CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211765Orig1s000

NON-CLINICAL REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 211765
Submission date: 12/26/2018
Drug: ubrogepant
Applicant: Allergan Sales, LLC
Indication: acute treatment of migraine with or without aura in adults

Reviewing Division: Division of Neurology 2

Discussion:
The pharm/tox reviewer and supervisor found the nonclinical information for ubrogepant adequate to support approval for the above indication.

Two-year studies in Wistar Han and CD-1 mice were conducted with ubrogepant. The executive carcinogenicity assessment committee concluded that the studies were adequate and that there were no drug-related neoplasms in either study.

An appropriate Established Pharmacologic class for ubrogepant is Calcitonin Gene-Related Peptide Receptor Antagonist.

Conclusions:
The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. I agree that the information is adequate to support approval from a pharm/tox perspective. I have provided comments on labeling separately.

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

/s/

PAUL C BROWN
12/18/2019 02:53:35 PM

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: December 17, 2019

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

Subject: NDA 211-765 (ubrogepant, AGN-241688)

NDA 211-765 was submitted as a 505(b)(1) application by Allergan Sales, LLC on December 26, 2018, to support marketing approval of ubrogepant, a calcitonin gene-related peptide (CGRP) receptor antagonist, for the "acute treatment of migraine with or without aura in adults." Clinical development of ubrogepant for the proposed indication was conducted by Allergan under IND 113924.

The sponsor conducted a standard battery of nonclinical studies to support clinical development and an NDA for ubrogepant. In addition, the sponsor conducted studies to investigate the potential for ubrogepant to constrict human coronary arteries and to further assess the risk of hepatotoxicity.

The nonclinical studies were reviewed by Dr. Nesti (Pharmacology/Toxicology NDA Review and Evaluation, NDA 211975, December 17, 2019). (Dr. Nesti's review references those conducted by Dr. D. Charles Thompson under IND 113924.) Based on the review, Dr. Nesti concludes the nonclinical data are adequate and support approval of the NDA.

Summary of selected (key) nonclinical findings

The primary pharmacology studies conducted characterize ubrogepant as an antagonist at the mouse, rat, rabbit, rhesus monkey, and human CGRP receptors, with greater in vitro binding affinity and more potent in vivo functional (capsaicin-induced vasodilation) effects in human and rhesus monkey compared to mouse (binding data only), rat, and New Zealand White rabbit. (The mouse and rat strains used for the in vitro binding assays were not specified; Sprague-Dawley rat was used in the functional assay.) Ubrogepant exhibited selectivity for the CGRP receptor, as evidenced by substantially lower potency at the human adrenomedullin (AM) 1 and 2, calcitonin, and amylin (AMY) 1 and 3 receptors, and the lack of notable off-target binding (except for the dopamine transporter) in a comprehensive panel of in vitro binding assays.

Distribution of radioactivity to the CNS (cerebellum, cerebrum, medulla, olfactory bulbs, spinal cord), following an acute oral 5-mg/kg dose of ^{14}C-ubrogepant to Wistar and Long Evans rats, was low 0.006-0.12 µg*eq/g tissue (LLOQ = 0.006 µg*eq/g tissue) at the tissue T_{max} (1-3 hrs postdose). Consistent with these data, ubrogepant exhibited low (0-16%) CGRP receptor occupancy in rhesus monkey brain, at plasma concentrations of 53-203 nM.

In humans, one major circulating metabolite was identified, M15, a glucuronide of a methylated catechol. M15 accounted for ~13 and 30% of total drug-related material in human circulation 1 and 3 hrs, respectively, following a single 50-mg oral dose of ubrogepant. According to the sponsor's Pharmacology Written Summary, M15 exhibited in vitro binding affinity for the human CGRP receptor, with a K_i of 265 nM. Based on this, the sponsor concluded M15 is not pharmacologically active, although the mean C_{max} in humans at the recommended human dose of 200 mg/day is ~320 ng/mL. M15 accounted for ≤5% and approximately 75% of drug-related material in Wistar rat and rhesus monkey plasma, respectively, following an acute oral dose (rat: 5 mg/kg; monkey: 10 mg/kg) of ^{14}C-ubrogepant. Although M15 exposure was low in rat, which was used for eproductive and developmental toxicology and carcinogenicity studies, M15 is not an acyl glucuronide and, therefore, is not considered to pose a risk of toxicity.

The general toxicity of orally administered ubrogepant was assessed in CD-1 mouse (3-month), Wistar rat (7- and 14-day, 1-, 3-, and 6-month), and rhesus monkey (3- and 9-month) GLP-compliant studies. No acute toxicity studies were conducted.

In rat, the most consistent findings among studies were reductions in body weight gain, increases in ALT (≤3.2-fold), and histopathology changes in parathyroid gland (vacuolation) and small intestine (epithelial vacuolation). In the 6-month study (0, 5, 20, and 160 mg/kg/day), the NOAEL was 20 mg/kg/day, which was associated with plasma exposures (AUC) of 13.2 and 17.9 µM*hr in males and females, respectively; however, no serious or unmonitorable toxicity was observed up to the highest dose tested, which was associated with plasma exposures (AUC) of 153 and 128 µM*hr in males and females, respectively.

In monkey, oral administration of ubrogepant at doses up to 150 mg/kg/day for 3 months or up to 175 mg/kg/day for 9 months resulted in no evidence of drug-related toxicity. In fact, the 9-month study was notable for the paucity of spontaneous findings reported. A review of the histopathology individual animal line listings was conducted by an internal board-certified veterinary pathologist, who concluded the lack of typical background findings was likely due to a high threshold for reporting. The highest doses tested were associated with plasma exposures (AUC) of 126-97.8 and 273-376 µM*hr, respectively.

In addition to the pivotal toxicity studies of ubrogepant, the sponsor conducted in vitro assays to assess the potential for coronary artery vasoconstriction and to further investigate the potential for hepatotoxicity. In the in vitro study using human distal coronary, middle meningeal, and cerebral arteries, ubrogepant inhibited αCGRP-induced vasodilation but did not induce vasoconstriction at concentrations up to 100 µM.

In the investigative hepatotoxicity assays using HepG2 (human hepatocellular carcinoma) cells and HepaRG spheroids (a metabolically active system) and a proprietary in silico analysis

system, the effects of ubrogepant were compared to those of two other CGRP receptor antagonists, for which development was discontinued because of hepatotoxicity. The results indicated that ubrogepant inhibited bile acid transporters, inhibited HepG2 oxygen consumption rate in a concentration-dependent manner (suggesting the potential to induce mitochondrial toxicity), and exhibited "a modest induction of oxidative stress in HEPG2 cells," considered an effect of ubrogepant itself rather than metabolite(s). Based on "Eight different clinical protocols of ubrogepant…investigated in SimPops," the sponsor concluded that …despite in vitro results, no ALT elevations were predicted for any of the protocols tested…indicating that ubrogepant would be safe at doses up to 10-fold higher than the clinical dose in the hepatic safety clinical study (dosing 100 mg 2 days on, 2 days off for 56 days, 28 total doses)." The maximum recommended clinical dose for the proposed indication (acute migraine) is 200 mg/day, suggesting a 5-fold safety margin with a similar dosing regimen.

A standard battery of reproductive and development toxicology studies was conducted for ubrogepant: fertility and early embryonic development (0, 20, 80, and 160 mg/kg), embryofetal development (0, 1.5, 5. 25, and 125 mg/kg), and pre- and postnatal development (0, 25, 60, and 160 mg/kg) in Wistar rat, and an embryofetal development in New Zealand White rabbit (2 studies; 0, 15, 45, 75, and 250 mg/kg). (For comparison, plasma exposure (AUC) in human at the maximum recommended human dose (MRHD) of 200 mg/day is 4.4 µM*hr.)

In the fertility and early embryonic development study, ubrogepant (0, 20, 80, and 160 mg/kg/day) was administered orally prior to mating and continuing in females through gestation day (GD) 7; drug-treated males and females were mated with drug-naive females and males, respectively. No adverse effects on reproductive performance or fertility parameters were observed. Toxicokinetic (TK) data were not collected. However, in the 6-month toxicity in rat, the 160 mg/kg dose was associated with plasma exposures (AUC) of 153 and 128 µM*hr in males and females, respectively.

In the embryofetal development (EFD) study in rat, ubrogepant (0, 1.5, 5, 25, and 125 mg/kg/day) was administered orally on gestation days (GD) 6-20. No adverse effects on EFD were observed at plasma exposures (AUC) up to 198 µM*hr. In rabbit, two EFD studies were conducted. In both studies, ubrogepant was administered orally at doses of 0, 15, 45, 75, and 250 mg/kg on GDs 7-20. A repeat study was needed because of the inadequate number of pregnant dams (<16) in several groups (including control) in the first study; however, there was an increase in abortion and embryofetal mortality in surviving litters at the high dose. In the repeat study, the high-dose group was terminated on GDs 19-22 because of litter loss (blood in cage, abortions) and maternal toxicity (body weight loss, reduced food consumption); as a result, no litter data are available for that dose. The NOAEL (75 mg/kg) for adverse embryofetal development effects in rabbit was associated with a plasma exposure (AUC) of 36.6 µM*hr.

