CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214846Orig1s000

NON-CLINICAL REVIEW(S)

PHARMACOLOGY/TOXICOLOGY SECONDARY REVIEW

NDA #:	214846 (IND 131161)
Supporting Document #:	SDN #1; eCTD 0001
Received Date:	June 1, 2020
PDUFA Goal Date:	June 1, 2021
Sponsor:	Myovant Sciences GMBH
Drug:	Relugolix, estradiol and norethindrone acetate
Proposed Tradename:	MYFEMBREE
Pharmacologic Class:	Gonadotropin-releasing hormone receptor antagonist (relugolix); estrogen (estradiol); progestin (norethindrone acetate)
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Secondary Reviewer:	Kimberly Hatfield, PhD
Tertiary Reviewer:	Mukesh Summan, PhD, DABT
Primary Reviewer:	Laurie McLeod-Flynn, PhD, DABT
Pharm/Tox Division:	Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (DPT-RPURM)
Clinical Review Division:	Division of Urology, Obstetrics and Gynecology (DUOG)
Recommendation on Regulatory Action:	Approval
Review Date:	May 5, 2021

I agree with the nonclinical reviewer that there are no nonclinical concerns for the safety of relugolix plus estradiol and norethindrone acetate (relugolix + E2/NETA), and that Pharmacology/Toxicology supports the approval of MYFEMBREE for the treatment of heavy menstrual bleeding associated with uterine fibroids under NDA 214846.

MYFEMBREE is formulated as a fixed dose combination tablet containing 40 mg relugolix, 1 mg E2 and 0.5 mg NETA. The intended mechanism of action has three parts: 1) relugolix binds pituitary GnRH receptors, thereby reducing luteinizing hormone and follicle-stimulating hormone release, and consequently the production of estrogen (to improve symptoms of uterine fibroids); 2) E2 serves as an exogenous estrogen to reduce the increase in bone resorption and bone loss that can occur due to the decrease in circulating estrogen from relugolix alone; and 3) NETA serves as an exogenous progestin to protect the uterus from the potential adverse endometrial effects of unopposed estrogen.

Relugolix is a New Molecular Entity (NME) for this obstetrical indication, but was recently approved as a standalone product (120 mg) for the treatment of adult patients with advanced prostate cancer (ORGOVYX; NDA 214621; December 2020). Both E2 and NETA are approved estrogen and progestin components of multiple drug products, and the combination of E2/NETA is approved as the marketed product ACTIVELLA (1 mg/0.5 mg or 0.5 mg/0.1 mg tablets) for both the treatment of moderate to severe vasomotor symptoms due to menopause and for the prevention of postmenopausal osteoporosis.

A full nonclinical battery of studies were completed to support the nonclinical safety of relugolix as a GnRH receptor antagonist. In a 39-week study in monkeys, a NOAEL was established at 15 mg/kg (5198 ng*h/mL AUC; 26X the MRHD). A dose of 50 mg/kg/day relugolix resulted in liver toxicity (bile plug formations and yellowish brown pigment deposition in Kupffer cells) and systemic phospholipidosis. Females demonstrated decreased corpora lutea, decreased uterine weights, and cessation of menses. No NOAEL was observed for systemic phospholipidosis; however, minimal effects were observed at 1.5 mg/kg/day (1.1-fold). Phospholipidosis was not observed in clinical studies and is considered to be a rare occurrence in humans.

In a 26-week study in rats, a NOAEL was established at 30 mg/kg (1594 ng*h/mL AUC; 8X the MRHD) for males and 100 mg/kg (6630 ng*h/mL AUC; 33X the MRHD) for females. A dose of 300 mg/kg/day resulted in minimal eosinophilic crystals in the epididymal epithelium, phospholipidosis, and minimal focal hemorrhage in the liver. In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold less than in humans, and this study represented non-pharmacological targets of relugolix.

In human GnRH-receptor knock-in mice, twice daily oral doses of relugolix ≥100 mg/kg induced a constant diestrous phase and decreased ovarian and uterine weights in females, with reversibility after cessation of treatment. In male knock-in mice, decreased prostate, testis, and seminal vesicle weights were observed at twice daily doses ≥3 mg/kg, with reversibility for all but testis weight.

Reproductive and developmental toxicology studies showed no effect on female fertility (up to 1000 mg/kg/day; >300 times the MRHD), embryofetal toxicity in rabbits (abortion, total litter loss, or decreased number of live fetuses at 9 mg/kg/day; 0.5X the MRHD), but only maternal toxicity in rats in both an embryofetal development and pre/postnatal development study (decreased body weight gain and food consumption at 1000 mg/kg/day; 300X the MRHD).

Relugolix was not carcinogenic in mice or rats at exposures up to approximately 142 or 423 times the MRHD, based on AUC. No evidence of pre-neoplastic lesions was observed in 39-week studies in monkeys. Relugolix was not mutagenic based on a standard battery of genotoxicity studies.

For the E2/NETA component of MYFEMBREE, the applicant conducted a comparative bioavailability study to establish an adequate scientific bridge to ACTIVELLA, and is therefore able to rely on the Agency's previous findings of safety for ACTIVELLA as reflected in the product labeling. The nonclinical sections of labeling for the E2/NETA

components of MYFEMBREE will align with the ACTIVELLA approved drug product labeling.

In conclusion, the nonclinical profile of relugolix administered in combination with E2/NETA supports the clinical safety of MYFEMBREE. There are no anticipated concerns for use of MYFEMBREE when used clinically in females for the proposed indication.

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/

KIMBERLY P HATFIELD
05/10/2021 01:05:31 PM

MUKESH SUMMAN
05/10/2021 10:24:00 PM
I concur

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	214846
Supporting document/s:	eCTD 0001
Applicant's letter date:	1 June 2020
CDER stamp date:	1 June 2020
Product:	Relugolix, estradiol and norethindrone acetate
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Applicant:	Myovant Sciences GMBH
Review Division:	Division of Urology, Obstetrics and Gynecology
Reviewer:	Laurie McLeod-Flynn, Ph.D., D.A.B.T.
Supervisor/Team Leader:	Kimberly Hatfield, Ph.D.
Division Director:	Christine Nguyen, M.D.
Project Manager:	Maria Wasilik

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 214846 are owned by Myovant or are data for which Myovant has obtained a written right of reference. Any information or data necessary for approval of NDA 214846 that Myovant does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 214846.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Relugolix is an oral gonadotropin-releasing hormone (GnRH) receptor antagonist being developed in combination with estradiol (E2) and norethindrone acetate (NETA) for the treatment of heavy menstrual bleeding associated with uterine fibroids (proposed tradename MYFEMBREE). The combination is designed to maintain systemic E2 concentrations within a therapeutically effective range (to improve symptoms of uterine fibroids) while minimizing bone loss and vasomotor symptoms, without risking the endometrial hyperplasia associated with unopposed estrogen.

Relugolix (120 mg) was approved for treatment of adult patients with advanced prostate cancer in 2020 under NDA 214621 (Orgovyx), for which the nonclinical studies were previously reviewed.

Oriahnn, a combination of a gonadotropin-releasing hormone (GnRH) receptor antagonist (elagolix; 300 mg), estradiol (1 mg), and norethindrone acetate (0.5 mg), was approved in 2020 for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. Myfembree, a combination of relugolix (40 mg), estradiol (1 mg) and norethindrone acetate (0.5 mg), is similarly proposed for treatment of heavy menstrual bleeding associated with uterine fibroids in a reproductively capable population.

Although all nonclinical studies for relugolix were reviewed under NDA 214621 for prostate cancer, risk/benefit and nonclinical labeling are evaluated separately for this application.

1.2 Brief Discussion of Nonclinical Findings

Repeat-dose toxicity studies with relugolix were conducted in mice up to 13 weeks, in rats up to 26 weeks, and in monkeys up to 39 weeks. Monkey was the most sensitive species, with similar receptor binding affinity for relugolix as humans. This was noted in pharmacology studies which showed a significant difference in binding affinity of relugolix (TAK-385) to human, monkey and rat GnRH receptors, with high affinity for human (IC_{50} of 0.12 nM) and monkey (IC_{50} of 0.15 nM) GnRH receptors and a low affinity for rat GnRH receptors (IC_{50} of 2900 nM). As such, the binding affinity of relugolix for rat GnRH receptors is more than 1000-fold less than in humans, therefore the studies conducted in rats are primarily a toxicological assessment of non-pharmacological targets of relugolix.

In a 39-week study in monkeys, at 50 mg/kg/day relugolix (about 99.1-fold the exposure at the MRHD of 40 mg, based on AUC), liver toxicity (bile plug formations and yellowish brown pigment deposition in Kupffer cells) and systemic phospholipidosis were observed (decreasing following a 13-week recovery period). In females, decreased corpora lutea, decreased uterine weights, and cessation of menses were observed. No

adverse effect levels (NOAELs) were 15 mg/kg/day (26.2-fold) based on liver toxicity, 1.5 mg/kg/day (1.1-fold) based on decreased uterine weight and decreased corpora lutea, and 15 mg/kg/day (26.2-fold) for cessation of menses. No NOAEL was observed for systemic phospholipidosis; however, minimal effects were observed at 1.5 mg/kg/day (1.1-fold). No effects on cardiac parameters were observed in this study, and no effects were observed in a cardiac safety pharmacology study up to 30 mg/kg (estimated to be about 65 times the exposure at the MRHD of 40 mg, based on Cmax at first dose, in the 39-week study) in conscious male telemetered cynomolgus monkeys. At 100 and 300 mg/kg, effects on QT interval, QTc and PR interval were observed. Relugolix was shown in vitro to inhibit hERG channels with an IC_{50} of 9.7 µg/ml or about 373 times the clinical Cmax of 26 ng/ml at the MRHD of 40 mg.

In a 26-week study in rats, at 300 mg/kg/day (about 154-fold the exposure at the MRHD of 40 mg, based on AUC), minimal eosinophilic crystals in the epididymal epithelium, phospholipidosis, and minimal focal hemorrhage in the liver were observed. NOAELs were 100 mg/kg/day (about 33.5-fold) for liver effects and phospholipidosis in females, and 30 mg/kg/day (about 8.0-fold) for phospholipidosis (testicular) in males. Phospholipidosis was not observed in clinical studies and is considered to be a rare occurrence in humans. In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold less than in humans, and this study is a toxicological assessment of non-pharmacological targets of relugolix.

In human GnRH-receptor knock-in mice, administration of relugolix at oral doses of 100 mg/kg and above twice daily to female mice induced a constant diestrous phase and decreased ovarian and uterine weights, effects which were reversible following cessation of treatment. In male knock-in mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses 3 mg/kg and above twice daily for 28 days, effects which were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal.

Reproductive and developmental toxicology were studied in rats and rabbits.

In a fertility study in rats, no effect on female fertility was observed at up to 1000 mg/kg/day (greater than 300 times the MRHD of 40 mg daily in women). As noted above, the binding affinity of relugolix for GnRH receptors in rats is more than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix.

In an embryo-fetal development study in rabbits, oral administration of relugolix to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the MRHD of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH receptors is unknown.

In a similar embryo-fetal development study in rats, oral administration of relugolix to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. A NOAEL for maternal toxicity was 200 mg/kg/day (86 times the MRHD). No treatment related malformations were observed up to 1000 mg/kg/day. As noted above, the binding affinity of relugolix for GnRH receptors in rats is more than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy.

In a pre- and postnatal developmental study in pregnant and lactating rats, oral administration of relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times the MRHD), a dose in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD.)

Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low-dose estrogens and progestins as an oral contraceptive before conception or during early pregnancy.

Administration of a single oral dose of [^{14}C] relugolix (30 mg/kg) to fasted female rats on lactation Day 14 demonstrated that relugolix-derived radioactivity reached peak concentrations by 2 hours post-dose in both plasma and milk (9.7-fold milk-to-plasma accumulation ratio) and decreased to levels below the limit of quantification by 48 hours.

Carcinogenicity was studied in rats and mice.

Relugolix: Two-year carcinogenicity studies were conducted in mice at oral relugolix doses up to 100 mg/kg/day and in rats at doses up to 600 mg/kg/day. Relugolix was not carcinogenic in mice or rats at exposures up to approximately 142 or 423 times, respectively, the exposure in human females at the MRHD of 40 mg daily, based on AUC. No evidence of pre-neoplastic lesions was observed in 39-week studies in monkeys.

For the E2/NETA component of Myfembree, long-term continuous administration of natural and synthetic estrogens in certain animal species has long been known to increase the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. Risk assessment is typically based on human data.

Relugolix was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells or the in vivo rat bone marrow micronucleus assay.

Table 1. Safety Margins From Pivotal Toxicology Studies

Study	NOAEL	AUC_{0-24}	Safety Margin[1] (Based on AUC)
26-week rat study – Females	100 mg/kg oral	6630 ng•h/mL[2]	33X
26-week rat study – Males	30 mg/kg oral	1594 ng•h/mL[2]	8X
39-week monkey study	15 mg/kg oral	5198 ng•h/mL[2]	26X

[1] Exposure multiples were based on clinical pharmacokinetics analysis from Study MVT-601-042 (NDA Module 2.7.1, Table 19) where the clinical dose (40 mg) resulted in systemic exposure of AUC_{0-inf} =198.1 ng•h/mL.
[2] The combined male and female mean AUC_{0-24} value was used to determine the clinical safety margin.

Table 2. Reproductive and Developmental Toxicity Safety Margins

Study	Species	NOAEL	AUC_{0-24}	Safety Margin[1] (Based on AUC)
Fertility	Rat	1000 mg/kg oral	61133 ng•h/mL[2]	300X
Embryofetal Development	Rat	1000 mg/kg oral	61133 ng•h/mL[2]	300X
	Rabbit	3 mg/kg oral	25 ng•h/mL	0.1X
Pre-/Postnatal Development	Rat	1000 mg/kg oral	61133 ng•h/mL[2]	300X

[1] Exposure multiples were based on clinical pharmacokinetics analysis from Study MVT-601-042 (NDA Module 2.7.1, Table 19) where the clinical dose (40 mg) resulted in systemic exposure of AUC_{0-inf} =198.1 ng•h/mL.
[2] Toxicokinetics were not measured in this study but were estimated from a 4-week study in male and female rats (N=6). See rationale included with Table 3 in Appendix Section 13.1.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology recommends approval of this application.

1.3.3 Labeling

Sponsor proposed PLLR label 9.30.20:

INDICATIONS AND USAGE (Highlights)

[redacted] (b) (4)

8 USE IN SPECIFIC POPULATIONs

8.1 Pregnancy

Risk Summary

[redacted] (b) (4)

(b) (4)

In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures (b) (4) In both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures (b) (4) exposures in women at the (b) (4) respectively (*see Data*).

Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital (b) (4) defects (including cardiac anomalies and limb-reduction defects) following exposure to (b) (4) estrogens and progestins (b) (4) before conception or during early pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. There are insufficient data to conclude whether the presence of uterine fibroids reduces the likelihood of achieving pregnancy or increases the risk of adverse pregnancy outcomes. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

(b) (4)

Animal Data

(b) (4)

(b) (4)

In a pre- and postnatal developmental study in pregnant and lactating rats, (b) (4) no effect on pre- and postnatal development at doses up to 1000 mg/kg/day, (b) (4)

8.2 Lactation

(b) (4)

8.3 Females and Males of Reproductive Potential

Based on the mechanism of action, (b) (4) early pregnancy loss if MYFEMBREE is administered to pregnant women *[see Use in Specific Population (8.1),* (b) (4)

Pregnancy Testing

Exclude pregnancy before initiating treatment with MYFEMBREE. Perform pregnancy testing if pregnancy is suspected during treatment with MYFEMBREE *[see Warnings and Precautions* (b) (4)

Contraception

Advise (b) (4) women to use effective nonhormonal contraception during treatment with MYFEMBREE and for 1 week (b) (4) *[see Warnings and Precautions* (b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies were conducted with relugolix in (b) (4)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Mutagenesis

Relugolix was not mutagenic (b) (4) in vitro bacterial reverse mutation assay, the in vitro chromosomal aberration assay in Chinese hamster lung cells, (b) (4) the in vivo (b) (4) bone marrow micronucleus assay.

Impairment of Fertility

(b) (4)

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) (b) (4) organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, GI tract or testes) (b) (4) of relugolix in rats and monkeys (b) (4)

(b) (4)

Comparison of Sponsor proposed label and FDA proposed label, with mark-up.

INDICATIONS AND USAGE (Highlights)

Sponsor proposed	Edited version	FDA proposed
(b) (4)		(b) (4) of heavy menstrual bleeding associated with uterine fibroids. (1)

8 USE IN SPECIFIC POPULATIONs

8.1 Pregnancy

Risk summary

Sponsor proposed	Edited version	FDA proposed
Risk Summary (b) (4)	No changes proposed.	No changes made.

Sponsor proposed	Edited version	FDA proposed
Risk Summary (cont.) In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures (b) (4) . In both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures (b) (4) exposures in women at the (b) (4) respect vely (*see Data*).	Risk Summary (cont.) In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures (b) (4) about half those at the maximum recommended human dose (MRHD) of 40 mg. (b) (4). In both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures (b) (4) about half and approximately (b) (4) 300 times exposures in women at the (b) (4) MRHD, respect vely (*see Data*).	Risk Summary (cont.) In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures about half those at the maximum recommended human dose (MRHD) of 40 mg. In both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures about half and approximately 300 times exposures in women at the MRHD, respectively *(see Data)*.
		Orgovyx label: In an animal reproduction study, oral administration of relugolix to pregnant rabbits during organogenesis caused embryo-fetal lethality at maternal exposures that were 0.3 times the human exposure at the recommended dose of 120 mg daily based on AUC (*see Data*).

Sponsor proposed	Edited version	FDA proposed
Risk Summary (cont.) Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital (b) (4) defects (including cardiac anomalies and limb-reduction defects) following exposure to (b) (4) estrogens and progestins (b) (4) before conception or during early pregnancy. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. There are insufficient data to conclude whether the presence of uterine fibroids reduces the likelihood of achieving pregnancy or increases the risk of adverse pregnancy outcomes. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.	No changes proposed.	No changes made.

Data

Sponsor proposed	Edited version	FDA proposed
(b) (4)	No changes proposed.	No changes made.

Sponsor proposed	Edited version	FDA proposed
Data *Animal Data* (b) (4)	Data *Animal Data* (b) (4) In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis (b) (4). Days 6 to 18 (b) (4) (b) (4) of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (b) (4) about half the human exposure at the maximum recommended human dose (MRHD) of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. (b) (4) (b) (4) No treatment related effects were observed at 3 mg/kg/day, (b) (4) fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH receptors is unknown. (b) (4) ~~(~~In a similar embryo-fetal development study, oral administration of relugolix to pregnant rats during the	Data *Animal Data* In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the maximum recommended human dose (MRHD) of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH receptors is unknown. In a similar embryo-fetal development study, oral administration of relugolix to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. A no adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (86 times the MRHD). In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related malformations were observed up to 1000 mg/kg/day.

(b) (4)	period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (b) (4) 300 times the MRHD), (b) (4) a dose at which maternal toxicity (decreaseds (b) (4) body weight gain and food consumption) was observed. , (b) (4) A no adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (b) (4) 86 times the MRHD). , (b) (4) . In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related malformations were observed up to 1000 mg/kg/day. (b) (4)	

Sponsor proposed	Edited version	FDA proposed
Data *Animal Data* (cont.) In a pre- and postnatal developmental study in pregnant and lactating rats, (b) (4) no effect on pre- and postnatal development at doses up to 1000 mg/kg/day. (b) (4)	Data *Animal Data* (cont.) In a pre- and postnatal developmental study in pregnant and lactating rats, orally administration (b) (4) of relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (b) (4) 300 times the MRHD), a dose in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD.), (b) (4) .	Data *Animal Data* (cont.) In a pre- and postnatal developmental study in pregnant and lactating rats, oral administration of relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times the MRHD), a dose in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD.)

8.2 Lactation

Sponsor proposed	Edited version	FDA proposed
Risk Summary There are no data on the presence of relugolix or its metabolites in human milk, the effects on the breastfed child, or the effects on mi k production. Relugolix was detected in milk in lactating rats (*see Data*). Detectable amounts of estrogen and progestin have been identified in the breast mi k of women receiving estrogen plus progestin therapy. (b) (4) [redacted] The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for MYFEMBREE and any potential adverse effects on the breastfed child from MYFEMBREE or from the underlying maternal condition.	No changes proposed.	No changes made.

Sponsor proposed	Edited version	FDA proposed
Data *Animal Data* (b) (4) [redacted]	Data *Animal Data* (b) (4) [redacted] and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose. (b) (4) [redacted]	Data *Animal Data* In lactating rats administered a single oral dose of 30 mg/kg radiolabeled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.
		Orgovyx label: In lactating rats administered a single oral dose of 30 mg/kg radiolabeled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.

8.3 Males and Females of Reproductive Potential

Sponsor proposed	Edited version	FDA proposed
Based on the mechanism of action, [redacted] early pregnancy loss if MYFEMBREE is administered to pregnant women *[see Use in Specific Population (8.1),* [redacted] Pregnancy Testing Exclude pregnancy before initiating treatment with MYFEMBREE. Perform pregnancy testing if pregnancy is suspected during treatment with MYFEMBREE *[see Warnings and Precautions* [redacted] Contraception Advise [redacted] women to use effective nonhormonal contraception during treatment with MYFEMBREE and for 1 week after discontinuing MYFEMBREE *[see Warnings and Precautions* [redacted] [redacted]	No changes proposed.	No changes made.

