

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 213006
Supporting document/s: SDN #2; eCTD #0000
Applicant's letter date: December 26, 2019
CDER stamp date: December 26, 2019
Product: Vibegron
Indication: Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency
Applicant: Urovant Sciences Inc.
Review Division: Division of Urology, Obstetrics and Gynecology
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Primary Reviewer: Laurie McLeod-Flynn, PhD, DABT
Acting Division Director: Christine Nguyen, MD
Project Manager: Nenita Crisostomo, RN

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Executive Summary

Introduction

Vibegron is a β -3 adrenergic receptor (AR) agonist indicated as a once-daily oral treatment for overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in men and women at a dose of 75 mg/day. The intended mechanism of action of vibegron is to activate β -3 AR and increase bladder capacity by relaxing the detrusor smooth muscle of the bladder during bladder filling. Vibegron is a new molecular entity and the second β -3 AR agonist to be developed for OAB. The original IND 106410 was initiated on January 29, 2010.

The following review serves as the secondary and tertiary nonclinical review to support the approval of this new molecular entity. The primary nonclinical review was completed by Dr. Laurie McLeod-Flynn (see nonclinical review in DARRTS dated October 20, 2020).

Brief Discussion of Nonclinical Findings

A complete nonclinical development program was conducted by the applicant for vibegron. Primary pharmacology studies indicated that vibegron is highly selective (>9000-fold) for β -3 AR over β -1 AR or β -2 AR in cell-based in vitro functional assays. Mechanistically, vibegron was shown to activate β -3 AR in the urinary bladder and increase bladder capacity by relaxing the detrusor smooth muscle during bladder filling. Relaxation was demonstrated in a bladder strip assay to be concentration-dependent with an EC_{50} of 3.0 μ M in rats and 0.087 μ M in humans. Vibegron was also found to be active in a number of nonclinical species (human ~ monkey < dog ~ rabbit < rat), and was primarily investigated for safety in rat, monkey, and dog. In vivo metabolism studies demonstrated that vibegron was extensively metabolized in both rat and monkey and had a similar metabolite profile in both species to that observed in humans.

Cardiac safety pharmacology studies in the rhesus monkey indicated that vibegron significantly increased heart rate, respiration rate and body temperature. While a no observed effect level (NOEL) for cardiac effects could not be determined in this study, a low dose (0.22-fold of the clinical exposure at 75 mg) resulted in only a transient increase in heart rate. Further evaluations of cardiac toxicity in the 9-month chronic study in monkeys confirmed these effects with transient ECG findings at the highest dose tested (75-fold the clinical AUC) that resolved after 24 hrs, along with marked increases in QRS duration and changes in QRS configuration. No QT interval prolongation was observed. Mid-dose (17-fold the clinical AUC) resulted only in slightly increased heart rates that resolved by 24 hrs. A NOEL for cardiac findings in the monkey was determined to be at a dose 2-fold of the clinical AUC (6-fold the clinical C_{max}). No histopathological correlates in the heart were observed at any dose in monkeys. Cardiac toxicity was also evaluated in an ancillary pharmacology study in dogs which showed transient decreases in mean arterial pressure and increases in

heart rate at all doses (>3-fold of C_{max} at the clinical dose of 75 mg), and small (<10%) increases in QRS interval at 14-fold the C_{max}. As in monkeys, no effects on QT interval were observed up to 116-fold the C_{max} of the clinical dose.

General toxicity of chronic oral administration of vibegron was adequately evaluated in rats (3 & 6 months) and monkeys (3 & 9 months). Other than ECG findings already described above in the monkey, the only toxicity of note was slight accumulation of brown fat in white adipose tissue (rats and monkeys; a pharmacologic effect common to β -3-AR agonists in animals) and slight increases in alkaline phosphatase in male rats. In rats, the NOAEL was determined to be 30 mg/kg/day (~ 21.3-fold AUC at the clinical dose of 75 mg) and in monkeys, a NOEL (due to ECG findings) was determined to be 25 mg/kg/day (6.4-fold C_{max} at the clinical dose of 75 mg, 2.1-fold AUC).

A complete genotoxicity battery was conducted and vibegron was determined not to be mutagenic in any assay. Two year carcinogenicity studies were also conducted in mice and rats, with no treatment-related malignancies observed in either species at adequate exposure margins (21-fold and 55-fold of the 75 mg clinical dose based on AUC in male and female mice respectively, and 18-fold and 117-fold of the 75 mg clinical dose based on AUC in male and female rats respectively).

Reproductive studies to examine fertility, embryofetal development, and pre- and postnatal development were also conducted in rats and rabbits. At about 898-fold the clinical dose (based on AUC), decreased maternal food consumption, reduced fetal body weight, and increased incidence of delayed skeletal ossification (skull, sternebra, metacarpal, and talus-calcaneus bones) were observed. At about 286-fold the clinical dose (based on AUC), no maternal or developmental toxicity was observed.

No embryo-fetal developmental toxicity was observed in rats at doses up to 300 mg/kg/day (1867-fold the AUC at the clinical dose) or in rabbits at doses up to 100 mg/kg/day (285-fold the AUC at the clinical dose). No developmental toxicity was observed in F1 rat offspring at doses up to 100 mg/kg/day (89-fold the AUC at the clinical dose). At extremely high exposure multiples in rabbits (300 mg/kg/day; 898-fold the AUC at the clinical dose), maternal toxicity (decreased food consumption) and fetal toxicity (reduced fetal body weight and an increased incidence of delayed skeletal ossification) were observed. Also at high exposure multiples in rats (500 mg/kg/day; 458-fold the AUC at the clinical dose), maternal toxicity was observed during gestation and lactation (decreased body weight gain and food consumption) along with developmental toxicity in F1 offspring (increased stillborn index, lethality, reduced viability and weaning indices, decreased body weight and body weight gains, low physical development differentiation indices, and effects on sensory function and reflexes).

Recommendations

Approvability

Pharmacology/toxicology supports approval of vibegron 75 mg for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency in both men and women.

Additional Nonclinical Recommendations

None

Labeling

Relevant toxicities regarding effects on reproduction and fertility, and the lack of mutagenicity and carcinogenicity have been adequately described in the proposed product labeling for vibegron.

11 Integrated Summary and Safety Evaluation

Vibegron has been adequately evaluated in nonclinical studies for pharmacology, pharmacokinetics and toxicology. Studies showed that vibegron is a selective agonist for the β -3 AR over β -1 and β -2 AR and demonstrated its intended pharmacologic function of relaxing the detrusor smooth muscle of the urinary bladder during bladder filling to increase bladder capacity. While vibegron initiated cardiac effects at multiple doses and across species (increased heart rate, respiration rate, QRS duration and altered QRS configuration), these findings did not correlate with any clinically significant findings in clinical trials with the intended oral dose of 75 mg. Vibegron did not prolong the QT interval to any clinically relevant extent at single clinical doses 5.3 times the clinical dose of 75 mg, and did not have any statistically or clinically significant effects on blood pressure at the recommended clinical dose. Vibegron also expressed minimal toxicities in chronic repeat dose studies, with safety margins of 21-fold and 2-fold in rats and monkeys respectively, based on AUC. The low margin in monkeys is primarily due to the observed ECG findings that were determined not to have a clinical correlation.

Vibegron was determined to not be mutagenic or carcinogenic, with no treatment-related malignancies observed at adequate exposure margins in 2-year studies in mice and rats. Reproductive findings showed maternal toxicity and indications of fetal/developmental toxicity, but at doses that represented significantly high margins of exposure >450-fold the clinical dose, based on AUC.

The extensive nonclinical information submitted in support of vibegron supports the safety of clinical use at a once daily oral dose of 75 mg in the intended male and female population of subjects with overactive bladder. There are no pending nonclinical concerns or issues regarding the chronic use of this product for the indication or intended population, and no additional studies are required. As such, pharmacology/toxicology supports approval of vibegron for treatment of overactive bladder.

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/s/

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Applicant: Urovant 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. (acting)
Project Manager: Nenita Crisostomo, RN

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Vibegron is the second beta-3 adrenergic agonist to be developed for treatment of overactive bladder (OAB). Some beta-3 adrenergic agonists have the potential, through overlapping interactions with beta-1 adrenergic receptors (AR), to have effects on heart rate. As such, the extensive set of nonclinical studies submitted by the sponsor included both acute and chronic studies of the cardiac effects of vibegron in monkeys, alone and in combination with antimuscarinics (e.g. tolterodine). No formal indication for vibegron in combination with antimuscarinics has yet been proposed.

1.2 Brief Discussion of Nonclinical Findings

Vibegron activated the human β_3 adrenergic receptor, increased cAMP levels and exhibited a high selectivity for β_3 -AR over β_1 -AR or β_2 -AR in cell based and in vitro functional assays.

In a bladder strip assay, vibegron induced relaxation of bladder smooth muscle in a concentration-dependent manner.

Vibegron was tested up to 9 months in monkeys and 6 months in rats. The monkey was shown to be pharmacologically similar in β_3 -AR activity compared to humans, while agonist activity at the rabbit and dog β_3 adrenergic receptors was approximately 10-fold less potent, and activity at the rat receptor was 100-fold less potent than in humans. Metabolite profiles in toxicology species were similar to those observed in humans.

No histopathological effects were observed in monkeys up to approximately 75 times the expected clinical exposure at the maximum recommended human dose (MRHD) of 75 mg vibegron (via AUC), except for slight accumulation of brown fat in white adipose tissue (a pharmacologic effect common to beta-3-adrenergic agonists in animals) and very slight cellular infiltration in the liver. A no effect level (NOEL) was observed at 25 mg/kg/day (6-fold Cmax, 2.1-fold AUC), based on ECG effects.

In rats, a no-adverse-effect level (NOAEL) was observed at about 21.3-fold the MRHD. Some brown fat accumulation was observed at this level of administration in male rats. At about 102-fold, one male was found dead in study week 12, and very slight or slight increases in alkaline phosphatase were observed. No other significant toxicities were observed.

In the 9-month monkey toxicology study, transient electrocardiographic findings (increases in QRS duration consistent with a ventricular conduction defect and P wave partially or fully hidden in the T wave of the preceding complex) were observed at approximately 2 hours post dose (generally resolved by 24 hours post dose) at a dose of about 114-fold the expected clinical exposure at the maximum recommended human dose (MRHD) of 75 mg (via Cmax). In animals where PR and QT intervals could be evaluated (1 female and 1 male on 1 or 2 occasions), no prolongation in QT interval

was observed. In these animals, there were marked increases in QRS duration and notable changes in QRS configuration, including "coving" of the S wave. Heart rates were slightly increased at 2 hours post dose but normalized by 24 hours. A NOEL for heart rate effects was observed at about 6-fold in this conscious monkey model. After nine months of treatment, no indication of cardiac histopathology was observed despite the ECG findings.

In a 3-month toxicology study in monkeys, 2 females were found dead at 181-fold the C_{max} at the MRHD of 75 mg (255-fold AUC). ECG changes were observed in all surviving males at this dose and it should be considered that these deaths may have been due to cardiac arrhythmias. A NOAEL for ECG changes was observed at 43-fold. QRS distortion was observed in males after approximately 3 weeks of dosing at the high dose (at approximately 1 hour and/or 24 hours postdosing), and after approximately 1 - 2 months of dosing at the mid dose. In 1 animal at the high dose, absence of P waves and PR prolongation were also observed. After approximately 2 months of dosing at about 104-fold, ECG changes were limited to QRS distortion. There were no histomorphological cardiac effects observed to correlate with ECG findings.

A cardiac safety pharmacology study was also conducted in rhesus monkeys using an escalating dose design. Heart rate, arterial blood pressure (systolic, diastolic, and mean pressure), electrocardiographic parameters (PR, QRS, and QT intervals), body temperature, respiratory rate, and depth of respiration were monitored via telemetry for approximately 24 hours post dose. QT interval was corrected for heart rate (QT_c) using an individual animal correction method (Miyazaki's correction). Blood samples were collected at 0 (pre-dose), 0.5, 1, 2, 4, 8, and 24 hours post dose. At exposures approximately 0.22-fold those at the MRHD of 75 mg and above, transient increased heart rate, increased respiration rate, and increased body temperature (a metabolic effect of β_3 -adrenergic receptor agonists observed in animals) were observed. Increases in uncorrected QT interval were also observed at all doses. Corrected QT (QT_c) changes, to account for changes in heart rate, did not reveal a dose relationship, which was interpreted to indicate that drug-related increases in QT interval were an artifact of increased heart rate. At about 2.7-fold and above, decreased PR interval was also observed (10 to 19%). At 135 mg/kg (42-fold C_{max}, 31-fold AUC), increased diastolic blood pressure (13 mmHg, 19%), respiration depth (7 mmHg, 103%), and QRS interval (6 msec, 12%) were also observed in addition to effects observed at lower doses. No NOEL for cardiac effects was observed in this study, but at the lowest dose, only a transient increase in heart rate was observed.

Preliminary studies were also conducted in dogs. Vibegron was administered intravenously to mixed breed anesthetized and vagotomized dogs. Heart rate, mean arterial pressure, and electrocardiographic parameters were monitored. Plasma concentrations were approximately 3, 8, 14, 26, and 116-fold C_{max} at the MRHD of 75 mg vibegron. Transient decreases in mean arterial pressure and increases in heart rate were observed at all doses (> 3-fold C_{max} at the MRHD). No effects on QT interval were observed up to 116-fold. At doses about 14-fold, small (<10 %) increases in QRS interval were observed.

In a 3-month oral combination toxicity study, monkeys were administered vibegron (about 23-fold), followed immediately by increasing doses of tolterodine (up to about 4-fold the MRHD). Tolterodine is an antimuscarinic bladder relaxant approved to treat frequent urination, urinary incontinence, or urinary urgency. At the high dose of tolterodine, one male was found dead following observations of distended abdomen, signs of stomach content aspiration, decreased heart rate at 2 hours (27%) and 24 hours post dose (42%), increased PR interval at 2 hours post dose (50%), and increased QT and QTc intervals at 2 hours (20% and 13%, respectively) and 24 hours post dose (56% and 30%, respectively). Effects on heart rate were observed in all dose groups. Vibegron did not appear to increase the exposure of tolterodine nor did tolterodine affect the exposure to vibegron.

In vitro, vibegron had no statistically significant effect on human potassium channel tail current, but at the maximum testable concentration of 365-fold the MRHD, it inhibited current by 21.4%.

In all, the cardiac effects of vibegron in monkeys, studied over acute and chronic periods, alone and in combination with tolterodine, should be viewed as the potential effects of vibegron after administration of very large clinical multiples of both drugs, in an animal model where pharmacokinetic profiles over time cannot be matched exactly with clinical pharmacokinetic profiles. Lethality was observed in the 3-month study in monkeys at 181-fold the MRHD of vibegron, but occurred in the 3-month vibegron/tolterodine combination study in monkeys at 23-fold the MRHD of vibegron and about 4-fold the MRHD of tolterodine. Increases in QRS distortion (conduction defects) were observed at greater than 100-fold the MRHD of vibegron in both the 3-month and the 9-month studies in monkeys. An increase in corrected QT interval was observed only in the 3-month vibegron/tolterodine combination study (along with 1 death at the high dose of tolterodine.) A NOEL for increases in heart rate was observed in the 9-month study in monkeys at about 6-fold the MRHD of vibegron; however small increases in heart rate were observed at about one fifth of the MRHD in the telemetered monkey pharmacology study, with continuous monitoring over 24 hours, possibly indicating a decreasing effect of vibegron on heart rate following prolonged administration. Similar effects to monkeys were observed in preliminary intravenous studies in dogs. Negligible risk for direct effects on human potassium channels were indicated in the in vitro hERG study, and no cardiac histopathology was observed in any study in either species. In all, although signals for increases in heart rate, conduction effects, increased QT interval (in combination with high doses of tolterodine) and sudden death were identified in monkeys, clinical risk assessment must ultimately rely on effects observed in clinical studies at therapeutic and supratherapeutic doses of vibegron alone and in combination with antimuscarinics.