In the pre- and postnatal development study in rat, ubrogepant, administered orally at doses of 0, 25, 60, and 160 mg/kg/day throughout gestation and lactation, resulted in reduced body weight at birth and during the lactation period in offspring at the mid and high doses, which were associated with maternal toxicity. No toxicokinetic data were collected. Plasma exposure (AUC) at the NOAEL (25 mg/kg/day) for adverse pre- and postnatal developmental effects was estimated (by the sponsor) based on TK data from a 14-day study in nonpregnant rat (23.2

µM*hr). However, in the preliminary and pivotal EFD studies in pregnant rats, the plasma AUCs at 25 mg/kg/day were 32.3 and 66.1 µM*hr, respectively.

Ubrogepant was negative in a standard battery of in vitro and in vivo genetic toxicology assays. In adequately designed and conducted 104-week oral carcinogenicity studies in CD-1 mouse (0, 5, 15, and 50 mg/kg/day) and Wistar rat (males: 0, 10, 30, and 100 mg/kg/day; females: 0, 10, 30, and 150 mg/kg/day), ubrogepant was negative for drug-related neoplasms. The highest dose tested in mice is similar to the maximum recommended human dose (MRHD) of 200 mg/day on a body surface area (mg/m^2) basis. Plasma exposure (AUC) at the highest doses tested in rats (108-122 µM*hr) is approximately 25 times that in humans (4.4 µM*hr) at the MRHD.

Conclusion and Recommendations

The nonclinical studies of ubrogepant are adequate to support approval of ubrogepant for the indication proposed.

A post-marketing requirement for a juvenile animal toxicology study of ubrogepant in appropriately aged animals is recommended to support clinical trials in the pediatric population under PREA, based, in part, on published studies of CGRP involvement in developmental processes (e.g., Dememes D, Broca C. Brain Res 108:59-67, 1998; Elefteriou F. Arch BIochem Biophys 473:231-236, 2008; Fitzgerald M. Brit J Anaesth 75:177-185, 1995; Hutson JM et al. Pediatr Surg Int 31:317-325, 2015; Lerner UH. J Musculoskelet Neuronal Interact 6(1):87-95, 2006; Sample SJ et al. PLoS One 9(12):e113959, doi:10.1371/journal.pone.0113959.)

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

/s/

LOIS M FREED
12/17/2019 03:41:14 PM

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:	211765
Supporting documents:	1
Applicant's letter date:	December 26, 2018
CDER stamp date:	December 26, 2018
Product:	Ubrelvy (ubrogepant)
Indication:	Acute treatment of migraine with or without aura in adults
Applicant:	Allergan
Review Division:	DN2
Reviewer:	Edmund Nesti, PhD
Supervisor:	Lois Freed, PhD
Acting Division Director:	Nicholas Kozauer, M.D.
Project Manager:	Emilios Papanastasiou, PharmD

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Ubrogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist. The CGRP receptor is expressed in peripheral and central nervous system tissues, including those implicated in migraine pain. During a migraine episode CGRP levels increase, which induce vasodilation and nociceptive signaling though the CGRP receptor. It is hypothesized that inhibiting CGRP receptor activity will also inhibit migraine pain. Ubrogepant is indicated for acute treatment of migraine pain. The proposed maximum human dose is 200 mg/day.

1.2 Brief Discussion of Nonclinical Findings

In vitro, ubrogepant inhibited CGRP binding to the CGRP receptor with K_Is in the low pM range for human and monkey and low nM range for mouse, rat, rabbit, and dog.

In animal efficacy models, ubrogepant inhibited relaxation of capsaicin-induced dermal vasodilation (a CGRP-mediated response) with a low pM EC_{50} in monkey; in rat and rabbit, inhibition occurred at low nM and low µM $EC_{50s,}$ respectively. In human cranial arteries, ubrogepant inhibited CGRP-induced vasodilation dose dependently, up to approximate 25% at 1 µM.

In *in vitro* off-target binding assays, ubrogepant was found to bind the dopamine transporter (DAT), with an IC_{50} of 6 µM.

Ubrogepant was negative in an *in vitro* hERG assay. There were no effects on respiratory or cardiovascular parameters at oral doses up to 75 mg/kg or 300 mg/kg, respectively, in telemetered Rhesus monkeys. In *ex vivo* vasoactivity studies, ubrogepant (up to 100 µM) did not induce constriction of the human distal coronary artery, middle meningeal, or cerebral arteries. Neurobehavioral assessments in mice (100 mg/kg) and rats (up to 250 mg/kg) were negative.

Ubrogepant was administered orally in all toxicology studies. In the 6-month rat (up to 160 mg/kg) and 9-month monkey (up to 175 mg/kg) studies, there were no adverse findings. The safety margins based on AUC at the highest doses tested were 34- and 78-fold in rat and monkey, respectively, relative to that at the maximum recommended human dose (MRHD) of 200 mg/day.

In genetic toxicology assessments, ubrogepant was negative in OECD-compliant Ames, *in vitro* chromosomal aberration, and *in vivo* rat bone marrow micronucleus assays. Ubrogepant was negative in 104-week mouse (up to 50 mg/kg) and rat (up to 100(M) and 150(F)) carcinogenicity studies, according to the FDA statistical analysis. However, the mouse study was not adequate because the safety margin based on AUC at the highest dose tested was less than 25-fold the MRHD.

There were no ubrogepant-related findings in the fertility and early embryonic development study (up to 160 mg/kg) in rat. The safety margin based on AUC at the highest dose tested was 34-fold the MRHD.

In the rat embryofetal development study (up to 125 mg/kg) there were no ubrogepant related findings. The safety margin based on AUC at the highest dose tested was 48-fold the MRHD.

In the rabbit embryofetal development study (0, 15, 45, 75, or 250 mg/kg), the HD group had to be sacrificed due to blood in the cage, abortion, and a decrease in

mean body weights (70 g). The 75 mg/kg group also had blood in the cage. The NOAEL in dams was 45 mg/kg, with a safety margin based on AUC of 3-fold at the MRHD. The fetal NOAEL was 75 mg/kg, with a safety margin based on AUC of 9-fold the MRHD.

In the prenatal and postnatal developmental study (0, 25, 60, 160 mg/kg) in rat, the NOAEL was 25 mg/kg for both dams and pups based on MD and HD reductions in maternal mean body weight gain of approximately 85% and decreases in pup body weight of up to 11% (MD) and 20% (HD). The safety margin at the NOAEL based on AUC for both was 16-fold the MRHD.

1.3 Recommendations

1.3.1 Approvability

The nonclinical NDA package supports approval of ubrogepant.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of ubrelvy in pregnant women. (b) (4)

Animal data

(b) (4)

Sponsor

Risk Summary

There are no adequate data on the developmental risk associated with the use of UBRELVY in pregnant women. (b) (4)

Animal Data

(b) (4)

12.1 Mechanism of Action

Ubrelvy binds to the calcitonin gene-related peptide (CGRP) receptor and antagonizes CGRP receptor function.

Sponsor

(b) (4)

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

(b) (4)

Mutagenesis

Ubrelvy was negative in *in vitro* ((b) (4)). and *in vivo* (rat bone marrow micronucleus) assays.

Impairment of Fertility
Oral administration of ubrelvy (0, (b) (4), 20, 80, or 160 mg/kg/day) to male or female rats (b) (4) resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) at the highest dose tested (b) (4) approximately 3 (b) (4) times that in humans at the MRHD.

Sponsor

Carcinogenicity
(b) (4)

Mutagenicity
Ubrogepant was negative in the Ames test, chromosomal aberration test in Chinese Hamster Ovary cells, and in the in vivo rat bone marrow micronucleus test.

Impairment of Fertility
(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number
1374248-77-7
Generic Name
Ubrogepant (b) (4)
Code Name
AGN-241688, MK-1602, L-004740060-005X, L-004740060, C11052503-H MKW-1222, RA1
Chemical Names (IUPAC)
(3'*S*)-*N*-((*3S*,*5S*,*6R*)-6-methyl-2-oxo-5-phenyl-1-(2,2,2-trifluoroethyl)piperidin-3-yl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3 carboxamide
Molecular Formula/Molecular Weight

Molecular Formula	Molecular Weight
$C_{29}H_{26}F_3N_5O_3$ (as free base anhydrate)	549.557 g/mol
(b) (4)	

Sponsor's table

Structure or Biochemical Description

Sponsor's figure

Pharmacologic Class
Calcitonin gene-related peptide (CGRP) receptor antagonist.

2.2 Relevant INDs, NDAs, BLAs, and DMFs

IND 113924

2.3 Drug Formulation

Table 1 Components and Quantitative Composition of Ubrogepant Tablets, 100 mg

Component	Quality Standard	Function	Unit Dose Composition	
			%w/w	(mg/tablet)
Ubrogepant	In-house[a]	Drug substance	10.00	100.0[b]
Polyvinylpyrrolidone/ Vinyl acetate copolymer	USP/NF	(b) (4)		
Vitamin E polyethylene glycol succinate	USP/NF			
Mannitol	USP/NF			
Microcrystalline cellulose	USP/NF			
Sodium chloride	USP/NF			
Croscarmellose sodium	USP/NF			
Colloidal silicon dioxide	USP/NF			
Sodium stearyl fumarate	USP/NF			
Total			**100**	**1000**

a Per section 3.2.S.4.1 Specification (b) (4)

b (b) (4)

Sponsor's Table

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

(b) (4) should be controlled to (b) (4)% for the drug product. A general toxicity study of 90 days' duration in one species will be needed to qualify (b) (4) at the proposed limit of (b) (4)% for the drug product. Justification should be provided for the species selected.

