	4.00	6210	0.0958
	8	250	1069	1.00	15226	0.155	557	2.00	11775	0.120

NA Not applicable.
Note: AUC_{0-24} is equivalent to AUC_{0-t}.

Toxicokinetic Parameters for (S,S)-M18 and (S,R)-M18 in Plasma of Pregnant Rats

Interval	Dose Group	COL-144 Dose Level (mg/kg/day)	(S,S)-M18 C_{max} (ng/mL)	(S,S)-M18 T_{max} (hr)	(S,S)-M18 AUC_{0-24} (ng•hr/mL)	(S,S)-M18 M:P Ratio AUC_{0-24}	(S,R)-M18 C_{max} (ng/mL)	(S,R)-M18 T_{max} (hr)	(S,R)-M18 AUC_{0-24} (ng•hr/mL)	(S,R)-M18 M:P Ratio AUC_{0-24}
GD 6	6	100	1036	8.00	16270	0.736	69.7	8.00	1212	0.0548
	7	175	767	8.00	15057	0.506	72.8	8.00	1311	0.0441
	8	250	1563	8.00	25077	0.682	116	8.00	2020	0.0549
GD 17	6	100	1004	8.00	14620	0.505	88.2	8.00	1355	0.0468
	7	175	1135	8.00	19456	0.300	124	8.00	2069	0.0319
	8	250	1614	8.00	30253	0.309	157	4.00	3231	0.0330

NA Not applicable.
Note: AUC_{0-24} is equivalent to AUC_{0-t}.

Sponsor's tables

Dosing Solution Analysis

Mean dosing solution concentrations were within ±10% of nominal.

Necropsy

In the sacrificed MD dam, there was a kidney mass, a dilated kidney pelvis, and urinary bladder calculi. At the HD, uterine weights were reduced.

GROUP MEAN UTERUS WEIGHTS

0	100 mg/kg	175 mg/kg	250 mg/kg
98.56 g	103.49 g	94.22 g	**82.72 g**

Cesarean Section Data (corpora lutea, resorptions, implantation sites, sex ratio, dead fetuses, and pre and post implantation losses)

There were no drug-related findings.

Offspring (Fetal Weights, Malformations, Anomalies (External, Visceral, and Skeletal))

Fetal weights were decreased at the HD (14%), and there was a dose-related delay in skeletal ossification at the MD and HD. There were no drug-related skeletal variations at the low dose; therefore, the sponsor only included the MD and HD findings in the table below.

Text Table 1: Skeletal Variations

Variation	Control (litter mean percent)[a]		175 mg/kg/day (litter mean percent)		250 mg/kg/day (litter mean percent)		(b) (4) HCD (2008-2009 GD 21) (range, litter mean percent)	
	Fetal	Litter	Fetal	Litter	Fetal	Litter	Fetal	Litter
Incomplete ossification of the skull	0	0	2.9*	17	4.0*	12	0.0-0.7	0.0-8.0
5th sternebrae unossified	1.3	8	7.1*	25	23**	52**	0.0-1.9	0.0-12.0
6th sternebrae unossified	0	0	0	0	2.6	8.0	0.0-0.6	0.0-4.0
5th/6th sternebrae, incomplete ossification	0.6	4.0	2.1	8.3	12**	48**	0.6-4.7	4.0-28.0
Other sternebrae, unossified	0	0	0	0	6.6**	16	0.0-0.6	0.0-4.0
Other sternebrae, incomplete ossification	0	0	0	0	7.9**	40**	0.0-0.6	0.0-4.0
Sternebrae, asymmetrically ossified	0	0	0.7	4.2	2.0	8.0	0.0-0.6	0.0-4.0
5th/6th sternebrae, bipartite	0	0	0	0	2.6	16	0.0-0.9	0.0-4.0
Other sternebrae bipartite	0	0	0	0	6.6**	20*	0.0-0.7	0-4.2
Wavy/bent ribs	0	0	15**	46**	22**	60**	0.0-1.6	0.0-8.0
13th rudimentary ribs	1.3	4.0	2.9	17	9.9**	44**	0.0-5.4	0.0-20.0
Incomplete ossification of ribs	0	0	2.1	8.3	3.3*	16	0.0-0.3	0.0-4.0
7th cervical ribs	0	0	0	0	2.0	12	0.0-0.6	0.0-8.0

* = p≤0.05; ** = p≤0.01

a. Litter Mean Percent = the group mean of the percent of fetuses within each litter exhibiting the fetal abnormality.

Sponsor's table

Study title: Oral Gavage Tolerability and Dose Range-finding Developmental Toxicity and Toxicokinetic Study with COL-144 in Rabbits

Study no.:	7874-134
Study report location:	EDR
Conducting laboratory and location:	CoLucid Pharmaceuticals, Inc. 2530 Meridian Parkway, Suite 300 Durham, North Carolina 27713
Date of study initiation:	April 26, 2011
GLP compliance:	No
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, Lot# 77056-02, and purity 101.2%