The label for Detrol® LA (tolterodine tartrate extended release capsules) states that “in dogs, changes in the QT interval (slight prolongation of 10% to 20%) were observed at a suprapharmacologic dose of 4.5 mg/kg, which is about 68 times higher than the recommended human dose. In clinical trials of normal volunteers and patients, QT

interval prolongation was observed with tolterodine immediate release at doses up to 8 mg (4 mg bid) and higher doses were not evaluated.”

Mutagenesis

Vibegron was not mutagenic in in vitro microbial reverse mutation (Ames) assays, showed no genotoxic activity in an in vitro human peripheral blood lymphocyte chromosomal aberration assay, and did not increase the frequency of micronucleated polychromatic erythrocytes in an in vivo rat bone marrow micronucleus assay.

Carcinogenesis

In mice, oral administration of vibegron at 21-fold the exposure of the MRHD of 75 mg in males and 55-fold in females for two years did not cause treatment-related malignancies.

In rats, oral administration of vibegron at 18-fold the exposure of the MRHD of 75 mg in males and 117-fold in females for two years did not cause treatment-related malignancies.

Reproductive toxicity

In fertility and general reproductive toxicity studies conducted in rats, the NOEL for fertility parameters in female and male rats was about 275-fold the systemic exposure at the MRHD of 75 mg. General toxicity (body weight loss) and decreased fertility parameters were observed in female rats at about 1867-fold.

In an embryo-fetal developmental toxicity study in rats, pregnant rats were treated with daily oral doses of vibegron from days 6 to 20 of gestation. At about 1867-fold the MRHD, maternal body weight loss and lethality were observed. At about 267-fold the MRHD, no maternal or developmental toxicity or teratogenicity was observed.

In an embryo-fetal developmental toxicity study in rabbits, pregnant rabbits were treated with daily oral doses of vibegron from days 7 to 20 of gestation. At about 898-fold the MRHD, decreased maternal food consumption, reduced fetal body weight, and increased incidence of delayed skeletal ossification (skull, sternebra, metacarpal, and talus-calcaneus bones) were observed. At about 286-fold the MRHD, no maternal or developmental toxicity was observed.

In a pre- and post-natal developmental toxicity study, pregnant or lactating rats were treated with daily oral doses of vibegron from day 6 of gestation through day 20 of lactation. At about 458-fold the MRHD, decreased maternal body weight gain was observed during gestation (along with decreased food consumption) and during lactation. Developmental toxicity was observed in F1 offspring (increased stillborn index, lethality, reduced viability on Lactation Day 4, decreased weaning index, decreased body weight and body weight gains, low physical development differentiation indices [piliation, incisor eruption, eye opening, and/or preputial separation], and effects on

sensory function and reflexes) at this dose. At about 89-fold the MRHD, decreased maternal body weight gain was observed during lactation. NOAELs were observed at about 9-fold the MRHD for maternal toxicity, and 89-fold for developmental toxicity.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/toxicology supports approval of vibegron 75 mg for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

1.3.2 Additional Non Clinical Recommendations

No additional recommendations are being made.

1.3.3 Labeling

Division and sponsor agreed upon labeling for nonclinical-related sections of the Prescribing Information (PI):

INDICATIONS AND USAGE

GEMTESA is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency (1)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

In animal studies, no effects on embryo-fetal development were observed following administration of vibegron during the period of organogenesis at exposures approximately 275-fold and 285-fold greater than clinical exposure at the recommended daily dose of GEMTESA (b) (4) in rats and rabbits, respectively. Delayed fetal skeletal ossification was observed in rabbits at approximately 898-fold clinical exposure, in the presence of maternal toxicity. In rats treated with vibegron during pregnancy and lactation, no effects on offspring were observed at 89-fold clinical

exposure. Developmental toxicity was observed in offspring at approximately 458-fold clinical exposure, in the presence of maternal toxicity (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies carry some risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively.

Data

Animal Data

In an embryo-fetal developmental toxicity study (b) (4) pregnant rats were treated with daily oral doses of 0, 30, 100, 300, or 1000 mg/kg/day vibegron during the period of organogenesis (Days 6 to 20 of gestation.) These doses were associated with systemic exposures (AUC) 0-, 9-, 89-, 275-, and 1867-fold higher, respectively, than in humans treated with the recommended daily dose of GEMTESA (75 mg vibegron). No embryo-fetal developmental toxicity was observed at doses up to 300 mg/kg/day. Treatment with the high dose of 1000 mg/kg/day was discontinued due to maternal toxicity.

In an embryo-fetal developmental toxicity study (b) (4) pregnant rabbits were treated with daily oral doses of 0, 30, 100, or 300 mg/kg/day vibegron during the period of organogenesis (Days 7 to 20 of gestation.) These doses were associated with systemic exposures (AUC) 0-, 86-, 285-, and 898-fold higher, respectively, than in humans treated with the recommended daily dose of GEMTESA (b) (4). No embryo-fetal developmental toxicity was observed at doses of vibegron up to 100 mg/kg/day. Maternal toxicity (decreased food consumption) and reduced fetal body weight and an increased incidence of delayed skeletal ossification, were observed at 300 mg/kg/day.

In a pre- and post-natal developmental toxicity study, pregnant or lactating rats were treated with daily oral doses of 0, 30, 100, or 500 mg/kg/day vibegron from day 6 of gestation through day 20 of lactation. These doses were associated with estimated systemic exposures (AUC) 0-, 9-, 89-, and 458-fold higher, respectively, than in humans treated with the recommended daily dose of GEMTESA (b) (4). No developmental toxicity was observed in F1 offspring at doses up to 100 mg/kg/day. Maternal toxicity was observed during lactation (decreased body weight gain) at doses ≥ 100 mg/kg/day and during gestation (decreased body weight gain and food consumption) at 500 mg/kg/day. Developmental toxicity was observed in F1 offspring (increased stillborn index, lethality, reduced viability and weaning indices, decreased body weight and body weight gains, low physical development differentiation indices, and effects on sensory function and reflexes) at 500 mg/kg/day.

8.2 Lactation

Risk Summary

(b) (4)

(b) (4)

When a single oral dose of radiolabeled vibegron was administered to postnatal nursing rats, radioactivity was observed in milk (see Animal Data).

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GEMTESA and any potential adverse effects on the breastfed infant from GEMTESA or from the underlying maternal condition.

Data

Animal Data

In a lactational transfer study (b) (4) lactating rats were treated with a single oral dose of 10 mg/kg radiolabeled [³H] vibegron on postpartum day 10. Levels of radioactivity were determined in milk and plasma collected at 1, 4, 12, and 24 after dosing. The C_{max} of total radioactivity in milk and plasma were observed at 9 and 2 hours after dosing, respectively, with a maximum milk-to-plasma concentration ratio of 2.2 observed at 12 hours after dosing. Vibegron elimination from milk showed a similar trend as that from plasma. The radioactivity concentration in milk at 24 hours after administration was approximately 25% of the C_{max}.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Vibegron is a selective human beta-3 adrenergic receptor (AR) agonist (b) (4). Activation of the beta-3 AR increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No carcinogenicity was observed in long-term studies conducted in mice and rats treated with daily oral doses of vibegron for approximately 2 years. In the mouse carcinogenicity study, CD-1 mice were treated with daily oral doses of vibegron up to 90 mg/kg/day in males and up to 150 mg/kg/day in females, corresponding to estimated systemic exposures (AUC) 21- and 55-fold higher, respectively, than in humans treated with the recommended daily dose of GEMTESA (b) (4). In the rat carcinogenicity study, Sprague Dawley rats were treated with daily oral doses of vibegron up to 30 mg/kg/day in males and up to 180 mg/kg/day in females, corresponding to systemic exposures (AUC) 18- and 117-fold higher, respectively, than in humans treated with the recommended daily dose of GEMTESA (b) (4).

Mutagenesis

Vibegron was not mutagenic in *in vitro* microbial reverse mutation assays, showed no evidence of genotoxic activity in an *in vitro* human peripheral blood lymphocyte chromosomal aberration assay, and did not increase the frequency of micronucleated polychromatic erythrocytes in an *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

In fertility/general reproductive toxicity studies conducted in rats, females were treated with daily oral doses of 0, 30, 100, 300, or 1000 mg/kg/day vibegron and males were treated with daily oral doses of 0, 10, 30, or 300 mg/kg/day vibegron. No effects on fertility were observed in female or male rats at doses up to 300 mg/kg/day, associated with systemic exposure (AUC) at least 274-fold higher than in humans treated with the recommended daily dose of GEMTESA (b) (4). General toxicity, decreased fecundity, and decreased fertility were observed in female rats at 1000 mg/kg/day, associated with estimated systemic exposure 1867-fold higher than in humans treated with the recommended daily dose of GEMTESA (b) (4).

2 Drug Information

2.1 Drug

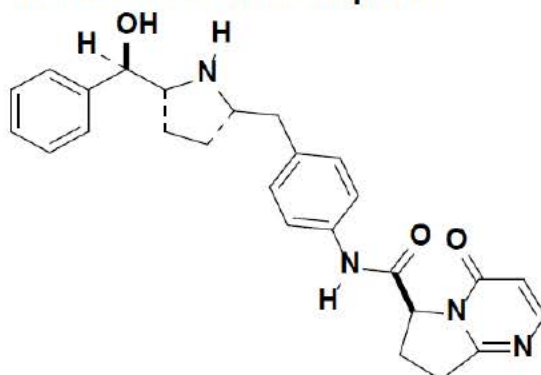
CAS Registry Number: 1190389-15-1

Generic Name: vibegron

Code Name: MK-4618, KRP-114V, RVT-901

Chemical Name: (6S)-N-(4-([(2S,5R)-5-[(R)-hydroxy(phenyl)methyl]pyrrolidin-2-yl] methyl)phenyl)-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-a]pyrimidine-6-carboxamide

Molecular Formula/Molecular Weight: C₂₆H₂₈N₄O₃ / 444.538 g/mol

Structure or Biochemical Description**Pharmacologic Class:** Beta-3-adrenergic agonist**2.2 Relevant INDs, NDAs, BLAs and DMFs**

IND 106410

2.3 Drug Formulation**Composition of Vibegron 75 mg Tablets (sponsor's table)**

Composition of Vibegron 75 mg Tablets (Sponsor's table)			
Component	Quality Standard	Component Function	Quantitative Composition (mg/tablet)
Vibegron	In-house	Active ingredient	75.00
Mannitol	USP/NF	(b) (4)	(b) (4)
Microcrystalline Cellulose (b) (4)	NF, Ph.Eur		
Croscarmellose Sodium	NF, Ph.Eur		
Hydroxypropyl Cellulose	NF, Ph.Eur		
Magnesium Stearate	NF, Ph.Eur		
(b) (4)			
Total Coated Tablet Weight (mg)			

Abbreviations: NF=National Formulary; Ph.Eur.=European Pharmacopoeia; USP= United States Pharmacopeia

(b) (4)

Quantitative Composition of Film Coating Material (Table 2)

Quantitative Composition of Film Coating Material (Table 2)		
(b) (4)	Quality Standard	Weight/Weight %
Lactose Monohydrate	NF, Ph.Eur, JP	(b) (4)
(b) (4) Hypromellose	USP, Ph.Eur, JP, ChP	
Titanium Dioxide	USP, Ph.Eur, JP, ChP, FCC	
Triacetin	USP, Ph.Eur, ChP, FCC	
FD&C Blue#2/ (b) (4)	Aluminum Lake	
JECFA, JSFA		
(b) (4)		

Abbreviations: NF=National Formulary; Ph.Eur.=European Pharmacopoeia; USP= United States Pharmacopoeia; JP=Japanese Pharmacopoeia; JSFA=Japan's Specifications and Standards for Food Additives; JECFA=Joint Evaluation Committee on Food Additives; ChP=Chinese Pharmacopoeia; FCC=Food Chemicals Codex

2.4 Comments on Novel Excipients

No novel excipients were used.

2.5 Comments on Impurities/Degradants of Concern

A limit of (b) (4) µg/day (b) (4) ppm) for individual impurities and (b) (4) µg/day (b) (4) ppm) for total impurities have been set as acceptance criteria for 2 genotoxic impurities (b) (4) and additional non-genotoxic impurities, detected in vibegron batches.

2.6 Proposed Clinical Population and Dosing Regimen

Vibegron is proposed for treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in men and women at a daily oral dose of 75 mg/day.

2.7 Regulatory Background

Vibegron is a new molecular entity and the second beta-3 adrenergic agonist to be developed for overactive bladder. The original IND 106410 was initiated on January 29, 2010.

3 Studies Submitted**3.1 Studies Reviewed**

Oral Cardiovascular and Respiratory Telemetry Study in Monkeys (Study no.: TT #09-5605) p. 29

Six-Month Oral Toxicity Study in Rats p. 58

Nine-Month Oral Toxicity Study in Cynomolgus Monkeys p.60

Three-Month Oral Toxicity Study in Rats p.72

Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys p.76

Effect of MK-4618 on Cardiovascular Function in Anesthetized Dogs p.45

MK-4618: Electrophysiological Evaluation on hERG Channel Current Stably Expressed in CHO Cells p.28

Microbial Mutagenesis Assay p.97

Chromosome Aberration Test in Human Blood Lymphocytes p.105

Assay for Micronucleus Induction in Rat Bone Marrow From a 14-Day Oral Toxicity Study p.106

Two-Year Oral Carcinogenicity Study in CD1 Mice p.108

Two-Year Oral Carcinogenicity Study in Rats with Six-Month Toxicokinetic Evaluation p.112

Oral Fertility Study in Male Rats p.119

Oral Fertility Study in Female Rats p.120

Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rats p.123

Oral Embryo-Fetal Developmental Toxicity and Toxicokinetic Study in Rabbits p.125

Study for Effects of KRP-114V on Pre- and Postnatal Development, including Maternal Function by Oral Administration in Rats p.128

Consideration of milk transfer in rats following administration of [³H] KRP-114V p.58

4 Pharmacology

4.1 Primary Pharmacology

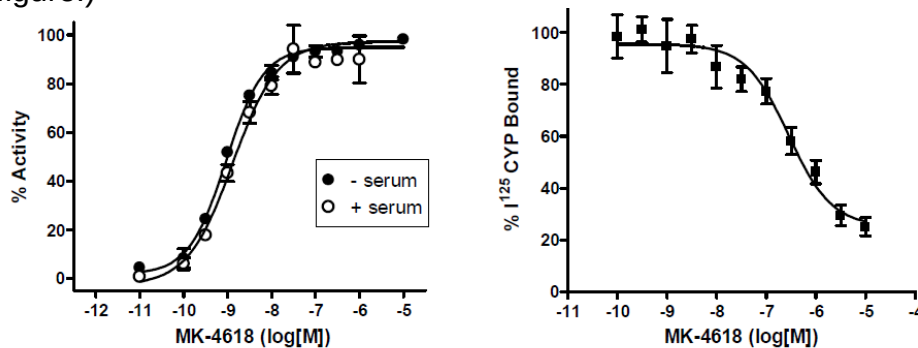
Study title: In Vitro Activity of MK-4618 at β Adrenergic Receptors (AR) (Merck PD0001, 2010)

In a standard competition binding assay, using membranes prepared from recombinant cells expressing β_1 , β_2 or β_3 -adrenergic agonists and from cell lines stably expressing rat, rhesus and dog β_3 -AR receptors, the degree of activation and EC_{50} relative to a full agonist (isoproterenol) were measured. The potency and efficacy at the rat, rhesus and dog receptors were determined in the presence of 40% serum from the appropriate species, using otherwise identical protocols.