2.6 Proposed Clinical Population and Dosing Regimen

Adults with migraine with or without aura. Recommended dose: 50 mg or 100 mg taken orally. If needed, a second dose may be administered at least 2 hours after the initial dose. The maximum daily dose is 200 mg.

2.7 Regulatory Background

Nonclinical comments

Meeting	Date
End-of Phase 2	March 17, 2016
Type B Pre-NDA	August 30, 2018
Agreed iPSP	December 8, 2016

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology

- *In vitro* binding and cellular activity studies.
- *In vivo* CGRP receptor occupancy assessment in monkey.
- *In vivo* and *ex vivo* pharmacodynamic assessments in rat, rabbit, and monkey.

Secondary Pharmacology

- *In vitro* off target binding assays

Safety Pharmacology

- Electrophysiological evaluation of hERG channel activity
- *In vivo* neurologic (mouse and rat), cardiovascular (rat and monkey), and respiratory (monkey) assessments.
- *Ex vivo* vasoactivity assessments using human distal coronary artery, middle meningeal, and cerebral arteries.

Pharmacokinetics

- Liquid chromatography with tandem mass spectrometric (LC-MS/MS) detection method validation studies for ubrogepant in plasma (mouse, rat, rabbit, and monkey) and milk (rat).
- Single and repeat dose (PO) absorption studies conducted in mouse, rat, rabbit, and monkey.
- Whole-body autoradiography in rat following a single oral dose
- Mouse plasma protein binding assessment.
- CSF/plasma assessment following a single oral dose in monkey
- *In vitro* drug metabolism assays

- *In vivo* metabolism profiling of mouse, rat, rabbit, and monkey plasma.
- Excretion assays in rat, rabbit, and monkey.
- *In vitro* interaction and inhibition studies with human transporters.

General toxicology

- Dose rang-finding studies in rat and monkey
- Pivotal 6- and 9-months PO studies in rat and monkey, respectively.

Genetic toxicology

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

Carcinogenicity

- 2-year studies in mouse and rat.

Reproductive and Development toxicology

- Fertility and early embryonic development PO study in rat.
- Embryo-fetal development PO studies in rat and rabbit.
- Pre and postnatal development PO study in rat.

Special toxicology studies

- 1-month rasH2 WT toxicology studies in mice.
- *In vitro* hepatotoxicity study
- 3-day PO phototoxicity study

3.2 Studies Not Reviewed

Self-administration, drug discrimination, and physical dependence studies

3.3 Previous Reviews Referenced

IND 113924, D. Charles Thompson, Ph.D., April 13, 2012.

4 Pharmacology

4.1 Primary Pharmacology

In *in vitro* assays, ubrogepant inhibited [^{125}I]CGRP binding to the CGRP receptor with K_is in the 70 to 80 pM range for human and monkey and 10 to 47 nM for mouse, rat, rabbit, and dog. In cells expressing human or monkey CGRP receptor, ubrogepant inhibited CGRP stimulated cAMP response with EC_{50}s of 70 and 80 pM, respectively.

In efficacy models, ubrogepant inhibited relaxation of capsaicin-induced dermal vasodilation (a CGRP mediated response) in the rat (EC_{50}=3 nM), rabbit (EC_{60} 20 µM), and monkey (EC_{50}=3 pM), and inhibited of CGRP-induced relaxation of human cranial arteries dose dependently (up to ~25% at 1 µM).

4.2 Secondary Pharmacology

Ubrogepant was found to bind the dopamine transporter (DAT) (IC_{50} 5.6 µM) in an off-target binding assay with a panel of approximately 100 ion channels (including hERG), receptors, and enzymes. No other meaningful binding was observed at 10 µM ubrogepant.

In a receptor selectivity assay, ubrogepant was found to have at least 100-fold more potency (CGRP stimulated cAMP response) for the hCGRP receptor over human adrenomedullin 1 and 2, calcitonin, and Amylin 1 and 3.

4.3 Safety Pharmacology

In an electrophysiological evaluation of hERG channel current, the IC_{50} for inhibition by ubrogepant was 63 µM.

The cardiovascular and respiratory effects of orally administered ubrogepant were assessed in telemetered monkeys. There were no effects on respiratory parameters at doses up to 75 mg/kg and no effects on cardiovascular parameters at doses up to 300 mg/kg.

In *ex vivo* studies, ubrogepant (up to 100 µM) did not induce constriction of the human distal coronary, middle meningeal, or cerebral arteries.

Neurobehavioral assessments (modified Irwin FOB) were made in CD-1 mice (100 mg/kg) and Wistar Han (WH) rats (up to 250 mg/kg) after oral administration of ubrogepant. No drug-related findings were reported in either species.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Liquid chromatography with tandem mass spectrometric (LC-MS/MS) detection methods were validated for ubrogepant in mouse, rat, rabbit, monkey, and human plasma, and milk in rat.

Following oral administration to rats and monkeys, [^{14}C]ubrogepant was approximately 23% bioavailable and was widely distributed to most tissues and milk (rat) at similar concentrations to blood. Brain, bone, eye lens, and spinal cord had

negligible drug concentrations. Approximately 80% of [^{14}C]Ubrogepant was recovered. It was primarily excreted through the urine (15%), bile (32%), and feces (32%).

Ubrogepant was primarily metabolized by CYP3A4. The major circulating human metabolite was M15; however, it is a non-acyl glucuronide and, therefore, was of little toxicological significance.

Ubrogepant is a substrate of uptake transporters, OATP1B1, OATP1B3, and OAT1, and efflux transporters, Pgp and BCRP.

The plasma half-life of ubrogepant was approximately 2 hours in rat and 4 hours in monkey. Exposure (C_{max} and $AUC_{0\text{-}24\ h}$) increased approximately dose proportionally after oral administration in mouse, rat, rabbit, and monkey.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Nonpivotal toxicology studies

Study	Animal	Number/Sex	Daily (PO) Dose mg/kg	Assessment	Findings
7-Day W/ Recovery (12-1061)	Rat, WH	18 F/C 30 F/Drug	0 or 500	Clinical signs body weights, TK histopathology (TEM, small intestine)	Very slight to moderate epithelial cell vacuolation in the small intestine that resolved in recovery.
7-Day (11-2529)	Rat, WH	5 F/group	0, 500, or 750	Clinical signs body weights, clinical chemistry, TK, gross and histopathology (TEM, small intestine)	Decrease in body weight gain (44% LD & 59 % HD); epithelial cell vacuolation of the small intestine (negative: Oil-red-O) and parathyroid gland (LD & HD), tubular dilation of the kidney (LD & HD).
14-Day W/ micronucleus and FOB assays (11-1068)	Rat, WH	10/sex/group	0, 5, 25, or 250	Clinical signs body weights, food consumption, clinical chemistry, FOB, micronucleus, TK, gross and histopathology	Decrease in body weight gain (~50 % HD); epithelial cell vacuolation of the small intestine and parathyroid gland (HD)
1-Month tolerability (10-2545)	Rat, WH	5 F/group	0, 10 (28-D), 40 (28-D), or 250 (7-D)	Clinical signs body weights, food consumption, clinical chemistry, TK, gross and histopathology	No adverse drug-related findings.
1-Month (13-6002)	Rat, WH	10/sex/group	0, 250, 500, or 1000	Clinical signs body weights, food consumption, ophthalmic, clinical chemistry, TK, gross and histopathology	Abdominal distension (HD), dose- related decreases in body weight gain (up to 43%), epithelial cell vacuolation of the small intestine and parathyroid gland (LD-HD).
3-Month (11-1079)	Rat, WH	10/sex/group	0, 5, 20, or 100	Clinical signs body weights, food consumption, ophthalmic,	Decreases body weight gain (14%, HDM), epithelial cell vacuolation of the small intestine and

				clinical chemistry, TK, gross and histopathology	parathyroid gland (all MD and HD)
9-Day: 3 days at at each dose (10-1111)	Rhesus Monkey	2 F/drug; 2 M/C	0, 3, 30, or 300	Clinical signs body weights, food consumption, clinical chemistry, TK, and histopathology	Medial necrosis of small arteries within the small intestine and the large intestine (cecum) were noted in 1 of 2 monkeys.
3-Month (11-1080)	Rhesus Monkey	3/sex/group	0, 5, 15, 150	Clinical signs body weights, food consumption, ophthalmic, ECG, clinical chemistry, TK, gross and histopathology	No drug-related findings.

TK for Nonpivotal Studies

Study	Dose (mg/kg)	Assessment	C_{max} (µM)*	$AUC_{0\text{-}24\ h}$ (µM*h)*
7-Day, rat (12-1061)	500	D7	29[a]	427[a]
7-Day, rat (11-2529)	500	D7	44[a]	749[a]
	700	D7	42[a]	566[a]
14-Day, rat (11-1068)	5	D14	0.41/0.62	1.91/3.41
	25	D14	2.9/2.9	14/23
	250	D14	18/25	124/261
1-Month, rat (10-2545)	10	D28	1.2[a]	4.6[a]
	40	D28	7.4[a]	30[a]
	250	D7	29[a]	344[a]
1-Month, rat (13-6002)	250	W5	23/31	200/170
	500	W5	26/33	304/325
	1000	W5	35/43	504/552
3-Month, rat (11-1079)	5	W13	0.25/0.38	1.16/1.72
	20	W13	0.83/2.06	11/14
	100	W13	4.21/6.31	30/38
9-Day: 3 days at each dose, monkey (10-1111)	3	D3	0.18[a]	0.71[a]
	30	D6	4[a]	18[a]
	300	D9	31[a]	161[a]
3-Month, monkey (11-1080)	5	W13	0.43/0.41	1.68/1.56
	15	W13	2/3	9/9
	150	W13	19/16	126/98

*Male/female, except as specified: [a]female

Summary of nonpivotal toxicology findings.