12 Clinical Pharmacology

Sponsor proposed	Edited version	FDA proposed
Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to [redacted]	Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors [redacted] thereby reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), [redacted]	Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thereby reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), [redacted] Estradiol acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. As a component of MYFEMBREE, the addition of exogenous estradiol may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from relugolix alone. Progestins such as norethindrone act by binding to nuclear receptors that are expressed in progesterone-responsive

(b) (4)	(b) (4) (b) (4) - As a component of MYFEMBREE, the addition of (b) (4) may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from relugolix alone. Progestins such as (b) (4) –by binding to nuclear receptors that are expressed in progesterone-responsive tissues. As a component of MYFEMBREE, norethindrone may protect the uterus from the potential adverse endometrial effects of unopposed estrogen. (b) (4) (b) (4)	tissues. As a component of MYFEMBREE, norethindrone may protect the uterus from the potential adverse endometrial effects of unopposed estrogen.

		Orgovyx label: Relugolix is a nonpeptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thereby, reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and consequently testosterone.
		Oriahnn label: E2 acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. As a component of ORIAHNN, the addition of exogenous estradiol may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from elagolix alone. Progestins such as NETA act by binding to nuclear receptors that are expressed in progesterone responsive tissues. As a component of ORIAHNN, NETA may protect the uterus from the potential adverse endometrial effects of unopposed estrogen.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Sponsor proposed	Edited version	FDA proposed
(b) (4) Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.	Two-year carcinogenicity studies were conducted (b) (4) Relugolix was not carcinogenic in mice or rats at exposures up to approximately 142 or 423 times, respectively, the exposure in human females at the MRHD of 40 mg daily, based on AUC. (b) (4) E2/NETA Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.	Relugolix Two-year carcinogenicity studies were conducted in mice at oral relugolix doses up to 100 mg/kg/day and in rats at doses up to 600 mg/kg/day. Relugolix was not carcinogenic in mice or rats at exposures up to approximately 142 or 423 times, respectively, the exposure in human females at the MRHD of 40 mg daily, based on AUC. E2/NETA Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.
		Orgovyx label: Two-year carcinogenicity studies were conducted in mice at oral relugolix doses up to 100 mg/kg/day and in rats at doses up to 600 mg/kg/day. Relugolix was not carcinogenic in mice or rats at

		exposures up to approximately 75 or 224 times, respectively, the human exposure at the recommended dose of 120 mg daily based on AUC.

Mutagenesis

Sponsor proposed	Edited version	FDA proposed
Relugolix was not mutagenic (b) (4) (b) (4) the in vitro bacterial reverse mutation assay, the in vitro chromosomal aberration assay in Chinese hamster lung cells, and the in vivo mouse bone marrow micronucleus assay.	Relugolix was not mutagenic (b) (4) (b) (4) in the in vitro bacterial reverse mutation (Ames) assay~~,~~ or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells, (b) (4) or the in vivo rat (b) (4) bone marrow micronucleus assay.	Relugolix was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells or the in vivo rat bone marrow micronucleus assay.
		Orgovyx label: Relugolix was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells or the in vivo rat bone marrow micronucleus assay.

Impairment of Fertility

Sponsor proposed	Edited version	FDA proposed
(b) (4)	In a fertility (b) (4) 1000 mg/kg/day~~,~~ (b) (4) 300 times the MRHD of 40 mg daily in women). In rats, the binding affinity of relugolix for GnRH receptors is greater than 1000 fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix. (b) (4) In a 39-week toxicology study ~~i~~in monkeys, a decreases in the frequency of menses was (b) (4) observed in female monkeys at 50 mg/kg/day (b) (4) 99 times the MRHD of 40 mg daily in women, based on AUC), (b) (4) which was partially reversed following a 13-week recovery period. There were no significant effects on male	In a fertility study in rats, no effect on female fertility was observed at up to 1000 mg/kg/day (300 times the MRHD of 40 mg daily in women). In rats, the binding affinity of relugolix for GnRH receptors is greater than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix. In human GnRH-receptor knock-in mice, administration of relugolix at oral doses of 100 mg/kg and above twice daily to female mice induced a constant diestrous phase and decreased ovarian and uterine weights, effects which were revers ble following cessation of treatment. In male knock-in mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses 3 mg/kg and above twice daily for 28 days, effects which were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal. In a 39-week toxicology study in monkeys, a decrease in the frequency of menses was observed in female monkeys at 50 mg/kg/day (99 times the MRHD of 40 mg daily in women, based on AUC), which was partially reversed following a 13-week recovery period. There were no significant effects on male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human

	reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human exposure at a dose of 120 mg daily in men, based on AUC) (b) (4) [redacted]	exposure at a dose of 120 mg daily in men, based on AUC).
		Orgovyx label: In human GnRH-receptor knock-in male mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses ≥ 3 mg/kg twice daily for 28 days. The effects of relugolix were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal. In a 39-week repeat-dose toxicity study in monkeys, there were no significant effects on male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human exposure at the recommended dose of 120 mg daily based on AUC).

13.2 Animal Toxicology and/or Pharmacology

Sponsor proposed	Edited version	FDA proposed
Phospholipidosis (intracellular phospholipid accumulation) (b) (4) [redacted] organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, GI tract or testes) (b) (4) [redacted]	Phospholipidosis (intracellular phospholipid accumulation) (b) (4) [redacted] -was observed in multiple organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, GI tract or testes) after repeated ora (b) (4) [redacted] administration of (b) (4) [redacted] relugolix in rats and monkeys. (b) (4) [redacted] In a rat 26-week toxicity study, (b) (4) phospholipidosis was observed (b) (4) at doses (b) (4) of 100 mg/kg/day (approx mately 30 times the exposure at the MRHD of 40 mg daily in women based on AUC (b) (4)	Phospholipidosis (intracellular phospholipid accumulation) was observed in multiple organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, GI tract or testes) after repeated oral administration of relugolix in rats and monkeys. In a rat 26-week toxicity study, phospholipidosis was observed at doses of 100 mg/kg (approximately 30 times the exposure at the MRHD of 40 mg daily in women based on AUC) and above. In a monkey 39-week toxicity study, this effect was observed at doses of 1.5 mg/kg (approximately equal to the MRHD) and above and demonstrated evidence of revers bility after cessation

(b) (4)	(b) (4) and above. In a monkey 39-week toxicity study, (b) (4) s this effect was observed (b) (4) at doses (b) (4) -of1.5 mg/kg/day (approximately equal to the MRHD- (b) (4) and above and demonstrated evidence of reversibility (b) (4) The significance of (b) (4) this finding in humans is unknown. (b) (4)	of treatment. The significance of this finding in humans is unknown.
		Orgovyx label: Phospholipidosis (intracellular phospholipid accumulation) was observed in multiple organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, gastrointestinal tract or testes) after repeated oral administration of relugolix in rats and monkeys. In a rat 26-week toxicity study, phospholipidosis was observed at doses ≥ 100 mg/kg (approximately 18 times the human exposure at the recommended dose based on AUC). In a monkey 39-week toxicity study, this effect was observed at doses ≥ 1.5 mg/kg (approximately 0.6 times the human exposure at the recommended dose based on AUC) and demonstrated evidence of reversibility after cessation of treatment. The significance of this finding in humans is unknown.

FDA proposed (clean):

INDICATIONS AND USAGE (Highlights)

(b) (4)

(1)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MYFEMBREE is contraindicated in pregnancy *[see Warnings and Precautions* (b) (4) *.* Based on findings from animal studies and its mechanism of action, MYFEMBREE may cause early pregnancy loss. Discontinue MYFEMBREE if pregnancy occurs during treatment *[see Warnings and Precautions* (b) (4) *and Clinical Pharmacology (12.1)]..*

The limited human data with the use of MYFEMBREE in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).*

In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures about half those at the maximum recommended human dose (MRHD) of 40 mg. In both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures about half and approximately 300 times exposures in women at the MRHD, respectively *(see Data).*

Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to estrogens and progestins before conception or during early pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. There are insufficient data to conclude whether the presence of uterine fibroids reduces the likelihood of achieving pregnancy or increases the risk of adverse pregnancy outcomes. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the maximum recommended human dose (MRHD) of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH receptors is unknown.

In a similar embryo-fetal development study, oral administration of relugolix to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. A no adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (86 times the MRHD). In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related malformations were observed up to 1000 mg/kg/day.

In a pre- and postnatal developmental study in pregnant and lactating rats, oral administration of relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times the MRHD), a dose in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD.)

8.2 Lactation

Risk Summary

There are no data on the presence of relugolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Relugolix was detected in milk in lactating rats (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen plus progestin therapy and can reduce mild production in breast-feeding females. This reduction is less likely to occur once breast-feeding is well established (b) (4)

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for MYFEMBREE and any potential adverse effects on the breastfed child from MYFEMBREE or from the underlying maternal condition.

Data
Animal Data

In lactating rats administered a single oral dose of 30 mg/kg radiolabeled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.

8.3 Females and Males of Reproductive Potential

Based on animal data and the mechanism of action, MYFEMBREE can cause early pregnancy loss if MYFEMBREE is administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

MYFEMBREE may delay the ability to recognize the occurrence of a pregnancy because it may reduce the intensity, duration, and amount of menstrual bleeding *[see Warnings and Precautions* (b) (4) Exclude pregnancy before initiating treatment with MYFEMBREE. Perform pregnancy testing if pregnancy is suspected during treatment with MYFEMBREE and discontinue treatment if pregnancy is confirmed *[see Contraindications (4) and Warnings and Precautions* (b) (4) *.*

Contraception

(b) (4)

Advise (b) (4) of reproductive potential to use effective nonhormonal contraception during treatment with MYFEMBREE and for 1 week (b) (4)

8.4 Pediatric Use

Safety and effectiveness of MYFEMBREE in patients (b) (4) have not been established.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

MYFEMBREE is a combination of relugolix, estradiol (E2), and norethindrone acetate (NETA).

Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thereby reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), (b) (4)

Estradiol acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. As a component of MYFEMBREE, the addition of exogenous estradiol may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from relugolix alone.

Progestins such as norethindrone act by binding to nuclear receptors that are expressed in progesterone-responsive tissues. As a component of MYFEMBREE, norethindrone may protect the uterus from the potential adverse endometrial effects of unopposed estrogen.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Relugolix
Two-year carcinogenicity studies were conducted in mice at oral relugolix doses up to 100 mg/kg/day and in rats at doses up to 600 mg/kg/day. Relugolix was not carcinogenic in mice or rats at exposures up to approximately 142 or 423 times, respectively, the exposure in human females at the MRHD of 40 mg daily, based on AUC.

E2/NETA
Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Mutagenesis

Relugolix was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells or the in vivo rat bone marrow micronucleus assay.

Impairment of Fertility

In a fertility study in rats, no effect on female fertility was observed at up to 1000 mg/kg/day (300 times the MRHD of 40 mg daily in women). In rats, the binding affinity of relugolix for GnRH receptors is greater than 1000 fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix.

In human GnRH-receptor knock-in mice, administration of relugolix at oral doses of 100 mg/kg and above twice daily to female mice induced a constant diestrous phase and decreased ovarian and uterine weights, effects which were reversible following cessation of treatment. In male knock-in mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses 3 mg/kg and above twice daily for 28 days, effects which were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal.

In a 39-week toxicology study in monkeys, a decrease in the frequency of menses was observed in female monkeys at 50 mg/kg/day (99 times the MRHD of 40 mg daily in

women, based on AUC), which was partially reversed following a 13-week recovery period. There were no significant effects on male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human exposure at a dose of 120 mg daily in men, based on AUC).

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) was observed in multiple organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, GI tract or testes) after repeated oral administration of relugolix in rats and monkeys. In a rat 26-week toxicity study, phospholipidosis was observed at doses of 100 mg/kg (approximately 30 times the exposure at the MRHD of 40 mg daily in women based on AUC) and above. In a monkey 39-week toxicity study, this effect was observed at doses of 1.5 mg/kg (approximately equal to the MRHD) and above and demonstrated evidence of reversibility after cessation of treatment. The significance of this finding in humans is unknown.

2 Drug Information

2.1 Drug

MYFEMBREE is a combination of relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, indicated for the treatment of heavy menstrual bleeding associated with uterine fibroids.

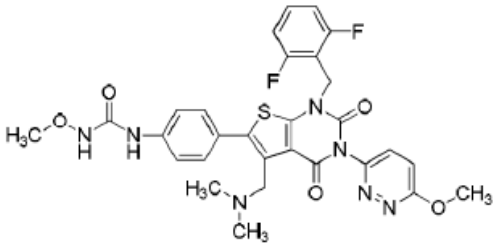
Generic Name: relugolix, E2/NETA

Code Name: TAK-385

Chemical Name: N-(4-[2,6-diflurobenzyl)-5-[(dimethylamino)methy]-1,2,3,4-tetrahydro-3-(6-methoxypyridazin-3-yl)-2,4-dioxothieno[2,3-d]pyrimidin-6yl]-N-methoxyurea); Urea, N-[4-[1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-1,2,3,4-tetrahydro-3-(6-methoxy-3-pyridazinyl)-2,4-dioxothieno[2,3-d]pyrimidin-6-yl]phenyl]-N'-methoxy-

Molecular Formula/Molecular Weight: $C_{29}H_{27}F_2N_7O_5S$/ 623.63

Structure or Biochemical Description



Pharmacologic Class: GnRH antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

(b) (4)

IND 131161 (Treatment of women with heavy menstrual bleeding associated with uterine fibroids)

(b) (4)

IND 118736 (Advanced, relapsed, or metastatic prostatic cancer)
NDA 214621 (Treatment of adult patients with advanced prostate cancer)

2.3 Drug Formulation

Relugolix is formulated as a fixed-dose combination (FDC) tablet containing 40 mg relugolix, 1 mg estradiol (E2) and 0.5 mg norethindrone acetate (NETA).

Quantitative Composition of RELUGOLIX/E2/NETA FDC Tablets

Component	Quality Standard	Function	Composition	
			(% w/w)	(mg/Tablet)
Core Tablet				
Relugolix	In-house	Active ingredient	(b) (4)	40.0
Estradiol	In-house[a]	Active ingredient		1.0[b]
Norethindrone acetate	In-house[a]	Active ingredient		0.5
Mannitol	USP-NF/Ph. Eur.	(b) (4)		(b) (4)
Sodium starch glycolate	USP-NF/Ph. Eur.			
Hydroxypropyl cellulose	USP-NF/Ph. Eur.			
Lactose monohydrate	USP-NF/Ph. Eur.			
Magnesium stearate	USP-NF/Ph. Eur.			
(b) (4)				
Film-Coated Tablet				
(b) (4)				

Abbreviations: Ph. Eur = European Pharmacopoeia; qs = quantum sufficit; USP-NF = United States Pharmacopoeia–National Formulary.
a In-house standard is based on USP-NF/Ph. Eur. and includes the manufacturer-specific testing outlined in Sections S.4.1 (estradiol) and S.4.1 (norethindrone acetate).

(b) (4)

2.5 Comments on Impurities/Degradants of Concern

TAK-385 related substances (b) (4) were assessed for their mutagenic potential using Multiple Computer Automated Structure Evaluation, MCASE (version 2.00; database module:A20, Salmonella Mutagenicity- NTP & A2C, Salmonella Mutagenicity – Gene Tox.) and Deductive Estimation of Risk from Existing Knowledge, DEREK for Windows (version 11.0.0 + Takeda 2.0). (b) (4) was not evaluated because its level in the drug product is significantly below the identification threshold as per ICH Q3B(R2). Based on these analyses, (b) (4) was found to possess mutagenic potential and to be of concern, whereas (b) (4) were negative in all the evaluations. A battery of in vitro and in vivo genotoxicity studies were conducted with (b) (4), to support a weight-of-evidence genotoxicity evaluation, and a CDER genotoxicity consult concluded

that the impurity (b) (4) did not pose a genotoxic risk for human subjects when present at levels up to (b) (4) µg/day.

Relugolix (containing (b) (4) at (b) (4) %) was not carcinogenic in 2-year mouse and rat studies.

2.6 Proposed Clinical Population and Dosing Regimen

Relugolix/E2/NETA is proposed for daily oral use of 40 mg/1 mg/0.5 mg in premenopausal females, for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids), with use limited to 24 months due to the risk of continued bone loss (which may not be reversible).

2.7 Regulatory Background

Relugolix (120 mg) was approved for treatment of adult patients with advanced prostate cancer in 2020 under NDA 214621 (Orgovyx), for which the pivotal toxicology studies were previously reviewed.

Oriahnn, a combination of a gonadotropin-releasing hormone (GnRH) receptor antagonist (elagolix), estradiol (1 mg), and norethindrone acetate (0.5 mg), was approved in 2020 for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology		
Binding affinity of TAK-385 for GnRH receptors.	TAK-385-00090	p.30
Antagonistic activity of TAK-385 for human GnRH receptor in a human GnRH receptor expressing CHO cell system	TAK-385-00091	p.31
Antagonistic activity of TAK-385 for monkey receptor in a monkey GnRH receptor expressing	TAK-385-00092	p.31
Suppression of the hypothalamic-pituitary-gonadal axis by a novel, orally active small molecule gonadotropin-releasing hormone (GnRH) antagonist, TAK-385, in female human GnRH receptor knock-in mice.	TAK-385-00103	p.32
Suppression of a hypothalamus-pituitary-gonadal axis by a novel, orally active small molecule gonadotropin-releasing hormone (GnRH) antagonist, TAK-385, in male human GnRH receptor knock-in mice.	TAK-385-00105	p.32
Safety pharmacology study of TAK-385: Effects on hERG current	TAK-385-00072	p.32

Effects on the cardiovascular system in conscious monkeys	TAK-385-00071	p.33
Toxicology		
Four-week oral gavage toxicity study of TAK-385 in rats	TAK-385-00107	p.36
Twenty-six-week oral gavage toxicity study of TAK-385 in rats	TAK-385-000145	p.36
Four-week gavage toxicity of TAK-385 in monkeys	TAK-385-00102	p.38
Thirty-nine-week oral gavage toxicity study of TAK-385 in monkeys with a 13-week recovery period	TAK-385/00144	p.38
Bacterial reversion assay with TAK-385	TAK-385-00093	p.46
Cytogenetic Assay with TAK-385 in Chinese Hamster Lung (CHL) Cells.	TAK-385-00068	p.47
Micronucleus Assay with TAK-385 in rats	TAK-385-00094	p.48
Thirteen-week oral gavage range-finding toxicity study of TAK-385 in mice	TAK-385-00119	p.49
Twenty-four-month oral gavage carcinogenicity study of TAK-385 in mice	TAK-385-10217	p.49
Twenty-four-month oral gavage carcinogenicity study of TAK-385 in rats	TAK-385-10218	p.55
Effects of TAK-385 on Fertility and Early Embryonic Development to Implantation in Rats	TAK-385-00113	p.66
Effects of TAK-385 on Embryo-Fetal Development in Rats	TAK-385-00110	p.69
Effects of TAK-385 on embryo-fetal development in rabbits	TAK-385-00115	p.71
Effects of TAK-385 on Pre- and Postnatal Development, including Maternal Functions in Rats	TAK-385-300136	p.78
Lacteal secretion of [^{14}C]TAK-385 in rats	TAK-385-1272	p.35

3.2 Studies Not Reviewed

Studies reviewed under NDA 214621

ADME	
Tissue distribution ([^{14}C]-relugolix) in male albino rat	TAK-385-00081
Tissue distribution ([^{14}C]-relugolix) in female albino rat	TAK-385-00082
Tissue distribution ([^{14}C]-relugolix) in male pigmented rat	TAK-385-00083
Whole body autoradiography ([^{14}C]-relugolix) in male rats	TAK-385-12448
Whole body autoradiography ([^{14}C]-relugolix) in female rats	TAK-385-12449
Plasma protein binding of ([^{14}C]-relugolix)	TAK-385-00084
Fetoplacental transfer ([^{14}C]-relugolix)	TAK-385-12711
In vitro metabolite profiling ([^{14}C]-relugolix)	TAK-385-00040
Characterization of TAK-385 metabolites	TAK-385-00085
In vivo single-dose metabolite profiling ([^{14}C]relugolix)	TAK-385-00088

Single-dose ([^{14}C]relugolix) in rats	TAK-385-00074/76
Single-dose ([^{14}C]relugolix) in monkeys	TAK-385-00077
Inhibition in Recombinant CYPs	TAK-385-12714
Phenotyping in recombinant CYPs	TAK-385-00041
Gut microbiota-mediated metabolism ([^{14}C]-relugolix)	TAK-385-12402
Permeability in Caco-2 cells	TAK-385-10172
Pharmacology	
Secondary pharmacology battery of TAK-385	TAK-385-00054
Safety pharmacology study of CNS in rats	TAK-385-00069
Safety pharmacology study of respiratory system in rats	TAK-385-00070
Other	
Phospholipidosis biomarker study in rats	TAK-385-13010
Phototoxicity (NRU assay) in BALB/3T3 cells	TAK-385-00013
Phototoxicity in (b) (4):SKH1-hr hairless mice	TAK-385-00112

3.3 Previous Reviews Referenced

NDA 214621 (21 December 2020), Nonclinical Section by Claudia Miller (b) (4)

4 Pharmacology

Primary Pharmacology

Study title: Binding affinity of TAK-385 for GnRH receptors. (Study No. TAK-385-00090)

The in vitro binding affinity of TAK-385 for GnRH receptors was compared to GnRH, TAP-144 (leuprolide acetate, a GnRH agonist), cetrorelix (a GnRH antagonist) and TAK-013 (an alternate drug candidate) using human, monkey or rat GnRH receptors expressed in CHO cell membranes and inhibition of binding of ^{125}I-TAP-144.