MK-4618 activated the human β_3 -AR and increased cAMP levels, with an EC_{50} of 1.1 nM and 87% activation relative to isoproterenol. MK-4618 had >9000-fold selectivity for β_3 -AR over β_1 -AR or β_2 -AR in cell-based in vitro functional assays. A small serum shift was observed in the presence of 40% human serum.

MK-4618 inhibited binding of ^{125} I-CYP to human β_3 -AR-expressing CHO cells in a concentration dependent manner with an IC_{50} of 193 nM. It did not appear to bind to either β_1 or β_2 adrenergic receptors.

Effects of MK-4618 on cAMP increase relative to isoproterenol (A) and ^{125} I-CYP binding (B) in CHO cells expressing human β_3 adrenergic receptors (sponsor's figure.)



Functional and binding activity of MK-4618 at human β_3 , β_1 and β_2 adrenergic receptors

Subtype	Functional	Binding
	EC_{50} , nM (% activation, n)	IC_{50} , nM (n)
β_3 - 40%serum	1.1 ± 0.5 (84%, 7)	193 ± 41 (5)
β_3 + 40%serum	1.7 ± 0.9 (102%, 15)	N.D.
β_1	>10000 (5%, 3)	>20000 (2)
β_2	>10000 (7%, 3)	>20000 (2)

Mean $\pm$ SEM.

N.D., not determined.

(Sponsor's table)

Rhesus monkey was shown to be pharmacologically similar in response to humans. Binding affinity for rat and dog β_3 adrenergic receptors was weaker.

Potency and species specificity of MK-4618 at β_3 -AR (sponsor's table.)

Species	40% serum	EC ₅₀ , nM (% activation, n)
Rhesus monkey	-	1.7 ± 1.0 (108%, 7)
	+	3.1 ± 1.3 (98%, 7)
Rat	-	86 ± 35 (83%, 8)
	+	122 ± 33 (89%, 6)
Dog	-	11 ± 4.2 (82%, 8)

Mean ± SEM.

Study title: Radioligand Binding, and Cellular assays of the activity of the test compound(s) RV 901 (MK-4618) and Mirabegron (RVT-901-9009, 2017)

Stimulation by MK-4618 at β_3 adrenergic receptors was found to be similar to mirabegron in HEK-293 cells. Inhibition at β_1 -AR and β_2 -AR was found to be similar for both compounds and minimal.

Significant responses ($\geq 50\%$ inhibition or stimulation) in primary assays (sponsor's table.)

Cat #	Assay Name	Species	Cell Name	Conc.	Criteria	Resp.	Ag.	Ant.	IC ₅₀ /EC ₅₀ *
Compound: Mirabegron, PT #: 1211533									
302200	Adrenergic β_3 , Adenylyl Cyclase	hum	HEK-293	10 nM	$\geq \pm 50\%$		60%	ND	10.0 ± 0.56 nM
Compound: RV 901 (MK-4618), PT #: 1211532									
302200	Adrenergic β_3 , Adenylyl Cyclase	hum	HEK-293	3 nM	$\geq \pm 50\%$		59%	ND	2.13 ± 0.25 nM

Study title: Antagonist and agonist primary screen (Urovant, RVT-901-9008, 2017)

MK-4618 and mirabegron were tested in DiscoverX patented biosensor assays for G-protein coupled receptor activation, endocytosis, and calcium mobilization. For antagonist and agonist assays, data was normalized to the maximal and minimal response observed in the presence of control ligand (phenylephrine for arrestin-mediated receptor activation, epinephrine for arrestin-mediated endocytosis, and A61603 for calcium flux) and vehicle. Similar results were obtained for MK-4618 and mirabegron (sponsor's table.)

Compound Name	Project ID	Assay Name	Assay Format	Assay Target	Conc (uM)	Value 1	Value 2	Average Value	Std Deviation	% Efficacy
Mirabegron	URO001-01-c-00001-000-00	Calcium Flux	Agonist	ADRA1A	0.1	107.8	110.2	109	1.7	-1.1
Mirabegron	URO001-01-c-00001-000-00	Calcium Flux	Agonist	ADRA1A	1	110.8	110.9	110.8	0.1	-0.4
Mirabegron	URO001-01-c-00001-000-00	Calcium Flux	Agonist	ADRA1A	10	110.5	111.7	111.1	0.8	-0.3
Mirabegron	URO001-01-c-00001-000-00	Calcium Flux	Antagonist	ADRA1A	0.1	279.5	289.4	284.4	7	3.6
Mirabegron	URO001-01-c-00001-000-00	Calcium Flux	Antagonist	ADRA1A	1	279.4	291.5	285.5	8.6	3
Mirabegron	URO001-01-c-00001-000-00	Calcium Flux	Antagonist	ADRA1A	10	267	282.5	274.8	11	9.1
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1B	0.1	137760	141400	139580	2573.9	0.8
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1B	1	141960	149520	145740	5345.7	1.4
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1B	10	148680	156520	152600	5543.7	2.1
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1B	0.1	694400	805280	749840	78404	-9.5
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1B	1	674520	711200	692860	25936.7	0.7
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1B	10	450800	458640	454720	5543.7	43.4
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1D(82-572)	0.1	8400	8680	8540	198	-1.7
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1D(82-572)	1	9520	9800	9660	198	0.8
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1D(82-572)	10	9800	10640	10220	594	2
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1D(82-572)	0.1	34720	36400	35560	1187.9	0.3
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1D(82-572)	1	35000	38640	36820	2573.9	-4.7
Mirabegron	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1D(82-572)	10	23520	29120	26320	3959.8	36.8
RVT-901	URO001-01-c-00001-000-00	Calcium Flux	Agonist	ADRA1A	0.1	111.4	112	111.7	0.4	-0.1
RVT-901	URO001-01-c-00001-000-00	Calcium Flux	Agonist	ADRA1A	1	111.2	111.2	111.2	0	-0.3
RVT-901	URO001-01-c-00001-000-00	Calcium Flux	Agonist	ADRA1A	10	110.3	111.2	110.8	0.6	-0.4
RVT-901	URO001-01-c-00001-000-00	Calcium Flux	Antagonist	ADRA1A	0.1	288.1	291.5	289.8	2.4	0.6
RVT-901	URO001-01-c-00001-000-00	Calcium Flux	Antagonist	ADRA1A	1	287.8	292	289.9	3	0.5
RVT-901	URO001-01-c-00001-000-00	Calcium Flux	Antagonist	ADRA1A	10	286.4	286.6	286.5	0.1	2.4
RVT-901	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1B	0.1	138880	146720	142800	5543.7	1.2
RVT-901	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1B	1	128800	135800	132300	4949.7	0.1
RVT-901	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1B	10	121240	126000	123620	3365.8	-0.7
RVT-901	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1B	0.1	697480	725760	711620	19997	-2.7
RVT-901	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1B	1	663320	679840	671580	11681.4	4.5
RVT-901	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1B	10	486360	532560	509460	32668.3	33.6
RVT-901	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1D(82-572)	0.1	7280	8400	7840	792	-3.2
RVT-901	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1D(82-572)	1	8960	10920	9940	1385.9	1.4
RVT-901	URO001-01-c-00001-000-00	Arrestin	Agonist	ADRA1D(82-572)	10	8960	8960	8960	0	-0.8
RVT-901	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1D(82-572)	0.1	34720	37800	36260	2177.9	-2.5
RVT-901	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1D(82-572)	1	34720	35840	35280	792	1.4
RVT-901	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1D(82-572)	10	29120	31080	30100	1385.9	21.9
Tamsulosin hydrochloride	URO001-01-c-00001-000-00	Calcium Flux	Antagonist	ADRA1A	0.1	118.5	120.7	119.6	1.6	97
Tamsulosin hydrochloride	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1B	0.1	133000	133560	133280	396	101.1
Tamsulosin hydrochloride	URO001-01-c-00001-000-00	Arrestin	Antagonist	ADRA1D(82-572)	0.1	8960	9800	9380	594	103.9

Study title: RVT-901: Assessment of Agonist Activity in Human β_3 Stably Expressing CHO Cell line and Rabbit β_3 Transiently Transfected CHO Cell Line (Merck, RVT-901-9004, 2013)

The relevance of rabbit as a toxicological test species was assessed in cell culture. The rabbit β_3 -AR ORF was cloned into a constitutive mammalian expression system and transiently transfected into CHO cells via the standard lipofectamine transfection protocol. Agonist activity of isoproterenol and MK-4618 was assessed at 72 hours post-infection. In parallel, agonist activity was assessed in human β_3 -AR stably expressed in CHO cells and CHO parental cell lines transfected with mock plasmid. Agonist activity was measured via the LANCE cAMP assay, a time-resolved fluorescence resonance energy transfer (FRET) immune assay that specifically measures cAMP production upon modulation of adenyl cyclase activity.

Isoproterenol exhibited agonist activity against both human (EC_{50} =31 nM) and rabbit (EC_{50} =60 nM) β_3 -AR under the conditions of this in vitro assay.

MK-4618 demonstrated potent activity against both human (EC_{50} =1.2 nM) and rabbit β_3 -AR (EC_{50} =9.6 nM).

Although MK-4618 is approximately 8-fold more potent toward human β_3 -AR than rabbit β_3 -AR, rabbit is concluded to be an appropriate test species.

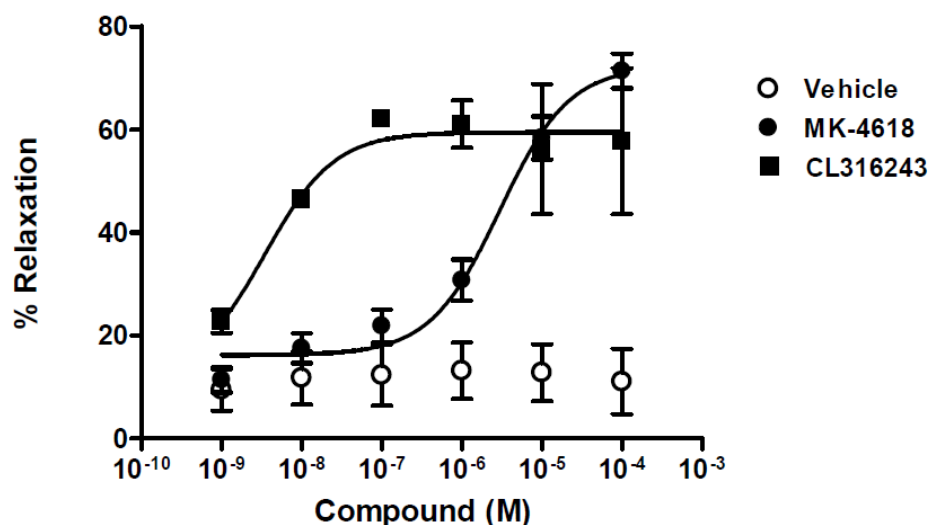
Summary of Agonist Activity (EC₅₀ and % Max) for Isoproterenol and RVT-901 (sponsor's table.)

	Human	Rabbit	Parental CHO
Isoproterenol	31 nM (100%)	60 nM (87%)	>10000 nM (23%)
RVT-901	1.2 nM (100%)	9.6 nM (97%)	>10000 nM (16%)

Study title: MK-4618 Induced Relaxation of Rat Bladder Smooth Muscle (Merck, PD002, 2010)

MK-4618 was evaluated in an in vitro rat bladder strip assay to examine functional relaxation of bladder smooth muscle induced by MK-4618. MK-4618 induced the relaxation of pre-contracted bladder smooth muscle in a concentration-dependent manner, with an EC₅₀ of 3.0 μ M and a maximum relaxation of 71% at 100 μ M. CL316243 was used as a positive control (rat in vitro β_3 -AR EC₅₀ of 5.9 nM). The maximum relaxation achieved for MK-4618 was similar to effects of CL316243 (57%), however the potency was lower for MK-4618 compared to CL316243 (EC₅₀, 3.5 nM)

Relaxation response in rat urinary bladder smooth muscle to MK-4618 and CL316243. Compounds were titrated on KCl-induced contraction (sponsor's figure.)

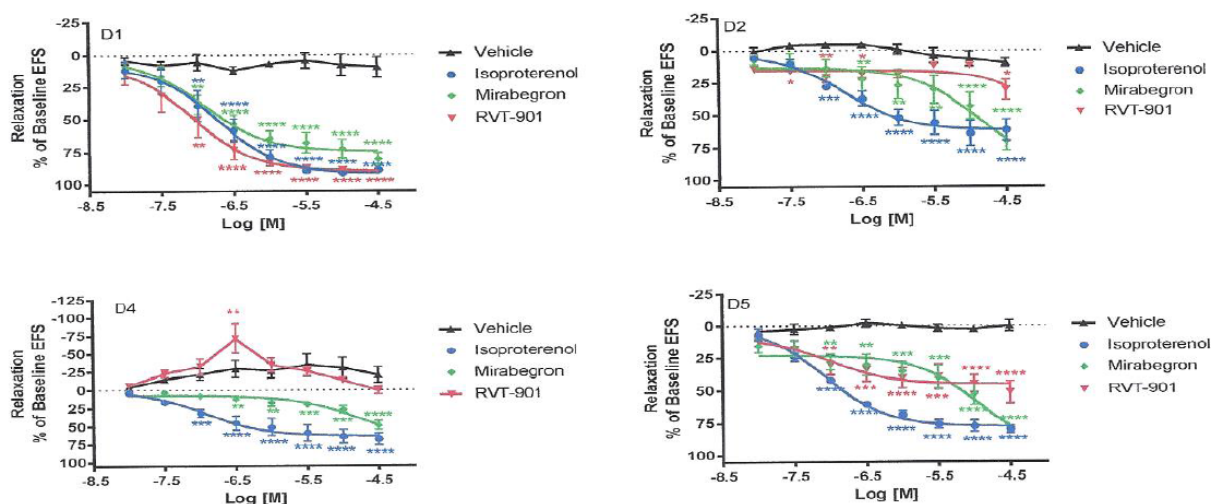


Study title: Study to Assess the Effects of Test Compounds on the Contractility of Electrically Stimulated Human Bladder Strips (Urovant, CDY001, 2017)

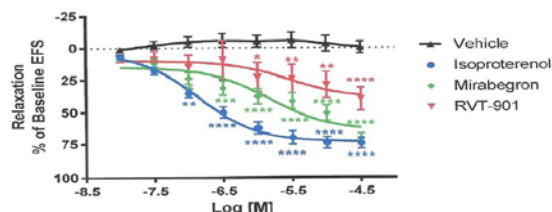
In bladder strips isolated from healthy urinary bladder of 4 human donors, the effects of RVT-901 on contractions induced by electrical field stimulation (EFS) were studied. In 4 donors, addition of isoproterenol, a non-selective beta adrenergic agonist, and mirabegron, a selective beta3-adrenergic agonist, caused a significant decrease in amplitude of EFS evoked human bladder muscle contractions, in a dose dependent manner, compared to vehicle. In two of the four donors tested, RVT-901 also decreased

the amplitude of EFS evoked contractions in a dose dependent manner compared to vehicle.

Effect of RVT-901 on the contractility of human isolated bladder muscle strips - individual donor responses (sponsor's figure.)



Effect of RVT-901 on the contractility of human isolated bladder muscle strips - combined mean data from four donors (sponsor's figure.)