Species	Finding	C_{max} µM	$AUC_{0\text{-}24\ h}$ µM*h
Rat	Abdominal distention	35/43	504/552
	Epithelial vacuolation in the small intestine and the parathyroid	2[b]	13[b]
	Decrease in body weight gain 14 to 59%	5 – 44[b]	34 – 740[b]
Monkey	Medial necrosis of small arteries within the small intestine and the large intestine (cecum)	31[a]	161[a]

*Male/female, except as specified: [a]female; [b]combined

Study title: Six-Month Oral Toxicity Study in Rats

Study no.:	12-1045
Study report location:	EDR
Conducting laboratory and location:	Merck Research Laboratories West Point, Pennsylvania
Date of study initiation:	March 6, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Ubrogepant, lot # L-004740060-005X006, purity 100%

Key Study Findings

The NOAEL was the HD (C_{max} 11046 ng/mL; AUC_{last} 85108 ng*h/mL).

Methods

Doses:	0, 5, 20, or 160 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	2 mL/kg
Formulation/Vehicle:	100% Polyethylene Glycol 400
Species/Strain:	Rat, Wistar Han
Number/Sex/Group:	15/sex/group
Age:	6 weeks
Weight:	F: 86.4 to 125.0 g; M: 99.2 to 141.1 g
Satellite groups:	TK
Unique study design:	None
Deviation from study protocol:	There were minor deviations which did not affect study validity.

Observations and Results

Mortality and Clinical Signs

There were no drug-related findings.

Body Weights and Food Consumption

At the HD, there were decreases in body weight gain (up to 20%), compared to controls, which correlated with decreases in food consumption.

Ophthalmoscopy

There were no drug-related findings.

ECG

Not assessed.

Hematology, Clinical Chemistry, and Urinalysis

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

There were no drug-related findings.

Histopathology

Adequate Battery
Yes

Peer Review
Yes

Histological Findings
At the HD, there was epithelial cell vacuolation in the small intestinal and parathyroid gland (see sponsor's table).

	Females			Males		
Dose, mg/kg/day	5	20	160	5	20	160
Number of Animals	15	15	15	15	15	15
Histomorphology (Incidence)						
Small intestine	NE			NE		
Epithelium, vacuolation		-	14		-	14
Parathyroid gland	NE			NE		
Vacuolation		-	8		-	4
- = No test article-related change. NE = Group not examined.						

Special Evaluation

None

Toxicokinetics

Exposure (C_{max} and $AUC_{0\text{-}24\ h}$) values were similar between sexes and increased approximately dose proportionally in Week 13 (see sponsor's table).

Summary Mean (± SE) Plasma MK-1602[a] Toxicokinetic Parameters in Rats Following a Dose of MK-1602: Study Week 13

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
5	Female	3.59 ± 0.455	0.912 ± 0.217	2.0 ± NC
	Male	2.55 ± 0.409	0.382 ± 0.0412	2.0 ± NC
	All	3.07 ± 0.344	0.647 ± 0.154	2.0 ± NC
20	Female	17.9 ± 2.64	4.45 ± 2.06	1.0 ± NC
	Male	13.2 ± 2.02	2.01 ± 0.164	1.0 ± NC
	All	15.6 ± 1.63	3.23 ± 1.07	1.0 ± NC
160	Female	128 ± 13.2	23.7 ± 7.41	2.0 ± NC
	Male	153 ± 10.2	17.2 ± 2.16	1.0 ± NC
	All	141 ± 11.1	18.3 ± 4.59	2.0 ± NC

Dosing Solution Analysis

All dosing formulations were within ±10 of nominal.

Study title: Nine-Month Oral Toxicity Study in Rhesus Monkeys

Study no.:	12-1045
Study report location:	EDR
Conducting laboratory and location:	Merck Research Laboratories West Point, Pennsylvania
Date of study initiation:	March 5, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Ubrogepant, lot # L-004740060-005X006, purity 100%

Key Study Findings

The NOAEL was the HD (C_{max} 20040 ng/mL; AUC_{last} 196170 ng*h/mL).

Methods

Doses:	0, 5, 20, or 175 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	2 mL/kg
Formulation/Vehicle:	100% Polyethylene Glycol 400
Species/Strain:	Rhesus Monkeys
Number/Sex/Group:	4/sex/group
Age:	1 to 3 years
Weight:	M: 2.9 to 3.5 kg; F: 2.7 to 3.8 kg
Satellite groups:	TK
Unique study design:	None
Deviation from study protocol:	There were minor deviations which did not affect study validity.

Observations and Results

Mortality and Clinical Signs

There were no drug-related findings.

Body Weights and Food Consumption

There were no drug-related findings.

Ophthalmoscopy

There were no drug-related findings.

ECG

There were no drug-related findings.

Hematology, Clinical Chemistry, and Urinalysis

There were no drug-related findings.

Gross Pathology

There were no drug-related findings.

Organ Weights

There were no drug-related findings.

Histopathology

Adequate Battery
Yes

Peer Review
Yes

Histological Findings
There were no drug-related findings.

Special Evaluation

None

Toxicokinetics

Plasma exposures (C_{max} and $AUC_{0\text{-}24\ h}$) were similar between sexes. Exposures increased greater than dose proportionally from 5 to 20 mg/kg and approximately dose proportionally from 20 to 175 mg/kg on Day 1 and in Week 13. Exposures increased greater than dose proportionally in Week 39 (see sponsor's table).

Summary Mean (± SE) Plasma MK-1602[a] Toxicokinetic Parameters in Monkeys Following a Dose of MK-1602 : Study Day 1

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
5	Female	1.86 ± 0.139	0.558 ± 0.120	1.0 ± 0.0
	Male	1.56 ± 0.280	0.341 ± 0.0722	1.8 ± 0.25
	All	1.71 ± 0.156	0.449 ± 0.0767	1.4 ± 0.18
20	Female	22.4 ± 5.00	5.98 ± 1.08	1.5 ± 0.29
	Male	12.4 ± 3.13	2.72 ± 0.664	1.8 ± 0.25
	All	17.4 ± 3.31	4.35 ± 0.851	1.6 ± 0.18
175	Female	225 ± 115	24.4 ± 12.2	3.5 ± 0.50
	Male	281 ± 116	25.9 ± 7.89	4.5 ± 1.3
	All	253 ± 76.4	25.1 ± 6.74	4.0 ± 0.65

[a]MK-1602 plasma concentrations from all control group animals on Study Day 1 were below the lower limit of quantitation of the bioanalytical method (LLQ = 0.009 µM).

Summary Mean (± SE) Plasma MK-1602[a] Toxicokinetic Parameters in Monkeys Following a Dose of MK-1602 : Study Week 13

Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
5	Female	1.31 ± 0.154	0.346 ± 0.115	1.8 ± 0.25
	Male	1.35 ± 0.152	0.335 ± 0.0750	1.5 ± 0.29
	All	1.33 ± 0.100	0.341 ± 0.0635	1.6 ± 0.18
20	Female	16.0 ± 3.99	3.84 ± 1.24	2.5 ± 0.50
	Male	12.4 ± 4.04	2.80 ± 0.965	1.3 ± 0.25
	All	14.2 ± 2.71	3.32 ± 0.755	1.9 ± 0.35
175	Female	119 ± 59.6	13.1 ± 5.68	3.0 ± 0.58
	Male	230 ± 103	26.0 ± 11.1	3.5 ± 0.50
	All	175 ± 59.1	19.6 ± 6.28	3.3 ± 0.37

Summary Mean (± SE) Plasma MK-1602[a] Toxicokinetic Parameters in Monkeys Following a Dose of MK-1602 : Study Week 39				
Dose (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
5	Female	1.52 ± 0.200	0.297 ± 0.0634	2.0 ± 0.71
	Male	1.52 ± 0.312	0.207 ± 0.0460	3.0 ± 0.58
	All	1.52 ± 0.171	0.252 ± 0.0400	2.5 ± 0.46
20	Female	12.6 ± 4.35	2.66 ± 1.23	2.0 ± 0.0
	Male	11.6 ± 4.68	1.74 ± 0.523	2.0 ± 0.0
	All	12.1 ± 2.97	2.20 ± 0.643	2.0 ± 0.0
175	Female	376 ± 102	38.2 ± 6.60	4.0 ± 0.0
	Male	273 ± 80.4	28.2 ± 6.14	3.5 ± 0.50
	All	325 ± 63.3	33.2 ± 4.58	3.8 ± 0.25

[a]MK-1602 plasma concentrations from all control group animals in Study Week 39 were below the lower limit of quantitation of the bioanalytical method (LLQ = 0.009 µM).

Dosing Solution Analysis

All dosing formulations were within ±10 of nominal.

7 Genetic Toxicology

Ubrogepant was negative in OECD-compliant Ames, *in vitro* chromosomal aberration, and *in vivo* rat bone marrow micronucleus assays.