Methods

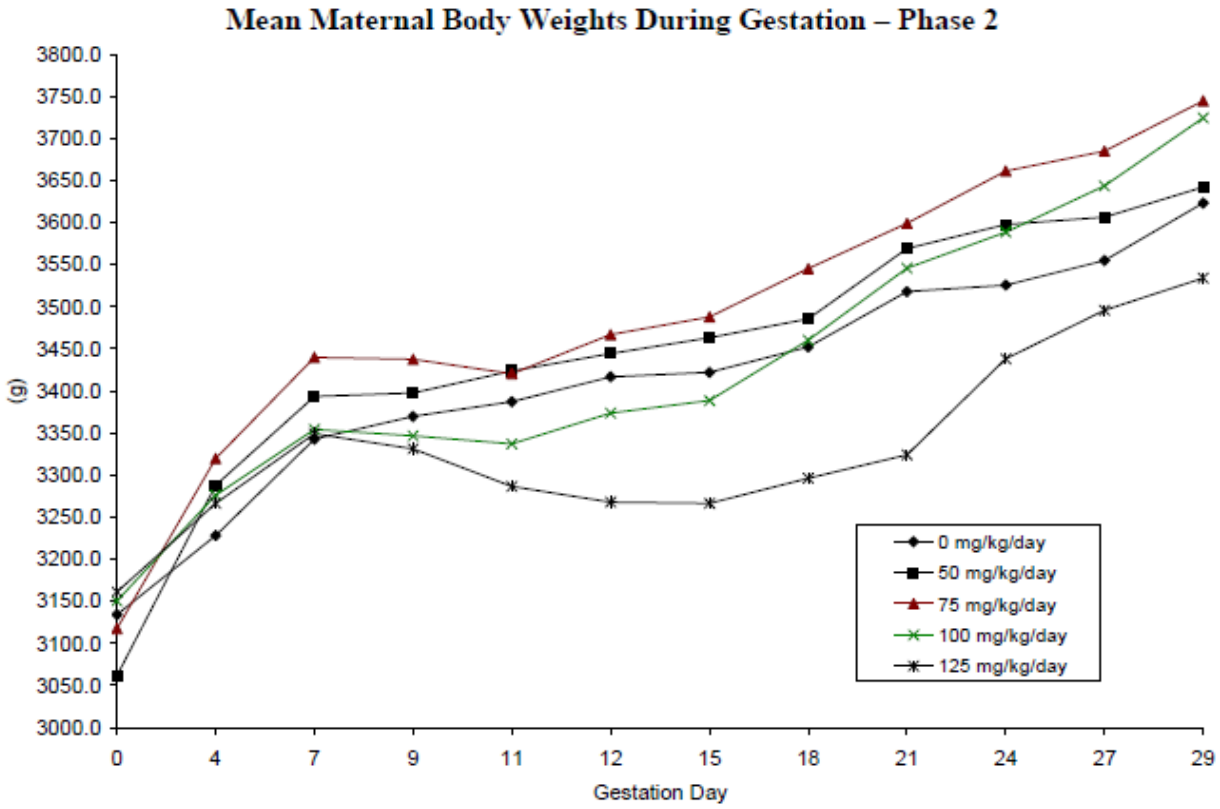
Doses:	Nonpregnant animals: Part 1: 0, 5, 10, 20, or 40 mg/kg Part 2: 0, 50, 75, or 100 mg/kg Pregnant animals: 0, 50, 75, 100, or 125 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	0.25% (w/v) methylcellulose in water
Species/Strain:	Rabbits /Hra:(NZW)SPF rabbits
Number/Sex/Group:	Nonpregnant part 1 & 2: 3/group Pregnant: 6/group Pregnant TK: 3/group
Satellite groups:	None
Study design:	In Parts 1 and 2, animals were dosed for 7 days and sacrificed on Day 8 without necropsy. Pregnant (main and TK) animals were dosed from GD 7 to 20 and sacrificed on GD 29 with necropsy.
Deviation from study protocol:	There were minor deviations, with no impact on study validity.

Key Study Findings

Nonpregnant animals were assessed for mortality, clinical signs, body weight, food consumption, and TK. There were no drug-related findings at ≤75 mg/kg. At the HD in Part 2, there was a decrease in mean body weight gain (64%), compared to controls, which correlated with a decrease in food consumption.

Pregnant animals were assessed for mortality, clinical observations, maternal body weight, food consumption, necropsy, TK, cesarean section, and fetal external evaluations. One HD TK animal died on GD 11 due to gavage error. At the HD, reduced body weight and body weight gain were observed throughout dosing; body weight

effects correlated with a decrease in food consumption (23 to 55%) and mean fetal body weight (7.7%).



Sponsor's figure

Mean Maternal Body Weight Changes

GD	0 mg/kg	50 mg/kg	75 mg/kg	100 mg/kg	125 mg/kg
7 to 21	175	176	159	192	-25
21 to 29	105	73	146	179	210
0 to 29	489	581	627	574	373

Plasma lasmiditan exposure (C_{max} and $AUC_{0\text{-}24\ h}$) increased greater than dose proportionally on GD 7 and approximately dose proportionally on GD 20, with no accumulation. M3 and M7 exposures increased greater than dose proportional on GD 7; on GD 20, increases in mean C_{max} were less than dose proportional and mean $AUC_{0\text{-}24\ h}$ increases were dose proportional. M8 and (S,S)-M18 exposure increased approximately dose proportionally. (S,R)-M18 C_{max} increased approximately dose proportionally, while $AUC_{0\text{-}24\ h}$ increased greater than dose proportionally. M7 and M8 accumulated after repeat dosing, while M3, (S,S)-M18, and (S,R)-M18 did not.

Mean Toxicokinetic Parameters for COL-144 and M3 in Rabbit Plasma

Dose Group	COL-144 Dose Level (mg/kg/day)		COL-144 C_{max} (ng/mL)	COL-144 AUC_{0-24} (ng·hr/mL)	COL-144 T_{max} (hr)	M3 C_{max} (ng/mL)	M3 AUC_{0-24} (ng·hr/mL)	M3 T_{max} (hr)	M3 M/P ratio AUC_{0-24}
Gestation Day 7									
7	50	Mean	164	528	0.500	234	603	0.750	1.17
		SD	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	2	2	2	2
8	75	Mean	426	1261	0.500	859	1490	0.500	1.29
		SD	261	380	0	185	272	0	0.55
		N	3	3	3	3	3	3	3
9	100	Mean	774	2720	0.833	828	1979	0.667	0.802
		SD	624	1544	0.289	686	967	0.289	0.279
		N	3	3	3	3	3	3	3
10	125	Mean	939	3084	0.500	1559	3005	0.500	0.982
		SD	783	1172	0	1478	1466	0	0.254
		N	3	3	3	3	3	3	3
Gestation Day 20									
7	50	Mean	522	1092	0.500	463	625	0.500	0.659
		SD	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	2	2	2	2
8	75	Mean	561	1711	0.667	576	1116	0.667	0.706
		SD	90	598	0.289	203	316	0.289	0.313
		N	3	3	3	3	3	3	3
9	100	Mean	521	1900	1.00	635	1453	0.500	0.754
		SD	393	836	0.87	499	711	0	0.038
		N	3	3	3	3	3	3	3
10	125	Mean	678	2281	0.500	715	1678	0.500	0.754
		SD	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	2	2	2	2

NA - Not applicable.