Calculated EC₅₀ concentrations of RVT-901 and Mirabegron

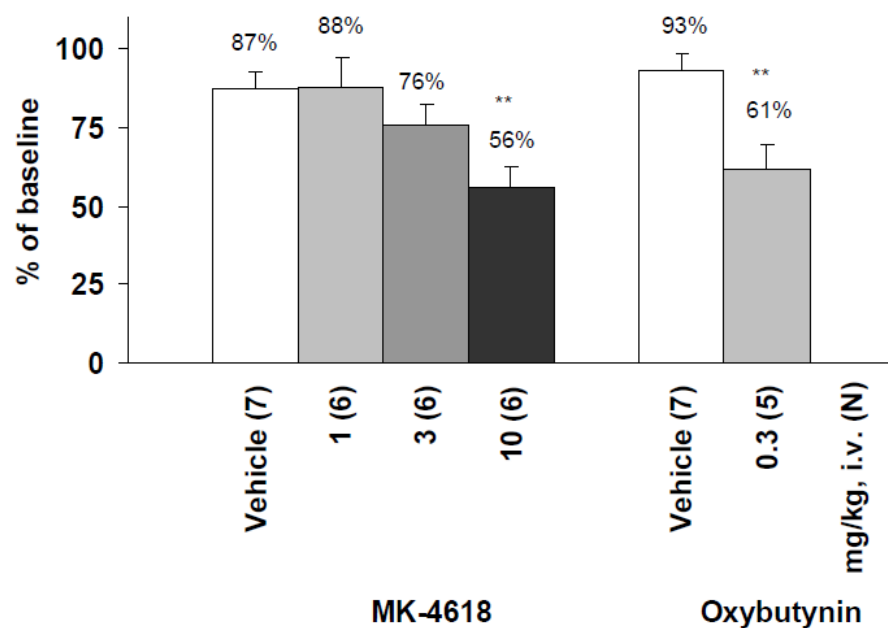
	RVT-901 Log EC ₅₀	RVT-901 EC ₅₀	Mirabegron Log EC ₅₀	Mirabegron EC ₅₀
Donor 1	-7.08	0.0832	-6.912	0.1226 uM
Donor 2	NA	NA	-4.933	11.668 uM
Donor 4	NA	NA	-4.825	14.962 uM
Donor 5	-7.014	0.097 uM	-4.939	11.508 uM
Combined	-7.06	0.087 uM	-5.83	1.479 uM

Study title: Effect of MK-4618 in the Rat Bladder Hyperactivity Model (Merck, PD003, 2010)

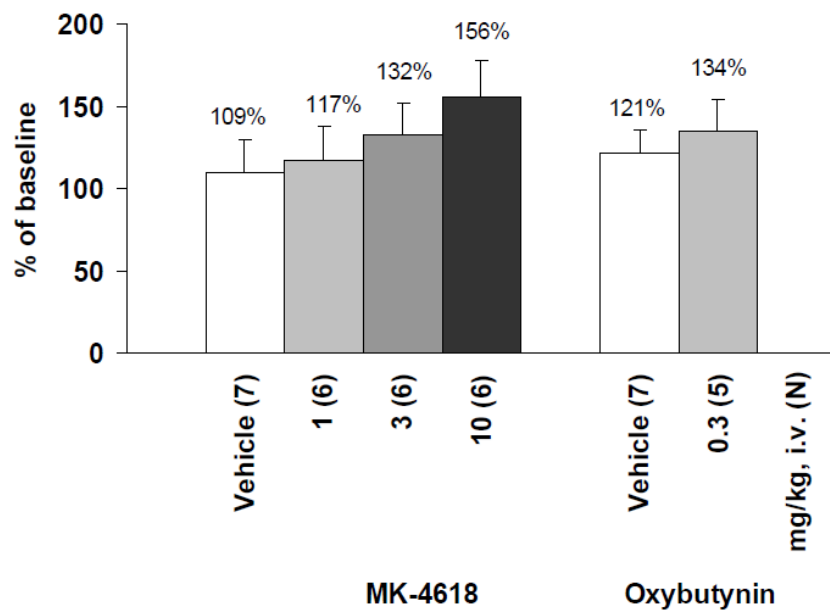
In a rat bladder overactivity model using intravesical acetic acid infusion, MK-4618 caused dose-dependent decrease in micturition pressure with a maximum decrease (56%) comparable to oxybutynin (61%). The minimum effective dose of MK-4618 in decreasing micturition pressure was 10 mg/kg (mean plasma concentration of 57 µM).

Effect of MK-4618 on micturition pressure (A) and functional bladder capacity (B) in the rat acetic acid-induced bladder hyperactivity model (sponsor's figure.)

A



B



Effect of MK-4618 on plasma glycerol levels (adipose tissue) (sponsor's table.)

	Dose (mg/kg)	n	Plasma glycerol (μM)
Vehicle	-	7	158 ± 20
MK-4618	1	6	524 ± 34**
	3	6	457 ± 83**
	10	6	640 ± 43**

Plasma levels of MK-4618 and mirabegron after constant rate infusion (sponsor's table).

Compound	Dose (mg/kg)	n	Plasma level (μmol/L)
MK-4618	1	6	5
	3	6	25
	10	6	57

Study title: Effect of MK-4618 on Plasma Glycerol and Free Fatty Acids Levels in Anesthetized Rats (Merck, PD004, 2010)

MK-4618 dose-dependently increased plasma glycerol and FFA levels in anesthetized rats; however, glycerol elevation was observed even at the lowest dose, which did not cause bladder effect (minimal effective dose 10 mg/kg IV) in this model.

Effect of MK-4618 on plasma glycerol and free fatty acid (FFA) levels in anesthetized rats (sponsor's table.)

	Dose (mg/kg)	Glycerol (μM)	FFA (mEq/mL)
Vehicle	-	92 ± 25	0.16 ± 0.03
MK-4618	0.1	239 ± 8	0.23 ± 0.03
	0.3	358 ± 52**	0.33 ± 0.08
	1	457 ± 56**	0.37 ± 0.05*
	3	525 ± 63**	0.44 ± 0.02**
	10	515 ± 72**	0.45 ± 0.05**

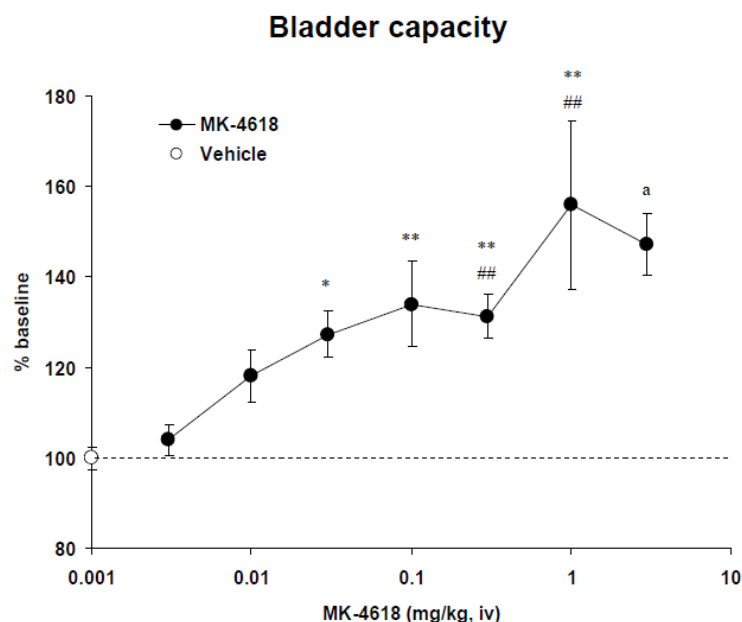
Study title: Effect of MK-4618 on the Cystometric Parameters and Serum Glycerol Levels in Anesthetized Rhesus Monkeys (Merck, PD005, 2010)

In a rhesus monkey cystometry model, MK-4618 PK/PD parameters of bladder function and adipose tissue were measured and compared.

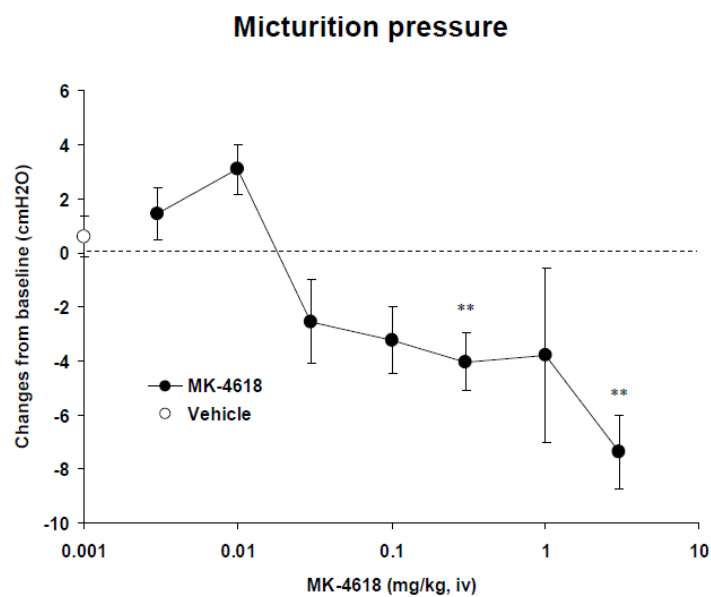
MK-4618 increased bladder capacity in a dose-dependent manner with mean effective dose 0.03 mg/kg and maximum bladder capacity increase $156 \pm 19\%$ of baseline bladder capacity. Micturition pressure was significantly decreased at 0.3 and 3 mg/kg. Bladder compliance was increased at doses greater than 0.1 mg/kg. serum glycerol levels also increased dose-dependently. The EC₅₀s for increased bladder capacity and increased serum glycerol were 2.9 and 9.9 nM, respectively.

Effect of MK-4618 on the bladder capacity (A), maximum intravesical pressure (B) and bladder compliance (C) in rhesus monkeys (sponsor's figure.)

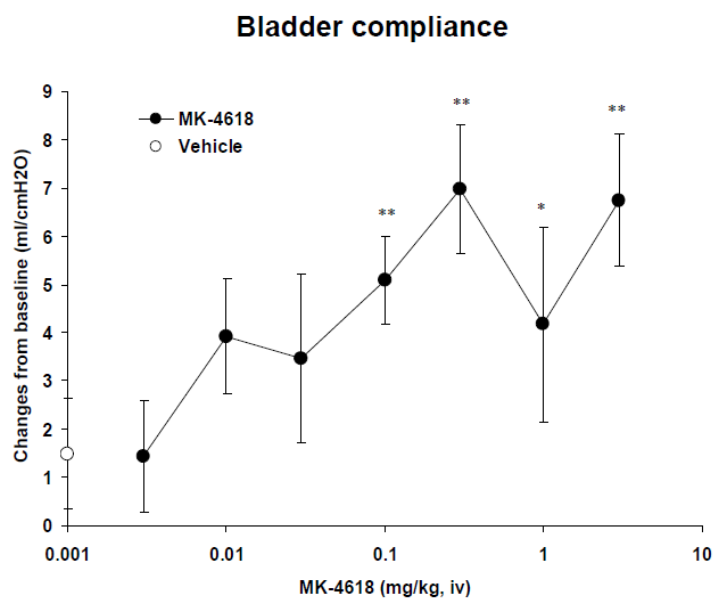
A



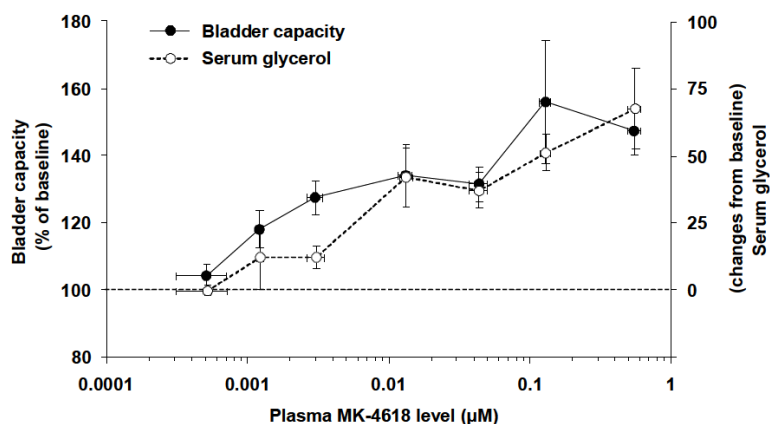
B



C



PK/PD relationship for MK-4618 for both bladder capacity and serum glycerol levels (sponsor's figure.)



EC₅₀ values of MK-4618 for bladder capacity and serum glycerol increase in female rhesus monkeys (sponsor's table.)

Parameter	EC ₅₀ , nM	(95% CI)
Bladder	2.9	(1.0-6.8)
Glycerol	9.9	(1.8-53.6)

Study title: In Vivo Selectivity of MK-4618 to β_3 -AR in Rhesus Monkeys (Merck, PD006, 2010)

In vivo selectivity of MK-4618 to β_3 -AR was examined using anesthetized male rhesus monkeys. Serum glycerol and free fatty acid (FFA) levels increased dose-dependently.

Effect of MK-4618 on Serum Glycerol and FFA in Anesthetized Rhesus Monkeys (sponsor's table.)

	Dose (mg/kg)	Glycerol (µM)	FFA (mEq/ml)
Vehicle	-	3.3	0.05
MK-4618	0.001	34.8 ± 9.3	0.90 ± 0.11
	0.01	88.9 ± 2.2	1.43 ± 0.11
	0.1	140.2 ± 8.2	1.87 ± 0.25
	1	175.4 ± 19.9	2.17 ± 0.40

4.2 Secondary Pharmacology

Study title: MRL Report PD007

Significant responses ($\geq 50\%$ inhibition or stimulation) were noted in the following primary assays: (sponsor's table.)

PRIMARY BIOCHEMICAL ASSAY	SPECIES	CONC.	% INH.	IC ₅₀ *	K _i	n _H
Protein Serine/Threonine Kinase, PRKCA (PKC α)	hum	100 μ M	-79			
Adrenergic β_3	hum	10 μ M	53	4.13 μ M	3.1 μ M	0.440
Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	hum	10 μ M	89	1.14 μ M	0.606 μ M	1.2

Protein Serine/Threonine Kinase, PRKCA (PKC α)

Source: Human recombinant insect Sf9 cells

Substrate: 250 ug/mL Histone

Vehicle: 1% DMSO

Pre-Incubation Time/Temp: 15 minutes @ 25 C

Incubation Time/Temp: 10 minutes @ 25 C

Incubation Buffer: 20 mM HEPES, 8 mM MgCl, 0.08 mM CaCl, 100 ug/ml

Phosphatidylserine, 20 ug/ml Diacylglycerol

Quantitation Method: Quantitation of [³²P]Histone

Significance Criteria: > 50% of max stimulation or inhibition

Adrenergic β_3

Source: Human recombinant HEK-293 cells

Ligand: 0.5 nM [¹²⁵I] Cyanopindolol

Incubation Time/Temp: 90 minutes @ 25 C

Incubation Buffer: 20 mM Tris-HCl, pH 7.4, 120 mM NaCl, 2 mM MgCl, 50 mg/l

Ascorbate, 4 mg/l BSA

Vehicle: 1% DMSO

Non-Specific Ligand: 1000 uM Alprenolol

K_D: 1.5 nM

Bmax: 0.55 pmol/mg Protein

Specific Binding: 80%

Quantitation Method: Radioligand Binding

Significance Criteria: $\geq 50\%$ of max stimulation or inhibition

Transporter, Serotonin (5-Hydroxytryptamine) (SERT)

Source: Human recombinant HEK-293 cells

Ligand: 0.15 nM [¹²⁵I] RTI-55

Vehicle: 1% DMSO

Incubation Time/Temp: 3 hours @ 4 C

Incubation Buffer: 50 mM Tris-HCl, pH 7.4, 100 mM NaCl 1 uM Leupeptin 10 uM PMSF

Non-Specific Ligand: 10 uM Imipramine

K_D: 0.17 nM

B_{max}: 0.41 pmole/mg Protein

Specific Binding: 95%

Quantitation Method: Radioligand Binding

Significance Criteria: $\geq 50\%$ of max stimulation or inhibition

Study title: MRL Report PD009

No significant response ($\geq 50\%$ inhibition or stimulation) was noted in the potassium channel assay:

ASSAY NAME	REFERENCE COMPOUND	HISTORICAL		n _H	CONCURRENT	
		IC ₅₀	K _i		BATCH *	IC ₅₀
Potassium Channel [K _A]	Dendrotoxin	0.089 nM	0.069 nM	0.9	232109	0.033 nM

Potassium Channel [K_A]

Source: Wistar Rat cerebral cortex

Ligand: 10 pM [¹²⁵I] Dendrotoxin

Vehicle: 1% DMSO

Incubation Time/Temp: 30 minutes @ 4 C

Incubation Buffer: 50 mM Tris-HCl, pH 7.4, 20 mM NaCl, 0.3% BSA

Non-Specific Ligand: 10 nM Dendrotoxin

K_D: 0.035 nM

B_{max}: 0.22 pmol/mg Protein

Specific Binding: 70% *

Quantitation Method: Radioligand Binding

Significance Criteria: $\geq 50\%$ of max stimulation or inhibition

Study title: Serotonin Reuptake Inhibition and Cellular Phospholipidosis Activities of MK-4618 (Study no. PD008, 2010)

MK-4618 was tested in the cellular assays for serotonin reuptake inhibition in hSERT and accumulation of phospholipids.