TAK-385 exhibited a high affinity for human (IC_{50} of 0.12 nM) and monkey (IC_{50} of 0.15 nM) GnRH receptors and a low affinity for rat GnRH receptors (IC_{50} of 2900 nM), in the absence of fetal bovine serum (FBS), and a 3-fold decrease in binding for all three species in the presence of 40% FBS. The binding of TAK-385 to human GnRH receptor was higher than for cetrorelix, leuprolide acetate (TAP-144) or GnRH. Values in the table below are expressed as IC_{50} (nM) in the presence of 0% or 40% FBS:

Compound	Human		Monkey		Rat	
	0	40	0	40	0	40
GnRH	31	17	17	7.5	26	24
TAP-144	2.9	3.0	2.0	2.3	0.36	0.48
Cetrorelix	0.85	1.2	0.28	0.53	0.25	0.38
TAK-013	0.089	1.6	0.18	1.3	1500	18000
TAK-385	0.12	0.33	0.15	0.32	2900	9800

TAK-013 is an analog of TAK-385
Sponsor's table

Study title: Antagonistic activity of TAK-385 for human GnRH receptor in a human GnRH receptor expressing CHO cell system (Study No. TAK-385-00091)

TAK-385 antagonism of arachidonic acid release was measured in vitro in CHO cells expressing human GnRH receptors. The IC_{50} and IC_{90} (nM) of TAK-385, cetrorelix, and TAK-013 for inhibition of ^{3}H-arachidonic acid release, in the absence and presence of 40% human plasma, are shown in table below:

Compound	No human plasma		40% human plasma	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}
TAK-385	0.32	2.6	1.6	18
Cetrorrelix	0.67	4.6	4.5	75
TAK-013	0.068	0.78	3.4	270

Sponsor's table

Study title: Antagonistic activity of TAK-385 for monkey receptor in a monkey GnRH receptor expressing (Study No. TAK-385-00092)

TAK-385 antagonism of arachidonic acid release was measured in vitro in CHO cells expressing monkey GnRH receptors. The IC_{50} and IC_{90} (nM) of TAK-385 and cetrorelix for inhibition of ^{3}H-arachidonic acid release, in the absence and presence of 40% human plasma, are shown in table below:

Compound	No monkey plasma		40% monkey plasma	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}
TAK-385	16	77	230	1700
Cetrorelix	0.78	3.0	12	49

Sponsor's table

Although TAK-385 appeared more selective for human than for monkey receptors, the monkey model was judged to be acceptable.

Study title: Suppression of a LH release by single oral administration of a novel non-peptide gonadotropin-releasing-hormone antagonist, TAK-385, in castrated cynomolgus monkeys (Study No. TAK-385-00095)

Nine castrated adult cynomolgus monkeys were administered a single oral dose of 0, 1, or 3 mg/kg of TAK-385, followed in 2 weeks by 0, 0.1, or 0.3 mg/kg TAK-385. Luteinizing hormone (LH) in plasma was measured using a dispersed mouse testicular cell bioassay at 0, 1, 2, 4, 8, 24, and 48 hours.

TAK-385 decreased plasma LH levels at doses of 1 (up to 24 hours) and 3 mg/kg (up to 48 hours, the last time point measured). No effect was observed at 0.1 or 0.3 mg/kg.

Study title: Suppression of the hypothalamic-pituitary-gonadal axis by a novel, orally active small molecule gonadotropin-releasing hormone (GnRH) antagonist, TAK-385, in female human GnRH receptor knock-in mice. (Study No. TAK-385-00103)

The effects of chronic administration of TAK-385 on HPG axis were evaluated using female human GnRH receptor (GnRHR) knock-in mice. TAK-385 (100 mg/kg, twice daily) for 4 weeks induced constant diestrous, decreased ovarian and uterine weights, and down-regulated pituitary GnRHR mRNA expression. Effects were reversible following cessation of treatment. No difference in cancellous or cortical bone density between intact, OVX and TAK-385-treated mice were observed. No effect was observed at 30 mg/kg/day, while 200 mg/day was similar in effect to 100 mg/kg/day.

Study title: Suppression of a hypothalamus-pituitary-gonadal axis by a novel, orally active small molecule gonadotropin-releasing hormone (GnRH) antagonist, TAK-385, in male human GnRH receptor knock-in mice. (Study no. TAK-385-00105)

The effects of chronic administration of TAK-385 on HPG axis were evaluated using male human GnRH receptor (GnRHR) knock-in mice (N=8/group) for 28 days.
Group 1 was administered the vehicle (0.5% methylcellulose containing 6 mg/mL citric acid), group 2 was castrated, and groups 3, 4 and 5 were administered oral TAK-385 (3, 10 or 30 mg/kg/day).

Decreased ventral prostate weight (up to 84% relative to body weight) and seminal vesicle weight (up to 91% relative to body weight) were observed at 3 mg/kg TAK-385 and above. Effects were reversible, except for decreased testis weight, which did not fully recover after 28 days of drug withdrawal. Similar effects were observed in castrated mice at 10 mg/kg/day or greater. Pituitary human GnRH mRNA expression was decreased up to 80% (similar to castrated mice) in knock-in mice at 10 mg/kg/day and greater.

Safety Pharmacology

Title: Safety pharmacology study of TAK-385: Effects on hERG current (Study No. TAK-385-00072, (b) (4) 2006, GLP)

In HEK-293 cells stably expressing the human ether-à-go-go–related gene (hERG) channel, using the whole cell clamp method (n=5/group) at room temperature, the IC_{50}

of TAK-385 was shown to be 9.7 µg/ml or about 373 times the Cmax of 26 ng/ml at the MRHD of 40 mg.

Test substance	Vehicle (0.1 vol% DMSO)	TAK-385			Positive control (E-4031)
Concentration (ug/ml)	0	0.3	3	30	0.051[1]
Number of cells	5	5	5	5	5
Rate of residual current (%)[2]	96.8	93.5	77.0	20.8	7.5
% inhibition[3]		3.4	20.5	78.5	
Conclusion	Inhibition at 3 ug/ml or more	IC_{50}: 9.7 ug/ml			

1. 0.1 umol/L
2. % of value after treatment relative to that before treatment
3. Inhibition rate corrected for the mean vehicle value
Sponsor's table

Title: Safety pharmacology study of TAK-385: Effects on the cardiovascular system in conscious monkeys (Study No. TAK-385-00071, (b) (4) 2006, GLP)

Male cynomolgus monkeys (N=4, 4 years 5 months to 4 years 11 months old) were administered a single oral dose (telemetered, crossover design, 7-day intervals between doses) of 0, 30, 100, or 300 mg/kg.

At 100 mg/kg (about 161 times Cmax at the MRHD of 40 mg), statistically significant increases in QT interval (up to 51 msec) and QTc (up to 47 msec) were observed at 8 hours, compared to vehicle; significant increases in QT and QTc were also seen at 300 mg/kg (about 484 times) at 8 hours. Prolonged QTc interval (up to 26 msec) was also observed at 1 hour at both 100 and 300 mg/kg. Minimal (up to 4 msec) but statistically significant differences in PR interval were observed at 4 hours and 24 hours at 30 mg/kg (about 65 times) and above. No effect on cardiac parameters was observed at 30 mg/kg. No effects on systolic, diastolic, or mean blood pressure, heart rate, PR interval, or QRS duration were observed at any dose.

Dosing	Single oral dosing (crossover design)			
Measurement method	Telemetry			
Time points	0.5 hours before and 1, 2, 4, 8, and 24 hours after dosing			
Test substance	Vehicle [1]	TAK-385		
Dose levels (mg/kg)	0	30	100	300
Dosage volume (ml/kg)	5	5	5	5
Systolic blood pressure [mmHg]	-	-	-	-
Diastolic blood pressure [mmHg]	-	-	-	-
Mean blood pressure [mmHg]	-	-	-	-
Heart rate [beats/min]	-	-	-	-
Electrocardiograms PR interval, QRS duration, QT and QTc intervals	-	-	Prolongation of QT at 8 hours after dosing (51 ms*) and QT_c at 4 hours after dosing (62 ms*)	Prolongation of QT at 8 hours after dosing (37 ms*) and QT_c at 4 hours after dosing (36 ms*).
General physical condition	-	-		Vomiting (n=1)
Conclusion	Prolongation of QT and QT_c intervals was noted at 100 mg/kg and above			

1= 0.5% methylcellulose solution containing 6 mg/ml citric acid
- = no treatment-related changes
* = maximum mean differences of these parameters from corresponding vehicle values
Sponsor's table

Toxicokinetics (Monkey Study no. TAK-385-00102): Human Cmax: 26.0 ng/mL

		Male (N=3)			Female (N=3)			Total (N=6)		
Dose (mg/kg/day)	No. of dosing	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng·h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng·h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng·h/mL)
5	1st	1.7 (0.6)	83.2 (56.9)	407 (270)	2.7 (1.2)	131.8 (101.1)	554 (409)	2.2 (1.0)	107.5 (78.0)	480 (320)
	28th	1.3 (0.6)	299.0 (111.3)	1383 (461)	1.3 (0.6)	234.2 (103.6)	835 (253)	1.3 (0.5)	266.6 (102.5)	1109 (448)
10	1st	1.0 (0.0)	770.1 (168.6)	3239 (392)	2.0 (1.7)	425.7 (326.7)	1731 (1207)	1.5 (1.2)	597.9 (299.4)	2485 (1152)
	28th	1.0 (0.0)	730.3 (162.6)	3132 (442)	1.0 (0.0)	565.9 (256.0)	2602 (814)	1.0 (0.0)	648.1 (211.9)	2867 (654)
20	1st	2.0 (0.0)	816.8 (402.8)	4479 (1740)	1.7 (0.6)	1424.7 (265.6)	5637 (525)	1.8 (0.4)	1120.8 (451.6)	5058 (1313)
	28th	1.7 (0.6)	1053.8 (472.7)	5078 (2172)	1.3 (0.6)	1228.6 (226.5)	5609 (819)	1.5 (0.5)	1141.2 (345.0)	5344 (1497)
100	1st	3.3 (1.2)	3965.8 (2097.6)	34184 (14773)	2.7 (1.2)	4425.3 (1000.0)	33741 (9031)	3.0 (1.1)	4195.5 (1491.1)	33963 (10954)
	28th	3.3 (1.2)	4198.7 (1120.8)	34942 (12200)	3.3 (1.2)	4554.0 (355.7)	35609 (5030)	3.3 (1.0)	4376.4 (768.7)	35276 (8354)

Sponsor's table

5 Pharmacokinetics/ADME/Toxicokinetics

Nonclinical Toxicokinetics

Table 3: Toxicokinetics – 4-week oral gavage toxicity study in rats

		Male (N=3)			Female (N=3)			Total (N=6)		
Dose (mg/kg/day)	No. of dosing	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)
10	1st	2.7 (1.2)	2.3 (1.0)	15 (6)	4.0 (0.0)	4.1 (4.7)	19 (20)	3.3 (1.0)	3.2 (3.2)	17 (14)
	29th	3.3 (1.2)	10.9 (0.5)	63 (16)	2.7 (1.2)	32.4 (22.0)	97 (42)	3.0 (1.1)	21.7 (18.2)	80 (34)
30	1st	3.3 (1.2)	39.6 (21.7)	185 (70)	4.0 (0.0)	32.1 (17.0)	176 (78)	3.7 (0.8)	35.9 (17.9)	180 (66)
	29th	3.3 (1.2)	113.1 (77.6)	532 (283)	2.0 (0.0)	168.8 (83.0)	516 (170)	2.7 (1.0)	141.0 (78.1)	524 (209)
300	1st	4.0 (0.0)	1809.5 (1145.2)	8995 (4632)	3.3 (1.2)	1357.2 (393.8)	7444 (2709)	3.7 (0.8)	1583.4 (805.0)	8220 (3498)
	29th	4.0 (0.0)	1218.8 (577.1)	9412 (3671)	2.7 (1.2)	1985.5 (552.1)	12318 (6668)	3.3 (1.0)	1602.1 (656.9)	10865 (5070)
2000	1st	8.0 (4.0)	7544.0 (823.3)	131232 (23615)	14.7 (8.3)	5730.1 (994.2)	75681 (14470)	11.3 (6.9)	6637.1 (1285.9)	103457 (35109)
	29th*	12.0 (-)	12160.4 (-)	186591 (-)	8.0 (-)	13029.1 (-)	157754 (-)	10.0 (-)	12594.8 (-)	172173 (-)

Source: NDA Module 4.2.3.2 (Study TAK-385-00107)

The toxicokinetic evaluation for the 4-week rat study above were also used to estimate the toxicokinetics for the reproductive and developmental toxicity studies in the rat, where no toxicokinetic evaluations were conducted. A high dose of 1000 mg/kg/day was determined to be the rat NOAEL in the reproductive and developmental toxicity studies, a dose that was not examined in the 4-week rat study. As such, the nonclinical reviewer extrapolated the AUC at 1000 mg/kg/day from both 2000 mg/kg and 300 mg/kg values in the following way (using the male and female combined "Total" values as listed in the table at Day 29):

AUC at 2000 mg/kg/day / 2 = AUC at 1000 mg/kg/day

AUC at 300 mg/kg/day * 3.33 = AUC at 1000 mg/kg/day

2000 mg/kg AUC = 172713 ng•h/mL / 2 = 86086 ng•h/mL at 1000 mg/kg

300 mg/kg AUC = 10865 ng•h/mL * 3.33 = 36180 ng•h/mL at 1000 mg/kg

Average of both extrapolated values = (86086 + 36180) / 2 = 61133 ng•h/mL at 1000 mg/kg

This extrapolated value is not much different from the AUC at 1000 mg/kg/d in rat at 13 weeks (79209 ng•h/mL). A 4-week extrapolated AUC was used instead of the measured 13-week AUC for the reproductive and developmental toxicity studies because a duration of 4-weeks was more representative of the dosing period than 13 weeks.

Table 4: Toxicokinetics - 4-week oral gavage toxicity study in monkeys

Dose	No. of	Male (N=3)			Female (N=3)			Total (N=6)		
		Tmax	Cmax	AUC_{0-24h}	Tmax	Cmax	AUC_{0-24h}	Tmax	Cmax	AUC_{0-24h}
(mg/kg/day)	dosing	(h)	(ng/mL)	(ng·h/mL)	(h)	(ng/mL)	(ng·h/mL)	(h)	(ng/mL)	(ng·h/mL)
5	1st	1.7 (0.6)	83.2 (56.9)	407 (270)	2.7 (1.2)	131.8 (101.1)	554 (409)	2.2 (1.0)	107.5 (78.0)	480 (320)
	28th	1.3 (0.6)	299.0 (111.3)	1383 (461)	1.3 (0.6)	234.2 (103.6)	835 (253)	1.3 (0.5)	266.6 (102.5)	1109 (448)
10	1st	1.0 (0.0)	770.1 (168.6)	3239 (392)	2.0 (1.7)	425.7 (326.7)	1731 (1207)	1.5 (1.2)	597.9 (299.4)	2485 (1152)
	28th	1.0 (0.0)	730.3 (162.6)	3132 (442)	1.0 (0.0)	565.9 (256.0)	2602 (814)	1.0 (0.0)	648.1 (211.9)	2867 (654)
20	1st	2.0 (0.0)	816.8 (402.8)	4479 (1740)	1.7 (0.6)	1424.7 (265.6)	5637 (525)	1.8 (0.4)	1120.8 (451.6)	5058 (1313)
	28th	1.7 (0.6)	1053.8 (472.7)	5078 (2172)	1.3 (0.6)	1228.6 (226.5)	5609 (819)	1.5 (0.5)	1141.2 (345.0)	5344 (1497)
100	1st	3.3 (1.2)	3965.8 (2097.6)	34184 (14773)	2.7 (1.2)	4425.3 (1000.0)	33741 (9031)	3.0 (1.1)	4195.5 (1491.1)	33963 (10954)
	28th	3.3 (1.2)	4198.7 (1120.8)	34942 (12200)	3.3 (1.2)	4554.0 (355.7)	35609 (5030)	3.3 (1.0)	4376.4 (768.7)	35276 (8354)

Mean (S.D.)

Source: NDA Module 4.2.3.2 (Study no. TAK-385-00102)

Table 5: Toxicokinetics - 26-week oral gavage toxicity study in rats

Dose	No. of	Male (N=3)			Female (N=3)			Total (N=6)		
		Tmax	Cmax	AUC_{0-24h}	Tmax	Cmax	AUC_{0-24h}	Tmax	Cmax	AUC_{0-24h}
(mg/kg/day)	dosing	(h)	(ng/mL)	(ng·h/mL)	(h)	(ng/mL)	(ng·h/mL)	(h)	(ng/mL)	(ng·h/mL)
10	1st	2.0 (0.0)	2.3 (0.7)	13 (4)	3.3 (1.2)	6.9 (8.7)	23 (21)	2.7 (1.0)	4.6 (6.1)	18 (14)
	177th	4.0 (0.0)	38.0 (15.1)	212 (70)	2.7 (1.2)	62.1 (27.0)	249 (80)	3.3 (1.0)	50.0 (23.6)	230 (70)
30	1st	4.0 (0.0)	65.4 (73.9)	350 (345)	2.0 (0.0)	94.3 (72.6)	296 (156)	3.0 (1.1)	79.9 (67.4)	323 (241)
	177th	3.3 (1.2)	246.7 (41.2)	1653 (474)	4.7 (3.1)	257.1 (86.8)	1534 (39)	4.0 (2.2)	251.9 (61.0)	1594 (308)
100	1st	4.0 (0.0)	630.7 (116.7)	2937 (860)	2.7 (1.2)	621.7 (199.8)	2771 (990)	3.3 (1.0)	626.2 (146.4)	2854 (834)
	177th	4.0 (0.0)	875.0 (518.1)	7152 (4589)	2.0 (0.0)	1199.7 (189.7)	6109 (870)	3.0 (1.1)	1037.4 (391.6)	6630 (3009)
300	1st	3.3 (1.2)	1129.1 (301.8)	6155 (1609)	4.0 (0.0)	1127.6 (107.4)	6754 (1359)	3.7 (0.8)	1128.4 (202.6)	6455 (1372)
	177th	6.0 (3.5)	2911.2 (523.5)	34077 (12262)	6.7 (4.6)	2541.1 (603.7)	26951 (1000)	6.3 (3.7)	2726.2 (603.7)	30514 (8705)

Mean (S.D.)

Source: NDA Module 4.2.3.2 (Study no. TAK-385-00145)

Table 6: Toxicokinetics - 39-week oral gavage toxicity study in monkeys

Dose	No. of	Male (N=4)			Female (N=4)			Total (N=8)		
		Tmax	Cmax	AUC_{0-24h}	Tmax	Cmax	AUC_{0-24h}	Tmax	Cmax	AUC_{0-24h}
(mg/kg/day)	dosing	(h)	(ng/mL)	(ng·h/mL)	(h)	(ng/mL)	(ng·h/mL)	(h)	(ng/mL)	(ng·h/mL)
1.5	1st	2.0 (1.4)	20.2 (10.4)	103 (44)	1.0 (0.0)	26.0 (21.0)	91 (58)	1.5 (1.1)	23.1 (15.7)	97 (48)
	273rd	1.3 (0.5)	55.7 (13.0)	264 (72)	1.3 (0.5)	50.2 (37.5)	190 (71)	1.3 (0.5)	53.0 (26.2)	227 (77)
5	1st	1.5 (0.6)	181.1 (215.1)	717 (638)	1.5 (0.6)	212.9 (59.5)	932 (201)	1.5 (0.5)	197.0 (147.1)	824 (452)
	273rd	1.8 (0.5)	230.1 (129.0)	1087 (334)	1.0 (0.0)	333.9 (56.7)	1554 (353)	1.4 (0.5)	282.0 (107.6)	1321 (404)
15	1st	2.3 (1.3)	1002.4 (485.0)	4173 (1471)	2.3 (1.3)	608.4 (376.7)	3021 (1216)	2.3 (1.2)	805.4 (453.9)	3597 (1393)
	273rd	1.8 (0.5)	989.8 (34.5)	5046 (409)	2.0 (0.0)	895.0 (95.9)	5349 (213)	1.9 (0.4)	942.4 (83.8)	5198 (343)
50*	1st	2.0 (0.0)	2815.9 (910.0)	16813 (8835)	2.5 (0.9)	2810.2 (1195.6)	16251 (6278)	2.3 (0.7)	2813.1 (1026.4)	16532 (7410)
	273rd	2.0 (0.0)	3048.5 (838.5)	19906 (6692)	3.1 (1.2)	2472.7 (1345.4)	19369 (9372)	2.6 (1.0)	2760.6 (1123.0)	19637 (7871)

Mean (S.D.)

*: Male, N=8; Female, N=8; Total, N=16

Source: NDA Module 4.2.3.2 (Study TAK-385-00144)

Clinical Pharmacokinetics
The pharmacokinetic parameters of relugolix, unconjugated estradiol, unconjugated and total estrone, and norethindrone after administration of a single dose of MYFEMBREE (fasted conditions) to healthy postmenopausal women under fasted conditions are summarized below.

Table 7: Pharmacokinetic Parameters of Relugolix, Unconjugated Estradiol, and Norethindrone After Single Dose Administration of MYFEMBREE

Parameter	Relugolix (40 mg)	Unconjugated Estradiol (1 mg)	Norethindrone (0.5 mg)
$AUC_{0\text{-}inf}$ (ng·hr/mL or pg·hr/mL), mean (SD)	198.1 (111.6)	818.7 (334.4)	17.5 (8.5)
C_{max} (ng/mL or pg/mL), mean (SD)	26.0 (18.2)	28.0 (19.2)	3.6 (1.4)
T_{max} (hr), median (min, max)	2.00 (0.25, 5.00)	7.00 (0.25, 24.00)	1.0 (0.50, 4.00)

Source: NDA Module 2.7.1, Table 19
Abbreviations: AUC = area under the concentration-time curve; $AUC_{0\text{-}inf}$ = AUC from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; E2 = estradiol; NET = norethindrone; T_{max} = time to maximum observed concentration.