Mean Toxicokinetic Parameters for M7 and M8 in Rabbit Plasma

Dose Group	COL-144 Dose Level (mg/kg/day)		M7 C_{max} (ng/mL)	M7 AUC_{0-24} (ng·hr/mL)	M7 T_{max} (hr)	M7 M/P ratio AUC_{0-24}	M8 C_{max} (ng/mL)	M8 AUC_{0-24} (ng·hr/mL)	M8 T_{max} (hr)	M8 M/P ratio AUC_{0-24}
Gestation Day 7										
7	50	Mean	9.31	40.4	0.750	0.0838	8800	61475	1.00	122
		SD	NA	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	2	2	2	2	2
8	75	Mean	26.8	117	0.500	0.103	15133	133632	0.833	119
		SD	6.8	35	0	0.051	802	29816	0.289	67
		N	3	3	3	3	3	3	3	3
9	100	Mean	80.3	813	2.83	0.299	17867	190573	3.33	89.1
		SD	81.8	929	2.02	0.328	2183	24614	1.15	50.9
		N	3	3	3	3	3	3	3	3
10	125	Mean	46.2	265	1.67	0.0935	20500	241791	3.33	93.1
		SD	50.1	120	2.02	0.0442	3928	32316	1.15	58.3
		N	3	3	3	3	3	3	3	3
Gestation Day 20										
7	50	Mean	156	657	0.500	0.677	13550	78497	1.00	80.3
		SD	NA	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	2	2	2	2	2
8	75	Mean	218	1401	0.667	0.858	18100	156697	1.33	100
		SD	42	258	0.289	0.176	1609	18521	0.58	42
		N	3	3	3	3	3	3	3	3
9	100	Mean	244	1438	1.00	0.767	22500	235684	2.67	130
		SD	162	622	0.87	0.238	5336	68479	1.15	22
		N	3	3	3	3	3	3	3	3
10	125	Mean	227	1969	0.750	0.940	26850	283578	2.00	132
		SD	NA	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	2	2	2	2	2

NA – Not Applicable

Mean Toxicokinetic Parameters for (S,S)-M18 and (S,R)-M18 in Rabbit Plasma

Dose Group	COL-144 Dose Level (mg/kg/day)		(S,S)-M18 C_{max} (ng/mL)	(S,S)-M18 AUC_{0-24} (ng·hr/mL)	(S,S)-M18 T_{max} (hr)	(S,S)-M18 M/P ratio AUC_{0-24}	(S,R)-M18 C_{max} (ng/mL)	(S,R)-M18 AUC_{0-24} (ng·hr/mL)	(S,R)-M18 T_{max} (hr)	(S,R)-M18 M/P ratio AUC_{0-24}
Gestation Day 7										
7	50	Mean	155	1384	4.00	2.70	284	2525	4.00	5.09
		SD	NA	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	2	2	2	2	2
8	75	Mean	242	2544	2.67	2.16	466	4693	2.67	4.05
		SD	46	202	1.15	0.72	38	322	1.15	1.65
		N	3	3	3	3	3	3	3	3
9	100	Mean	298	3212	3.33	1.61	558	6234	3.33	3.09
		SD	37	238	1.15	1.18	102	560	1.15	2.18
		N	3	3	3	3	3	3	3	3
10	125	Mean	275	3847	4.67	1.46	581	8065	3.33	3.13
		SD	80	751	3.06	0.87	92	1315	1.15	2.06
		N	3	3	3	3	3	3	3	3
Gestation Day 20										
7	50	Mean	147	1321	2.00	1.23	282	2574	2.00	2.60
		SD	NA	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	2	2	2	2	2
8	75	Mean	260	2901	2.67	1.81	474	5076	3.33	3.23
		SD	63	773	1.15	0.66	54	666	1.15	1.26
		N	3	3	3	3	3	3	3	3
9	100	Mean	390	4565	3.33	2.57	598	7112	2.67	3.93
		SD	118	1400	1.15	0.81	154	2014	1.15	0.64
		N	3	3	3	3	3	3	3	3
10	125	Mean	346	4355	4.00	2.08	691	8716	4.00	4.05
		SD	NA	NA	NA	NA	NA	NA	NA	NA
		N	2	2	2	2	2	2	2	2

NA - Not applicable.

Sponsor's tables

Study title: Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetic with COL-144 in Rabbits

Study no.:	8220235
Study report location:	EDR
Conducting laboratory and location:	CoLucid Pharmaceuticals, Inc. 2530 Meridian Parkway, Suite 300 Durham, North Carolina 27713
Date of study initiation:	July 22, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, Lot# 77056-02, and purity 101.9%

Methods

Doses:	0, 50, 75, or 115 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	0.25% (w/v) methylcellulose in water.
Species/Strain:	Rabbits/Hra:(NZW)SPF
Number/Sex/Group:	20/group
Satellite groups:	None
Study design:	Lasmiditan was administered from Gestation Day 7 to 20. Animals were sacrificed and necropsied on Day 29.
Deviation from study protocol:	Rabbit fetal skeletons were over processed and could not be evaluated. The study was repeated.

Key Study Findings

Dams were evaluated for mortality, clinical observations, maternal body weight, and food consumption. One HDF aborted on GD 21. There were dose-related clinical signs of few or no feces and thin appearance. There were dose-related reductions in body weight gain of 16, 50, and 95 %, compared to control, at 50, 75, and 115 mg/kg, respectively, between GD 7 and 21, which resolved between GD 21 and 29. At the HD, these findings correlated with decreases in food consumption (GD 7 to 21, up to 25%).

Cesarean section data included the number of corpora lutea, uterine examinations for numbers of live and dead fetuses, early or late resorptions, and abnormalities. There were no drug-related findings.

Fetuses were weighed and evaluated for external and visceral abnormalities. There were no drug related findings.