MK-4618 had an IC₅₀ >9.5 μ M (low activity) in the hSERT functional assay for serotonin reuptake inhibition, using fluoxetine as a positive control.

MK-4618 had weak activity in a phospholipidosis cellular assay (A₅₀ >70 μ M) using the fluorescent labeled phospholipid probe NBD-PE (Bhandari et al., 2008) in HepG2 cells, with 10 μ M amiodarone as a positive control.

4.3 Safety Pharmacology

Study title: Fourteen-Day Oral Toxicity Study in Rats with Functional Observational Battery (FOB) Study no. TT #09-1065

Methods

Doses: 0, 2, 20, or 1000 mg/kg/day of MK-4618 (base)
Frequency of dosing: Once daily via oral gavage
Formulation/Vehicle: 20% polyethylene glycol 400 in deionized water
Species/Strain: Crl:CD(SD) rats, 10/sex/group

Observations and Results

Mortality/ Clinical Signs

At 1000 mg/kg/day, unscheduled deaths were observed beginning Study Day 5 following decreased activity and skin turgor, distended abdomen and urine staining. The cause of death was considered to be drug aspiration/reflux. Physical signs included salivation, distended abdomen, urine staining, and red color muzzle staining (primarily in females.)

Body Weights/ Food Consumption

At 1000 mg/kg/day, body weight loss in females and decreases in body weight gain in males were associated with transiently decreased food consumption.

Hematology/ Clinical Chemistry

At 1000 mg/kg/day, slight decreases in leukocytes (42%) and primary lymphocytes (43%) were observed. In males, very slight decreases in platelets (21%), reticulocytes (23%) and neutrophils (30%) were also observed. In females, a very slight increase in fibrinogen (65%) was observed. Decreases in triglycerides (up to 72%), very slight decreases in cholesterol (23%, females), very slight increases in chloride (2%), increases in ALT (69%, up to 3-fold elevations in some animals) and BUN (individual females), and very slight decreases in total protein (9%), and albumin (8%) were also observed. Very slight increases in urinary protein (females) and very slight to slight increases in urine volume were observed.

Histopathology

At 1000 mg/kg/day, inflammation of nasopharynx, focal inflammation of lungs and an accumulation of foamy alveolar macrophages, consistent with aspiration/reflux were observed. Myocardial degeneration in heart and fibrosis in liver was observed in one rat.

Functional Observational Battery

Neurobehavioral effects were observed after a single oral dose at 20 mg/kg (about 9-fold) and 1000 mg/kg (about 1671-fold): decreased locomotion (decreased line crosses and rears), abnormal gait and abnormal posture. At 1000 mg/kg, palpebral closure, constricted pupil size, decreased muscle tone, and decreased body temperature were observed. In one animal, gasping and sternal recumbency was noted.

Toxicokinetics

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Rats Following Dosing of MK-4618 : Study Week 2				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
2	Female	1.14 $\pm$ 0.277	0.254 $\pm$ 0.113	1.0 $\pm$ NC
	Male	0.454 $\pm$ 0.0274	0.122 $\pm$ 0.00896	2.0 $\pm$ NC
	All	0.799 $\pm$ 0.165	0.175 $\pm$ 0.0622	1.0 $\pm$ NC
20	Female	32.7 $\pm$ 4.10	8.07 $\pm$ 2.31	2.0 $\pm$ NC
	Male	28.6 $\pm$ 2.82	10.1 $\pm$ 1.36	2.0 $\pm$ NC
	All	30.7 $\pm$ 2.71	9.09 $\pm$ 1.30	2.0 $\pm$ NC
1000	Female	5770 $\pm$ 306	315 $\pm$ 13.4	4.0 $\pm$ NC
	Male	4950 $\pm$ 233	266 $\pm$ ID	4.0 $\pm$ NC
	All	5450 $\pm$ 260	295 $\pm$ 17.5	4.0 $\pm$ NC

NC = Not Calculated

ID = Insufficient Data

^a MK-4618 concentrations in plasma from all control group animals at 2 hours post-dose were below the lower limit of quantitation of the bioanalytical method.

*Sponsor table

Study title: MK-4618: Electrophysiological Evaluation on hERG Channel Current Stably Expressed in CHO Cells (Study no. TT #09-4709)

In CHO-K1 Chinese Hamster Ovary cells, at a concentration of 31 μ M (112-fold the MRHD of 75 mg using C_{max})(N=5), MK-4618 had no statistically significant effect on hERG channel tail current, but at the maximum testable concentration of 101 μ M (365-fold)(N=4), it inhibited hERG current by 21.4%.

Study title: Oral Cardiovascular and Respiratory Telemetry Study in Monkeys (Study no.: TT #09-5605)

Key Study Findings:

- At 2.5 mg/kg (0.22-fold the MRHD of 75 mg by C_{max}, 0.16-fold by AUC) and above, transient increased heart rate (58 to 112 bpm, 38 to 79%), increased respiration rate (5 to 8 breaths/minute, 14 to 31%), and increased body temperature (0.3 to 0.4°C) were observed. Increases in uncorrected QT interval were also observed at all doses. Corrected QT (QT_c) changes, to account for changes in heart rate, did not reveal a dose relationship, which was interpreted to indicate that drug related increases in QT interval were an artifact of increased heart rate.
- At 15 mg/kg (2.7-fold C_{max}, 1.3-fold AUC) and above, decreased PR interval was also observed (10 to 19%).

- At 135 mg/kg (42-fold C_{max}, 31-fold AUC), increased diastolic blood pressure (13 mmHg, 19%), respiration depth (7 mmHg, 103%), and QRS interval (6 msec, 12%) were also observed in addition to effects observed at lower doses.
- No no-effect level for cardiac effects was observed in this study. However, at 2.5 mg/kg, no increase in PR interval was observed to coincide with the observed transient increase in heart rate.

Methods

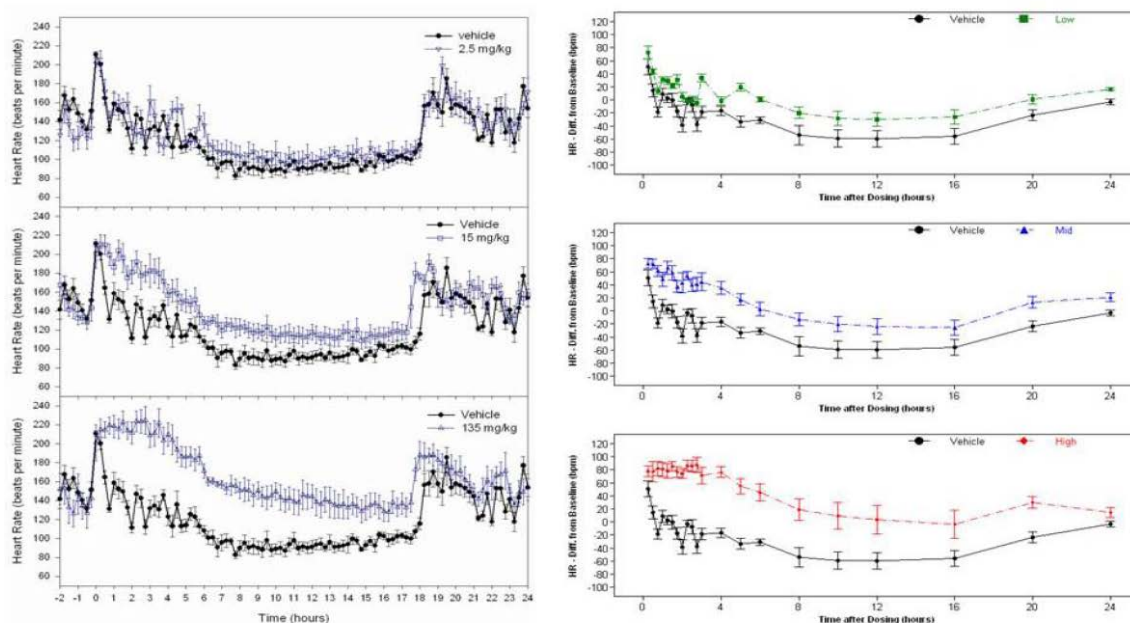
Doses: 0, 2.5, 15 and 135 mg/kg
Frequency of dosing: Once daily
Route of administration: Oral, gavage
Formulation/Vehicle: 20% polyethylene glycol 400 + HCl salt (pH = 2.5 ± 0.2)(5 mL/kg)
Species/Strain: Rhesus monkeys, 2/sex/group
Age/weight: Approximately 3 to 7 years, 7.1 to 9.4 kg
Unique study design: In an escalating dose design, heart rate, arterial blood pressure (systolic, diastolic, and mean pressure), electrocardiographic parameters (PR, QRS, and QT intervals), body temperature, respiratory rate, and depth of respiration were monitored via telemetry for approximately 24 hours postdose. QT interval was corrected for heart rate (QT_c) using an individual animal correction method (Miyazaki's correction).

Observations and Results

Heart rate:

At 2.5 mg/kg, increases in heart rate ranged from 15 to 53 beats per minute (bpm) (10 to 37%), peaking at about 3 hours post dose (lasting from approximately 2.5 hours to 16 hours post dose). At 15 mg/kg, increases ranged from 24 to 82 bpm (17 to 57%), peaking at about 2 hours post dose (lasting from approximately 30 minutes to 24 hours post dose). At 135 mg/kg, increases ranged from 52 to 112 bpm (35 to 79%), peaking at 2 hours post dose (lasting from approximately 30 minutes to 24 hours post dose).

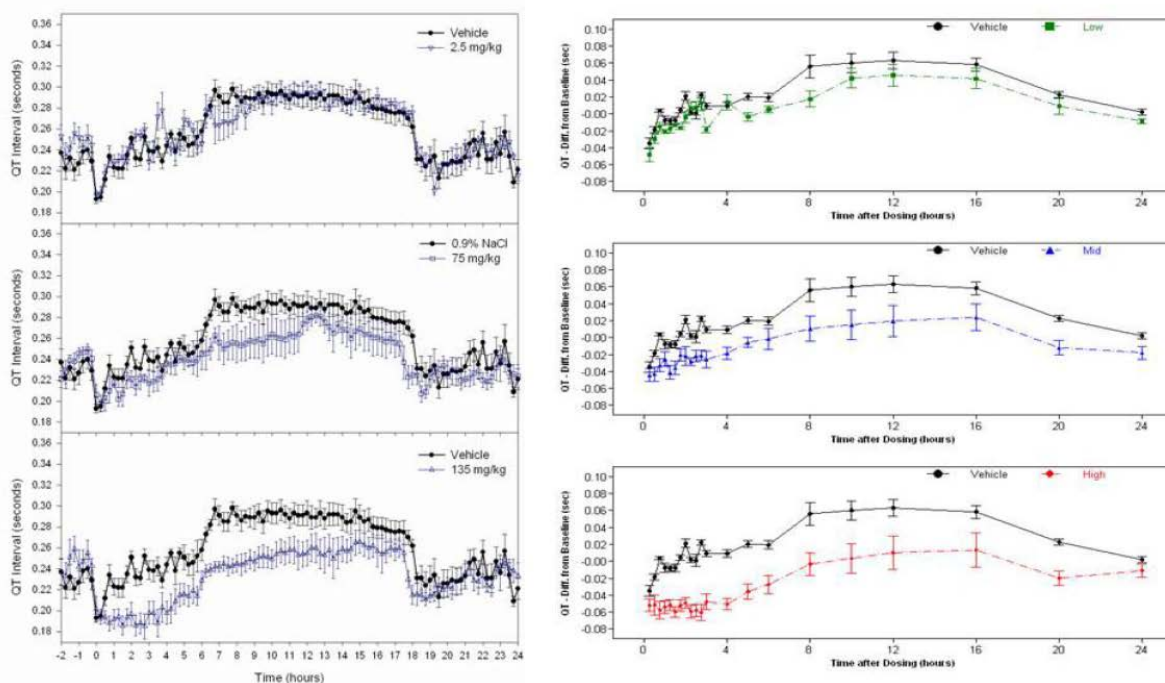
Effect of 2.5, 15, and 135 mg/kg MK-4618 on Heart Rate in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)



QT interval:

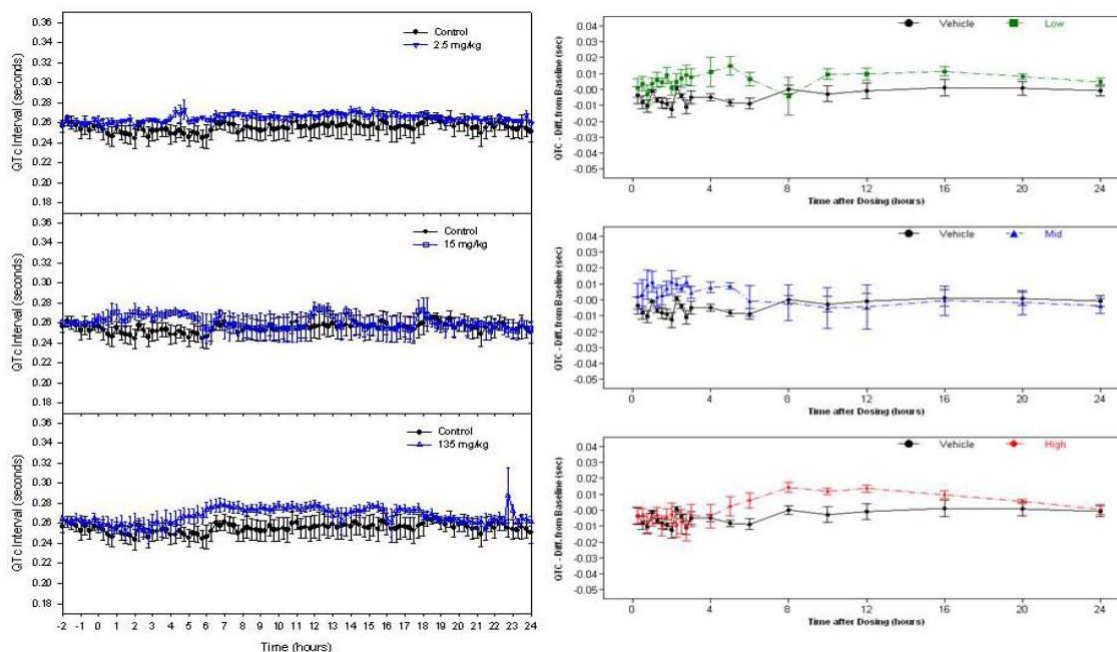
At 2.5 mg/kg, decreases in QT interval ranged from 4 to 39 milliseconds (2 to 17%). At 15 mg/kg, decreases ranged from 33 to 45 milliseconds (13 to 20%). At 135 mg/kg, decreases ranged from 22 to 82 milliseconds (9 to 34%).