(Based on Pharmacology/Toxicology IND Review and Evaluation, IND 113924, D. Charles Thompson, Ph.D., April 13, 2012)

8 Carcinogenicity

Dose-range finding studies

Study	Animal	Number	Daily (PO) Dose mg/kg	Assessment	Findings
3-month (11-6035)	mouse	~10/sex/group	0, 0.5, 1, 5, 20, or 100	Clinical signs body weights, food consumption, clinical chemistry, TK, gross and histopathology	decreases in body weight gain in HDF (17%); centrilobular hepatocellular hypertrophy at ≥20 mg/kg/day in M.
3-month (12-6044)	mouse	~10 M/group	0, 200, 400, or 750	Clinical signs body weights, food consumption, clinical chemistry, TK, gross and histopathology	Decrease in body weight gain (~27%, MD & HD). Very slight to moderate epithelial cell vacuolation of the small intestine at all doses.
3-month (13-1093)	mouse	50/sex/group	0, 100, 200, or 400	Clinical signs body weights, food consumption, clinical chemistry, TK, gross and pathology	There were no drug-related findings.

TK from Dose-range finding Studies

Study	Dose mg/kg	Assessment (Week)	C_{max} µM (M/F)	$AUC_{0\text{-}24\ h}$ µM*h (M/F)
3-month mouse (11-6035)	0.5	13	0.37/0.33	0.75/0.59
	1	13	0.82/0.51	1.61/1.18
	5	13	4/3	12/10
	20	13	9/9	45/39
	100	13	16/21	130/190
3-month mouse (12-6044)	200	13	18 M	272 M
	400	13	32 M	495 M
	750	13	28 M	387 M
3-month mouse (13-1093)	100	5	12/11	136/101
	200	5	2/1	239/143
	400	5	2/1	267/285

Study title: Two-Year Oral Carcinogenicity Study in Mice

Study no.:	12-1109
Study report location:	EDR
Conducting laboratory and location:	Merck Research Laboratories West Point, Pennsylvania
Date of study initiation:	July 5, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Ubrogepant, lot # L-004740060-005X006, purity 100%
CAC concurrence:	Yes. HDM: a predicted >25-fold plasma AUC margin to the 50 mg/day dose in humans HDF: a reduction in body weight gain at 100 mg/kg in the 13-week dose-ranging study.

Methods

Doses:	0 (vehicle), 0 (vehicle), 5, 15, or 50 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	10% polysorbate 80 in deionized water
Basis of dose selection:	“exposure multiples relative to the clinical therapeutic dose”
Species/Strain:	Mouse, Crl:CD1(ICR)
Number/Sex/Group:	Main: 50/sex/group; TK: 6/sex/group
Age:	Approximately 5 weeks
Animal housing:	Up to 3 mice per cage
Paradigm for dietary restriction:	None
Dual control employed:	None
Interim sacrifice:	None
Satellite groups:	TK
Deviation from study protocol:	There were minor deviations which did not affect study validity.

Observations and Results

Mortality

Observations were made daily.

There were no drug-related findings.

Clinical Signs

Observations were made weekly.

There were no drug-related findings.

Body Weights

Once per week during Weeks 1 – 4 and then once every 4 weeks thereafter.

There were no drug-related findings.

Food consumption

Not assessed.

Gross Pathology

There were no drug-related findings.

Histopathology

Complete battery of tissues
Yes

Peer Review
Yes

Signed pathologist report
Yes

Neoplastic
There were no drug-related findings.

Non-neoplastic
Epithelial cell vacuolation of the small intestine (duodenum) observed in 2 early sacrificed female mice at HD.

Toxicokinetics

Drug plasma concentrations were assessed at 1 and 2 hours post dose during Weeks 5 and 27. Drug concentrations were similar between sexes and increased dose proportionally between 5 and 50 mg/kg. Drug did not accumulate after repeat dosing.

Summary Mean (± SE) Plasma MK-1602[a] Concentrations (µM) in Mice Following a Dose of MK-1602 in Study Week 5			
Dose (mg/kg/day)	Sex	Time (hr) 1	2
Vehicle	Female	0.00 ± 0.00	NC
	Male	0.00 ± 0.00	NC
	All	0.00 ± 0.00	NC
5	Female	1.89 ± 0.471	1.05 ± 0.222
	Male	2.45 ± 0.211	1.38 ± 0.239
	All	2.17 ± 0.262	1.22 ± 0.163
15	Female	4.74 ± 0.439	2.72 ± 0.282
	Male	5.23 ± 0.235	4.26 ± 0.232
	All	4.98 ± 0.248	3.49 ± 0.380
50	Female	9.03 ± 1.12	6.07 ± 0.574
	Male	7.63 ± 0.578	7.80 ± 1.04
	All	8.33 ± 0.644	6.94 ± 0.659

NC = Not Calculated

[a]MK-1602 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.017 µM) of the bioanalytical method.

Summary Mean (± SE) Plasma MK-1602[a] Concentrations (µM) in Mice Following a Dose of MK-1602 in Study Week 27			
Dose (mg/kg/day)	Sex	Time (hr) 1	2
Vehicle	Female	0.00 ± 0.00	NC
	Male	0.00 ± 0.00	NC
	All	0.00 ± 0.00	NC
5	Female	1.35 ± 0.672	0.601 ± 0.200
	Male	3.14 ± 0.359	1.87 ± 0.257
	All	2.25 ± 0.526	1.23 ± 0.319
15	Female	2.96 ± 0.665	1.73 ± 0.236
	Male	4.27 ± 0.320	3.81 ± 0.425
	All	3.61 ± 0.440	2.77 ± 0.512
50	Female	8.62 ± 0.749	5.64 ± 0.791
	Male	7.10 ± 2.02	6.24 ± 2.95
	All	7.86 ± 1.02	5.94 ± 1.37

NC = Not Calculated

[a]MK-1602 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.018 µM) of the bioanalytical method.

Sponsor's tables

Dosing Solution Analysis

The mean concentration of the ubrogepant formulations were ±15% of nominal.

Study title: Two-Year Oral Carcinogenicity Study in Rats with Six-Month Toxicokinetic Evaluation

Study no.:	12-1079
Study report location:	EDR
Conducting laboratory and location:	Merck Research Laboratories West Point, Pennsylvania
Date of study initiation:	June 1, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Ubrogepant (sponsor's table)

Lot Numbers	Purity (expressed as Potency As Is)
L-004740060-005X006	99.8 percent by HPLC
L-004740060-005X014	99.8 percent by HPLC
L-004740060-005X013	99.9 percent by HPLC
L-004740060-005X015	100.0 percent by HPLC

CAC concurrence:	Yes. A reduction in body weight gain in males at 100 mg/kg and a predicted 25-fold margin in HDF to the MRHD (50 mg/day).
Doses:	0 (vehicle), 0 (vehicle), 10, 30, 100 (M), or 150 (F) mg/kg
Frequency of dosing:	Daily
Dose volume:	2 mL/kg
Route of administration:	Oral
Formulation/Vehicle:	100% polyethylene glycol 400
Basis of dose selection:	"…exposure multiples relative to the clinical therapeutic dose and the FDA Executive Carcinogenicity Assessment Committee (CAC) recommendation."
Species/Strain:	Rat, Wistar Han
Number/Sex/Group:	Main: 50/sex/group; TK 6/sex/group
Age:	36 days
Animal housing:	Social housing
Paradigm for dietary restriction:	*Ad libitum*
Dual control employed:	None
Interim sacrifice:	None
Satellite groups:	TK
Deviation from study protocol:	There were minor deviations which did not affect study validity.

Observations and Results

Mortality

Observations were made daily.

There were no drug-related findings.

Clinical Signs

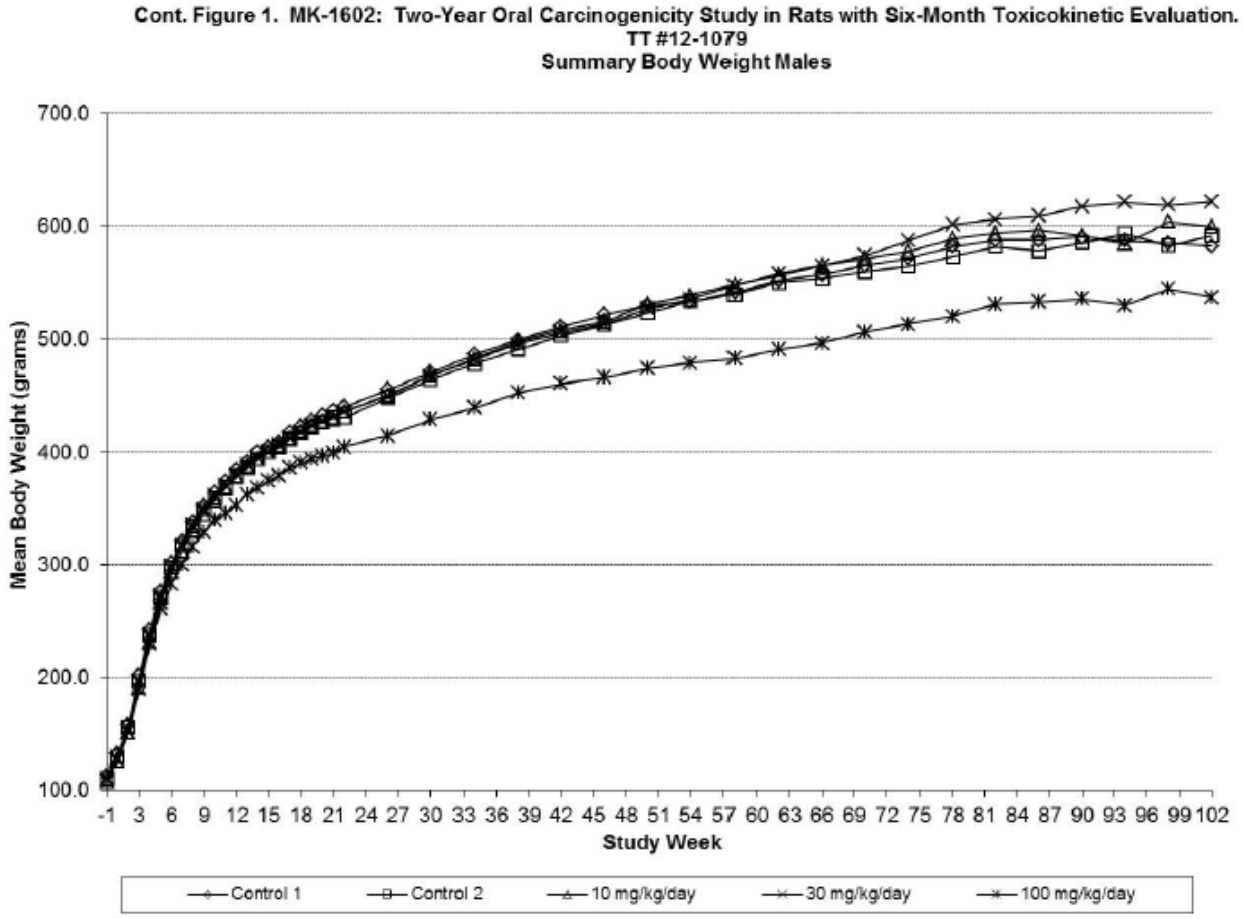
Observations were made weekly.