The maternal NOAEL was the MD, based on abortion and decreases in body weight gain during the dosing period at the HD. The fetal NOAEL was the HD.

Study title: Oral Gavage Study for Effects on Embryo-fetal Development and Toxicokinetic with COL-144 in Rabbits

Study no.:	8223068
Study report location:	EDR
Conducting laboratory and location:	CoLucid Pharmaceuticals, Inc. 2530 Meridian Parkway, Suite 300 Durham, North Carolina 27713
Date of study initiation:	January 21, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, Lot# 77056-02, and purity 101.9%

Key Study Findings

The maternal and fetal NOAEL was the LD (C_{max}: 584 ng/mL; $AUC_{0\text{-}24\ h}$: 2545 ng*h/mL), based on decreased fetal body weight, abortion, skeletal variations, and post implantation loss at higher doses.

Methods

Doses:	0, 50, 75, or 115 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	0.25% (w/v) methylcellulose in water.
Species/Strain:	Rabbits/Hra:(NZW)SPF
Number/Sex/Group:	Main study: 20/group; TK: 3/group
Satellite groups:	TK
Study design:	Lasmiditan was administered from Gestation Day (GD) 7 to 20. Animals were sacrificed and necropsied on GD 29.
Deviation from study protocol:	There were minor deviations that did not affect study validity

Mortality and Clinical Signs

Observations were made twice daily.

One MDF was sacrificed due to markedly reduced food consumption and body weight loss. One HDF aborted on GD 22 after showing an extended period of low food consumption and few or no feces. One CF, 1 LDF, and 1 HDF were found dead with signs of gavage error.

Body Weight and Food Consumption

Recordings were made twice weekly.

At the HD, there were reductions in body weight, body weight gain, and food consumption, compared to control, occurred during the dosing period (GD 7 to 20). These reductions partially resolved post dose.

Mean Maternal Body During Gestation (g)

Day	0 mg/kg	50 mg/kg	75 mg/kg	115 mg/kg
0	3446	3440	3523	3495
7 (Dosing Day 1)	3579	3519	3631	3607
18 (Dosing Day 18)	3713	3575	3678	3467
29 (Post dosing)	3896	3646	3844	3724

Mean Food Consumption During Gestation (g)

Day	0 mg/kg	50 mg/kg	75 mg/kg	115 mg/kg
7 to 21	149.0	122.5	121.2	72.2**

* = ≤0.05; ** = ≤0.01

Toxicokinetics

Plasma exposures (C_{max} and $AUC_{0\text{-}24\ h}$) for lasmiditan and its metabolites (M3, M7, M8, (S,S)-M18 and (S,R)-M18) increased approximately dose proportionally. After repeat dosing, exposure accumulated for lasmiditan and metabolites M3, M7, M8, (S,R)-M18 and (S,S)-M18.

Mean Toxicokinetic Parameters for COL-144 and M3 in Rabbit Plasma

Dose Group	COL-144 Dose Level (mg/kg/day)		COL-144 C_{max} (ng/mL)	COL-144 T_{max} (hr)	COL-144 $AUC_{0\text{-}24}$ (ng·hr/mL)	M3 C_{max} (ng/mL)	M3 T_{max} (hr)	M3 $AUC_{0\text{-}24}$ (ng·hr/mL)	M3 M:P Ratio $AUC_{0\text{-}24}$
Gestation Day 7									
6	50	Mean	510	0.500	1196	650	0.500	1090	0.920
		SD	124	0	210	148	0	119	0.103
		N	3	3	3	3	3	3	3
7	75	Mean	640	0.500	1512	983	0.500	1539	1.07
		SD	230	0	553	173	0	249	0.23
		N	3	3	3	3	3	3	3
8	115	Mean	1161	0.500	3698	1312	0.500	2705	0.783
		SD	286	0	1703	313	0	801	0.203
		N	3	3	3	3	3	3	3
Gestation Day 20									
6	50	Mean	584	0.833	2545	672	0.833	1832	0.797
		SD	162	0.289	961	185	0.289	207	0.305
		N	3	3	3	3	3	3	3
7	75	Mean	964	0.667	2614	1103	0.667	1935	0.740
		SD	624	0.289	918	631	0.289	673	0.029
		N	3	3	3	3	3	3	3
8	115	Mean	1158	1.00	4286	840	0.667	1961	0.642
		SD	1040	0.87	3284	571	0.289	600	0.405
		N	3	3	3	3	3	3	3

Mean Toxicokinetic Parameters for M7 and M8 in Rabbit Plasma

Dose Group	COL-144 Dose Level (mg/kg/day)		M7 C_{max} (ng/mL)	M7 T_{max} (hr)	M7 AUC_{0-24} (ng·hr/mL)	M7 M:P Ratio AUC_{0-24}	M8 C_{max} (ng/mL)	M8 T_{max} (hr)	M8 AUC_{0-24} (ng·hr/mL)	M8 M:P Ratio AUC_{0-24}
Gestation Day 7										
6	50	Mean	23.9	0.500	81.7	0.0689	10923	1.33	104492	91.3
		SD	1.7	0	8.8	0.0066	1004	0.58	24947	33.5
		N	3	3	3	3	3	3	3	3
7	75	Mean	36.5	0.500	192	0.121	13467	1.67	124539	91.1
		SD	13.0	0	120	0.043	208	2.02	19306	37.8
		N	3	3	3	3	3	3	3	3
8	115	Mean	53.1	0.500	365	0.0970	15600	2.17	193456	65.3
		SD	20.8	0	225	0.0234	3857	1.76	44801	45.4
		N	3	3	3	3	3	3	3	3
Gestation Day 20										
6	50	Mean	305	1.00	1588	0.640	14567	1.33	119252	49.4
		SD	67	0	506	0.118	404	0.58	24612	12.5
		N	3	3	3	3	3	3	3	3
7	75	Mean	330	0.667	1797	0.740	17633	1.17	139173	55.6
		SD	90	0.289	279	0.276	5255	0.76	21002	10.0
		N	3	3	3	3	3	3	3	3
8	115	Mean	392	1.00	2946	0.613	28667	3.00	365343	162
		SD	342	0.87	2611	0.166	3557	1.73	95554	176
		N	3	3	3	3	3	3	3	3