Effect of 2.5, 15, and 135 mg/kg MK-4618 on QT Interval in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (no correction for heart rate) (sponsor's figure.)



Using Miyazaki's correction for heart rate in individual animals, an increase in QTc interval at 2.5 mg/kg showed a mean peak increase of 23 milliseconds (9%) at 6 hours post dose (2 to 12 hours). At 15 mg/kg, increases in QTc interval ranged from 9 to 24 milliseconds (4 to 9%), peaking at 2 hours (1.5 to 6 hours.) At 135 mg/kg, increases in QTc interval ranged from 4 to 15 milliseconds (2 to 6%), peaking at 12 hours post dose (4 to 16 hours.)

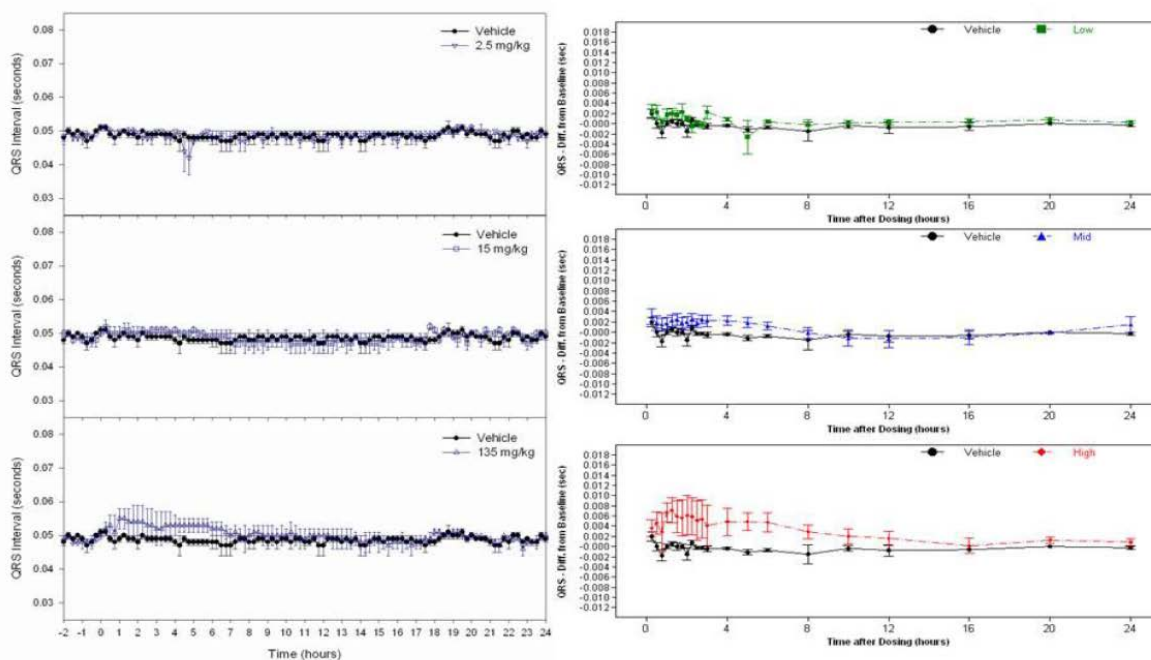
Effect of 2.5, 15, and 135 mg/kg MK-4618 on QTc Interval (Miyazaki's Correction) in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)



QRS interval:

At 135 mg/kg, increases in QRS interval of 2.4 to 6 milliseconds (4 to 12 %) were observed from 30 minutes to 12 hours postdose. No effects on QRS interval were observed at 2.5 or 15 mg/kg.

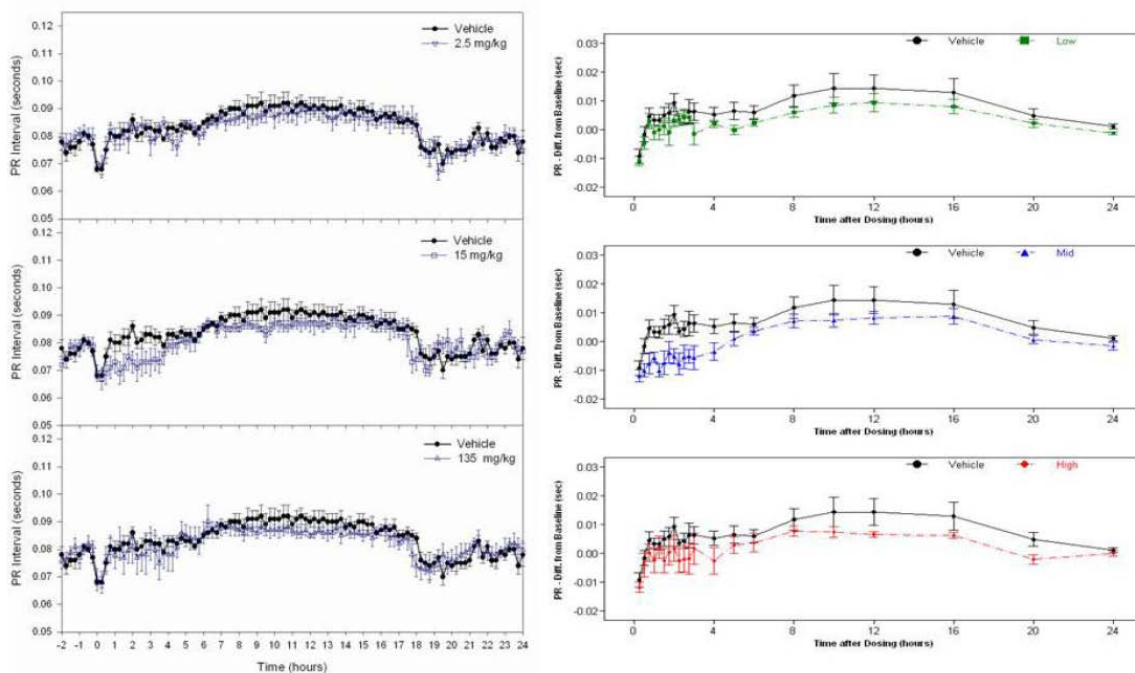
Effect of 2.5, 15, and 135 mg/kg MK-4618 on QRS Interval in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)



PR interval:

At 15 mg/kg, decreases in PR interval ranged from 6 to 14 milliseconds (7 to 19%) from approximately 30 minutes to 20 hours post dose. At 135 mg/kg, decreases in PR interval ranged from 1.2 to 9 milliseconds (2 to 10%) until 24 hours post dose. No effect was observed at 2.5 mg/kg.

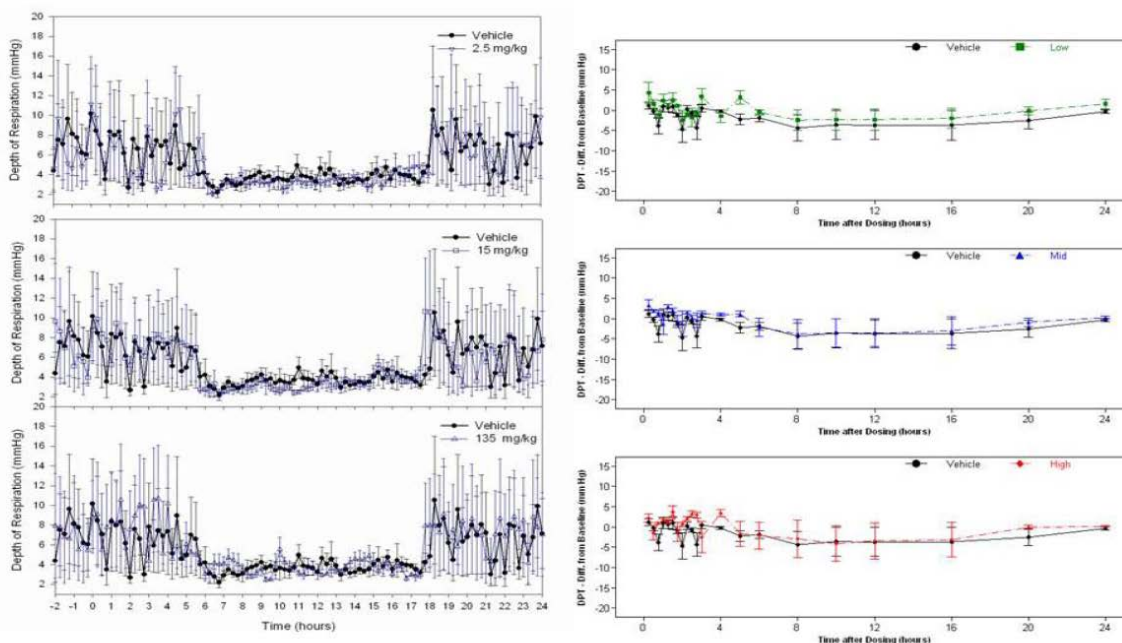
Effect of 2.5, 15, and 135 mg/kg MK-4618 on PR Interval in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)



Depth of respiration:

At 135 mg/kg, increases in depth of respiration of 3.2 to 7 mmHg (51 to 103%) were observed from approximately 30 minutes to 4 hours post dose. No effects were observed at 2.5 or 15 mg/kg.

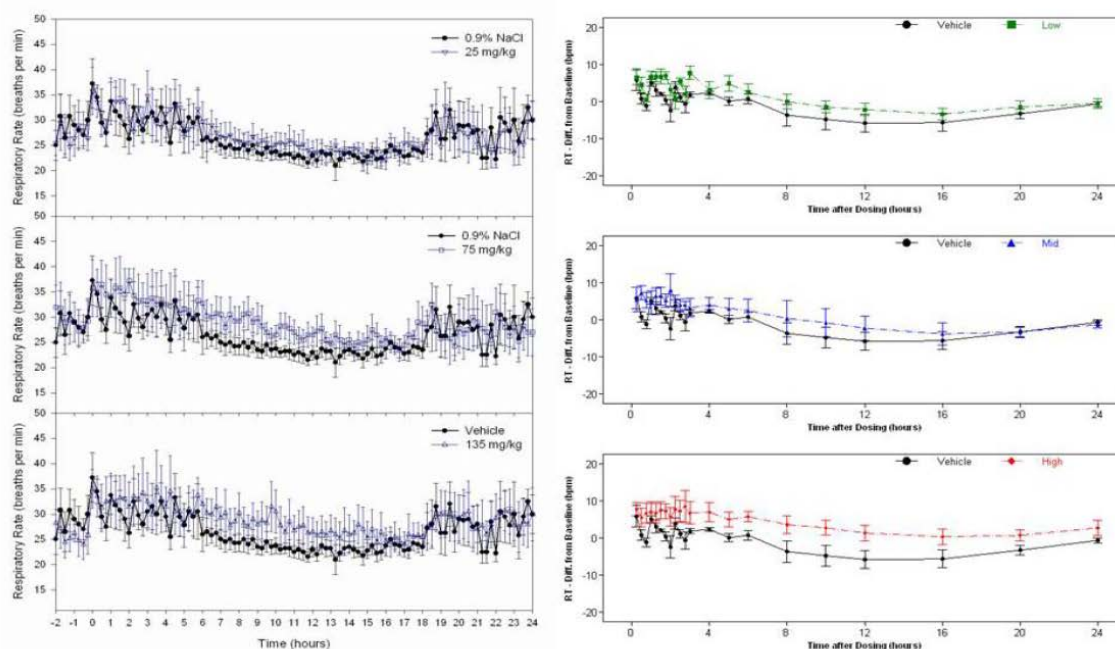
Effect of 2.5, 15, and 135 mg/kg MK-4618 on Depth of Respiration in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)



Rate of respiration:

At, 2.5 mg/kg, increases in respiration of 2 to 7 breaths per minute (5 to 24%) were observed until approximately 20 hours post dose. At 15 mg/kg, increases of 2 to 5 breaths per minute (5 to 14%) were observed until approximately 20 hours. At 135 mg/kg, increases in rate of respiration of 2 to 8 breaths per minute (9 to 31%) were observed until approximately 24 hours post dose.

Effect of 2.5, 15, and 135 mg/kg MK-4618 on Rate of Respiration in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)

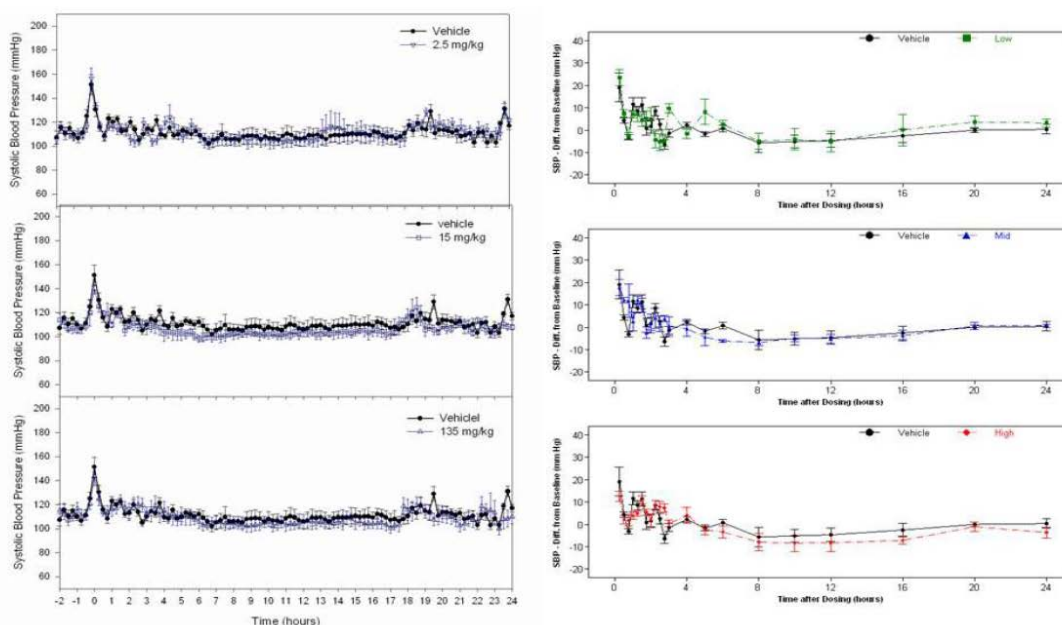


Blood pressure:

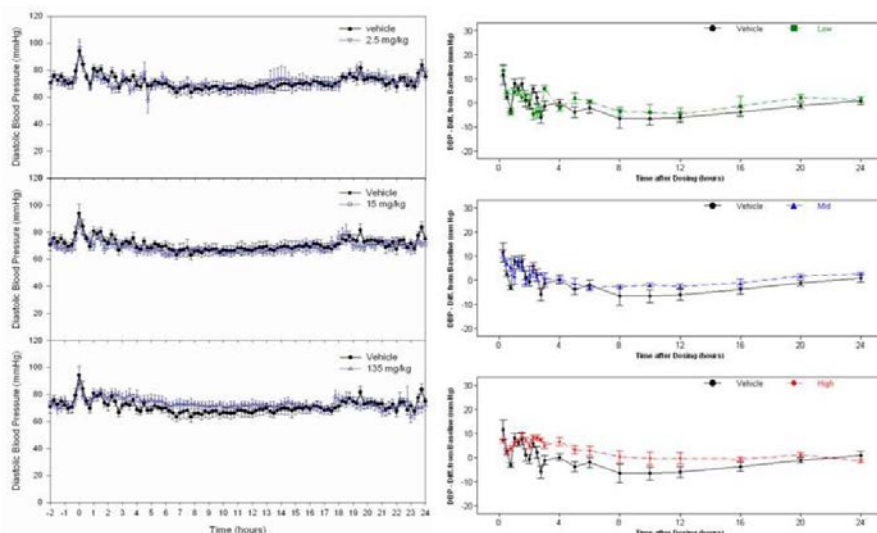
At 135 mg/kg, a peak increase in diastolic blood pressure 13 mmHg (19%) was observed at approximately 2.5 hours post dose (2 to 16 hours) from approximately 2 hours to 16 hours after dosing, coinciding with an increase in heart rate.