There were no drug-related findings.

Body Weights

Once per week during Weeks 1 – 22 and then once every 4 weeks thereafter.

In HDM, there was a 10% decrease in body weight gain compared to the controls.



Sponsor's figure

Food Consumption

Not assessed.

Gross Pathology

There were no drug-related findings.

Histopathology

Complete battery of tissues
Yes

Signed pathologist report
Yes

Peer Review
Yes

Neoplastic
Based on the FDA statistical analysis, ubrogepant was not carcinogenic.

Non-neoplastic
There were dose-dependent increases in epithelial cell vacuolation in the small intestine.

Toxicokinetics

Exposure (C_{max} and $AUC_{0\text{-}24\ h}$) was generally higher in females than males. Exposure increased approximately dose proportionally in both sexes.

Summary Mean (± SE) Plasma MK-1602 Toxicokinetic Parameters in Rats Following a Dose of MK-1602 : Study Week 13

Dose[a] (mg/kg/day)	Sex	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
10	Female	10.9 ± 3.16	6.41 ± 3.39	0.50 ± NC
	Male	5.40 ± 1.46	0.665 ± 0.193	0.50 ± NC
30	Female	32.0 ± 12.0	8.84 ± 5.27	0.50 ± NC
	Male	26.1 ± 2.72	4.46 ± 1.76	0.50 ± NC
100	Male	108 ± 30.9	20.9 ± 4.39	1.0 ± NC
150	Female	122 ± 22.7	27.1 ± 4.48	1.0 ± NC

NC = Not Calculated

[a]MK-1602 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.013 µM) of the bioanalytical method in Study Weeks 13 and 27.

Sponsor's table

Dosing Solution Analysis

The mean concentration of the ubrogepant formulations was ±15% of nominal.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Oral Fertility Study in Female and Male Rats

Study no.:	12-7150
Study report location:	EDR
Conducting laboratory and location:	Merck Research Laboratories West Point, Pennsylvania
Date of study initiation:	March 29, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Ubrogepant, lot # L-004740060-005X006, and purity: 100%

Key Study Findings

The NOAEL was the HD.

Methods

Doses:	0, 5, 20, 80, or 160 mg/kg
Frequency of dosing:	Daily
Dose volume:	2 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	100% polyethylene glycol 400
Species/Strain:	Rat, Crl:WI(HAN)
Number/Sex/Group:	20/sex/group
Satellite groups:	None
Study design:	Animals were dosed 14 days prior to cohabitation, during cohabitation, and in females through Gestation Day (GD) 7.
Deviation from study protocol:	There were minor deviations which did not affect study validity.

Observations and Results

Mortality

Assessment were made daily.

There were no drug-related deaths.

Clinical Signs

There were no drug-related physical signs.

Body Weight

Assessments were made approximately twice weekly.

There were no drug-related findings.

Food Consumption

Assessments were made every 3 days.

There were no drug-related findings.

Toxicokinetics

Not assessed.

Dosing Solution Analysis

All dosing formulations were within ±10% of nominal.

Necropsy

There were no drug-related findings.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Pre and Post Implantation Loss, and Live and Dead Fetuses)

There were no drug-related findings.

Sperm Count and Motility analysis and Epididymal Sperm Head Quantitation.

There were no drug-related findings.

9.2 Embryofetal Development

Summary of range-finding study in rat

A preliminary oral embryofetal developmental toxicology and TK study was conducted in WH rats. Oral doses of ubrogepant (0, 1.5, 5, 25, or 250 mg/kg;12/group) were administered from GDs 6 through 20. Dams were assessed for mortality, physical signs, body weight and food consumption. Embryofetal assessments consisted of viability, weight, sex, and external and visceral morphology. The HD group was sacrificed early on GD 16 or 17 due to decreased mean body weight gain (75%) and decreased mean food consumption (up to 48%), compared to controls. There were no drug-related findings at doses ≤25 mg/kg.

Plasma exposure ($AUC_{0\text{-}24\ h}$) increased approximately dose proportionally up 25 mg/kg, and greater than dose proportionally between 25 and 250 mg/kg. C_{max} increased dose proportionally across all dose levels.

Summary Mean (± SE) Plasma MK-1602 Toxicokinetic Parameters in Rats Following Dosing of MK-1602: Gestation Day 15

Dose (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
1.5	1.41 ± 0.193	0.334 ± 0.0775	1.3 ± 0.25
5	7.14 ± 0.936	1.13 ± 0.205	2.0 ± 0.71
25	32.3 ± 1.79	6.97 ± 1.03	1.0 ± 0.0
250	585 ± 58.1	48.0 ± 10.4	5.0 ± 1.0

Sponsor's Table

Study title: Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats

Study no.:	12-7040
Study report location:	EDR
Conducting laboratory and location:	Merck Research Laboratories West Point, Pennsylvania
Date of study initiation:	January 20, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Ubrogepant, lot # L-004740060-005X005, Purity: 99.6%

Key Study Findings

The maternal and fetal NOAEL was the HD (Dams: C_{max}: 16 µM; $AUC_{0\text{-}24\ h}$: 198 µM* h).

Methods

Doses:	0, 1.5, 5, 25, or 125 mg/kg
Frequency of dosing:	Daily
Dose volume:	2 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	100% polyethylene glycol 400
Species/Strain:	Rat/WI(HAN)
Number/Sex/Group:	24/C group; 28/drug group
Satellite groups:	TK
Study design:	Ubrogepant was administered on GDs 6 through 20. Animals were sacrificed on GD 21. TK assessments were made on on GD 15.
Deviation from study protocol:	None reported.

Observations and Results

Mortality

Assessments were made daily.

F_0: There were no drug-related findings.

Clinical Signs

Assessments were made daily.

F_0: There were no drug-related findings.

Body Weight

Recording were made every two days.

F_0: There were no drug-related findings.

Food Consumption

Recording were made every two days.

F_0: There were no drug-related findings.

Toxicokinetics

Plasma exposure (C_{max} and $AUC_{0\text{-}24\ h}$) increase greater than dose proportionally from 1.5 to 25 mg/kg and less than dose proportionally from 25 to 125 mg/kg.

Summary Mean (± SE) Maternal Plasma MK-1602 Toxicokinetic Parameters in Rats Following Dosing of MK-1602: Gestation Day 15

Dose[a] (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
1.5	1.04 ± 0.216	0.232 ± 0.101	1.0 ± NC
5	6.51 ± 1.06	1.32 ± 0.333	1.0 ± NC
25	66.1 ± 7.54	10.0 ± 0.975	1.0 ± NC
125	198 ± 20.7	15.5 ± 2.78	1.0 ± NC

[a] MK-1602 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.013 µM) of the bioanalytical method.

NC = Not Calculated

Sponsor's table

Dosing Solution Analysis

All dosing formulations were within ±10% of nominal.

Necropsy

F_0: There were no drug-related findings.

Cesarean Section Data (implantation Sites, corpora lutea, live fetuses, and Pre- and Post-Implantation Loss, etc.)

There were no drug-related findings.

Offspring (Malformations, Variations (external, visceral, coronal, and skeletal), sex ratio, weight, etc.)

There were no drug-related findings.

Summary of range-finding study in rabbit

A preliminary oral embryofetal development and TK study was conducted in New Zealand White rabbits. Oral doses of (0, 3, 15, 45, or 250 mg/kg,12/group) were administered on GDs 7 through 20. Animals were assessed for corpora lutea, pre and post implantation loss, placental morphology, mortality, weight, sex ratio, external and visceral morphology, and maternal TK. At the HD, there was a 26% increase in post implantation loss compared to 4.4% in control animals. There were no other drug related findings.

Plasma exposure (C_{max} and $AUC_{0\text{-}24\ h}$) increased greater than dose proportionally between 3 and 15 mg/kg, and approximately dose proportionally between the 15, 45, and 250 mg/kg groups.