Mean Toxicokinetic Parameters for (S,S)-M18 and (S,R)-M18 in Rabbit Plasma

Dose Group	COL-144 Dose Level (mg/kg/day)		(S,S)-M18 C_{max} (ng/mL)	(S,S)-M18 T_{max} (hr)	(S,S)-M18 AUC_{0-24} (ng·hr/mL)	(S,S)-M18 M:P Ratio AUC_{0-24}	(S,R)-M18 C_{max} (ng/mL)	(S,R)-M18 T_{max} (hr)	(S,R)-M18 AUC_{0-24} (ng·hr/mL)	(S,R)-M18 M:P Ratio AUC_{0-24}
Gestation Day 7										
6	50	Mean	175	2.67	1866	1.64	381	2.67	4059	3.58
		SD	27	1.15	574	0.69	83	1.15	1472	1.67
		N	3	3	3	3	3	3	3	3
7	75	Mean	243	4.00	2709	1.99	538	4.00	5742	4.18
		SD	43	0	437	0.84	50	0	1186	1.84
		N	3	3	3	3	3	3	3	3
8	115	Mean	366	4.00	4479	1.51	648	3.33	8004	6.03
		SD	114	0	1097	0.98	223	1.15	2403	3.20
		N	3	3	3	3	3	3	3	3
Gestation Day 20										
6	50	Mean	297	2.67	2893	1.17	396	3.33	4347	1.77
		SD	23	1.15	799	0.18	65	1.15	1324	0.39
		N	3	3	3	3	3	3	3	3
7	75	Mean	307	2.33	3192	1.28	474	2.67	4716	1.92
		SD	104	1.53	539	0.28	84	1.15	313	0.53
		N	3	3	3	3	3	3	3	3
8	115	Mean	743	4.67	10813	5.06	944	3.33	13265	6.51
		SD	180	3.06	4288	6.02	398	1.15	6679	8.21
		N	3	3	3	3	3	3	3	3

NA Not applicable.

Sponsor's tables

Dosing Solution Analysis

Dosing formulations were within ±15% of nominal.

Necropsy

There were no drug-related findings in dams.

Cesarean Section Data (corpora lutea, resorptions, implantation sites, sex ratio, dead fetuses, and pre and post implantation losses)

At the HD, there were increases in early, late, and total resorptions and post implantation loss.

MEAN % RESORPTIONS AND POSTIMPANTATION LOSS

Finding	0 mg/kg	50 mg/kg	75 mg/kg	115 mg/kg
Resorptions: Total	1.3	0.0	2.1	**11.3**
Early	0.7	0.0	2.1	**5.7**
Late	0.6	0.0	1.7	**5.6**
Postimplantation Loss	1.3	0.0	3.8	**11.3**

Offspring (Fetal Weights, Malformations, Anomalies (External, Visceral, and Skeletal)

Fetal weights were decreased (14%) at the HD. Cardiovascular defects of the ventricular septum and stenosis of the ascending aorta occurred in fetuses of 11 and 6% of litters, respectively, at the HD. There was a drug-related delay in skeletal ossification, demonstrated by a significant increase (30%) of unossified 5th sternebra, which was outside the historical control range (2.4 to 28%), at the HD. One HD fetus had absent/partially absent bones in the skull and multiple external malformations including open eye, meningocele, and flexed paws.

MEAN FETAL WEIGHTS (g)

0 mg/kg	50 mg/kg	75 mg/kg	115 mg/kg
41.35	38.85	39.28	**35.69**

9.3 Prenatal and Postnatal Development

Study title: Oral Gavage Study for Effects on Pre- and Post-natal Development, Including Maternal Function with COL-144 in Rats

Study no.:	8220236
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 16, 2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Lasmiditan, Lot 77056-02, and purity 101.9%

Key Study Findings

The NOAEL was the MD, based on postnatal death, stillbirth, and decreased litter size at the HD.

Methods

Doses:	0, 100, 150, or 225 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.25% (w/v) methylcellulose in water
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	F_0: 25 mated females per group F_1: 25/sex/group
Satellite groups:	None
Study design:	At dosing initiation, animals were 12 weeks old (GD 6 through LD 20 for females), and body weights ranged from 209 to 271 g. Lasmiditan was administered daily via oral gavage to F_0 rats from implantation through weaning.
Deviation from study protocol:	There were minor deviations that did not affect study validity.

Observations and Results

F_0 Dams

Survival: Observations were made twice daily.

There was one HDF sacrificed due to moribund condition and failing to completely deliver a litter. At the HD, there was an increased number of stillborn pups.

Stillborn Pups

Dose	0 mg/kg	100 mg/kg	150 mg/kg	225 mg/kg
Total Pups	124	91	92	155
Stillborn	9	2	3	35**
%	7.2	2.2	3.3	22

** = P≤0.01

Clinical signs: Detailed observations were made twice weekly.

At the HD, there were drug related findings consisting of an increase in the gestation period (HD: 22.6 days, C: 21.7 days, and HC: 21.6 to 21.9 days), prolonged deliveries, and a reduction in delivered pups. Underdeveloped mammary glands were observed in dams at the HD (4/14). 10 dams were removed from the study due to loss of litters, which corresponded with a lack of milk in the pups' stomach.

Delivered Pups

0 mg/kg	100 mg/kg	150 mg/kg	225 mg/kg
316	290	302	270

Body weight: Recordings were made twice weekly from GD 0 to LD 21.

During gestation, there were dose-related decreases in body weight and body weight gain at the MD and HD.

Mean Body Weight on Gestation Day 20

Dose	0 mg/kg	100 mg/kg	150 mg/kg	225 mg/kg
g	359.3	365.1	354.4	347.1
%	-	2	-1	-3

Mean Body Weight Gain Gestation Day 0-20

Dose	0 mg/kg	100 mg/kg	150 mg/kg	225 mg/kg
g	152.6	159.6	147.3	140.2
%	-	4	-4	-8

Food consumption: Recordings were made twice weekly from GD 4 to GD20.