No dose related or biologically significant effects on systolic blood pressure or mean blood pressure were observed.

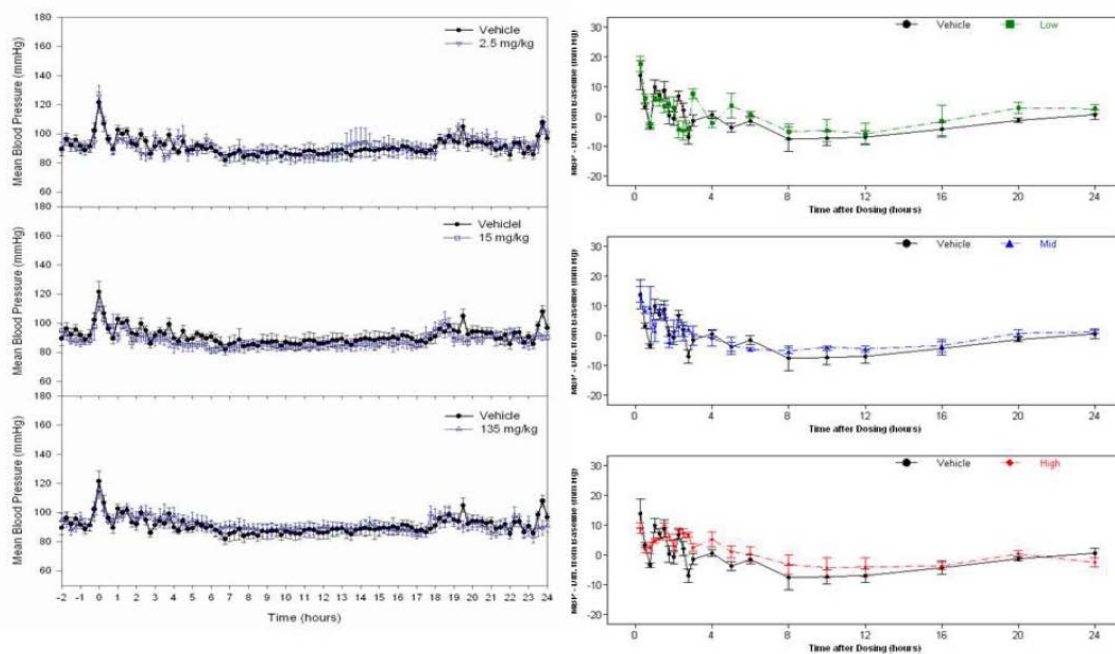
Effect of 2.5, 15, and 135 mg/kg MK-4618 on Systolic Blood Pressure in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)



Effect of 2.5, 15, and 135 mg/kg MK-4618 on Diastolic Blood Pressure in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)



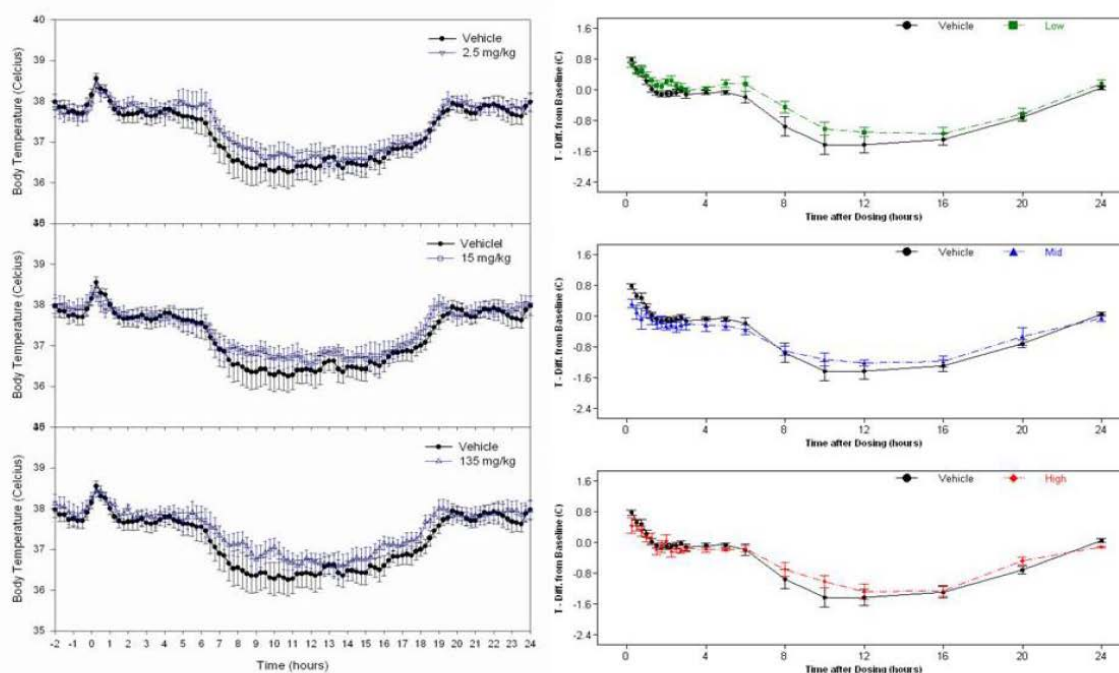
Effect of 2.5, 15, and 135 mg/kg MK-4618 on Mean Blood Pressure in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)



Body temperature:

Increases in body temperature of $+0.4^{\circ}\text{C}$, $+0.3^{\circ}\text{C}$ and $+0.4^{\circ}\text{C}$ were observed from 5 to 16 hours, 7 to 18 hours and 5 to 20 hours post dose at 2.5, 15 and 135 mg/kg, respectively.

Effect of 2.5, 15, and 135 mg/kg MK-4618 on Body Temperature in Conscious Monkeys: Untransformed Data (Left Panel) and Baseline-Transformed Data (Right Panel) for Vehicle/Control Versus Test Article (Dosing at Time 0) (sponsor's figure.)



Toxicokinetics

After the telemetry phase ended, blood samples were collected from all monkeys at 0 (pre-dose), 0.5, 1, 2, 4, 8, and 24 hours postdose after doses of 2.5, 15 and 135 mg/kg MK-4618. At a clinical dose of 75 mg/day vibegron, a C_{max} of 123 ng/mL (0.277 μM) and an $\text{AUC}_{0-24\text{h}}$ of 1450 ng•h/mL (3.26 $\mu\text{M}\cdot\text{hr}$) were observed in Study RVT-901-1002.

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Monkeys Following a Dose of MK-4618				
Dose (mg/kg)	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
2.5	Female	0.492 $\pm$ ID	0.0492 $\pm$ ID	0.75 $\pm$ ID
	Male	0.551 $\pm$ ID	0.0703 $\pm$ ID	1.5 $\pm$ ID
	All	0.521 $\pm$ 0.0245	0.0598 $\pm$ 0.00760	1.1 $\pm$ 0.31
15	Female	3.84 $\pm$ ID	0.602 $\pm$ ID	1.5 $\pm$ ID
	Male	4.66 $\pm$ ID	0.886 $\pm$ ID	0.75 $\pm$ ID
	All	4.25 $\pm$ 0.306	0.744 $\pm$ 0.0851	1.1 $\pm$ 0.31
135	Female	103 $\pm$ ID	12.6 $\pm$ ID	3.0 $\pm$ ID
	Male	102 $\pm$ ID	10.8 $\pm$ ID	2.0 $\pm$ ID
	All	102 $\pm$ 6.92	11.7 $\pm$ 0.568	2.5 $\pm$ 0.50

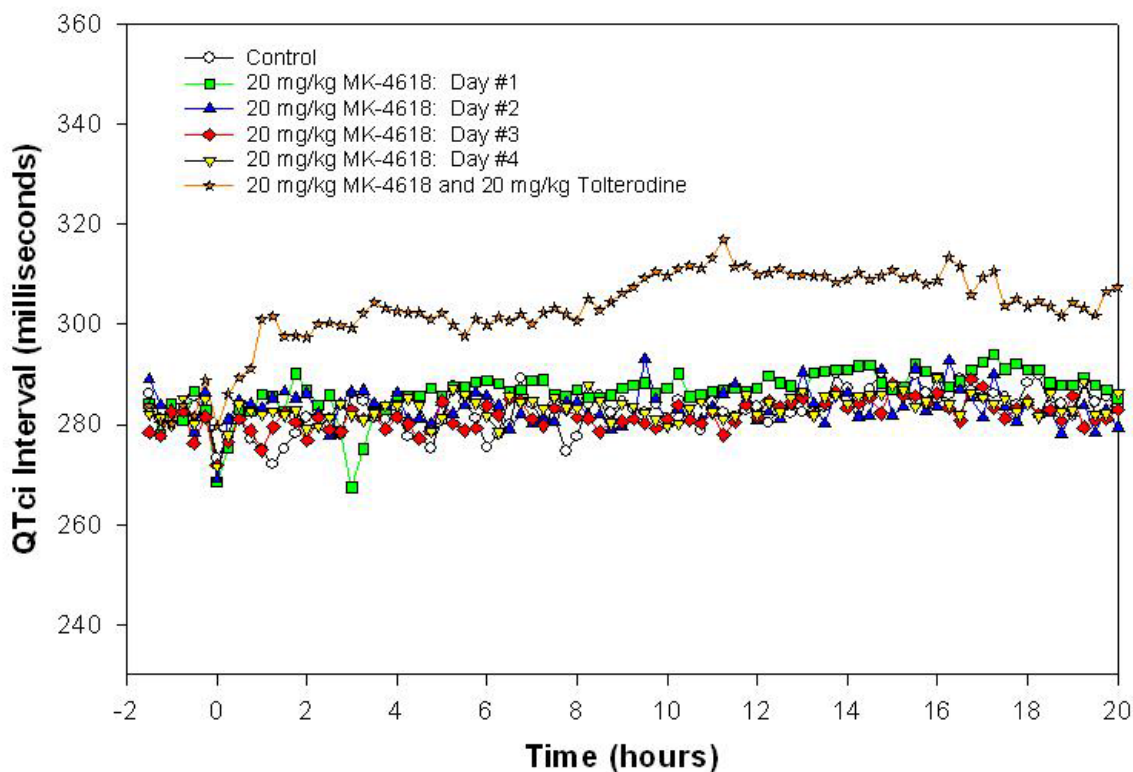
ID = Insufficient Data

*Sponsor's figure

Nonclinical Study Report: MK-4618 and tolterodine: Exploratory oral repeat dose telemetry study in monkeys with assessment of concomitant dosing with tolterodine (Report TT #10-5855).

Rhesus monkeys (n=4) received a single oral dose of the vehicle (time-matched control), followed by four consecutive daily doses of 20 mg/kg MK-4618 (about 5-fold the exposure of the MRHD of 75 mg by C_{max}) on Days 1 to 4 and then by a concomitant dose of 20 mg/kg MK-4618 and 20 mg/kg tolterodine (about 24-fold the exposure at the MRHD of 75 mg by C_{max}) on treatment Day 5. The combination of drugs elicited increases in heart rate and decreases in PR interval that were similar to those that occurred on Days 2 to 4 of treatment with 20 mg/kg MK-4618 alone and no effect on uncorrected QT interval. After correction of the QT interval for heart rate variation (QTc interval) increases in QTc interval (10%) were noted relative to the vehicle control. Arterial blood pressure was increased 10 to 15 mmHg on Day 5 following treatment with the combination.

Day-By-Day Comparison of the Effects of Repeat Administration of 20 mg/kg MK-4618 and Concomitant Dosing with 20 mg/kg MK-4618 and 20 mg/kg Tolterodine on QTc Interval in Rhesus Monkeys (Untransformed Continuous 15-Min Mean Data) (sponsor's figure.)

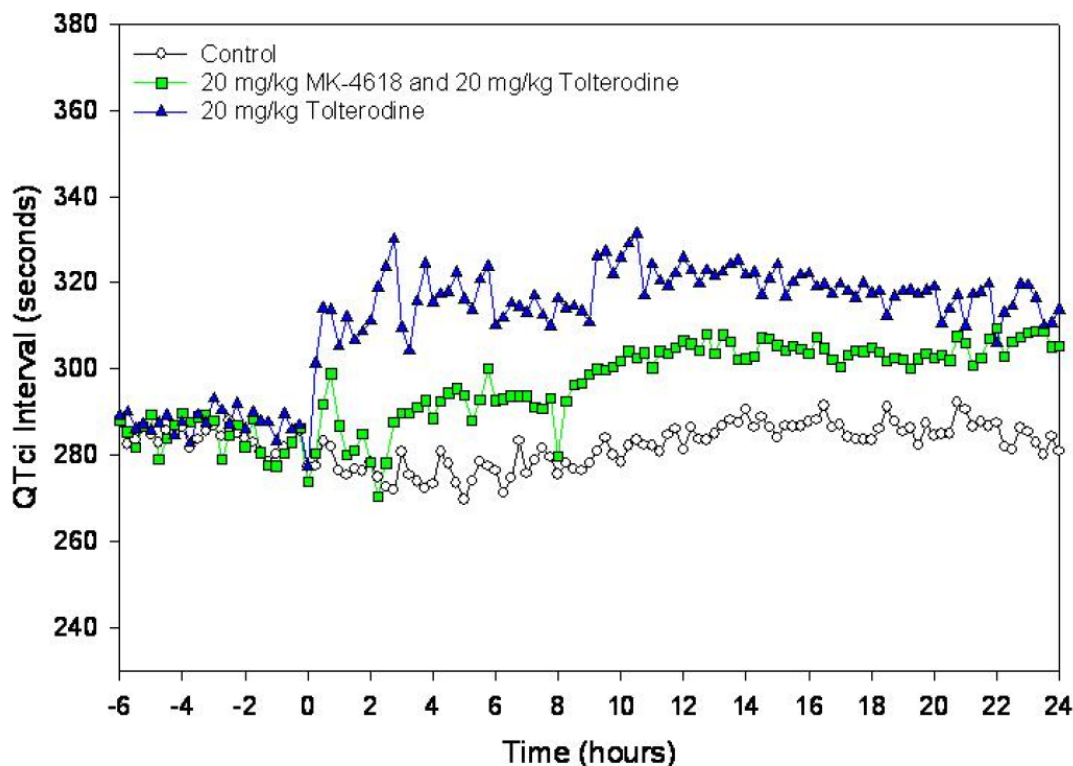


Rhesus monkeys (n=4) received a single oral dose of the vehicle (time-matched control), followed by four consecutive daily doses of 20 mg/kg MK-4618 on Days 1 to 4 to assess tachyphylaxis. On Day 5, the monkeys received doses of 20 mg/kg MK-4618 and 20 mg/kg tolterodine (an anti-muscarinic agent) concomitantly to assess the cardiovascular effects of their co-administration. The monkeys were dosed at approximately the same time (Time 0) on all dosing occasions (~9:30 AM). Continuous 15-min means for the four monkeys are presented over the duration of the 20-hr post dose monitoring period.