Study Title: Lacteal secretion of [^{14}C]TAK-385 in rats (Study# TAK-385-1272)

Administration of a single oral dose of [^{14}C]relugolix (30 mg/kg) to fasted female rats (N=5) on lactation Day 14 demonstrated that relugolix-derived radioactivity reached peak concentrations by 2 hours post-dose in both plasma (0.441± 0.327 µg equiv/mL) and milk (4.262 ± 5.192 µg equiv./mL) (9.7-fold milk-to-plasma accumulation ratio) and decreased to levels below the LOQ (0.057 µg ± 0.038 equiv/mL) by 48 hours.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Twenty-six-week oral gavage toxicity study of TAK-385 in rats

Study no.: TAK-385-000145
Conducting laboratory and location: (b) (4)
Date of study initiation: 6 March 2007
GLP compliance: yes
QA statement: yes
Drug, lot #, and % purity: TAK-385, Lot no. M285-002, 98.7% pure

Key Study Findings

At 300 mg/kg/day (about 154-fold the exposure at the MRHD of 40 mg), minimal eosinophilic crystals in the epididymal epithelium, minimal foam cell infiltration in the testicular interstitium (indicative of phospholipidosis), minimal foam cell infiltration in the lungs (phospholipidosis), minimal scattered hepatocyte vacuolation (phospholipidosis) and minimal focal hemorrhage in the liver were observed. Minimal foam cell infiltration in the testicular interstitium (indicative of phospholipidosis) was also observed at 100 mg/kg/day (about 33.5-fold). No adverse effect levels were 30 mg/kg/day (about 8.0-fold) for males and 100 mg/kg/day for females (about 33.5-fold) based on phospholipidosis. No adverse effect levels were 100 mg/kg/day (about 33.5-fold for males and females), based on liver effects.

Methods

Doses:	0, 10, 30, 100, 300 mg/kg/day (based on mortality and phospholipidosis, with accompanying necrosis in many organs, at 2000 mg/kg/day in a 4-week oral study, with no effect at 300 mg/kg/day)
Frequency of dosing:	daily
Route of administration:	Oral, gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Crl:CD(SD) rats (Sprague-Dawley)
Number/Sex/Group:	15 (5/sex/group for recovery)
Age:	6 weeks
Weight:	188 – 236 g (males) and 145 – 225 g (females)
Satellite groups:	5/sex/group for toxicokinetics

Observations and Results

Mortality

No treatment related deaths occurred. One control (male) died in Week 15 of spontaneous lymphoid leukemia.

Clinical Signs

At 300 mg/kg/day, cloudy urine was observed from Week 15 in a few males and from Week 19 in females until the end of the administration period.

Body Weights

No treatment related effects were observed.

Feed Consumption

No treatment related effects were observed.

Ophthalmoscopy

No treatment related effects were observed.

Hematology

No treatment related effects were observed.

Clinical Chemistry

No treatment related effects were observed.

Urinalysis

At 300 mg/kg/day, urine volume was increased compared to control (110%).

Gross Pathology

Enlargement of liver and spleen, dark red foci in the lungs and excess fluid in the abdominal cavity were observed in the male (control) animal that died prematurely.

Organ Weights

At 300 mg/kg/day, absolute weight of testes (8%) and liver (females) were increased (10%).

Histopathology

In the epididymides, at 300 mg/kg/day, minimal eosinophilic crystals in the epithelium were observed in 7 animals.

In the testes, at 100 and 300 mg/kg/day, minimal foam cell infiltration in the interstitium, indicative of phospholipidosis, was observed in 7 and 13 animals, respectively.

In the lungs, at 300 mg/kg/day, minimal foam cell infiltration was observed in 8 males and 6 females (5 males and 3 females controls exhibited phospholipidosis.)

In liver, at 300 mg/kg/day, 1 male exhibited minimal scattered hepatocyte vacuolation, indicative of phospholipidosis and minimal focal hemorrhage.

Toxicokinetics

Parameter	Stage	Male - Dosage level (mg/kg/day)				Female - Dosage level (mg/kg/day)			
		10	30	100	300	10	30	100	300
Tmax (h)	1st dosing	2.0	4.0	4.0	3.3	3.3	2.0	2.7	4.0
	177th "	4.0	3.3	4.0	6.0	2.7	4.7	2.0	6.7
Cmax (ng/mL)	1st dosing	2.3	65.4	630.7	1129.1	6.9	94.3	621.7	1127.6
	177th "	38.0	246.7	875.0	2911.2	62.1	257.1	1190.7	2541.1
AUC0-24h (ng.h/mL)	1st dosing	13	350	2937	6155	23	296	2771	6754
	177th "	212	1653	7152	34077	249	1534	6109	26951

Sponsor's table

Study title: Thirty-nine-week oral gavage toxicity study of TAK-385 in monkeys with a 13-week recovery period.

Study no.:	TAK-385-00144
Conducting laboratory and location:	(b) (4)
Date of study initiation:	9 March 2007
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	TAK-385, Lot No. M285-002, 98.7% pure

Key Study Findings

At 50 mg/kg/day (about 99.1-fold the exposure at the MRHD of 40 mg, based on AUC), effects on the liver included bile plug formations and yellowish brown pigment deposition in Kupffer cells (along with increases in liver enzymes; increased alkaline phosphatase was also observed at 5 and 15 mg/kg/day without histopathological correlate.) Findings related to systemic phospholipidosis included foam cells in the lymphatic sinus of the mesenteric lymph nodes and in the lymphatic sinus of the submandibular lymph nodes, vacuolation of parietal cells in the stomach, increased tingible body macrophages (TBM) in the stomach; lymphoid follicles; bone marrow; germinal center of spleen; lymphoid follicles of the submandibular lymph nodes, mesenteric lymph nodes, cecum and colon; and in the lymphoid follicles of the duodenum, ileum and rectum. Following a 13-week recovery period, foam cells in the lymphatic sinus of the mesenteric lymph nodes, vacuolation of parietal cells in the stomach and yellowish brown pigment deposition in Kupffer cells in the liver were still evident. Decreased corpora lutea were observed in all females following dosing but were not evident following recovery.

At 15 mg/kg/day (about 26.2-fold), findings related to systemic phospholipidosis were foam cells in the lymphatic sinus of the mesenteric lymph nodes and in the lymphatic sinus of the submandibular lymph nodes, vacuolation of parietal cells in the stomach, increased TBM in the stomach, lymphoid follicles, bone marrow, germinal center of spleen, and in the lymphoid follicles of the submandibular lymph nodes, mesenteric lymph nodes, cecum and colon. Decreased corpora lutea were reported in all females.

At 5 mg/kg/day (6.7-fold), findings related to systemic phospholipidosis were limited to foam cells in the lymphatic sinus of the mesenteric lymph nodes and in the lymphatic sinus of the submandibular lymph nodes, vacuolation of parietal cells in the stomach, and increased TBM in the stomach. Decreased corpora lutea were reported in 3 of 4 females.

At 1.5 mg/kg (1.1-fold), findings related to systemic phospholipidosis were limited to the mesenteric lymph nodes.

A no adverse effect level (NOAEL) was 15 mg/kg/day (26.2-fold) based on liver toxicity. No NOAEL was observed for systemic phospholipidosis (increase in foamy cells, tangible body macrophages and cell vacuolation); minimal effects were observed at 1.5

mg/kg/day (1.1-fold.) In females, 1.5 mg/kg/day (1.1-fold) was a no effect level for decreased uterine weight and decreased corpora lutea, and 15 mg/kg/day (26.2-fold) was a no effect level for cessation of menses.

Methods

Doses:	0, 1.5. 15, and 50 mg/kg/day (based on hepatotoxicity (increased AST and ALT, bile plugs, single cell necrosis and yellowish brown pigment deposition in hepatocytes and Kupffer cells) at 100 mg/kg/day in a 4-week study
Frequency of dosing:	daily
Route of administration:	Oral, gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Monkey, cynomolgus
Number/Sex/Group:	4
Age:	3 years
Weight:	2.20 – 4.85 kg (males) and 2.00 – 3.40 kg (females)
Satellite groups:	4/sex/group in control and HD for recovery

Observations and Results

Mortality

No deaths occurred during the study.

Clinical Signs

At 50 mg/kg/day, menses (N=8 females) were not observed from Day 13 until the end of dosing. During the recovery period, menses resumed for 3 of 4 females. Cloudy (turbid) urine was observed from Week 1 until the end of dosing.

Body Weights/ Feed Consumption

No treatment related effects were observed.

Hematology

Effects included decreases in reticulocyte count and/or ratio (females,15 mg/kg: Week 26, males, 50 mg/kg: Week 39, females, 50 mg/kg: Weeks 26 and 39), decreases in neutrophil count and ratio, increases in the lymphocyte ratio (females,15 and 50 mg/kg: Week 39), with no notable changes in white blood cell count.

Hematology parameters in monkeys

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	1.5	5	15	50	0	1.5	5	15	50
HGB (g/dL)										
__pretrx	14.0	14.4	13.6	13.6	14.2	14.4	14.1	13.4	14.5	13.9
__Week 13	14.0	14.2	13.7	12.9* (8%)	13.9	13.8	13.5	13.1	14.2	13.5
__Week 26	14.1	14.0	13.7	13.0* (8%)	13.8* (2%)	13.9	13.6	13.4	14.5	14.0
__Week 39	13.7	13.9	13.6	12.9	13.6	13.7	12.9	12.8	13.8	13.4
__RWeek 13	13.4				14.2	14.1				13.2* (6%)
HCT (%)										
__pretrx	43.3	44.7	41.7	41.9	44.7	45.5	43.0	42.4	44.8	43.5
__Week 13	44.3	45.5	43.9	41.1* (7%)	44.4	44.6	42.6	43.0	46.1	43.3
__Week 26	45.7	45.2	44.1	42.7* (6%)	44.9	46.6	44.0	44.5	47.2	46.4
__Week 39	43.5	43.8	43.2	41.3	43.5	44.8	41.4	42.1	44.3	43.3
__RWeek 13	44.4				46.4	47.0				43.4* (8%)
MCH (pg)										
__pretrx	24.6	24.4	23.9	24.0	23.8	24.1	24.6	24.5	25.4	24.5
__Week 13	23.9	23.8	22.9	22.8	23.4	23.5	23.8	23.7	24.1	23.6
__Week 26	24.6	24.5	24.3	23.2* (6%)	24.1	23.8	24.2	24.5	24.7	24.0
__Week 39	24.5	24.4	23.7	23.2	23.9	23.7	24.0	24.2	24.7	24.0
__RWeek 13	23.4				23.4	22.8				23.4
Retic. (10^9/L)										
__pretrx	73.7	57.1	80.3	64.5	64.1	76.9	62.5	74.9	72.2	66.2
__Week 13	72.9	55.9	65.7	66.8	51.6	83.4	55.3	69.1	65.5	73.4
__Week 26	57.7	44.9	60.7	49.9	47.7	56.5	38.9	48.4	40.9* (28%)	39.4* (30%)
__Week 39	60.6	48.0	52.8	48.9	38.9* (36%)	53.4	43.7	50.2	50.7	39.7* (26%)
__RWeek 13	129				64.9	54.5				40.7
Retic. (%)										
__pretrx	1.3	1.0	1.4	1.1	1.1	1.3	1.1	1.4	1.3	1.2
__Week 13	1.3	0.9	1.1	1.2	0.9	1.5	1.0	1.2	1.1	1.3
__Week 26	1.0	0.8	1.1	0.9	0.9	1.0	0.7	0.9	0.7* (30%)	0.7* (30%)
__Week 39	1.1	0.9	0.9	0.9	0.7* (36%)	0.9	0.8	1.0	0.9	0.7
__RWeek 13	2.3				1.1	0.9				0.7
Neutrophil (%)										
__pretrx	35.9	25.0	36.3	39.0	25.0	41.9	38.9	44.7	29.9	44.7
__Week 13	28.1	31.2	31.8	28.8	26.8	37.2	38.1	37.1	25.0	33.0
__Week 26	33.0	29.3	27.6	32.3	28.4	34.3	38.4	35.2	20.0	27.5
__Week 39	29.8	29.4	33.3	32.2	22.4	39.3	36.6	43.0	18.2* (54%)	25.0* (36%)
__RWeek 13	20.8				17.2	30.7				34.9
Lymph. (%)										
__pretrx	59.9	70.5	58.5	56.1	69.7	52.7	55.9	50.2	65.1	50.8
__Week 13	66.5	63.8	62.9	65.9	67.1	57.1	55.5	57.7	69.8	61.5
__Week 26	62.0	66.1	67.5	62.2	65.8	59.7	55.5	59.4	74.7	66.9
__Week 39	64.8	66.3	62.5	61.0	72.3	55.1	57.2	51.8	75.7* (37%)	69.1* (25%)
__RWeek 13	73.5				77.3	63.2				59.5
Neut.(10^3/µl)										
__pretrx	3.73	2.78	3.28	3.59	3.02	6.93	4.13	5.30	3.47	5.70
__Week 13	3.85	4.69	3.53	2.80	3.50	5.54	5.26	3.87	3.31	4.60
__Week 26	4.07	3.66	2.63	2.93	3.40	4.32	4.74	3.36	2.28	2.79
__Week 39	2.84	3.27	2.94	2.54	2.47	4.85	3.88	4.19	1.83* (62%)	2.24* (54%)
__RWeek 13	2.58				1.71	2.93				3.04
Lymph.(10^3/µl)										
__pretrx	7.04	8.17	6.63	4.95	7.87	7.24	5.60	5.61	8.09	5.59
__Week 13	10.1	9.52	7.31	6.09	8.62	8.47	6.72	5.91	8.87	7.02
__Week 26	8.46	8.44	7.32	5.52	7.45	7.36	6.96	5.44	8.54	6.91
__Week 39	7.48	7.45	6.18	4.76	7.57	6.51	6.52	4.38	7.47	6.52
__RWeek 13	9.99				7.64	5.78				5.51

Clinical Chemistry

During the dosing period, alkaline phosphatase (ALP) was increased in females in the 5, 15 and 50 mg/kg/day groups, and aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total cholesterol were increased in males and females in

the 50 mg/kg/day groups (Weeks 13, 26, and 39.) Increases in phospholipids (PL) were observed at 50 mg/kg/day in males (Week 26) and females (Week 39.)

Clinical chemistry parameters in monkeys

	Males (mg/kg/day)					Females (mg/kg/day)				
	0	1.5	5	15	50	0	1.5	5	15	50
ALP (U/L)										
__pretrx	1846	1757	1548	2050	1902	1302	1632	1630	1407	1446
__Week 13	2208	1973	1803	2081	1950	1343	1398	1603*	1847*	1518*
__Week 26	2060	1601	1865	2004	1756	1098	1147	1316*	1595*	1468*
__Week 39	1912	1723	1878	1995	1868	899	974	1082	1352*	1331*
__RWeek 13	1828				2252	819				967
AST (U/L)										
__pretrx	28	22	27	25	26	28	25	29	23	28
__Week 13	26	21	22	24	44*	26	25	31	22	44*
__Week 26	25	19	21	22	45*	26	25	28	22	42*
__Week 39	24	20	24	21	48*	35	26	48	24	46*
__RWeek 13	26				31	23				24
ALT (U/L)										
__pretrx	38	28	38	37	31	42	39	45	38	48
__Week 13	34	27	36	40	169*	54	48	43	32	213*
__Week 26	31	28	27	40	177*	49	48	49	36	207*
__Week 39	31	29	34	34	201*	74	71	85	45	236*
__RWeek 13	39				26	66				40
Tchol(mg/dL)										
__pretrx	122	119	126	129	137	119	131	124	135	129
__Week 13	129	112	137	132	157*	119	132	115	146	161*
__Week 26	128	103	128	127	164*	124	135	121	146	165*
__Week 39	119	102	125	131	169*	122	127	122	149	163*
__RWeek 13	113				140	137				153
PLs (mg/dL)										
__pretrx	182	180	191	184	189	195	199	182	194	188
__Week 13	197	202	218	204	226	207	223	179	241	236
__Week 26	207	189	221	216	238	195	215	178	231	244*
__Week 39	198	188	219	204	247*	207	215	211	241	243
__RWeek 13	178				197	202				225
IP (mg/dL)										
__pretrx	5.05	4.83	4.03	4.71	5.53	3.47	4.55	3.73	3.85	3.67
__Week 13	5.56	5.06	4.79	4.54*	4.75*	4.04	4.85	4.13	4.67	4.48
__Week 26	5.22	4.20	3.83*	3.85*	4.33*	4.40	4.39	4.36	4.66	4.44
__Week 39	4.91	4.17	4.09*	3.89*	4.36*	3.31	4.04	2.71	4.46	3.59
__RWeek 13	6.62				6.56	4.21				4.63
Cl (mEq/L)										
__pretrx	109.2	108.2	112.5	111.5	109.9	108.9	110.6	111.8	109.8	108.6
__Week 13	107.7	106.5	107.8	110.1	108.7	110.2	110.9	110,0	110.1	109.7
__Week 26	109.7	112.5	110.9	111.9	111.3	110.5	111.2	111.3	110.6	112.4*
__Week 39	107.8	110.1	109.1	111.3	111.4*	109.5	111.4	111.6	111.0	111.9*
__RWeek 13	109.2				110.0	111.4				112.0

Ophthalmoscopy/ Electroretinography

No treatment related effects were observed.

ECG

No treatment related effects were observed.

Urinalysis

Cloudy urine was observed at 50 mg/kg/day.

Gross Pathology

Dark brownish discoloration of the liver was observed in 3 males and all females in the 50 mg/kg group at necropsy.

Organ Weights

Decreases in the absolute and relative weights of the ovaries were observed in females at 5, 15, and 50 mg/kg/day.

Histopathology

At 50 mg/kg/day, effects on the liver included bile plug formations and yellowish brown pigment deposition in Kupffer cells. Findings related to systemic phospholipidosis included foam cells in the lymphatic sinus of the mesenteric lymph nodes and in the lymphatic sinus of the submandibular lymph nodes, vacuolation of parietal cells in the stomach, increased tingible body macrophages (TBM) in the stomach, lymphoid follicles, bone marrow, germinal center of spleen, lymphoid follicles of the submandibular lymph nodes, mesenteric lymph nodes, cecum and colon, and in the lymphoid follicles of the duodenum, ileum and rectum. Following a 13-week recovery period, foam cells in the lymphatic sinus of the mesenteric lymph nodes, vacuolation of parietal cells in the stomach and yellowish brown pigment deposition in Kupffer cells in the liver were still evident. Decreased corpora lutea were observed in all females following dosing but were not evident following recovery.

At 15 mg/kg/day, findings related to systemic phospholipidosis were foam cells in the lymphatic sinus of the mesenteric lymph nodes and in the lymphatic sinus of the submandibular lymph nodes, vacuolation of parietal cells in the stomach, increased TBM in the stomach, lymphoid follicles, bone marrow, germinal center of spleen and in the lymphoid follicles of the submandibular lymph nodes, mesenteric lymph nodes, cecum and colon. Decreased corpora lutea were reported in all females.

At 5 mg/kg/day (6.7-fold), findings related to systemic phospholipidosis were foam cells in the lymphatic sinus of the mesenteric lymph nodes and in the lymphatic sinus of the submandibular lymph nodes, vacuolation of parietal cells in the stomach, and increased TBM in the stomach. Decreased corpora lutea were reported in 3 of 4 females.

At 1.5 mg/kg (1.1-fold), findings related to systemic phospholipidosis were limited to the mesenteric lymph nodes.

No evidence of drug related neoplasms or pre-neoplastic changes were observed after 39 weeks in monkeys.