During gestation, there were decreases in food consumption at the HD.

Mean Food Consumption During Gestation (g)

Dose	0 mg/kg	100 mg/kg	150 mg/kg	225 mg/kg
Days 4 - 20	29.9	30.1	29.5	27.8*

* = P≤0.05

Uterine content: There were no drug-related findings.

Necropsy observation: Examinations were performed on dams that terminated prematurely.

There were no drug-related findings.

Toxicokinetics: None

Dosing Solution Analysis Dosing formulations were within ±10% of nominal.

F_1 Generation

Survival: On LD 0, live pups were weighed and examined for external abnormalities. The number of live pups/sex/litter were recorded weekly through LD 21.

One HD dam was euthanized in a moribund condition after an incomplete delivery on GD23.

Over 1/3 of the HD litters had no surviving pups by LD 4.

Clinical signs: Recordings were made weekly until necropsy.

HD pups had thin appearance.

Body weight: Recordings were made weekly until necropsy.

HD pups had reduced body weights compared to controls during the lactation period (16%, Day 21) and through adulthood (11% (M), Day 110; 12% (F), GD 20).

Food consumption: There was no milk in the stomach of 4/14 HD pups.

Physical development: Pups were assessed for pinna unfolding (LD 1), hair growth (LD 7), incisor eruption (LD 7), eye opening (LD 11), and auditory startle (Day 21). After weaning, vaginal opening (PND 30) and balanopreputial separation (PND 35).

At the HD, pups had accelerated eye opening and a delay in the appearance of hair growth.

Mean Age Pups Reach Developmental Endpoint (Day).

Dose	0 mg/kg	100 mg/kg	150 mg/kg	200 mg/kg
Eye opening	15.17	15.00	15.00	14.07
Hair growth	14.17	13.92	14.00	15.71

There were no additional drug-related findings.

Neurological assessment: Locomotor activity (PND 22 and ~PND 45), pupillary reflexes (PND 22) and learning, memory, and reverse, learning (water maze, PND 35) were assessed in approximately ~25/sex/group.

There were no drug-related findings.

Reproduction: The conception indices: fertility indices, gestation duration, implantation sites, number of pups delivered, and number of live and dead pups, were assessed.

There were decreases in the number of implantation sites, pups delivered, and the number of live pups per litter.

Delivery and Litter Findings

Dose	0 mg/kg	100 mg/kg	150 mg/kg	200 mg/kg	HC
Mean Implantation Sites	14.56	16.38	14.64	11.89*	13.68-16.76
Mean Pups Delivered	14.17	15.58	14.64	10.97**	12.37-16.24
Mean Live Pups/Litter	13.78	15.42	14.64	10.72*	12.00-16.00

* = P≤0.05; ** = P≤0.01
HC = Historical Control

10 Special Toxicology Studies

Lasmiditan was tested in a GLP and QC Bovine Corneal Opacity and Permeability assay. It was found to severely irritate corneas at 200 mg/mL.

In a GLP and QC *In vitro* Balb/c 3T3 neutral red uptake phototoxicity assay, lasmiditan was found not to be phototoxic at concentrations up to approximately 100 µg/mL.

The renal toxicity of lasmiditan was assessed in a 4-week toxicology study in male Fischer rats (4/group: 0, 60, and 100 mg/kg, oral gavage). Mortality, physical examination, body weight, food consumption, hematology, clinical chemistry, urinalysis, kidney weight, kidney histopathology, and TK were assessed. Findings consisted of dose-related medullary tubular degeneration and regeneration of the cortical tubule. At the HD, there was an increase in kidney weight, which correlated with dose-related increases in urinary renal epithelial cell count. Histopathology of the kidney showed the collecting duct epithelium had increased vacuolation consisting of lipid droplets and autophagosomes, occasional necrotic cells, and intracellular apoptotic bodies. Exposure (C_{max} and $AUC_{0\text{-}24\ h}$) increased less than dose proportionally (see sponsor's table).

Plasma Concentration (ng/mL) and Pharmacokinetic Parameters for 573144 in Fischer Rats Following Multiple (21 days) Oral Administration, as the Hydrochloride Salt

Dose (mg/kg)		60	100
Time (hr)	0	0	0
	0.5	1270	2120
	1	1550	1800
	2	1300	2260
	4	1020	1340
	8	1140	1880
	24	171	322
AUC 0-24h		19576	31196
Cmax		1550	2260
Tmax (hr)		1	2

The hemolytic potential of lasmiditan was assessed in rat, beagle dog, and human blood in a GLP study. Lasmiditan was found be hemolytic at serum plasma concentrations >0.71 mg/mL, which is 23,000-fold greater than C_{max} at the maximum recommended human dose (200 mg).

11 Integrated Summary and Safety Evaluation

Lasmiditan is a serotonin 5-HT_{1F} receptor agonist indicated for the acute treatment of migraine with or without aura in adults. The proposed maximum clinical dose is 200 mg/day.

Pharmacology. In *in vitro* binding and functional assays, lasmiditan had low nanomolar affinity and activity at the 5-HT_{1F} receptor. Binding affinity was similar among mouse, rat, rabbit, dog, and human 5-HT_{1F} receptors.