Summary Mean (± SE) Plasma MK-1602 Toxicokinetic Parameters in Rabbits Following Dosing of MK-1602: Gestation Day 15/16

Dose (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
3	0.188 ± ID[a]	0.0483 ± ID[a]	2.0 ± ID[a]
15	5.23 ± 3.54	2.41 ± 2.07	1.7 ± 0.33
45	15.0 ± 4.60	4.14 ± 1.75	1.7 ± 0.33
250	175 ± 59.3	23.9 ± 3.39	4.7 ± 0.67

ID = Insufficient Data.
[a] n=2.

Sponsor's table

Study title: Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits

Study no.:	12-7050
Study report location:	EDR
Conducting laboratory and location:	Merck Research Laboratories West Point, Pennsylvania
Date of study initiation:	February 13, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Ubrogepant, lot # L-004740060-005X009, purity: 99.8%

Methods

Doses:	0, 15, 45, 75, or 250 mg/kg
Frequency of dosing:	Daily
Dose volume:	1 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	100% polyethylene glycol 400

Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	Main: 14/group; TK: 9/group
Satellite groups:	TK
Study design:	Ubrogepant was administered on GDs 7 to 20 to main study animals, and on GDs 7 to 15 to TK animals.
Deviation from study protocol:	There were minor deviations which did not affect study validity.

Observations and Results

Mortality and Clinical Signs

Observations were made daily.

There were no drug-related findings.

Body Weight

Recording were made every 3 days.

From GD 7 to 11 in the 75 and 250 mg/kg groups, there was a transient decrease in body weight gain of 46 and 65%, respectively.

Food Consumption

Recording were made every 3 days.

There were no drug-related findings.

Toxicokinetics

Plasma exposure (C_{max} and $AUC_{0\text{-}24\ h}$) increased approximately dose proportionally.

Summary Mean (± SE) Plasma MK-1602 Toxicokinetic Parameters in Rabbits Following a Dose of MK-1602 : Gestation Day 15

Dose[a] (mg/kg/day)	$AUC_{0\text{-}24\ hr}$ (µM•hr)	C_{max} (µM)	T_{max} (hr)
15	4.72 ± 0.603	0.648 ± 0.169	2.5 ± 0.50
45	16.9 ± 6.50	3.18 ± 1.08	2.5 ± 0.50
75[b]	27.7 ± 2.55	5.47 ± 0.323	4.0 ± 0.0
250	140 ± 38.5	17.0 ± 2.59	4.5 ± 0.50

[a] MK-1602 plasma concentrations were above the LLQ in 8 of 24 samples from control animals. These values were about 2% to 45% of the mean Cmax values of the 15 mg/kg/day dose group.

[b] N =3

Sponsor's Table

Dosing Solution Analysis

All dosing formulations were within ±10% of nominal.

Necropsy

There were no drug-related findings.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, Corpora Lutea, Live Fetuses etc.)

There were no drug-related findings. There was a lower pregnancy rate, which resulted in a 22% decrease in the number of litters assessed in all groups.

Offspring (Malformations, Variations (Placenta, External, Visceral, Skeletal and Coronal), Sex, and weight etc.)

There were no drug-related findings.

Study title: Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits

Study no.:	12-7290
Study report location:	EDR
Conducting laboratory and location:	Safety Assessment and Laboratory Animal Resources Merck Research Laboratories West Point, Pennsylvania
Date of study initiation:	June 21, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Ubrogepant, lot # L-004740060-005X006, purity: 100%.

Key Study Findings

The NOAEL was 45 mg/kg (maternal) and 75 mg/kg (fetal).

Methods

Doses:	0, 15, 45, 75, or 250 mg/kg
Frequency of dosing:	Daily
Dose volume:	1 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	100% polyethylene glycol 400
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	Main: 14/group; TK: 9/group
Satellite groups:	TK

Study design:	Ubrogepant was administered on GDs 7 to 20 to main study animals, and on GDs 7 to 15 to TK animals.
Deviation from study protocol:	There were minor deviations which did not affect study validity.

Observations and Results

Mortality

Observations were made daily.

The HD group was terminated between GDs 13 and 22 because of clinical signs and mean body weight loss.

Clinical Signs

Observations were made daily.

In the 75 mg/kg group, there was blood in the cage of 2/23 females, beginning on GD 17. In the HD group, there was blood in the cage of 13/23 females beginning on GD 17 and aborted tissue in 3 females on GD 20 or 21.

Body Weight

Recording were made every 3 days.

At the HD, mean body weight gain was -70 g, compared to +214 g in control animals, from GD 7 to 10.

Food Consumption

Recordings were made every 3 days.

At the HD, mean food consumption on GDs 8 and 13 was reduced by approximately 10%.

Toxicokinetics

Plasma exposure (C_{max} and $AUC_{0\text{-}24\ h}$) increased approximately dose proportionally, except for $AUC_{0\text{-}24\ h}$ between 75 and 250 mg/kg, which increased greater than dose proportionally.

Summary Mean (± SE) Maternal Plasma MK-1602 Toxicokinetic Parameters in Rabbits Following a Dose of MK-1602 : Gestation Day 15			
Dose (mg/kg/day)[a]	$AUC_{0\text{-}24\ hr}$ (μM•hr)	C_{max} (μM)	T_{max} (hr)
15[b]	5.65 ± 2.15	1.08 ± 0.245	1.7 ± 0.33
45[b]	13.9 ± 4.13	3.74 ± 1.39	1.3 ± 0.33
75	36.6 ± 6.00	6.15 ± 1.22	3.5 ± 0.50
250	226 ± 24.5	25.3 ± 1.87	3.5 ± 0.50

[a] MK-1602 concentrations in plasma from 3 control animals (animals #12-1039 and #12-1041 at 6 hr post-dose and animal #12-1042 at 4 hr post-dose) were above the lower limit of quantitation (LLQ = 0.009 μM) on Gestation Day 15. These values were approximately 2.2% or less of the mean C_{max} value of the low dose group (15 mg/kg/day) on Gestation Day 15.
[b] N = 3

Sponsor's table

Dosing Solution Analysis

All dosing formulations were within ±10% of nominal.

Necropsy

There were no drug-related findings.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, Corpora Lutea, Live Fetuses etc.)

There were no drug-related findings.

Offspring (Malformations, Variations (Placenta, External, Visceral, Skeletal and Coronal), Sex, and weight etc.)

There were no drug-related findings.

9.3 Prenatal and Postnatal Development

Study title: Oral Perinatal and Postnatal Developmental Study in Rats**,** Including a Postnatal Behavioral/Functional Evaluation

Study no.:	UBR-TX-03
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 22, 2017
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Ubrogepant, lot # P07143-031-H-P, purity: 100%

Key Study Findings

The NOAEL for both dams and pups was 25 mg/kg based on decreases in body weight.

Methods

Doses:	0, 25, 60, or 160 mg/kg
Frequency of dosing:	Daily
Dose volume:	2 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	100% Polyethylene Glycol 400
Species/Strain:	Rat/Wistar Han
Number/Sex/Group:	F_0: 25/group; F_1: 24/sex/group
Satellite groups:	None
Study design:	None
Deviation from study protocol:	There were minor deviations which did not affect study validity.

Observations and Results

F_0 Dams

Survival:	Observations were made twice daily. All animals survived to scheduled sacrifice.
Clinical signs:	Observations were made twice daily. There were no drug-related findings.
Body weight:	Recordings were made daily. In the MD and HD groups, mean body weight gain was reduced by 87 and 83%, respectively, between GDs 6 and 20, compared to controls. During Lactation Days 1 to 4, mean body weight gains were reduced 44 and 32% at the MD and HD, respectively.
Food consumption:	Recordings were made every 3 days. At the MD and HD, mean food consumption was reduced during GDs 6 to 18 by 91 and 85% of controls, respectively. During LDs 1 to 14, food consumption was reduced 91% (MD) and 87% (HD).
Uterine content:	There were no drug-related findings.
Necropsy observation:	There were no drug-related findings.
Toxicokinetics:	Not assessed.
Dosing Solution Analysis	All dosing formulations were within ±10% of nominal.

F_1 Generation

Survival:	Observations were made twice daily. There was no drug-related increase in mortality.
Clinical signs:	Observations were made daily. There were no drug-related findings.
Body weight:	Recordings were made daily. At the MD and HD, there were decreases in body weight of up to 11 and 20%, respectively, of controls.
Food consumption:	Recording were made approximately every 3 days. There were no drug-related findings.
Physical development:	Vaginal opening was assessed beginning on PND 28 and preputial separation beginning on PND 39. There were no drug-related findings.
Neurological assessment:	Passive avoidance evaluations were made beginning on PND 24. M-shaped water maze evaluations were made beginning on PND 70. There were no drug-related findings.
Reproduction:	During PNDs 94 through 99, rats were cohabitated. Ovarian and uterine examinations consisted of implantations sites. There were no drug-related findings.
Other:	Milk sample collection occurred on PND 14. Ubrogepant was detected in the milk of F_0 dams.