From the Orgovyx Nonclinical Review (Claudia Miller review, 21 December 2020)

Histopathology, dosing period

	Males					Females				
Doses (mg/kg/day)	0	1.5	5	15	50	0	1.5	5	15	50
n	4	4	4	4	4	4	4	4	4	4
Bone marrow (sternum)										
Increased in tangible body macrophage										
Slight				2	3				3	4
Bone marrow (femur)										
Increased in tingible body macrophage										
Slight				2	3				3	4
Spleen										
Increased in tingible body macrophage										
Slight				3	4				1	3
Enlargement of germinal center										
Slight		2	2	1	1			1		
Lymph node, submandibular										
Foam cell in lymphatic sinus										
Slight			1	3	4				3	3
Increased in tingible body macrophage										
Slight					2				3	2
Lymph node, mesenteric										
Foam cell in lymphatic sinus										
Slight		1	2	3	4		2	4	4	3
Increased in tingible body macrophage										
Slight				1	2				1	2
Submandibular gland										
Mononuclear cell infiltration										
Slight								1	1	2
Stomach										
Hemorrhage in mucosa										
Slight		3	3		1	1	2		1	
Increased in tingible body macrophage in lymphoid follicle										
Slight				3	2			3	3	2
Vacuolation in parietal cell										
Slight			1	2	4			1	4	3
Duodenum										
Increased in tingible body macrophage in lymphoid follicle										
Slight					2					
Pigment deposition										
Slight					1					
Hemorrhage in mucosa										
Slight										1
Ileum										
Increased in tingible body macrophage in lymphoid follicle										
Slight					1					1
Cecum										
Increased in tingible body macrophage in lymphoid follicle										
Slight									1	1
Pigment deposition										
Slight										1
Colon										
Hemorrhage in mucosa										
Slight		1	1		3					
Increased in tingible body macrophage in lymphoid follicle										
Slight					3				1	
Pigment deposition										
Slight			1		1					
Moderate										1
Rectum										
Increased in tingible body macrophage in lymphoid follicle										
Slight										1
Liver										
Bile thrombus										
Slight					2					1
Moderate					2					3
Fatty change of hepatocyte, diffuse										
Slight				1	1					
Subcapsular fibrosis										
Slight		1								
Yellowish brown pigment deposition in Kupffer cell										
Slight					1					
Moderate					1					3
Severe					2					1
Pancreas										
Hemorrhage in islet										
Slight			1	2	1					
Urinary bladder										

Mononuclear cell infiltration into submucosa Slight				1						
Thyroid Mononuclear cell infiltration Slight		1			1				1	
Adrenal Hyperplasia of cortical cell, focal Slight										1
Uterus Pigment deposition in mucosa Moderate									1	
Ovary Decrease of corpus luteum								3	4	4

Recovery

	Males		Females	
Doses (mg/kg/day)	0	50	0	50
n	4	4	4	4
Spleen Enlargement of germinal center Slight				1
Lymph node, submandibular Pigment deposition in medulla Slight				1
Lymph node, mesenteric Foam cell in lymphatic sinus Slight Pigment deposition in medulla Slight		1 1		1
Stomach Hemorrhage in mucosa Slight Vacuolation in parietal cell Slight		1		1
Duodenum Mononuclear cell infiltration into lamina propia of mucosa Slight		1		
Cecum Hemorrhage in mucosa Slight		1		
Liver Fatty change of hepatocyte, diffuse Slight Mononuclear cell foci		2		
Slight Yellowish brown pigment deposition in Kupffer cell Slight Moderate Severe		1 1 1		3 2 1
Pancreas Hemorrhage in islet Slight		1		1
Urinary bladder Mononuclear cell infiltration into submucosa Slight		1		
Thyroid Increase in large follicle Moderate		1		
Cerebrum Pigment deposition Slight				1

Toxicokinetics

Parameter		1.5 mg/kg	5 mg/kg	15 mg/kg	50 mg/kg
Tmax (h)	1st	2.0:1.0	1.5:1.5	2.3:2.3	2.0:2.5
	273rd	1.3:1.3	1.8:1.0	1.8:2.0	2.0:3.1
Cmax (ng/mL)	1st	20.2:26.0	181.1:212.9	1002.4:608.4	2815.9:2810.2
	273rd	55.7:50.2	230.1:333.9	989.8:895.0	3048.5:2472.7
AUC0-24h (ng.h/mL)	1st	103:91	717:932	4173:3021	16813:16521
	273rd	264:190	1087:1554	5046:5349	19906:19369

Sponsor's table

7 Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial reversion assay with TAK-385

Study no.:	TAK-385-00093
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7 August 2006
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	M285-001, 98.4% pure

Key Study Findings

TAK-385 was judged to be negative for mutagenicity under the conditions of this study.

Methods

Strains:	*S. typhimurium* (TA98, TA100, TA1535, and TA1537) and *E. coli* (WP2 *uvrA*)
Concentrations in definitive study:	Without S9 mix: 39.1, 78.1, 156, 313, 625, 1250 and 2500 ug/plate (TA100 and TA1535) 78.1, 156, 313, 625, 1250, 2500 and 5000 ug/plate (WP2uvrA, TA98 and TA1537). With S9 mix: 39.1, 78.1, 156, 313, 625, 1250 and 2500 ug/plate (TA100, TA1535 and TA1537) 78.1, 156, 313, 625, 1250, 2500 and 5000 ug/plate (WP2uvrA) 39.1, 78.1, 156,313,625,1250, 2500 and 5000 ug/plate (TA98)
Basis of concentration selection:	Dose-finding test using 1.5, 5, 15, 50, 150, 500, 1500 and 5000 ug/plate.
Negative control:	DMSO
Positive control:	2-(2-furyl)-3-(nitro-2 furyl) acrylamide (AF-2), sodium azide (NaN3), 2-amino-anthracene (2AA) and 9-aminoacridine hydrochloride (9-AA)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Pre-incubation method in the presence or absence of S9 mix; re-incubation period was 20 minutes followed by 48 hours of incubation.

Study Validity

Positive and negative controls responded as expected, using 2 plates/dose in a dose-finding test and a main test. Criteria for positive response was number of revertant colonies being greater than 2-fold of respective control value. No precipitate was observed at any dose in the presence or absence of S9 mix.

Results

No increase in the number of revertant colonies in the treated groups exceeded twice the number in the negative control in any test strain in the presence or absence of S9, and TAK-385 was judged to be negative for mutagenicity under the conditions of this study.

In Vitro Assays in Mammalian Cells

Study title: Cytogenetic Assay with TAK-385 in Chinese Hamster Lung (CHL) Cells.

Study no.:	06-166/GE
Conducting laboratory and location:	(b) (4)
Date of study initiation:	1 June 2006
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	M285-001, 98.4%

Key Study Findings

TAK-385 did not induce chromosomal aberrations under the conditions of this study.

Methods

Cell line:	Chinese Hamster Lung (CHL) cells
Concentrations in definitive study:	For metaphase analysis: 150, 200 and 250 ug/mL, for 6 hour pulse treatment without S9 mix; 300, 350, and 400 ug/mL for 6-hour pulse with S9 mix; and 26.2, 32.8, 41, 51.2 ug/mL for 24 hour continuous treatment.
Basis of concentration selection:	Excessive cytotoxicity was observed at 24-hours without S9 at 64 µg/mL.
Negative control:	DMSO
Positive control:	Mitomycin C and cyclophosphamide
Formulation/Vehicle:	DMSO
Incubation & sampling time:	1) Pulse treatment for 6 hours without S9 mix followed by an 18-hour expression period; 2) pulse treatment for 6 hours with S9 mix followed by an 18-hour expression

	period; and, 3) continuous treatment for 24 hours without S9 mix

Study Validity

Positive and negative controls responded as expected. Two separate assays were performed, using 1000 cells (200 metaphases) in each condition tested.

Results

No increase in chromosomal aberrations was observed at any dose under any condition tested, and TAK-385 was judged to be negative for genotoxicity under the conditions of this assay.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Micronucleus Assay with TAK-385 in rats

Study no:	B060606
Conducting laboratory and location:	(b) (4)
Date of study initiation:	29 August 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	M285-001, 98.4%

Key Study Findings

TAK-385 was judged to be negative for genotoxicity under the conditions of this assay.

Methods

Doses in definitive study:	500, 1000 and 2000 mg/kg/day
Frequency of dosing:	Daily, for 2 consecutive days
Route of administration:	Oral, gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.5 w/v% methylcellulose
Species/Strain:	Crl:CD(SD) rat, male, 7 weeks old
Number/Sex/Group:	5
Basis of dose selection:	No mortalities or clinical signs were observed. Body weight gain tended to be lower at 2000 mg/kg.
Negative control:	0.5 w/v% methylcellulose
Positive control:	cyclophosphamide

Study Validity

Bone marrow samples were collected 24 hours after final dose administration and 2000 immature erythrocytes (MNIEs) were examined. Positive and negative controls responded as expected.

Results

No increased incidence of micronucleated immature erythrocytes (MNIEs) was observed, and TAK-385 was judged to be negative for genotoxicity under the conditions of this assay.

Other Genetic Toxicity Studies

Impurities (b) (4) were assessed for their mutagenic potential using Multiple Computer Automated Structure Evaluation, MCASE (version 2.00; database module:A20, Salmonella Mutagenicity- NTP & A2C, Salmonella Mutagenicity – Gene Tox.) and Deductive Estimation of Risk from Existing Knowledge, DEREK for Windows (version 11.0.0 + Takeda 2.0). (b) (4) was not evaluated because its level in the drug product was significantly below the identification threshold as per ICH Q3B(R2). Based on these analyses, (b) (4) was found to possess mutagenic potential, and (b) (4) were negative in all in silico evaluations. A battery of in vitro and in vivo genotoxicity studies was conducted with (b) (4). Although (b) (4) was shown to be mutagenic in bacteria in the presence of rat S9 fractions (TAK-385-10011), additional in vitro genotoxicity studies in mammalian cells and in vivo studies in rodents with this impurity were negative (TAK-385-10075, TAK-385-10093, TAK-385-10081, and TAK-385-10082), and a weight-of-evidence evaluation concluded that the impurity (b) (4) did not pose a genotoxic risk for human subjects when present at levels up to (b) (4) µg/day. (b) (4)

8 Carcinogenicity

Study title: Twenty-four-month oral gavage carcinogenicity study of TAK-385 in mice.

Study no.:	TAK-385-10217
Study report location:	eCTD SDN 5
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 13, 2009 (Start of dosing: January 27, 2009 (Male) and January 29, 2009 (Female)
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	TAK-385, Lot number M285-005, 98.8% pure
CAC concurrence:	17 November 2008 protocol review

Key Study Findings

There were no dose-related increases in tumor incidence in either sex.

A statistically significant dose-related decrease in survival was seen in males but not in females. The pairwise comparisons did not show statistically significant increases in mortality in the treated groups compared to the vehicle control in either males or females.

A no effect level was 30 mg/kg/day for males, based on decreased survival and 100 mg/kg/day in females (highest dose tested.)

Adequacy of Carcinogenicity Study

Study design was adequate with the highest dose set at about 142-fold the exposure of a clinical dose of 40 mg/day via AUC.

Appropriateness of Test Models

The mouse is a commonly used model for 2-year assays.

Evaluation of Tumor Findings

No treatment-related neoplasms were observed.

Methods

Doses:	0, 10, 30, and 100 mg/kg/day
Frequency of dosing:	daily
Dose volume:	10 ml/kg
Route of administration:	Oral, gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution
Basis of dose selection:	In a preliminary 13-week oral gavage toxicity study conducted by the test facility (Study No. B061815; dose levels: 0, 200, 600, and 2000 mg/kg/day; 10 animals/sex/group), no abnormal clinical signs or obvious changes in the body weight or food consumption were noted at any dosage level. Slight anemic changes in the hematology test and the following histological changes were noted at 2000 mg/kg/day; necrosis of the tubular epithelium and basophilic tubule in the kidney, increased extramedullary hematopoiesis in the spleen, hyperplasia of the mucosal epithelium and inflammatory cell infiltration in the cecum and colon, and increased granulocytic hematopoietic cell in the bone marrow.
Species/Strain:	Mouse, B6C3F1 (b) (4)
Number/Sex/Group:	55 for the main s y
Age:	6 weeks; 21.5 to 25.6 g for males and 16.6 to 21.9 g for females
Animal housing:	Individual
Satellite groups:	17/sex/group for toxicokinetics on day 1 (4 for the day 1 toxicokinetic control group), and 28/sex/group for toxicokinetics at week 53 (8 for the week 53 toxicokinetic control group)

Observations and Results

Mortality

In males, a statistically significant dose-related decrease in survival was seen males. Survival was 85.4% 83.6%, 78.2%, and 70.9% for 0, 10, 30, and 100 mg/kg/day groups, respectively, and was within (or higher than) the background range of 58 to 74%. There were no treatment-related effects on mortality during the treatment period in females.

Number of animals that died or were euthanized in moribund condition

Sex	Male				Female			
Dose (mg/kg/day)	0	10	30	100	0	10	30	100
Number of animals	55	55	55	55	55	55	55	55
Death	3	2	7	3	3	4	1	1
Euthanized in moribund	5	7	5	13	10	10	15	9
Total/group	8	9	12	16	13	14	16	10
Survival rate (%)	85.4	83.6	78.2	70.9	76.4	74.5	70.9	81.8

Sponsor's table

Cause of death

Sex	Male				Female			
Dose (mg/kg/day)	0	10	30	100	0	10	30	100
Number of death or moribund sacrifice	8	9	12	16	13	14	16	10
Neoplastic								
Abdominal cavity								
Hemangiosarcoma	0	1	0	0	0	0	0	0
Rhabdomyosarcoma	0	0	0	0	1	0	0	0
Bone								
Osteosarcoma	1	0	0	0	0	0	0	0
Bone marrow, femur								
Hemangiosarcoma	0	0	0	0	0	0	1	0
Hematopoietic organ								
Histiocytic Sarcoma	1	0	0	2	2	2	3	2
Malignant lymphoma	1	3	4	4	3	5	3	3
Myeloid leukemia	0	0	0	0	0	1	0	0
Liver								
Hemangiosarcoma	1	0	0	0	0	0	1	0
Hepatocellular adenoma	1	0	0	0	0	0	0	0
Hepatocellular carcinoma	1	1	1	3	0	0	0	1
Mammary gland								
Mixed tumor, malignant	0	0	0	0	0	0	2	0
Oral cavity								
Squamous cell papilloma	1	0	0	0	0	0	0	0
Small intestine, duodenum								
Adenoma	0	1	0	0	0	0	0	0
Spleen								
Hemangiosarcoma	0	1	0	0	1	1	1	0
Subcutis								
Basal cell carcinoma	0	0	0	0	0	0	0	1
Fibrosarcoma	0	0	0	1	1	1	1	2
Fibrosarcoma, microchip related	0	1	0	2	4	2	2	0
Paraganglioma, malignant	0	0	0	1	0	0	0	0
Sarcoma, NOS, microchip related	0	0	1	0	0	0	0	0
Thoracic cavity								
Osteosarcoma	0	0	0	0	0	0	1	0
Non-neoplastic								
Glomerulopathy, hyaline	0	0	0	1	0	0	0	0
Hepatic necrosis	0	0	1	0	0	0	0	0
Peritonitis	0	0	0	0	0	0	1	0
Non-neoplastic								
Pyelonephritis	0	0	0	1	0	0	0	0
Panniculitis	0	1	0	0	0	0	0	0
Urological syndrome	1	0	5	1	0	0	0	0
Unknown	0	0	0	0	1	2	0	1

Sponsor's table

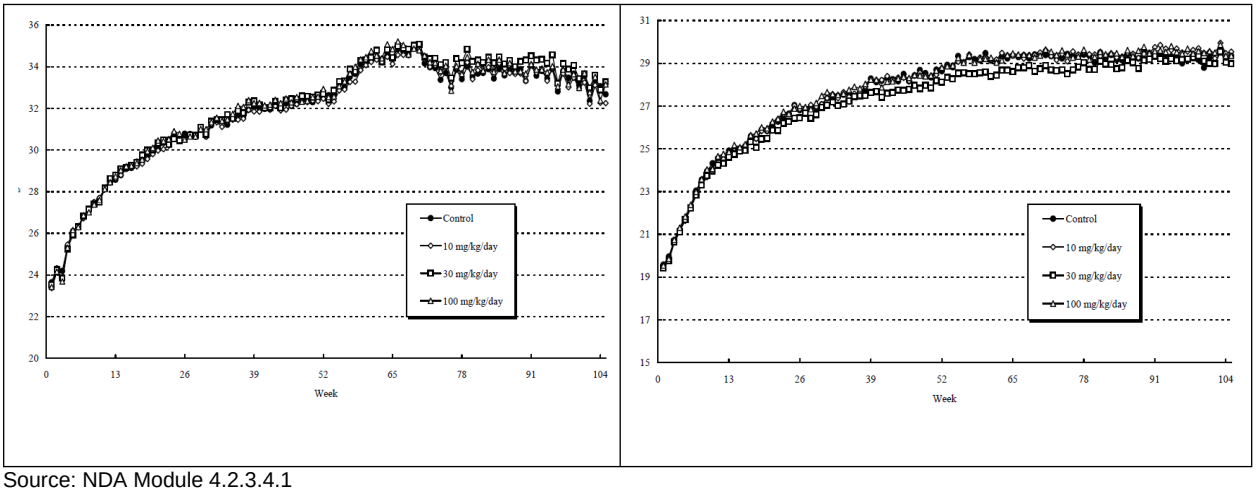
Clinical Signs

No treatment related effects were observed.

Body Weights

No treatment related effects were observed.

Body Weight in Males **Body Weight in Females**



Source: NDA Module 4.2.3.4.1

Feed Consumption

No treatment related effects were observed.

Gross Pathology

No treatment related effects were observed.

Histopathology

Neoplastic

Incidence of neoplasm

No treatment related effects were observed.

Sex	Male				Female			
Dose (mg/kg/day)	0	10	30	100	0	10	30	100
Number of animals	55	55	55	55	55	55	55	55
Total number of animals with neoplasm	41	41	33	40	40	34	31	36
Animals with multiple neoplasm	14	15	14	16	16	16	9	13
Animals with benign neoplasm	24	24	21	22	22	17	13	19
Animals with malignant neoplasm	25	31	20	27	29	27	23	20
Animals with metastatic neoplasm	12	14	11	16	22	20	11	13
Total number of neoplasm	57	64	51	65	67	58	43	50
Number of benign neoplasm	25	25	26	27	29	22	14	26
Number of malignant neoplasm	32	39	25	38	38	36	29	24

Sponsor's table

Vascular neoplasms in the femur bone marrow

Sex	Male				Female			
Dose (mg/kg/day)	0	10	30	100	0	10	30	100
Number of animals	55	55	55	55	55	55	55	55
Hemangioma	0	0	0	2*	0	0	0	0
Hemangiosarcoma	2	1	1	1	1	2	3	1
Hemangioma and/or hemangiosarcoma	2	1	1	3	1	2	3	1

*: Statistically significant ($p<0.05$)
Sponsor's table

Vascular neoplasm in any organs/tissues

Sex	Male				Female			
Dose (mg/kg/day)	0	10	30	100	0	10	30	100
Number of animals	55	55	55	55	55	55	55	55
Hemangioma	3	0	1	3	2	1	2	0
Hemangiosarcoma	7	5	3	3	3	5	3	2
Hemangioma and/or hemangiosarcoma	9	5	4	5	4	5	5	2

Sponsor's table

Non Neoplastic

No treatment related effects were observed.

Toxicokinetics

TK parameters (TAK-385; M:F)		Dose (mg/kg/day)		
		10	30	100
T_{max} (h)	Initial	1.0 : 1.0	1.0 : 1.0	2.0 : 2.0
	Week 53	1.0 : 2.0	1.0 : 1.0	1.0 : 2.0
C_{max} (ng/mL)	Initial	540.8 : 470.0	3034.8 : 2666.4	7357.5 : 7424.9
	Week 53	65.7 : 278.4	1737.9 : 1358.5	7255.3 : 9190.7
$AUC_{0\text{-}24\,h}$ (ng·h/mL)	Initial	1277 : 927	8331 : 6340	26791 : 27446
	Week 53	327 : 659	3371 : 3974	23954 : 32279

Sponsor's table

Dosing Solution Analysis

The test article was confirmed to be stable and homogeneous in the 1, 10, and 100 mg/mL formulations after storage for (b) (4)

At the initial (January 23, 2009), intermediate (January 25, 2010), and final (January 25, 2011) preparation, the dosing formulations were subjected to analysis to confirm the concentration and homogeneity of the test article by HPLC. Each dosing formulation was analyzed for 3 samples collected from the top, middle, and bottom layers.
As the results, the concentration and homogeneity of all dosing formulations satisfied the acceptable criteria (concentration: intended concentration (b) (4)%; C.V.: within (b) (4)%).

Study title: Twenty-four-month oral gavage carcinogenicity study of TAK-385 in rats.

Study no.:	TAK-385-10218
Study report location:	eCTD SDN 5
Conducting laboratory and location:	(b) (4)
Date of study initiation:	3 December 2008 (Start of dosing: December 17, 2008)
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	TAK-385, Lot Number M285-005, 98.8% pure
CAC concurrence:	17 November 2008 protocol review

Key Study Findings

There were no dose-related increases in tumor incidence in either sex.

A statistically significant dose-related decrease in survival was seen in males but not in females. The pairwise comparisons in males also showed statistically significant increases in mortality in the treated groups compared to the vehicle control.

Phospholipidosis (intracytoplasmic vacuoles in the affected parenchymal cells, infiltration of foamy macrophages and/or enlarged/pigmented macrophages) was observed at 200 mg/kg and above in males and at 600 mg/kg in females.

Nephrotoxicity was observed at 600 mg/kg.

The no-observed-effect-level (NOEL) was 30 mg/kg/day for males and 200 mg/kg/day for females.

Adequacy of Carcinogenicity Study

The study design was adequate with the high dose based on maximum tolerated dose in a 12-week study. The highest dose was about 423-fold the exposure of a clinical dose of 40 mg/day, based on AUC.

Appropriateness of Test Models

The rat is a commonly used model in 2-year studies.

Evaluation of Tumor Findings

No treatment-related neoplasms were observed.

Methods

Doses:	0, 10, 30, 200 and 600 mg/kg/day
Frequency of dosing:	daily
Dose volume:	10 ml/kg
Route of administration:	Oral, gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose
Basis of dose selection:	Based on mortality at 2000 mg/kg in the 4-week study, the highest dosage level was set at 600 mg/kg/day. The high, middle and low dosage levels were set at 200, 30 and 10 mg/kg/day.
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	60
Animal housing:	individual
Paradigm for dietary restriction:	NA
Interim sacrifice:	NA
Satellite groups:	5/sex/group for toxicokinetics
Deviation from study protocol:	In females in the control and at 600 mg/kg, survivors decreased to 19 in Week 100 of administration and were expected to decrease to less than 15 before reaching Week 104 of administration; all surviving females in each test group were therefore sacrificed in Week 102 (after 101-week administration period). No eCAC concurrence was located in DARRTS.

Observations and Results

Mortality

A statistically significant dose-related decrease in survival was seen in males but not in females. The pairwise comparisons in males also showed statistically significant increases in mortality in the treated groups compared to the vehicle control.