In vivo studies focused on trigeminal ganglia nociceptive neurotransmission because it is implicated as the origin of migraine pain and expresses 5-HT_{1F} receptors. The parameters assessed were protein extravasation (neuroinflammatory response), induction of c-fos, dural-evoked nociception transmission, CGRP release (*ex vivo*), and vasodilation. In the protein extravasation model, rats (4 M/group) were administered oral doses of lasmiditan (up to 10 mg/kg) 1 hour prior to electrical stimulation of the trigeminal nerve. The ID_{50} for inhibition of extravasation was $2x10^{-4}$ µg/kg at 1-hour post stimulation. In the c-fos expression model, rats (6-8 M/group) were given oral doses of lasmiditan (up to 100 µg/kg) 1 hour prior to stimulation. The number of c-fos positive cells was decreased dose dependently, with a maximum reduction of approximately 50% (1.5-hours post stimulation). In the assessment of dural-evoked trigeminovascular nociception, IV administration of 5 mg/kg lasmiditan (90 minutes prior to stimulation) to rats (5-10 M/group) produced a maximum decrease in the neuronal response of approximately 40% (at 90 min post stimulation). In the *ex vivo* assessment of CGRP release from the mouse trigeminovascular system, pretreatment with lasmiditan or sumatriptan (up to 30 µM, 10 minutes prior to stimulation) resulted in attenuation of CGRP release (~55%) after KCl challenge. In an assessment of the vasodilatory response, rats were dosed with IV lasmiditan or sumatriptan (up to 10 mg/kg) pre or post administration of IV capsaicin, periarterial electrical stimulation, or administration of α-CGRP. Both sumatriptan and lasmiditan inhibited dural artery vasodilation by approximately 70% in response to IV capsaicin and periarterial electrical stimulation. Neither sumatriptan nor lasmiditan inhibited α-CGRP-induced vasodilation. With no stimulation, sumatriptan dose-dependently increased mean arterial pressure and dural artery diameter, while lasmiditan did not.

Secondary Pharmacology. Lasmiditan *in vitro* binding affinity to 5-$HT_{1A, 2A, 1B, 2B, 2C, 1D, 1E, 6, and 7}$ was at least 250-fold lower compared to the 5-HT_{1F}. Lasmiditan and its major human metabolites M8 and M18 did not show binding at approximately 50 ion channels and receptors at concentrations ≤10 µM. In functional assays measuring current from different exogenously expressed $GABA_A$ isoforms (α1/β3/γ2, α2/β3/γ2, α3/β3/γ2, α4/β3/γ2, and α5/β3/γ2) in HEK293 cells, there were no agonist, antagonist, or PAM activities associated with lasmiditan at concentrations ≤100 µM.

In addition to the standard battery of secondary pharmacology studies, *in vivo* and *ex vivo* coronary artery vasoconstriction assessments were conducted to address the potential off-target cardiovascular effects of inhibiting the 5-HT_{1F} receptor. Vasoactivity studies found no lasmiditan (up to 100 µM) induced constriction of the rabbit saphenous vein, dog coronary or carotid artery, guinea pig atria and ileum, human internal mammary artery, or human proximal or distal coronary artery.

Safety Pharmacology. Lasmiditan, M8, and M18 were tested for their ability to inhibit hERG channel current in HEK cells. The IC_{50} (~3.0 µM, or 1170 ng/mL) for hERG inhibition was 4-fold higher than the human $C_{max, u}$ (299 ng/mL) for lasmiditan following a single oral 200 mg dose. IC_{50}s for M8 and M18 were greater than 30 µM, and therefore do not suggest a risk for hERG inhibition in humans.

In the *in vivo* single dose (0, 0.6, 2, or 6 mg/kg, 20-minute IV infusions) cardiovascular study in dogs (8/dose, 2 M and 6 F), inotropic state, systemic arterial pressures, heart rate, and electrocardiograms were recorded. There were no drug-related findings. ECG assessments in 2-, 4-, 13-, and 39-week PO and IV toxicology studies in dog also showed no drug-related findings.

A single dose (0, 0.1, 1, 4, or 12 mg/kg, IV) CNS safety pharmacology study of lasmiditan was conducted in mice (~10/M/group). In all animals, sensorimotor reactivity to auditory stimulus was increased. There were additional findings at the HD. The FOB assessment (Irwin,1968) identified a significant decrease in activity, which correlated with decreased core body temperature. The electroshock and pentylenetetrazol administration test identified an increase in the convulsive threshold. In the acetic acid test, IP administration of lasmiditan resulted in a reduced pain response (fewer writhes). In a 2-week toxicology study in dog (3/sex/group; 2, 6, or 15 mg/kg, IV), a neurological evaluation showed no drug-related findings.

In single-dose respiratory and renal system studies in rats (8/group), IV doses of lasmiditan (0, 1, 4, or 12 mg/kg) were assessed. There were no drug-related findings.

Pharmacokinetics. The major metabolites in humans were M8 and M18. These metabolites were adequately assessed in the nonclinical studies.

IV distribution studies in rat show that [^{14}C]lasmiditan crosses the blood brain barrier, with brain to plasma ratios of approximately 3 over a 24-hour period. The highest concentrations of lasmiditan were found in the urinary bladder and in the uveal tract of the eye. In distribution studies of the brain, the highest concentrations of lasmiditan were found in the pituitary gland, pineal gland, and cerebrospinal fluid. In pregnant rats, [^{14}C]lasmiditan concentrations were measurable in the fetus at 24 hours post dose.

In the plasma, approximately 55% of lasmiditan was protein bound in rat, dog, and human, and 90% in monkey.

[^{14}C]lasmiditan was primarily excreted in the urine, with only 28% excreted in the feces. After oral dosing to lactating rats, [^{14}C]lasmiditan was excreted into the milk, resulting in a milk-to-plasma AUC ratio of ~3.

Toxicology. General toxicology studies (IV and PO) were conducted in mouse, rat, and dog; reproductive and developmental studies were conducted in rat and rabbit; and carcinogenicity studies were conducted in rat and transgenic mouse.