10 Special Toxicology Studies

rasH2 WT mice studies

Study	Number	Daily (PO) Dose mg/kg	Assessment	Findings
1-month (11-6029)	~10/sex/group	0, 1, 5, 20, or 100	Clinical signs body weights, food consumption, clinical chemistry, TK, gross pathology	Slight centrilobular hepatocellular hypertrophy (5/10, HDM); very slight vacuolation of the intestinal epithelium (2/10 HDM).
1-month (12-6045)	~10/sex/group	0, 200, 500, or 1500	Clinical signs body weights, food consumption, clinical chemistry, TK, gross and pathology	Decrease in body weight gain in MD (35%) and HD (60%) females. Increases in neutrophils (up to 171%), lymphocytes (up to 173%), eosinophils (up to 300%), and monocytes (up to 600%) at the HD. Vacuolation of the intestinal epithelium (all doses).

TK: rasH2 WT mice studies

Study	Dose mg/kg	Assessment (Week)	C_{max} µM (M/F)	$AUC_{0\text{-}24\ h}$ µM*h (M/F)
1-month (11-6029)	1	4	0.58/0.67	1/1
	5	4	4/4	9/8
	20	4	7/10	21/40
	100	4	12/16	79/99
1-month (12-6045)	200	4	15/16	91/107
	500	4	17/20	126/183
	1500	4	24/31	324/377

The hepatotoxic potential of ubrogepant was assessed in bile acid transporter inhibition, mitochondria function, and oxidative stress assays; ubrogepant was not predicted to be hepatotoxic.

A 3-day oral gavage phototoxicity and bioanalysis evaluation of ubrogepant in female pigmented rats was conducted. Doses of 0, 10, and 40 mg/kg were assessed in 5 rats/group (for phototoxicity assessment). The phototoxicity animals were evaluated for viability, clinical signs, skin reactions, body weight, ophthalmological findings, and ocular histopathology. There were no drug-related findings. Plasma drug concentrations increased greater than dose proportionally.

Plasma Drug Concentrations 2 hours post dose on Day 3

Dose (mg/kg)	Mean Concentration (ng/mL)
0	0
10	787
40	4890

11 Integrated Summary and Safety Evaluation

Ubrogepant is a calcitonin gene-related peptide (CGRP) receptor antagonist. The CGRP receptor is expressed in peripheral and central nervous system tissues, including those implicated in migraine pain. During a migraine episode CGRP levels increase, which induce vasodilation and nociceptive signaling though the CGRP receptor. It is hypothesized that inhibiting CGRP receptor activity will also inhibit migraine pain. Ubrogepant is indicated for acute treatment of migraine pain. The proposed maximum human dose is 200 mg/day.

Primary Pharmacology. *In vitro*, ubrogepant inhibited [^{125}I]CGRP binding to the CGRP receptor with K_is in the low pM range for human and monkey and low nM range for mouse, rat, rabbit, and dog. In cells expressing human or monkey CGRP receptors, ubrogepant inhibited CGRP stimulated cAMP response with EC_{50}s in the low pM range.

In animal efficacy models, ubrogepant inhibited relaxation of capsaicin-induced dermal vasodilation (a CGRP mediated response) in the rat (EC_{50}=3 nM), rabbit (EC_{60} 20 µM), and monkey (EC_{50}=3 pM), and inhibited of CGRP-induced relaxation of human cranial arteries dose dependently (up to ~25% at 1 µM).

Secondary pharmacology. In an off-target binding assay with a panel of approximately 100 ion channels (including hERG), receptors, and enzymes, ubrogepant bound the dopamine transporter (DAT), with an IC_{50} of 5.6 µM. In a receptor selectivity assay, ubrogepant had at least 100-fold more potency (CGRP stimulated cAMP) for the human CGRP receptor over human adrenomedullin 1 and 2, calcitonin, and amylin 1 and 3. In a dedicated *in vitro* hERG assay, ubrogepant was negative.

Safety Pharmacology. In telemetered Rhesus monkeys, there were no effects on respiratory or cardiovascular parameters at oral doses up to 75 mg/kg or 300 mg/kg, respectively.

In *ex vivo* vasoactivity studies, ubrogepant (up to 100 µM) did not induce constriction of the human distal coronary artery, middle meningeal, and cerebral arteries.

Neurobehavioral assessments (modified Irwin FOB) after oral administration of ubrogepant to CD-1 mice (100 mg/kg) and WH rats (up to 250 mg/kg) showed no findings.

Pharmacokinetics. Plasma half-life for ubrogepant was approximately 2 hours in rat and 4 hours in monkey. Plasma exposure (C_{max} and $AUC_{0\text{-}24\ h}$) increased approximately dose proportionally after oral administration in mouse, rat, rabbit, and monkey.

The major circulating human metabolite was M15; however, it was a non-acyl glucuronide and, therefore, was of little toxicological significance.

Toxicology. In the general toxicology studies, ubrogepant was orally administered to Wistar Hanover (WH) rats and Rhesus monkeys at doses up to 1000 mg/kg and 300 mg/kg, respectively. In rats, there were decreases in mean body weight gain between 14% (100 mg/kg) and 59% (1000 mg/kg) and non-adverse vacuolation of the small intestine (20 to 1000 mg/kg). In monkeys, there was necrosis in the small arteries of the

small and large intestine (300 mg/kg). In the pivotal 6-month rat (5, 20, 160 mg/kg, 15/sex/group) and 9-month monkey (5, 20, 175 mg/kg, 4/sex/group) studies, the NOAELs were the HDs.

Genetic toxicology. Ubrogepant was negative in OECD-compliant Ames, *in vitro* chromosomal aberration, and *in vivo* rat bone marrow micronucleus assays.

Rat and Mouse Carcinogenicity. Based on the FDA statistical analysis, ubrogepant was not carcinogenic.

Carcinogenicity studies

Species	Duration	Dosing (mg/kg)
WH Rat (50/sex/group)	104-week	0(V), 0(V), 10, 30, 100(M), or 150(F)
CD-1 Mouse (50/sex/group)	104-week	0(V), 0(V), 5, 15, 50

Reproductive and Developmental Toxicology. In the pivotal fertility and early embryonic development study (0, 5, 20, 80 or 160 mg/kg PO) in WH rat (20/sex/group) there were no drug-related findings.

In the preliminary embryofetal development study (0, 1.5, 5, 25, or 250 mg/kg, PO) in WH rat (12/group), the HD group was sacrificed due to a 75% decrease in body weight gain, which correlated with decreased food consumption (up to 48%), compared to controls. In the pivotal embryofetal development study (0, 1.5, 5, 25, or 125 mg/kg, PO) in WH rat (approximately 28/group), there were no drug-related findings.

In the preliminary embryofetal development study (0, 15, 45, 75, or 250 mg/kg, PO) in New Zealand White rabbit (12/group), there was a 22% increase in post implantation loss, compared to control animals. Two pivotal embryofetal development studies (0, 15, 45, 75, or 250 mg/kg, PO) were conducted in New Zealand White rabbit (14/group). The first study was not an adequate, because there was a 22% decrease in the number of litters assessed in all groups. Findings consisted of transient (GDs 7 to 11) decreases in body weight gain of 46 and 65% in the 75 and 250 mg/kg group, respectively. In the second pivotal study, blood was observed in the cages of 2 75 mg/kg and 13 250 mg/kg animals. In the 250 mg/kg group, there were 3 abortions and a decrease in body weight gain of 70 g from GDs 7 to 10, compared to a 214 g increase during the same period in controls. The HD group was terminated between GDs 13 and 22 because of physical signs, abortion and body weight loss. The maternal NOAEL was 45 mg/kg and the fetal NOAEL was 75 mg/kg.

In the prenatal and postnatal developmental study (0, 25, 60, 160 mg/kg, PO) in WH rat (approximately 25/group, F_0 and F_1), the NOAEL was 25 mg/kg for both dams and pups based on: MD and HD reductions in maternal mean body weight gain of approximately 85% and 40% during the gestation and lactation periods, respectively, which correlated with decreases in food consumption; in pups, there were decreases in body weight of up to 11 and 20% of controls at the MD and HD, respectively.

Approvability. The nonclinical NDA package supports approval of ubrogepant.

Safety Margins

Study	Species	Dose mg/kg	C_{max} ng/mL	Margin	AUC_{last} ng*h/mL	Margin	Toxicity
6-Month General Toxicology	Rat	0, 5, 20, **160**	11046	18	85108	34	-
9-Month General Toxicology	Monkey	0, 5, 20, **175**	20040	33	196170	78	-
104-Week Carcinogenicity	Mouse	0, 5,15, **50**	5583*	9	48288*	19	-
104-Week Carcinogenicity	Rat	0,10, 30, **100(M)**, or **150(F)**	12615(M) 16358(F)	21(M) 27(F)	65189(M) 73640(F)	26(M) 29(F)	-
Fertility and Early Embryonic Development	Rat	0, 1.5, 5, 20, 80, **160**	11046**	18	85108**	34	-
Embryofetal Development	Rat	0, 1.5, 5, 25, or **125**	9356	16	119513	48	-
	Rabbit	0, 15, **45, 75**, or 250	Dam: 2257 Fetus: 3712	Dam: 4 Fetus: 6	Dam: 8390 Fetus: 22092	Dam: 3 Fetus: 9	Maternal: death, bleeding, abortion, and weight loss.
Pre-and Postnatal Development	Rat	0, **25**, 60, 160	6036**	10	39898**	16	Decreased body weight in dams and pups

Human 200 mg C_{max}: 600 ng/mL; AUC_{Last}: 2500 ng*h/mL
*Values were based on TK from a 3-month mouse study (11-6035).
**Values were taken from the 6-month toxicology study in rat.

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

/s/

EDMUND D NESTI
12/17/2019 10:52:31 AM

LOIS M FREED
12/17/2019 11:36:05 AM