Test article	Control*	TAK-385			
Dosage level (mg/kg/day)	0	10	30	200	600
Mortality (M:F)	26:42	40:35	41:35	40:37	35:42
Dosing period (weeks) (M:F)	104:101	104:101	104:101	104:101	104:101
Survival rate (%) (M:F)	56.7:30.0	33.3↓:41.7	31.7↓:41.7	33.3↓:38.3	41.7↓:30.0

Sponsor's table

Presumptive cause of death

Sex	Male					Female				
Dosage level (mg/kg/day)	0	10	30	200	600	0	10	30	200	600
No. of animals	60	60	60	60	60	60	60	60	60	60
No. of deaths	26	40	41	40	35	42	35	35	37	42
Tumor										
Adrenocortical tumor	0	1	0	0	0	0	1	0	0	0
Adrenomedullary tumor	0	0	0	2	0	0	0	0	0	0
Blood vessel tumor	0	0	0	0	1	0	0	0	0	0
Bone tumor	2	1	1	1	0	0	0	0	0	0
Histiocytic tumor	1	1	0	2	1	0	0	2	1	0
Leukemia, large granular lymphocytic	1	2	1	0	1	0	0	0	0	0
Leukemia, myeloid	0	0	1	0	1	0	0	0	0	1
Liver tumor	0	1	0	0	0	0	0	0	0	0
Mammary tumor	0	0	0	0	0	4	7	8	1	8
Malignant lymphoma	1	0	1	0	2	0	0	0	0	0
Neural tumor	0	0	0	0	1	0	0	0	0	0
Oral tumor	0	0	0	0	0	1	1	0	0	0
Pancreatic tumor	0	0	1	0	0	0	0	0	0	0
Pituitary tumor	10	13	18	12	10	34	24	22	32	29
Zymbal gland tumor	0	2	0	0	0	3	0	0	1	1
Prostate tumor	0	2	1	0	1	0	0	0	0	0
Subcutaneous tumor	1	3	0	5	1	0	0	0	0	2
Synovial tumor	0	0	0	0	0	0	0	1	0	0
Thymic tumor	1	0	0	0	1	0	0	0	0	0
Thyroid C cell tumor	0	0	0	0	1	0	0	0	0	0
Uterine tumor	/	/	/	/	/	0	1	0	0	0
Brain tumor	1	0	1	0	0	0	0	0	0	0
Non-tumor										
Poor clinical condition	3	1	2	1	8	0	1	2	1	1
Circulatory disturbance	0	1	0	1	0	0	0	0	0	0
Pituitary lesion	0	0	1	0	0	0	0	0	0	0
Brain lesion	0	0	1	0	0	0	0	0	0	0
DIC*	1	0	3	0	0	0	0	0	0	0
Foot lesion	3	2	4	2	3	0	0	0	0	0
Gastrointestinal lesion	0	1	0	0	0	0	0	0	0	0
Renal lesion	0	1	1	2	0	0	0	0	1	0
Sepsis	0	0	1	2	1	0	0	0	0	0
Urogenital tract lesion	0	1	1	4	1	0	0	0	0	0
Unclear	1	7	2	6	1	0	0	0	0	0

Values in the table indicate the number of animals that died/or were sacrificed as moribund due to respective lesions. /: Not applicable
*: Disseminated intravascular coagulation
Sponsor's table

Clinical Signs

No treatment-related clinical signs were observed.

No treatment-related palpable masses were observed.

Incidence summary of major clinical signs

Sex	Male					Female				
Dosage level (mg/kg/day)	0	10	30	200	600	0	10	30	200	600
No. of animals	60(26)	60(40)	60(41)	60(40)	60(35)	60(42)	60(35)	60(35)	60(37)	60(42)
Decrease, spontaneous movement	15(14)	23(23)	25(24)	15(15)	20(20)	32(31)	23(23)	24(24)	29(28)	34(33)
Prone/Lateral position	5(5)	4(4)	7(7)	6(6)	8(8)	5(5)	4(4)	4(4)	3(3)	6(6)
Bradypnea	17(17)	26(26)	25(25)	18(18)	25(25)	33(33)	21(21)	25(25)	29(29)	36(36)
Hypothermia	6(6)	4(4)	7(7)	6(6)	8(8)	3(3)	5(5)	5(5)	6(6)	8(8)
Paleness, skin	3(2)	7(7)	4(4)	7(6)	5(3)	3(3)	8(7)	9(7)	1(1)	7(7)
Swelling, hind limb and/or fore limb	7(2)	6(1)	11(9)	4(3)	8(5)	1(0)	2(0)	2(1)	2(0)	5(2)

Numbers in the table indicate the total number of animals with respective findings and numbers in parentheses indicate the number of the animals that died or were sacrificed as moribund.
Sponsor's table

Summary of palpable mass-bearers

Sex	Male					Female				
Dosage level (mg/kg/day)	0	10	30	200	600	0	10	30	200	600
No. of animals	60(26)	60(40)	60(41)	60(40)	60(35)	60(42)	60(35)	60(35)	60(37)	60(42)
Palpable mass	7(2)	15(11)	5(1)	13(8)	9(4)	32(20)	33(21)	40(23)	29(16)	33(23)
Callosity, limb plantar	38(14)	34(19)	34(22)	25(16)	30(11)	4(1)	6(2)	10(6)	8(1)	13(6)

Numbers in the table indicate the total number of animals with respective findings and numbers in parentheses indicate the number of the animals that died or were sacrificed as moribund.
Sponsor's table

Body Weights

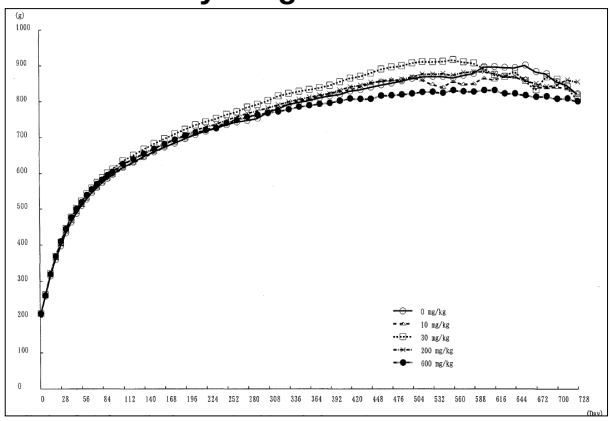
No treatment-related changes were observed; however, low body weight (slight, transient) was observed in males at 600 mg/kg between Weeks 86 and 94 (Days 602 and 658).

Summary of body weight

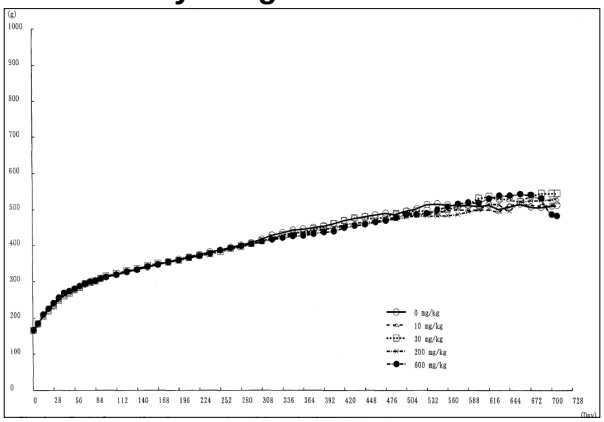
Sex	Dosage level (mg/kg/day)	Body weight [a)]				
		Week 13 (Day 91)	Week 26 (Day 182)	Week 52 (Day 364)	Week 78 (Day 546)	Week 104/101 (Day 728/707)
Male	0	586 ± 52	685 ± 72	804 ± 104	871 ± 137	822 ± 128
	10	585 ± 52	685 ± 71	808 ± 97	841 ± 101	824 ± 158
	30	601 ± 52	710 ± 74	834 ± 110	913 ± 139	807 ± 185
	200	592 ± 52	696 ± 68	813 ± 93	879 ± 105	855 ± 102
	600	595 ± 59	694 ± 79	790 ± 104	825 ± 110	801 ± 117
Female	0	309 ± 30	354 ± 39	447 ± 60	518 ± 93	514 ± 119
	10	310 ± 24	355 ± 35	433 ± 66	491 ± 78	522 ± 102
	30	309 ± 29	354 ± 36	439 ± 56	493 ± 89	547 ± 88
	200	309 ± 28	355 ± 35	437 ± 61	484 ± 98	534 ± 111
	600	308 ± 21	355 ± 31	428 ± 54	501 ± 82	484 ± 131

a): Mean ± S.D. (unit: g)
Sponsor's table

Body weight in Males



Body Weight in Females



Source: NDA Module 4.2.3.4.1

Feed Consumption

No treatment-related changes were observed.

Gross Pathology

An increased incidence of white foci in the lung was observed in both sexes at 600 mg/kg.

Incidence summary of treatment-related gross finding

Sex	Male					Female				
Dosage level (mg/kg/day)	0	10	30	200	600	0	10	30	200	600
No. of animals	60	60	60	60	60	60	60	60	60	60
Lung										
Focus, white	2	6	3	5	34	5	2	5	3	34

Sponsor's table

Histopathology

Neoplastic

There were no treatment-related increases in number of tumors.

Number of tumors and tumor bearers

Sex	Male					Female				
Dosage level (mg/kg/day)	0	10	30	200	600	0	10	30	200	600
No. of animals	60	60	60	60	60	60	60	60	60	60
No. of tumors	148	110	115	122	125	168	190	170	177	188
No. of benign tumors	120	87	91	96	96	114	117	101	118	126
No. of malignant tumors	28	23	24	26	29	54	73	69	59	62
No. of tumor bearing animals	57	57	54	49	53	59	58	60	59	60
No. of benign tumor bearers	49	50	50	46	45	57	56	53	56	55
No. of malignant tumor bearers	22	22	22	20	23	32	36	38	31	37
No. of multiple tumor bearers	39	33	35	38	36	46	46	45	42	45

Sponsor's table

Incidence summary of mammary tumor and subcutaneous

Sex	Female				
Dosage level (mg/kg/day)	0	10	30	200	600
No. of animals	60	60	60	60	60
Mammary gland					
Adenoma	0	0	1	1	1
Fibroadenoma	19	15	16	15	15
Fibroma	1	0	1	1	1
Adenolipoma	1	0	0	0	0
Adenocarcinoma arising in fibroadenoma	11	11	16	13	17
Adenocarcinoma	23	22	25	16	18
Mixed tumor, malignant	0	7*	3	1	5
Total with tumors including epithelial element	38	38	42	36	37
Total with tumors including mesenchymal element	25	28	30	25	27
Total with benign tumors	20	15	18	16	17
Total with malignant tumors	27	30	35	26	33
Total with tumors	38	38	42	36	37
Skin/subcutis					
Fibroma	0	0	0	0	1
Fibrosarcoma	0	0	0	0	2

Numbers in the table indicate the number of animals with respective tumors. *: p<0.01 (significantly different from the control group, common, Peto's test)
Sponsor's table

Historical data of malignant mixed tumor in the mammary gland

Recent 5 studies (total 310 females) [a]			Previous 9 studies (total 580 females) [b]		
N [c]	Rate (%)		N [c]	Rate (%)	
	Range	Average		Range	Average
8	1.4 - 3.3	2.6	1	0 - 1.7	0.2

a): Pathological examination ended between 2010 and 2011
b): Pathological examination ended between 2006 and 2010
c): No. of animals with respective tumor
Sponsor's table

An additive group composed of malignant elements originating from both epithelial and mesenchymal components, designated as "malignant mixed tumor," was observed in 0, 7, 3, 1 and 5 females at 0, 10, 30, 200 and 600 mg/kg, respectively. A tendency toward increase in incidence was observed in the 10, 30 and 600 mg/kg groups but not in the 200 mg group. Neither the sponsor nor the CDER statistical reviewer found a positive trend (P=0.2010), and in pairwise comparison, statistical significance was noted only at 10 mg/kg (P=0.0042). The incidence rates of malignant mixed tumor (11.7, 5.0 and 8.3%), were outside of the range of historical control data in the same laboratory in the last 5 years (0 - 3.3%, 890 females from 14 studies; average incidence rate 1.01%.)(The laboratory incidence in control animals has recently increased and the average incidence rate in historical control data from recent 5 studies was 2.6%, whereas that from previous 9 studies was 0.2%.) Malignant mixed tumor in the mammary gland observed in females at 10, 30 and 600 mg/kg was considered by the sponsor, nonclinical reviewer, and statisticians not to be treatment-related.

There was no significant effect of treatment on the incidence of other types of mammary tumors, subcutaneous fibroma or subcutaneous fibroadenoma, or in the combined incidences of mammary tumors including epithelial element (adenoma, fibroadenoma, adenolipoma, adenocarcinoma, adenocarcinoma arising in fibroadenoma and malignant

mixed tumor), mammary tumors including mesenchymal element (fibroadenoma, fibroma, adenolipoma, adenocarcinoma arising in fibroadenoma and malignant mixed tumor), all benign mammary tumors (adenoma, fibroadenoma, fibroma and adenolipoma), all malignant mammary tumors (adenocarcinoma, adenocarcinoma arising in fibroadenoma and malignant mixed tumor) or all mammary tumors.

Non Neoplastic

Treatment-related non-tumor findings were observed in the lungs (bronchus), trachea, kidneys, urinary bladder, stomach, duodenum, cecum, liver, pancreas, sublingual glands, submandibular glands, femoral and sternal bone marrow, spleen, mesenteric lymph node, submandibular lymph node, thymus, testes, epididymides, seminal vesicle, prostate, adrenals and femoral muscle.

Findings consistent with a diagnosis of phospholipidosis, characterized by intracytoplasmic vacuoles in the affected parenchymal cells, infiltration of foam cells (foamy macrophages) and enlarged/pigmented macrophages in various organs/tissues were observed for both sexes at 600 mg/kg.

Incidence summary of treatment-related non-tumors

Sex	Male					Female				
Dosage level (mg/kg/day)	0	10	30	200	600	0	10	30	200	600
No. of animals	60(26)	60(40)	60(41)	60(40)	60(35)	60(42)	60(35)	60(35)	60(37)	60(42)
Lung (bronchus)										
Foam cell infiltration, alveolar	28(10)	17(9)	22(14)	27(19)	54(32)	27(18)	23(13)	23(14)	30(20)	52(35)
minimal	26(10)	14(7)	21(13)	21(13)	17(12)	24(17)	20(11)	21(13)	26(18)	20(14)
mild	2(0)	3(2)	1(1)	6(6)	34(17)	3(1)	3(2)	2(1)	4(2)	32(21)
moderate	0	0	0	0	3(3)	0	0	0	0	0
Vacuolation, epithelium, alveolar	2(1)	1(1)	0	5(3)	46(26)	1(0)	0	0	2(1)	30(20)
minimal	1(0)	1(1)	0	4(2)	39(20)	1(0)	0	0	2(1)	29(19)
mild	1(1)	0	0	1(1)	7(6)	0	0	0	0	1(1)
Lipoproteinosis, alveolar	1(0)	1(1)	1(0)	4(3)	38(22)	7(3)	5(3)	2(1)	3(1)	37(23)
minimal	1(0)	1(1)	1(0)	4(3)	22(13)	7(3)	3(1)	1(0)	3(1)	15(9)
mild	0	0	0	0	14(8)	0	2(2)	1(1)	0	18(12)
moderate	0	0	0	0	2(1)	0	0	0	0	4(2)
Vacuolation, epithelium, bronchiolar	0	0	0	0	6(5)	0	0	0	0	1(1)
minimal	0	0	0	0	6(5)	0	0	0	0	1(1)
Trachea										
Vacuolation, epithelium, gland	0	0	0	0	2(2)	0	0	0	0	0
minimal	0	0	0	0	2(2)	0	0	0	0	0
Kidney										
Vacuolation, tubular cell	5(3)	4(4)	2(2)	8(8)	21(19)	5(5)	4(3)	1(1)	3(2)	17(14)
minimal	5(3)	4(4)	2(2)	8(8)	7(5)	4(4)	4(3)	1(1)	3(2)	13(10)
mild	0	0	0	0	10(10)	1(1)	0	0	0	4(4)
moderate	0	0	0	0	4(4)	0	0	0	0	0
Inflammation, focal, subcapsular	0	0	0	0	5(5)	0	0	0	0	0
minimal	0	0	0	0	1(1)	0	0	0	0	0
mild	0	0	0	0	4(4)	0	0	0	0	0
Hyaline droplet, tubular cell	3(2)	3(3)	2(2)	4(4)	18(15)	0	1(1)	4(4)	2(1)	6(6)
minimal	3(2)	2(2)	1(1)	2(2)	15(12)	0	1(1)	1(1)	2(1)	4(4)
mild	0	1(1)	1(1)	2(2)	0	0	0	3(3)	0	2(2)
moderate	0	0	0	0	3(3)	0	0	0	0	0
Urinary cast, granular	0	1(1)	0	0	11(11)	0	0	1(1)	0	2(2)
minimal	0	0	0	0	7(7)	0	0	1(1)	0	2(2)
mild	0	1(1)	0	0	4(4)	0	0	0	0	0
Hyperplasia, epithelium, papilla	15(3)	13(11)	11(8)	18(15)	41(25)	24(17)	21(13)	23(12)	23(14)	30(21)
minimal	14(2)	8(8)	11(8)	18(15)	23(17)	19(14)	20(12)	22(11)	19(12)	27(18)
mild	1(1)	5(3)	0	0	18(8)	5(3)	0	1(1)	4(2)	3(3)
moderate	0	0	0	0	0	0	1(1)	0	0	0
Hyperplasia, collecting duct, papilla	25(17)	25(23)	26(21)	31(29)	43(30)	22(17)	16(15)	15(13)	24(21)	21(18)
minimal	24(16)	19(17)	18(14)	22(21)	24(12)	21(16)	13(12)	11(9)	19(17)	18(15)
mild	1(1)	6(6)	8(7)	9(8)	19(18)	1(1)	3(3)	4(4)	5(4)	3(3)
Vacuolation, transitional cell	0	0	1(1)	0	6(5)	0	0	0	0	1(1)
minimal	0	0	1(1)	0	6(5)	0	0	0	0	1(1)
Urinary bladder										
Vacuolation, transitional cell	0	0	0	0	4(4)	0	0	0	0	0
minimal	0	0	0	0	2(2)	0	0	0	0	0
mild	0	0	0	0	2(2)	0	0	0	0	0

Stomach										
Vacuolation, epithelium, mucosal, glandular stomach	0	0	0	0	6(6)	0	0	0	0	4(4)
minimal	0	0	0	0	4(4)	0	0	0	0	4(4)
mild	0	0	0	0	2(2)	0	0	0	0	0
Intestine, duodenum										
Vacuolation, epithelium, gland	0	0	0	0	2(2)	0	0	0	0	2(2)
minimal	0	0	0	0	2(2)	0	0	0	0	2(2)
Intestine, cecum	n=59(25)	n=58(38)	n=56(37)	n=56(36)		n=59(41)	n=58(33)	n=54(29)	n=56(33)	
Vacuolation, epithelium, mucosal	0	2(2)	0	1(1)	9(8)	0	0	0	0	3(3)
minimal	0	2(2)	0	1(1)	9(8)	0	0	0	0	3(3)
Liver										
Vacuolation, epithelium, bile duct	0	0	0	0	43(26)	0	0	0	0	43(32)
minimal	0	0	0	0	38(21)	0	0	0	0	42(31)
mild	0	0	0	0	5(5)	0	0	0	0	1(1)
Vacuolation, Kupffer cell	0	0	0	0	3(3)	0	0	0	0	1(1)
minimal	0	0	0	0	2(2)	0	0	0	0	1(1)
mild	0	0	0	0	1(1)	0	0	0	0	0
Vacuolation, hepatocyte, pericanalicular	0	0	0	0	6(6)	0	0	0	0	1(1)
minimal	0	0	0	0	2(2)	0	0	0	0	0
mild	0	0	0	0	4(4)	0	0	0	0	1(1)
Altered cell focus, tigroid	28(7)	30(15)	28(15)	23(12)	42(19)	47(32)	45(23)	44(24)	49(30)	51(33)
minimal	28(7)	29(15)	28(15)	22(12)	37(19)	37(28)	32(18)	38(24)	45(28)	39(29)
mild	0	1(0)	0	1(0)	5(0)	9(4)	13(5)	6(0)	4(2)	10(4)
moderate	0	0	0	0	0	1(0)	0	0	0	2(0)
Pancreas										
Vacuolation, acinar cell	0	0	1(1)	0	9(9)	0	0	0	0	2(2)
minimal	0	0	1(1)	0	5(5)	0	0	0	0	1(1)
mild	0	0	0	0	4(4)	0	0	0	0	1(1)
Salivary gland, sublingual										
Vacuolation, acinar cell	0	0	0	0	4(4)	0	0	0	0	0
minimal	0	0	0	0	4(4)	0	0	0	0	0
Salivary gland, submandibular										
Hypertrophy, acinar cell	12(9)	16(15)	13(12)	17(12)	33(21)	25(25)	19(14)	23(22)	22(21)	21(18)
minimal	9(6)	14(13)	13(12)	17(12)	27(17)	22(22)	18(13)	19(18)	20(19)	18(15)
mild	3(3)	2(2)	0	0	6(4)	3(3)	1(1)	4(4)	2(2)	3(3)
Femoral bone marrow										
Infiltration, enlarged macrophage	0	0	0	0	13(12)	0	0	0	0	3(3)
minimal	0	0	0	0	5(4)	0	0	0	0	2(2)
mild	0	0	0	0	8(8)	0	0	0	0	1(1)
Sternal bone marrow										
Infiltration, enlarged macrophage	0	0	0	0	12(12)	0	0	0	0	2(2)
minimal	0	0	0	0	9(9)	0	0	0	0	2(2)
mild	0	0	0	0	3(3)	0	0	0	0	0

Numbers in the table indicate the total number of animals with respective findings and numbers in parentheses indicate the number of the animals that died or were sacrificed
Sponsor's table

Findings suggesting nephrotoxicity were observed for both sexes at 600 mg/kg.

Foam cell infiltration in the interstitium and brown pigmented macrophages in the testes and eosinophilic crystals in the epithelium in the cauda in the epididymides were observed at 200 mg/kg.

A no-observed-effect-level (NOEL) was estimated to be 30 mg/kg/day for males and 200 mg/kg/day for females.