General toxicology

General toxicology studies

Duration	Species	Number	Route	Dose mg/kg
5- or 14-Day	CD-1 mouse	5-day: 5 M/group 14-day: 10/sex/group	PO	5-day: 0, 10, 30, 50, 100, or 200 14-day: 0, 30, 100, 200, or 300
4-Week	CD-1 mouse	60/sex/group	PO	100 or 200
13-Week	CD-1 mouse	10/sex/group	PO	0, 30, 100, or 200
4-Day	SD Rat	3 F/group	IV	10, 25, or 55
2-Week	Fischer Rat	17/sex/group	IV	0, 4, 12, or 40
4-Day	Fischer Rat	3 M/group	PO	0, 50, 150, or 300
5-Day	Rat	3 M/group	PO	0, 10, 30, 60, 100, 250, or 300
14-Day	Fischer Rat	5/sex/group	PO	0, 30, 100, or 250
4-Week	CD-Rat	10-15/sex/group	PO	0, 10,30, 50, or 100
13-Week	CD-Rat	10-15/sex/group	PO	0, 10, 30, 50, 100, or 200
26-Week	CD-Rat	10-16/sex/group	PO	0, 10, 30, 50, 100, or 200
2-Week	Dog	3/sex/group	IV	2, 6, or 15
2-Week	Dog	1/sex/group	PO	0, 10, 20, 50, 60, 80, or 90
4-Week	Dog	3-5/sex/group	PO	0, 5, 10, 20, or 60
13-Week	Dog	3-5/sex/group	PO	0, 5, 10, 20, or 50
39-Week	Dog	4-6/sex/group	PO	0, 5, 10, 20, 30, or 50/40

Overall, drug-related death occurred at ≥200 mg/kg in mice; at ≥55 mg/kg (IV) and ≥50 mg/kg (PO) in rat; there were no drug-related deaths in dog. The most commonly observed clinical signs were CNS-related, i.e., tremors, ataxia, hypoactivity, recumbency, head shaking, clonic movements, and convulsions.

In the pivotal 26-week oral toxicology study in rat, there were deaths at 200 mg/kg (5/16) and 100 mg/kg (1/16), with no cause identified. Adverse CNS-related signs of convulsions and/or myoclonic jerking were observed at 200 mg/kg (3/16) and at 100 mg/kg (1/16). Convulsions at 200 mg/kg (2/16) persisted into the recovery period. There was a decrease in mean body weight (11%) in males at 200 mg/kg. There were nonreversible drug-related findings consistent with chronic progressive nephropathy (CPN) consisting of higher urine protein-to-creatinine ratio (200 mg/kg), higher UNAG-to creatinine ratio (200 mg/kg M), and lower urine specific gravity (200 mg/kg), which correlated with kidney lesions and increased kidney weights. Other drug-related histopathology findings included pigmentary inclusions associated with eosinophilic bodies in the cytoplasm of large motor neurons of the brain stem and spinal cord, which persisted into recovery animals at 200 mg/kg. Degenerative cardiomyopathy and increased heart weight were observed at the high dose (200 mg/kg), with increased severity in M and increased incidence in F. The NOAEL was 50 mg/kg.

In the pivotal 39-week oral toxicology study in dog, there were adverse CNS-related clinical signs consisting of tremors and hypoactivity at doses ≥40 mg/kg. The NOAEL was 30 mg/kg.

Genetic toxicology. Lasmiditan was negative in an OECD compliant Ames, *in vitro* chromosomal aberration, and *in vivo* mouse bone marrow micronucleus assays.

Rat and Tg.rasH2 Mouse Carcinogenicity. Based on the FDA statistical analysis, lasmiditan was not carcinogenic.

Carcinogenicity studies

Species	Duration	Dosing (mg/kg)
Rat (60/sex/group)	104-week	0, 10, 25, 75
Tg.rasH2 (25/sex/group)	26-week	M: 0, 20, 50, 150 F: 0, 25, 80, 250

Reproductive and Developmental Toxicology.

Reproductive and Developmental Toxicology Studies

Study	Species	Dosing (mg/kg)	
Fertility and Early Embryonic Development	Rat (22/sex/group)	Oral	M: 0, 100, 175 or 250/200 F: 0, 100, 150, or 200
Pilot Embryofetal Development	Rat (3/group)	IV	0, 10, 25, 55, or 75
Embryofetal Development	Rat (25/group)	IV	0, 5, 15, or 75
Pilot Embryofetal Development	Rabbit (5/group)	IV	0, 5, 20, or 40
Embryofetal Development	Rabbit (22/group)	IV	0, 5, 10, or 20
Pilot Embryofetal Development	Rat (6/group)	Oral	0, 5, 20, 50, or 100
Embryofetal Development	Rat (25/group)	Oral	0, 100, 175, or 250
Pilot Embryofetal Development	Rabbit (6/group)	Oral	Nonpregnant part 1: 0, 5, 10, 20, or 40 Nonpregnant part 2: 0, 50, 75, or 100 Pregnant: 0, 50, 75, 100, or 125
Embryofetal Development	Rabbit (20/group)	Oral	0, 50, 75, or 115
Embryofetal Development	Rabbit (20/group)	Oral	0, 50, 75, or 115
Pre- and Postnatal Development	Rat (F0: 25/group; F1: 25/sex/group)	Oral	0, 100, 150, or 225

In the pivotal fertility and early embryonic development study (PO) in rat, the HD was lowered from 250 to 200 mg/kg in males on Day 18 after a 3-day dosing holiday, due to 4 animal deaths, decreases in body weight, hypoactivity, ataxia, and labored respiration. The NOAEL was 200 mg/kg for both sexes.

In the embryofetal development studies (IV and PO) in rat, there were skeletal variations and drug-related decreases in maternal and fetal body weights. In the pivotal embryofetal development study (PO) in rat, the NOAEL was 175 mg/kg based on

decreases in fetal and maternal body weight (14% and up to 50%, respectively) and delayed skeletal ossification at the HD. In the pivotal embryofetal development study (PO) in rabbit, the NOAEL was the LD based on abortion (HD), dose-related increases in post implantation loss (MD & HD), and increases in cardiovascular defects (~10% of HD litters), and delayed skeletal ossification (~30% of HD litters).

In the pre-and postnatal development study (oral) in rat, the F_0 NOAEL was the MD based on a death during delivery, increase in the percentage of stillborn pups (22% compared to 7% in control), increase in the gestation period (1 day), and under developed mammary glands (4/14 HD dams were removed from the study due to loss of litters) at the HD. The F_1 NOAEL was the MD based on postnatal death (1/3 of the litters had no surviving pups), decreases in body weight during the lactation period (16%), and decreases in implantation sites (18%) and delivered pups (25%).

The nonclinical data support approval of lasmiditan.

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