Toxicokinetics

Dosage level (mg/kg/day)		0	10	30	200	600
Toxicokinetics (M:F) n=3 [b)]						
TAK-385						
T_{max} (h)	Day 1		4.0:2.7	3.3:3.3	4.0:3.3	4.0:4.0
	52 Week		4.0:2.7	2.7:2.7	4.0:4.0	8.0:6.7
C_{max} (ng/mL)	Day 1		1.9:11.4	109.3:86.7	795.2:887.4	2558.6:1967.0
	52 Week		28.2:32.6	246.6:350.5	1400.6:2049.9	7365.2:5667.9
AUC_{0-24h} (ng·h/mL)	Day 1		14:57	505:451	4747:5847	27817:22316
	52 Week		211:133	1467:1836	15465:18437	91900:75632

Sponsor's table

Dosing Solution Analysis

1, 10 and 100 mg/mL TAK-385 suspensions (vehicle: 0.5 w/v% methylcellulose solution) were stable and homogeneous for 24 hours at room temperature following 8 days in a cold place (2 to 8°C) using the same lot number of test article.

Analysis of the concentration and homogeneity of each dosing suspension, those actually used for dosing on the starting day of administration and in months 6, 12, 18 and 24, was done by the HPLC method at (b) (4) The proportion to the prescribed value ranged from (b) (4) to (b) (4) and the CV ranged from (b) (4) to (b) (4)%; both the concentration and homogeneity were confirmed to be within the acceptable range (concentration: (b) (4)% of the prescribed value, homogeneity: CV not exceeding (b) (4)%).

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Effects of TAK-385 on Fertility and Early Embryonic Development to Implantation in Rats

Study no.:	TAK-385-00113
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6 September 2006
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	TAK-385, Lot no. M285-001, 98.4% pure

Key Study Findings

There were no treatment-related effects on estrous cycling, fertility parameters, mating performance or embryonic findings on Day 15 of gestation after administration of doses up to 1000 mg/kg/day (greater than 300-fold the exposure of the MRHD of 40 mg, based on AUC) in rats. However, the binding affinity of relugolix for GnRH receptors in

rats is greater than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix. A NOAEL for general toxicity was 200 mg/kg/day (about 86-fold) and 1000 mg/kg/day for fertility and early embryonic development in this model.

Methods

Doses:	0, 40, 200, and 1000 mg/kg/day
Frequency of dosing:	daily
Dose volume:	10 ml/kg
Route of administration:	oral
Formulation/Vehicle:	0.5 w/v% methylcellulose solution (MC)
Species/Strain:	Rat, Crl:CD(SD)
Number/Sex/Group:	20
Study design:	Males were dosed once daily from Day 0 to Day 13, before mating, through the mating period (no longer than 3 weeks). Females were dosed once daily for 14 days, before mating through the mating period, until Day 6 of gestation. Non-mated females were dosed until Day 41.Dams were euthanized on Day 15 of gestation.

Group	Test article	Dosage level (mg/kg/day)	Dosage volume mL/kg/day)	Concentration (w/v%)	Number of animals
1	0.5% w/v% MC	-	10	-	20
2	TAK-385	40	10	0.4	20
3	TAK-385	200	10	2	20
4	Tak-385	1000	10	10	20

Sponsor's table

Dose justification: In a 4-week toxicity study, mortality was reported at 2000 mg/kg/day.

Observations and Results

Mortality

No mortality was observed.

Clinical Signs

No treatment related effects were observed.

Body Weight

A transient decrease in body weight gain in high dose males (52%) on Days 0 - 3 and a significant increase in body weight gain (41%) in high dose females on Days 10-13 of gestation were observed.

Feed Consumption

A decrease in food consumption (24%) on Days 0 to 1 of treatment in high dose males, an increase in food consumption (up to 8%) on Days 7 to 8 in all treated males, a decrease in food consumption (up to 19%) in high dose (pre-mating) females on Days 0

to 1 and Days 3 to 4 of treatment, and increased food consumption (10%) in high dose pregnant females on Days 0 to 1 were observed.

Estrous cycle
No treatment-related effects were observed in any treated group up to 1000 mg/kg/day.

Toxicokinetics

Although toxicokinetics were not measured in this study, toxicokinetics were estimated from a 4-week study in Crl:CD(SD) rats (N=6)

		Male (N=3)			Female (N=3)			Total (N=6)		
Dose (mg/kg/day)	No. of dosing	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)
10	1st	2.7 (1.2)	2.3 (1.0)	15 (6)	4.0 (0.0)	4.1 (4.7)	19 (20)	3.3 (1.0)	3.2 (3.2)	17 (14)
	29th	3.3 (1.2)	10.9 (0.5)	63 (16)	2.7 (1.2)	32.4 (22.0)	97 (42)	3.0 (1.1)	21.7 (18.2)	80 (34)
30	1st	3.3 (1.2)	39.6 (21.7)	185 (70)	4.0 (0.0)	32.1 (17.0)	176 (78)	3.7 (0.8)	35.9 (17.9)	180 (66)
	29th	3.3 (1.2)	113.1 (77.6)	532 (283)	2.0 (0.0)	168.8 (83.0)	516 (170)	2.7 (1.0)	141.0 (78.1)	524 (209)
300	1st	4.0 (0.0)	1809.5 (1145.2)	8995 (4632)	3.3 (1.2)	1357.2 (393.8)	7444 (2709)	3.7 (0.8)	1583.4 (805.0)	8220 (3498)
	29th	4.0 (0.0)	1218.8 (577.1)	9412 (3671)	2.7 (1.2)	1985.5 (552.1)	12318 (6668)	3.3 (1.0)	1602.1 (656.9)	10865 (5070)
2000	1st	8.0 (4.0)	7544.0 (823.3)	131232 (23615)	14.7 (8.3)	5730.1 (994.2)	75681 (14470)	11.3 (6.9)	6637.1 (1285.9)	103457 (35109)
	29th*	12.0 (-)	12160.4 (-)	186591 (-)	8.0 (-)	13029.1 (-)	157754 (-)	10.0 (-)	12594.8 (-)	172173 (-)

Necropsy

No treatment related effects were observed.

Fertility Parameters

No treatment related effects on the number of corpora lutea, number of implantations, pre-implantation loss rate or implantation index were observed. No treatment related effects on copulatory index, fertility index or mean copulatory interval were observed. No treatment related effects on the number of live embryos, number of post-implantation losses, embryo viability or post-implantation loss rate were observed.

Study title: Preliminary study for effects of TAK-385 on the estrous cycle in rats. (Study No. 06-161, Takeda, 2006)

In Crl:CD(SD) female rats (N=10/group, 10 weeks old), oral TAK-385 had no effect on estrous cycling (vaginal smears, stained with Giemsa's solution) up to at 1000 mg/kg/day after 14 days of treatment. No effect on ovary weights were observed. Effects on corpora lutea were not examined.

9.2 Embryonic Fetal Development

Study title: Effects of TAK-385 on Embryo-Fetal Development in Rats

Study no.: TAK-385-00110
Conducting laboratory and location: (b) (4)
Date of study initiation: 2006
GLP compliance: yes
QA statement: yes
Drug, lot #, and % purity: Relugolix, Lot # M285-001, 98.4% pure

Key Study Findings

At 1000 mg/kg/day (greater than 300-fold the exposure at the MRHD of 40 mg, based on AUC), decreases in maternal body weight gain and food consumption were observed. No treatment-related effects on maternal or fetal endpoints were observed. A no adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (about 86-fold). It should be noted that the binding affinity of relugolix for GnRH receptors in rats is greater than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix.

Methods

Doses: 0, 40, 200, and 1000 mg/kg/day
Frequency of dosing: daily
Dose volume: 10 ml/kg
Route of administration: Oral, gavage
Formulation/Vehicle: 0.5 w/v% methylcellulose solution (MC)
Species/Strain: Rat, Crl:CD(SD)
Number/Sex/Group: 20
Study design: Administration once daily from Day 6 to Day 17 of gestation

Group	Test article	Dosage level (mg/kg/day)	Dosage volume mL/kg/day)	Concentration (w/v%)	Number of animals confirmed to have copulated
1	0.5% w/v% MC	-	10	-	20
2	TAK-385	40	10	0.4	20
3	TAK-385	200	10	2	20
4	Tak-385	1000	10	10	20

Dose justification: In a 4-week toxicity study, mortality was reported at 2000 mg/kg/day.

Observations and Results

Mortality

No mortality was observed.

Clinical Signs

No treatment related effects were observed.

Body Weight

At 1000 mg/kg/day, decreased body weight (4%) was observed on Days 12, 14, 16 and 20 of gestation; decreased body weight gain was observed on Days 6 – 12 of gestation (21%) and on Days 18 – 20 of gestation (14%).

At 200 mg/kg/day, decreased body weight (4%) was observed on Day 20 of gestation; decreased body weight gain was observed on Days 18 – 20 (18%).

No effect on maternal body weight or body weight gain were observed at 40 mg/kg/day.

Body weight in dams

Dose (mg/kg) Days of gestation	Control		40		200		1000	
0	270.3±19.2	(19)	269.3±16.4	(20)	267.1±11.3	(19)	264.1±14.7	(20)
6	304.2±19.3	(19)	301.5±14.9	(20)	297.1±11.9	(19)	296.7±15.7	(20)
8	310.2±19.8	(19)	308.4±16.4	(20)	304.1±13.9	(19)	299.9±16.2	(20)
10	320.0±19.5	(19)	318.4±16.4	(20)	311.8±13.2	(19)	309.8±15.1	(20)
12	332.1±19.6	(19)	329.3±17.3	(20)	323.4±15.0	(19)	318.8±16.1#	(20)
14	341.5±19.7	(19)	340.0±18.8	(20)	332.9±17.4	(19)	327.2±16.6#	(20)
16	356.1±19.2	(19)	356.3±19.3	(20)	348.2±18.8	(19)	342.9±16.6#	(20)
18	384.3±20.9	(19)	384.7±22.4	(20)	373.0±21.4	(19)	370.9±17.6	(20)
20	420.5±24.5	(19)	419.3±24.3	(20)	402.7±26.6#	(19)	402.0±21.8#	(20)

Body weight gain in dams

Dose (mg/kg) Days of gestation	Control		40		200		1000	
0- 6	33.9±8.4	(19)	32.2±8.0	(20)	30.0±6.2	(19)	32.6±6.3	(20)
6-12	27.9±6.4	(19)	27.8±6.1	(20)	26.3±6.5	(19)	22.1±5.6#	(20)
12-18	52.2±9.2	(19)	55.4±9.9	(20)	49.6±11.0	(19)	52.1±6.4	(20)
6-18	80.1±14.3	(19)	83.2±15.2	(20)	75.9±13.7	(19)	74.2±9.1	(20)
18-20	36.2±5.3	(19)	34.6±4.9	(20)	29.7±8.1#	(19)	31.2±7.0#	(20)
0-20	150.2±25.1	(19)	150.0±22.8	(20)	135.6±22.9	(19)	137.9±17.6	(20)

Feed Consumption

Decreased food consumption was observed on gestation Days 6 to 7 (up to 29%) but improved by gestation Days 16 to 17 (to 6%.)

Toxicokinetics

Although toxicokinetics were not measured in this study, toxicokinetics were estimated from a 4-week study in Crl:CD(SD) rats (N=6)

		Male (N=3)			Female (N=3)			Total (N=6)		
Dose (mg/kg/day)	No. of dosing	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)
10	1st	2.7 (1.2)	2.3 (1.0)	15 (6)	4.0 (0.0)	4.1 (4.7)	19 (20)	3.3 (1.0)	3.2 (3.2)	17 (14)
	29th	3.3 (1.2)	10.9 (0.5)	63 (16)	2.7 (1.2)	32.4 (22.0)	97 (42)	3.0 (1.1)	21.7 (18.2)	80 (34)
30	1st	3.3 (1.2)	39.6 (21.7)	185 (70)	4.0 (0.0)	32.1 (17.0)	176 (78)	3.7 (0.8)	35.9 (17.9)	180 (66)
	29th	3.3 (1.2)	113.1 (77.6)	532 (283)	2.0 (0.0)	168.8 (83.0)	516 (170)	2.7 (1.0)	141.0 (78.1)	524 (209)
300	1st	4.0 (0.0)	1809.5 (1145.2)	8995 (4632)	3.3 (1.2)	1357.2 (393.8)	7444 (2709)	3.7 (0.8)	1583.4 (805.0)	8220 (3498)
	29th	4.0 (0.0)	1218.8 (577.1)	9412 (3671)	2.7 (1.2)	1985.5 (552.1)	12318 (6668)	3.3 (1.0)	1602.1 (656.9)	10865 (5070)
2000	1st	8.0 (4.0)	7544.0 (823.3)	131232 (23615)	14.7 (8.3)	5730.1 (994.2)	75681 (14470)	11.3 (6.9)	6637.1 (1285.9)	103457 (35109)
	29th*	12.0 (-)	12160.4 (-)	186591 (-)	8.0 (-)	13029.1 (-)	157754 (-)	10.0 (-)	12594.8 (-)	172173 (-)

Necropsy

No treatment-related effects were observed.
No treatment related effects on placental weight were observed. Fused placenta was observed (1 each) at 40 and 1000 mg/kg and was considered to be spontaneous.

Cesarean Section Data

No treatment related effects on the number of live fetuses, fetal viability index, number of embryo-fetal deaths, embryo-fetal mortality index, sex ratio or fetal body weight were observed.

Offspring

No external abnormalities were observed. No treatment related visceral abnormalities were observed. The mean frequency (%) of dilated ureter and convoluted ureter were higher in the 1000 mg/kg group compared to controls but the frequencies were within the range of the background control data. No treatment related skeletal abnormalities or variations were observed.

Study title: Effects of TAK-385 on embryo-fetal development in rabbits.

Study no.: TAK-385-00115
Conducting laboratory and location: (b) (4)
Date of study initiation: 11 October 2006
GLP compliance: yes
QA statement: yes
Drug, lot #, and % purity: Relugolix, Lot # M-285-001, 98.4% pure

Key Study Findings

At the high dose of 9 mg/kg/day (about 0.5-fold the clinical exposure in women at the MRHD of 40 mg), administered during the period of organogenesis, fetotoxicity, increased post-implantation loss, decreased number of live fetuses and low fetal viability rate were observed. No treatment related malformations, abnormalities, or variations were observed.

No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower, which is considered the NOAEL.

Methods

Doses:	0, 1, 3, and 9 mg/kg/day
Frequency of dosing:	daily
Dose volume:	5 ml/kg/day
Route of administration:	Oral, gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution (MC)
Species/Strain:	Rabbit, (b) (4):JW, 18 to 19 weeks old
Number/Sex/Group:	20
Study design:	Pregnant (b) (4):JW rabbits were dosed from Day 6 to Day 18 of gestation. Blood samples for TK were collected on Days 6 and 18 of gestation and euthanized on GD 28.

Group	Test or control article	Dosage level (mg/kg/day)	Dosage volume (mL/kg/day)	Concentration (w/v%)	Number of animals confirmed to have copulated*
1	0.5% w/v% MC	-	5	-	20
2	TAK-385	0.3	5	0.006	20
3	TAK-385	1	5	0.02	20
4	TAK-385	3	5	0.06	20
5	TAK-385	9	5	0.18	20

Sponsor's table

Justification for dose selection: In a range-finding study at doses of 8, 40, 200 and 1000 mg/kg/day, all animals at 1000 mg/kg/day died, and no pregnancies or implants were observed at 40, 200 or 1000 mg/kg/day. At 8 mg/kg group, in 2 of 6 animals, no pregnancy or implants were observed, and all fetuses from 2 of 4 pregnant animals died. Post-implantation loss and decreased number of live fetuses were also observed, and an increase in skeletal variations (full and short supernumerary ribs) was observed in fetuses. The high dose chosen for the definitive study was 9 mg/kg/day.

Observations and Results

Mortality

No dams died.

Clinical Signs

One dam in the control group (external genital bleeding on Days 19 and 20, followed by abortion Day 21) and 7 dams in the 9 mg/kg/day group aborted.

Body Weight / Feed Consumption

No treatment related effects on body weight or food consumption were observed in any group.

Toxicokinetics

Dose (mg/kg/day)	Day of gestation	Tmax (h)	Cmax (ng/mL)	AUC 0-24h (ng.h/mL)
0.3	6^{th} 18^{th}	- 0.5	0.0 0.4	0 0
1	6^{th} 18^{th}	0.5 0.5	1.6 3.6	2 6
3	6^{th} 18^{th}	0.5 0.5	5.5 12.8	14 25
9	6^{th} 18^{th}	0.7 0.5	25.3 53.3	56 106

Values are mean of N=3
Sponsor's table

Dosing Solution Analysis

Drug concentrations were confirmed by HPLC to be within the acceptable range of 100.0±10.0% of the target concentration (actual range: 92.6% to 107.0%) and to be stable under storage conditions.

Necropsy

One female in the control group aborted, and one female in the control group and 3 at 0.3 mg/kg/day were not pregnant. Liver discoloration was observed in 1 dam at 1 mg/kg/day, and complete litter loss was observed in 7 dams at 9 mg/kg/day.

Cesarean Section Data

At 9 mg/kg/day, litter loss was observed in 7 of 20 dams. Post-implantation loss was increased, and the number of live fetuses and fetal viability rate were decreased. No treatment related effects on number of corpora lutea, number of implantations, pre-implantation loss, sex ratio or fetal body weight were observed.

No treatment related effects were observed at 3 mg/kg/day or lower.

Gross pathological findings in dams and fetal findings

Dose (mg/kg) No. of dams	Control 18	0.3 17	1 20	3 20	9 20
No. of corpora lutea (A)	9.6±1.9	9.4±1.6	10.0±2.7	9.5±2.1	9.5±1.7
No. of implantations (B)	8.8±2.4	8.0±1.7	8.7±2.7	8.1±2.2	8.4±2.4
Preimplantation loss (%) ((A-B)/A)	9.8±11.0	14.1±15.1	13.3±13.0	14.3±18.1	12.6±21.1
Embryo/Fetus death					
No. of Embryo/Fetus deaths (D)	0.8±0.9	0.7±1.0	0.8±1.2	0.1±0.4@@	3.7±4.2
Postimplantation loss rate (%) (D/B)	9.4±10.6	7.8±11.5	8.4±11.3	2.5±11.2@@	43.9±45.4
Implantation site (%)	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	35.0±48.9$
Placental remnant (%)	8.4±9.7	5.7±9.4	6.5±10.6	2.5±11.2$	6.7±16.8$
Dead fetus (%)	1.0±4.2	2.1±4.8	1.9±3.9	0.0±0.0	2.2±5.4
Live fetus					
No. of live fetuses (C)	7.9±2.3	7.3±1.5	7.9±2.4	8.0±2.5	4.7±4.1$
Fetal viability rate (%) (C/B)	90.6±10.6	92.2±11.4	91.7±11.3	97.5±11.2@@	56.2±45.5
Sex ratio (Male/Total)	0.529±0.202	0.497±0.241	0.530±0.227	0.533±0.202	0.492±0.183
Body weight of fetus (g)					
Male	38.29±5.32	38.64±3.78	36.83±4.54	38.25±4.57	38.41±5.43
Female	37.52±5.40	38.60±3.63	36.43±5.11	35.75±4.78	36.66±5.42
Placental weight (g)					
Male	5.32±0.78	5.13±0.62	5.10±0.81	5.56±0.95	5.42±0.83
Female	5.11±0.94	5.32±0.94	4.93±0.98	5.24±1.00	5.27±0.66

@@ P<0.01 : Significantly different from the control by the Steel test
$ P<0.05 : Significantly different from control by the Shirley-Williams test

Sponsor's table

Offspring

External malformations:

At 9 mg/kg/day, meningoencephlocele, open eye, and absent claw were each observed in single fetuses. At 3 mg/kg/day, ectopia cordis with gastroschisis was observed in one fetus. No abnormalities were observed at 1 mg/kg/day or below. Due to the low incidence, each of these abnormalities was considered to be spontaneous.

External findings in fetuses and placental findings

Dose (mg/kg)	Control	0.3	1	3	9
No. of dams	18	17	20	20	13
No. of fetuses	143	124	157	159	93
External findings in fetuses					
Malformations (%)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.72 ± 3.20	2.78 ± 7.35$
Type and frequency (%)					
Meningoencephalocele	0.00	0.00	0.00	0.00	1.92
Open eye	0.00	0.00	0.00	0.00	1.92
Absent claw	0.00	0.00	0.00	0.00	0.85
Gastroschisis	0.00	0.00	0.00	0.72	0.00
Ectopia cordis	0.00	0.00	0.00	0.72	0.00
No. of placentae	143	124	157	159	93
Placental findings					
Abnormalities (%)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	1.92 ± 6.93
Type and frequency (%)					
Discolored placenta	0.00	0.00	0.00	0.00	1.92
Large placenta	0.00	0.00	0.00	0.00	1.92

$ P<0.05 : Significantly different from control by the Shirley-Williams test

Sponsor's table

From the Orgovyx Nonclinical Review (Claudia Miller review, 21 December 2020)

Necropsy findings: fetal, external

	Dose mg/kg/day				
Findings	0	0.3	1	3	9
No. examined litter/fetus	18/143	17/124	20/157	20/159	13/93
Meningoencephalocele					1/1[a]
Open eye					1/1[a]
Absent claw					1/1
Gastroschisis				1/1[a]	
Ectopia cordis				1/1[a]	

a occurred in the same fetus

Visceral abnormalities:

At 9 mg/kg/day, abnormal lung lobation, small gallbladder, and abnormal liver lobation were each observed in one fetus. At 3 mg/kg/day, microphthalmia, retroesophageal subclavian artery, narrow pulmonary trunk, right-sided aortic arch, ventricular septum defect, and persistent atrioventricular canal were each observed in one fetus. At 1 mg/kg/day, retroesophageal subclavian artery was observed in one fetus. At 0.3 mg/kg/day, no visceral abnormalities were observed. Due to the low incidence, all of these observations were judged to be spontaneous.

Visceral variations

At 3 mg/kg/day, dilated cerebral ventricle was observed in 2 fetuses and was judged to be spontaneous.

Visceral abnormalities and variations in fetuses

Dose (mg/kg)	Control	0.3	1	3	9
No. of dams	18	17	20	20	13
No. of fetuses	143	124	157	159	93
Abnormalities					
Mean frequencies (%)	0.62 ± 2.62	0.00 ± 0.00	0.72 ± 3.20	0.72 ± 3.20	1.82 ± 4.44
Type and frequency (%)					
Microphthalmia	0.00	0.00	0.00	0.72	0.00
Malpositioned subclavian branch	0.62	0.00	0.00	0.00	0.00
Retroesophageal subclavian	0.00	0.00	0.72	0.72	0.00
Narrowed pulmonary trunk	0.00	0.00	0.00	0.72	0.00
Right-sided aortic arch	0.00	0.00	0.00	0.72	0.00
Ventricular septum defect	0.00	0.00	0.00	0.72	0.00
Persistent atrioventricular canal	0.00	0.00	0.00	0.72	0.00
Abnormal lung lobation	0.00	0.00	0.00	0.00	0.96
Abnormal liver lobation	0.00	0.00	0.00	0.00	0.85
Small gallbladder	0.00	0.00	0.00	0.00	0.96
Variations					
Mean frequencies (%)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	1.11 ± 4.96	0.00 ± 0.00
Type and frequency (%)					
Dilated cerebral ventricle	0.00	0.00	0.00	1.11	0.00

Not significantly different from control

Sponsor's table

From the Orgovyx Nonclinical Review (Claudia Miller review, 21 December 2020)

Necropsy findings: fetal, visceral

	Dose mg/kg/day				
Findings	0	0.3	1	3	9
No. examined litter/fetus	18/143	17/124	20/157	20/159	13/93
Microphthalmia				1/1[a]	
Malpositioned subclavian branch	1/1				
Retroesophageal subclavian			1/1	1/1[a]	
Narrowed pulmonary trunk				1/1[a]	
Right-sighted aortic arch				1/1[a]	
Ventricular septum defect				1/1[a]	
Persistent atrioventricular canal				1/1[a]	
Abnormal lung lobation					1/1[a]
Abnormal liver lobation					1/1
Small gallbladder					1/1[a]
Dilated cerebral ventricle				1/2	

a occurred in the same fetus

Skeletal abnormalities:

At 9 mg/kg/day, fused sternebrae and absent phalanx were each observed in one fetus. At 3 mg/kg/day, misaligned thoracic vertebra with fused lumber arch, fused rib and absent rib were each observed in one fetus. Due to low incidences, all were judged to be spontaneous.

Skeletal variations:

No treatment related effects were observed.

Skeletal abnormalities and variations in fetuses

Dose (mg/kg)	Control	3	9
No. of dams	18	20	13
No. of fetuses	143	159	93
Abnormalities			
Mean frequencies (%)	0.00 ± 0.00	0.72 ± 3.20	1.71 ± 4.17
Type and frequency (%)			
Fused sternebra	0.00	0.00	0.85
Misaligned thoracic vertebra	0.00	0.72	0.00
Fused lumbar arch	0.00	0.72	0.00
Fused rib	0.00	0.72	0.00
Absent rib	0.00	0.72	0.00
Absent phalanx	0.00	0.00	0.85
Variations			
Mean frequencies (%)	21.58 ± 16.18	18.61 ± 26.82	26.48 ± 25.94
Type and frequency (%)			
Cervical rib	1.79	0.00	0.96
Asymmetry of sternebra	0.62	0.63	0.00
Dumbbell-shaped thoracic centrum	0.00	0.00	0.77
Splitting of thoracic centrum	0.00	0.00	0.77
Short rib	0.00	0.72	0.00
Full supernumerary rib	9.05	8.56	9.13
Short supernumerary rib	12.81	10.43	17.32
Supernumerary lumbar vertebra	3.02	0.56	6.32
No. of ossified			
Sacral and caudal vertebrae	18.74 ± 0.47	18.74 ± 0.46	18.59 ± 0.30

Not significantly different from control

Sponsor's table

From the Orgovyx Nonclinical Review (Claudia Miller review, 21 December 2020)

Necropsy findings: fetal, skeletal

	Dose mg/kg/day		
Findings	0	3	9
No. examined litter/fetus	18/143	20/159	13/93
Fused sternebra			1/1
Misaligned thoracic vertebra		1/1[a]	
Fused lumbar arch		1/1[a]	
Fused rib		1/1[a]	
Absent rib		1/1[a]	
Absent phalanx			1/1
Cervical rib	3/3		1/1
Asymmetry of sternebra	1/1	1/1	
Dumbbell-shaped thoracic centrum			1/1
Splitting of thoracic centrum			1/1
Short rib		1/1	

a: occurred in the same fetus

9.3 Prenatal and Postnatal Development

Study title: Effects of TAK-385 on Pre- and Postnatal Development, including Maternal Functions, in Rats

Study no.:	TAK-385-300136
Conducting laboratory and location:	(b) (4)
Date of study initiation:	6 June 2016
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	TAK-385, Lot no. M285-023, 99% pure

Key Study Findings

At 1000 mg/kg/day (greater than 300-fold the exposure of the MRHD of 40 mg, based on AUC), there were no effects on gestation length, number of implantation sites, gestation index, delivery, nursing, or necropsy findings, in the presence of decreased maternal body weight gain and food consumption. A no-observed-adverse-effect level was judged to be 100 mg/kg/day (about 34-fold) for maternal and fetal toxicity, development in F_1 pups, and reproductive functions in F_1 animals. The binding affinity of relugolix for GnRH receptors in rats is greater than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix.

Methods

Doses:	0, 20, 100, and 1000 mg/kg/day
Frequency of dosing:	daily
Dose volume:	10 ml/kg
Route of administration:	Oral, gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose solution
Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	18 or 19 pregnant females/ group
Study design:	Administration during the period from implantation to weaning (from Day 6 of gestation to Day 20 after delivery)

Observations and Results

Mortality, clinical signs, body weights, food consumption, necropsy, delivery/nursing conditions, gestation length, the number of implantation sites, and gestation index for F_0 dams; the number of live pups, external examination, sex ratio, stillbirths, birth index, viability, weaning index, clinical signs, body weights, physical development, and necropsy for F_1 pups; clinical signs, body weights, physical development, open-field test, spontaneous motor activity, learning ability, estrous cycle, pairing, fertility, pregnancy status, and necropsy for F_1 animals; and viability for F_2 embryos were measured in this study.

F_0 Dams

At 1000 mg/kg/day, body weight, body weight gain, and food consumption were low during the following periods: on Day 18 of gestation for body weight, from Days 8 to 10, 12 to 14, and 16 to 18 of gestation for body weight gain, and from Days 6 to 8, 8 to 10, and 10 to 12 of gestation for food consumption.

Body weights of F0 dams during gestation

Group	Control	TAK-385		
mg/kg	0	20	100	1000
Number of dams	18	18	18	19
Days of gestation				
0	234 ± 13	235 ± 13	234 ± 14	235 ± 11
6	269 ± 15	267 ± 14	268 ± 15	267 ± 13
8	276 ± 15	275 ± 14	277 ± 16	274 ± 14
10	288 ± 18	286 ± 15	287 ± 17	282 ± 15
12	297 ± 18	295 ± 15	297 ± 18	292 ± 15
14	307 ± 20	303 ± 17	305 ± 20	299 ± 16
16	325 ± 21	320 ± 18	323 ± 22	315 ± 17
18	354 ± 23	348 ± 20	350 ± 23	339 ± 17 W
20	379 ± 27	371 ± 21	376 ± 25	364 ± 25

Each value shows mean ± S.D. (g).
Significantly different from the control group (W: p<0.05 by Williams' test).

Body weights of F_0 dams during lactation

Group	Control	TAK-385		
mg/kg	0	20	100	1000
Number of dams	18	18	18	19
Days after delivery				
0	275 ± 24	270 ± 30	286 ± 22	271 ± 22
4	296 ± 20	288 ± 20 (17)	297 ± 18	289 ± 19
7	300 ± 20	295 ± 19 (17)	302 ± 20	300 ± 16
11	309 ± 19	302 ± 19 (17)	311 ± 17	312 ± 18
14	308 ± 20	306 ± 19 (17)	310 ± 17	314 ± 17
17	304 ± 19	303 ± 17 (17)	307 ± 15	314 ± 16
21	292 ± 18	290 ± 16 (17)	298 ± 17	308 ± 15 W

Each value shows mean ± S.D. (g).
Significantly different from the control group (W: p<0.05 by Williams' test). Figures in parentheses indicate number of dams.
Sponsor's table

Body weight gain in F_0 dams during gestation

Group	Control	TAK-385		
mg/kg	0	20	100	1000
Number of dams	18	18	18	19
Days of gestation				
0-6	35 ± 7	32 ± 6	34 ± 6	32 ± 7
6-8	6 ± 3	7 ± 3	9 ± 4	6 ± 5
8-10	12 ± 6	11 ± 4	10 ± 4	8 ± 4 W
10-12	9 ± 4	9 ± 5	10 ± 5	10 ± 5
12-14	10 ± 4	9 ± 3	8 ± 4	6 ± 5 W
14-16	19 ± 4	17 ± 4	18 ± 4	16 ± 5
16-18	29 ± 4	28 ± 7	27 ± 5	24 ± 5 W
18-20	24 ± 5	23 ± 6	26 ± 6	25 ± 12

Each value shows mean ± S.D. (g).
Significantly different from the control group (W: p<0.05 by Williams' test).
Sponsor's table

Body weight gain in F_0 dams during lactation

Group	Control	TAK-385		
mg/kg	0	20	100	1000
Number of dams	18	17	18	19
Days after delivery				
0-4	21 ± 14	15 ± 15	12 ± 15	18 ± 16
4-7	4 ± 7	7 ± 6	5 ± 7	11 ± 10 W
7-11	9 ± 7	8 ± 8	9 ± 6	12 ± 8
11-14	-2 ± 9	3 ± 9	-2 ± 8	2 ± 5
14-17	-3 ± 10	-2 ± 7	-3 ± 8	0 ± 8
17-21	-12 ± 11	-13 ± 9	-9 ± 7	-6 ± 12

Each value shows mean ± S.D. (g).
Significantly different from the control group (W: p<0.05 by Williams' test).
Sponsor's table

F_1 Generation

There were no adverse effects of the test article in the number of live pups at birth, sex ratio, the number of stillbirths, birth index, viability index on Day 4 after birth, weaning index, external abnormalities, clinical signs, body weight of either sex, morphological differentiation, reflex functions, or necropsy findings in the F1 pups.

There were no adverse effects of the test article in the clinical signs, body weight of either sex, morphological differentiation, open-field test, spontaneous motor activity, water multiple T-maze test, or necropsy findings in the F1 animals.

There were no adverse effects of the test article in clinical signs, estrous cycle, copulation index, copulatory interval, fertility index, the number of corpora lutea, the number of implantation sites, implantation rate, or necropsy findings.

There were no adverse effects of the test article in the number of pre-implantation losses, pre-implantation loss rate, the number of post-implantation losses, post-implantation loss rate, or the number of live embryos.

Toxicokinetics

Although toxicokinetics were not measured in this study, toxicokinetics were estimated from a 4-week study in Crl:CD(SD) rats (N=6)

		Male (N=3)			Female (N=3)			Total (N=6)		
Dose (mg/kg/day)	No. of dosing	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng•h/mL)
10	1st	2.7 (1.2)	2.3 (1.0)	15 (6)	4.0 (0.0)	4.1 (4.7)	19 (20)	3.3 (1.0)	3.2 (3.2)	17 (14)
	29th	3.3 (1.2)	10.9 (0.5)	63 (16)	2.7 (1.2)	32.4 (22.0)	97 (42)	3.0 (1.1)	21.7 (18.2)	80 (34)
30	1st	3.3 (1.2)	39.6 (21.7)	185 (70)	4.0 (0.0)	32.1 (17.0)	176 (78)	3.7 (0.8)	35.9 (17.9)	180 (66)
	29th	3.3 (1.2)	113.1 (77.6)	532 (283)	2.0 (0.0)	168.8 (83.0)	516 (170)	2.7 (1.0)	141.0 (78.1)	524 (209)
300	1st	4.0 (0.0)	1809.5 (1145.2)	8995 (4632)	3.3 (1.2)	1357.2 (393.8)	7444 (2709)	3.7 (0.8)	1583.4 (805.0)	8220 (3498)
	29th	4.0 (0.0)	1218.8 (577.1)	9412 (3671)	2.7 (1.2)	1985.5 (552.1)	12318 (6668)	3.3 (1.0)	1602.1 (656.9)	10865 (5070)
2000	1st	8.0 (4.0)	7544.0 (823.3)	131232 (23615)	14.7 (8.3)	5730.1 (994.2)	75681 (14470)	11.3 (6.9)	6637.1 (1285.9)	103457 (35109)
	29th*	12.0 (-)	12160.4 (-)	186591 (-)	8.0 (-)	13029.1 (-)	157754 (-)	10.0 (-)	12594.8 (-)	172173 (-)

Sponsor's table

11 Integrated Summary and Safety Evaluation

Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, reducing the release of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estrogen production, corpus luteum formation, and secretion of progesterone.

Estradiol acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. The addition of exogenous estradiol to this combination drug product is proposed to reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen from relugolix.

Progestins such as norethindrone act by binding to nuclear receptors that are expressed in progesterone-responsive tissues. The addition of norethindrone to this combination drug product is proposed to protect the uterus from the potential adverse endometrial effects of unopposed estrogen.

In human GnRH-receptor knock-in mice, administration of relugolix at oral doses of 100 mg/kg and above twice daily to female mice induced a constant diestrous phase and decreased ovarian and uterine weights, effects which were reversible following cessation of treatment. In male knock-in mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses 3 mg/kg and above twice daily for 28 days, effects which were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal.

Toxicology

Repeat-dose toxicity studies with relugolix were conducted in mice up to 13 weeks, in rats up to 26 weeks, and in monkeys up to 39 weeks. Monkey was the most sensitive species, and pharmacology studies showed a significant difference in binding affinity of relugolix to human, monkey and rat GnRH receptors, with high affinity for human and monkey GnRH receptors and a low affinity for rat GnRH receptors (more than 1000-fold less than in humans). Therefore the studies conducted in rats are primarily a toxicological assessment of non-pharmacological targets of relugolix.

In a 26-week study in rats, at 300 mg/kg/day (about 154-fold the exposure at the MRHD of 40 mg, based on AUC), minimal eosinophilic crystals in the epididymal epithelium, minimal foam cell infiltration in the testicular interstitium (indicative of phospholipidosis), minimal foam cell infiltration in the lungs (phospholipidosis), minimal scattered hepatocyte vacuolation (phospholipidosis) and minimal focal hemorrhage in the liver were observed. Minimal foam cell infiltration in the testicular interstitium (indicative of phospholipidosis) was also observed at 100 mg/kg/day (about 33.5-fold). No adverse effect levels were 30 mg/kg/day (about 8.0-fold) for males and 100 mg/kg/day for females, based on phospholipidosis. However, phospholipidosis was not observed in clinical studies and is considered to be a rare occurrence in humans. No adverse effect levels were 100 mg/kg/day (about 33.5-fold for males and females), based on liver effects.

In a 39-week study in monkeys, at 50 mg/kg/day (about 99.1-fold the exposure at the MRHD of 40 mg, based on AUC), effects on the liver included bile plug formations and yellowish-brown pigment deposition in Kupffer cells. Findings related to systemic phospholipidosis included foam cells in the lymphatic sinus of the mesenteric lymph nodes and in the lymphatic sinus of the submandibular lymph nodes, vacuolation of parietal cells in the stomach, increased tingible body macrophages (TBM) in the stomach, lymphoid follicles, bone marrow, germinal center of spleen, lymphoid follicles of the submandibular lymph nodes, mesenteric lymph nodes, cecum and colon and in the lymphoid follicles of the duodenum, ileum and rectum. Following a 13-week recovery period, some evidence of phospholipidosis and liver effects were still evident. Decreased corpora lutea were observed in all females following dosing at 5 (6.7-fold), 15 (26.2-fold) and 50 mg/kg/day, but were not observed following recovery. A no adverse effect level (NOAEL) was 15 mg/kg/day (26.2-fold) based on liver toxicity. No NOAEL was observed for systemic phospholipidosis (increase in foamy cells, tangible body macrophages and cell vacuolation); minimal effects were observed at 1.5 mg/kg/day (1.1-fold.) In females, 1.5 mg/kg/day (1.1-fold) was a no effect level for decreased uterine weight and decreased corpora lutea, and 15 mg/kg/day (26.2-fold) was a no effect level for cessation of menses. There were no significant effects on male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human exposure at a dose of 120 mg daily in men with prostate cancer, based on AUC). No effects on cardiac parameters were observed in this study, and no effects were observed in a cardiac safety pharmacology study up to 30 mg/kg (estimated to be about 65 times the exposure at the MRHD of 40 mg, based on Cmax at first dose in the

39-week monkey study) in conscious male telemetered cynomolgus monkeys. At 100 (161 times) and 300 mg/kg (484 times), effects on QT interval, QTc and PR interval were observed.

TAK-385 (relugolix) was shown in vitro to inhibit hERG channels with an IC_{50} 9.7 µg/ml or about 373 times the clinical Cmax of 26 ng/ml at the MRHD of 40 mg.

Relugolix metabolism and distribution were previously reviewed under NDA 214621 (21 December 2020, Claudia Miller). Parent drug is the major circulating metabolite, and all identified metabolites were formed in rats and monkeys.

Reproductive toxicity

In a fertility study in rats, no effects on female fertility were observed at up to 1000 mg/kg/day (greater than 300 times the MRHD of 40 mg daily in women). In rats, the binding affinity of relugolix for GnRH receptors is greater than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix.

In an embryo-fetal development study in rabbits, oral administration of relugolix to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the maximum recommended human dose (MRHD) of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower, therefore the NOAEL was considered 3 mg/kg/day. The binding affinity of relugolix for rabbit GnRH receptors is unknown, though based on the observation of pharmacologic effects of a GnRH receptor antagonist in this study compared to results in rats, the affinity is likely significantly greater in rabbits than in rats.

In a similar embryo-fetal development study in rats, oral administration of relugolix to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. A no adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (86 times the MRHD). In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related malformations were observed up to 1000 mg/kg/day.

In a pre- and postnatal developmental study in pregnant and lactating rats, oral administration of relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times the MRHD), a dose in which maternal toxicity was observed

(effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD.)

Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low-dose estrogens and progestins as an oral contraceptive before conception or during early pregnancy.

Administration of a single oral dose of [^{14}C] relugolix (30 mg/kg) to fasted female rats on lactation Day 14 demonstrated that relugolix-derived radioactivity reached peak concentrations by 2 hours post-dose in both plasma and milk (9.7-fold milk-to-plasma accumulation ratio) and decreased to levels below the limit of quantification by 48 hours.

Carcinogenicity

Relugolix: Two-year carcinogenicity studies were conducted in mice at oral relugolix doses up to 100 mg/kg/day and in rats at doses up to 600 mg/kg/day. Relugolix was not carcinogenic in mice or rats at exposures up to approximately 142 or 423 times, respectively, the exposure in human females at the MRHD of 40 mg daily, based on AUC. The impurity (b) (4) was present at (b) (4) % in these studies. In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold less than in humans and the binding affinity in mice was not studied. In monkeys, where the binding affinity is similar to humans, no evidence of pre-neoplastic lesions was observed in a 39-week study.

For the E2/NETA component of Myfembree, long-term continuous administration of natural and synthetic estrogens in certain animal species has long been known to increase the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. Risk assessment is typically based on human data.

Relugolix was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells or the in vivo rat bone marrow micronucleus assay.

12 Appendix/Attachments

Executive CAC Final Study Minutes
Date of Meeting: November 5, 2019

Committee: Paul Brown, PhD, OND IO, Acting Chair
Tim McGovern, PhD, OND IO, Member
Ron Wange, PhD, OND IO, Member
David Joseph, PhD, DGIEP, Alternate Member
Mukesh Summan, PhD, DBRUP, Pharm/Tox Supervisor
Laurie McLeod-Flynn, PhD, DBRUP, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

Application Type and Number(s): IND 131161
Drug Name: Relugolix (RVT-601) tablet form
Sponsor: Myovant Sciences, Ltd. GMBH c/o Myovant Sciences Inc.

Background

Relugolix is a GnRH antagonist being developed (b) (4) under IND 131161 for treatment of women with heavy menstrual bleeding associated with uterine fibroids. It was not genotoxic in a battery of assays.

Mouse Carcinogenicity Study

Relugolix was administered orally to B6C3F1/(b) (4) mice at 0, 10, 30, and 100 mg/kg/day (N = 55/sex/dose) in 0.5% w/v methylcellulose for 104 weeks.

Rat Carcinogenicity Study
Relugolix was administered orally to Crl:CD (SD) rats at 0, 10, 30, 200, and 600 mg/kg/day (N = 60/sex/dose) in 0.5% w/v methylcellulose for 104 weeks (males) or 101 weeks (females), due to non-dose-related decreases in survival in female rats.

Executive CAC Conclusions
Mouse:

- The Committee concurred that the carcinogenicity study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms observed in male and female mice.

Rat:

- The Committee concurred that the carcinogenicity study was adequate, noting prior approval of the protocol.

- The Committee concurred that there were no drug-related neoplasms observed in male and female rats.

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/

LAURIE L MCLEOD FLYNN
05/05/2021 09:12:21 AM

KIMBERLY P HATFIELD
05/05/2021 02:15:45 PM
I concur with the review and conclusions of Dr. McLeod-Flynn.