Nonclinical Study Report: MK-4618 and tolterodine: Exploratory oral cardiovascular telemetry study in monkeys to assess concomitant dosing of MK-4618 and tolterodine (Report TT #10-5856).

Rhesus monkeys (n=4) received a single oral dose of the vehicle or a concomitant dose of 20 mg/kg MK-4618 and 20 mg/kg tolterodine, followed by a dose of 20 mg/kg tolterodine alone (after a one-week wash-out period). Similar increases in systolic blood pressure, diastolic blood pressure and mean blood pressure ranging from (about 10 to 15 mmHg) were observed in both treatment arms. QTc interval prolongation was greater following tolterodine alone than with the combination, consistent with observed changes in heart rate. There was no potentiation of the heart rate effects observed with 20 mg/kg MK-4618 when administered concomitantly with tolterodine. It was concluded that the increases in blood pressure and QTc interval prolongation after a concomitant dose of 20 mg/kg MK-4618 and 20 mg/kg tolterodine were mediated by tolterodine and were not due to a drug/drug interaction.

Comparison of Concomitant Dosing of 20 mg/kg MK-4618 and 20 mg/kg Tolterodine Versus 20 mg/kg Tolterodine Alone on QTc Interval (Miyazaki's Correction) in Rhesus Monkeys (Untransformed 15-Min Means) (sponsor's figure.)

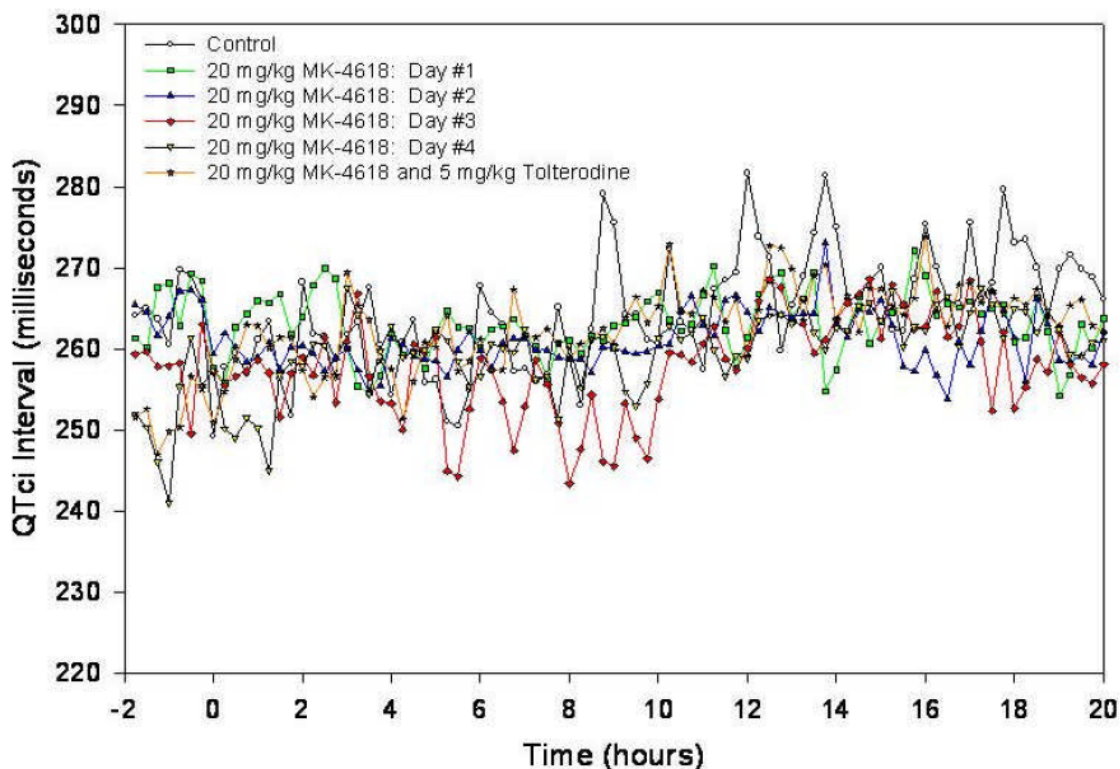


Rhesus monkeys (n=4) received a single oral dose of the vehicle alone to serve as a time-matched control. The animals were treated with a concomitant dose of 20 mg/kg MK-4618 and 20 mg/kg tolterodine, followed by a dose of 20 mg/kg tolterodine alone (after a one-week wash-out period). The monkeys were dosed at approximately the same time on each dose day, with dosing represented at Time 0. Telemetry data were recorded for 24 hrs post dose after administration of the vehicle and test article doses. Continuous 15-min means for the four animals are presented over the duration of the 24-hr post dose monitoring period.

Nonclinical Study Report: MK-4618 and tolterodine: Exploratory oral repeat dose telemetry study in monkeys with assessment of concomitant dosing with tolterodine (Report TT #10-5858).

In a second repeat dose study in monkeys, the QTc interval prolongation and increases in blood pressure were not observed when 20 mg/kg MK-4618 was dosed concomitantly with a lower dose of 5 mg/kg tolterodine (about 14-fold the exposure at the MRHD of 75 mg by C_{max}). Increases in heart rate were observed similar to the effects observed on Days 2 to 4 of treatment with 20 mg/kg MK-4618 alone.

Comparison of the Effects of Repeat Administration of 20 mg/kg MK-4618 and Concomitant Dosing With 20 mg/kg MK-4618 and 5 mg/kg Tolterodine on QTc Interval (Individual Animal Correction) in Rhesus Monkeys (sponsor's figure.)



Rhesus monkeys (n=4) received a single oral dose of the vehicle alone (time-matched control), followed by four consecutive daily doses of 20 mg/kg MK-4618 on Days 1 to 4 to assess tachyphylaxis. On Day 5, the monkeys received doses of 20 mg/kg MK-4618 and 5 mg/kg tolterodine (an anti-muscarinic agent) concomitantly to assess the cardiovascular effects of their co-administration. The monkeys were dosed at approximately the same time on all dosing occasions (~9:30 AM), with dosing represented at Time 0. Continuous 15-min means for the four monkeys are presented over the duration of the 20-hr post dose monitoring period.

Nonclinical Study Report: L-000753555: Exploratory oral pharmacology study in rhesus monkeys, 24-Mar-2010 (Report TT #10-1025).

An exploratory oral pharmacology study in rhesus monkeys was conducted at single oral doses of 1, 5, 10, 15, and 30 mg/kg of tolterodine. In this study, the $AUC_{0-24 \text{ hr}}$ at 5 mg/kg ranged from 1.71 to 2.42 $\mu\text{M}\cdot\text{hr}$ for tolterodine and 0.058 to 0.065 $\mu\text{M}\cdot\text{hr}$ for the 5-hydroxymethyl metabolite of tolterodine, with corresponding C_{max} values of 0.173 to 0.31 μM for tolterodine and 0.010 to 0.012 μM for the metabolite. The exposures at 20 mg/kg, exceeded 4 $\mu\text{M}\cdot\text{hr}$ for tolterodine and 0.13 $\mu\text{M}\cdot\text{hr}$ for the 5-hydroxymethyl metabolite with C_{max} values of 0.28 μM and 0.023 μM , respectively. The estimated exposure margins for $AUC_{0-24 \text{ hr}}$ for a 4 mg/day clinical dose of tolterodine in extensive metabolizers were estimated to be 11- and 30-fold for tolterodine and <1/1-fold for the

5-hydroxymethyl metabolite at single oral doses of 5 mg/kg and 20 mg/kg, respectively. The estimated exposure margins via C_{max} were 14- and 24-fold for tolterodine and 1- and 2-fold for the 5-hydroxymethyl metabolite at 5 mg/kg and 20 mg/kg, respectively.

Nonclinical Study Report: Ancillary Pharmacology: Effect of MK-4618 on Cardiovascular Function in Anesthetized Dogs. (Report TT #08-5311).

MK-4618 was administered sequentially (iv) to mixed breed anesthetized and vagotomized female dogs (N=3) at 1, 2, and 7 mg/kg (separated by 30 minutes). Heart rate, mean arterial pressure, and electrocardiographic parameters were monitored. Plasma concentrations were approximately 14, 36, and 116-fold C_{max} at the MRHD of 75 mg vibegron, respectively. Decreases in mean arterial pressure, increases in heart rate, decreases in PR interval, and small (<10 %) increases in QRS interval were observed at all doses.

Tabulated Summary of Cardiovascular Function (sponsor's table.)

Type of Study	GLP Study	Species/ Strain	Route	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Findings
Cardiovascular Function TT #08-5311	No	Dog/Mongrel (anesthetized, vagotomized, ventilated)	IV	Single dose	1, 2 & 7	3 F	At 1, 2 and 7 mg/kg: Decrease in MAP (-33, -31 and - 45%) Increase in HR (+28, +29 and +37%) Decrease in PR interval (-12, -13 and -12%) Increase in QRS interval (+10, +14 and +30%) <u>Peak average</u> <u>Plasma</u> <u>Concentrations:</u> 1 mg/kg = 4 µM. 2 mg/kg = 10 µM. 7 mg/kg = 32 µM

IV = Intravenous.

F = Female.

MAP = Mean Arterial Pressure

C_{max} = Maximum plasma concentration.

Nonclinical Study Report: Ancillary Pharmacology: Effect of MK-4618 on Cardiovascular Function in Anesthetized Dogs. (Report TT #08-5314).

MK-4618 was administered sequentially (iv) to mixed breed anesthetized and vagotomized female dogs (N=2) at 0.3, 0.7, and 2 mg/kg (separated by 30 minutes). Heart rate, mean arterial pressure, and electrocardiographic parameters were monitored. Plasma concentrations were approximately 3, 8, and 26-fold C_{max} at the MRHD of 75 mg vibegron. Transient decreases in mean arterial pressure and increases in heart rate were observed at all doses. No drug-related QT interval changes were observed.

Tabulated Summary of Cardiovascular Function (sponsor's table.)

Type of Study	GLP Study	Species/ Strain	Route	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Findings
Cardiovascular Function TT #08-5314	No	Dog/Mongrel (anesthetized, vagotomized, ventilated)	IV	Single dose	0.3, 0.7 & 2	2 F	Decrease in MAP in both dogs (~ -32%) at all doses. Peak HR increase (+11 and +32 %) & PR decrease (-8% and -22%) for individual dogs at 0.3 mg/kg <u>Peak average</u> <u>Plasma</u> <u>Concentrations:</u> 0.3 mg/kg = 0.9 µM. 0.7 mg/kg = 2.2 µM. 2 mg/kg = 7.1 µM

IV = Intravenous.

F = Female.

MAP = Mean arterial pressure

HR = Heart Rate

C_{max} = Maximum plasma concentration.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study title: Pharmacokinetics of MK-4618 in Sprague-Dawley Rats, Beagle Dogs, Rhesus Monkeys, and Cynomolgus Monkeys (Merck, 2010)

The pharmacokinetics of MK-4618 were studied following single intravenous and oral administration to rats, dogs, rhesus, and cynomolgus monkeys. Results are tabulated below.

Mean Pharmacokinetic Parameters of MK-4618 in Fasted Male Sprague-Dawley Rats, Beagle Dogs, and Rhesus and Cynomolgus Monkeys Following Intravenous Dosing (sponsor's table.)

Species	Dose (mg/kg)	AUC _{0-∞} (μM•hr)	CL _p (mL/min/kg)	Vd _{ss} (L/kg)	t _{1/2} (hr)
Rat (n=3)*	0.25	0.688 ± 0.175	14 ± 4	6.1 ± 1.2	6.8 ± 0.7
Dog (n=2)**	0.5	1.32	15	12	13
Rhesus Monkey** (n=2)	0.5	1.15	17	15	15
Cynomolgus Monkey** (n=2)	0.5	0.942	20	9.4	7.4
*MK-4618 was administered IV in EtOH:PEG 400:Acetate Buffer (2:5:3) or **EtOH:PEG 400:H ₂ O, (2:3:5) to fasted animals. Plasma concentrations of MK-4618 were determined using an LC-MS/MS assay following protein precipitation of plasma samples. Data represent average (n=2) or mean ± standard deviation (n=3).					

Mean Pharmacokinetic Parameters of MK-4618 in Fasted Male Sprague-Dawley Rats, Beagle Dogs and Rhesus and Cynomolgus Monkeys Following Oral Dosing (sponsor's table.)

Species	Dose (mg/kg)	AUC _{0-∞} (μM•hr)	C _{max} (μM)	T _{max} (hr)	F (%)
Rat (n=3)	2	1.08 ± 0.12	0.265 ± 0.158	0.083	20
Dog (n=2)	2	2.31	0.215	0.25 - 1	44
Rhesus Monkey (n=2)	2	1.07	0.102	2 - 4	23
Cynomolgus Monkey (n=2)	2	1.75	0.702	0.25 - 1	46
MK-4618 was administered P.O. in 0.5% methylcellulose + 0.02 SDS to fasted animals. Plasma concentrations of MK-4618 were determined using an LC-MS/MS assay following protein precipitation of plasma samples. Values represent average (n=2) or mean ± standard deviation (n=3).					

Study title: Plasma Protein Binding of MK-4618 in Wild Type rasH2 Mice and Dutch Belted Rabbits (Merck, 2011)

Plasma protein binding was determined by equilibrium dialysis with an incubation period of 4 hours at 37°C.

Plasma Protein Binding of MK-4618 in Wild Type rasH2 Mouse and Dutch Belted Rabbit (sponsor's table.)

Species	% Unbound		
	1 μ M	10 μ M	100 μ M
wild type rasH2 mouse	35 $\pm$ 3*	37 $\pm$ 2	39 $\pm$ 3
Dutch Belted rabbit	6 $\pm$ 0.4	6 $\pm$ 0.5	8 $\pm$ 0.9

* Mean $\pm$ standard deviation of triplicate measurements.

Study title: Quantitative Whole-Body Autoradiography of Long Evans Rats Following Oral Administration of ^{14}C -MK-4618 (Merck, Study no. 8233816, 2011)

Oral ^{14}C -MK-4618 was administered in 0.5% methylcellulose at 5 mg/kg and approximately 100 $\mu\text{Ci/kg}$ to Long Evans rats. Rats were euthanized at 2, 8, 12, 24, 48, 168, 336, and 840 hours postdose for quantitative whole-body autoradiography.

MK-4618-derived radioactivity was rapidly absorbed and extensively distributed into tissues. The highest concentrations of radioactivity were found in bile and urine. C_{max} in most tissues was reached at 2 hours postdose. After bile and urine, the tissues with the highest C_{max} were liver, uveal tract, stomach mucosa, small intestine, brown fat, and kidney cortex. By 168 hours postdose, MK-4618 was below detectable limits in all but twelve tissues; levels in the eye, meninges, preputial gland, testis, and uveal tract were measurable at 336 and 840 hours. Radioactivity in the lens of the eye and the non-circumventricular central nervous system tissues (cerebellum, cerebrum, medulla, olfactory lobe, and spinal cord) were below detectable levels. Elimination half lives ranged from 6.30 hours in bone marrow to 726 hours in meninges.

Concentrations of radioactivity in blood and tissues at specified times after a single oral administration of ^{14}C -MK-4618 to male Long Evans rats (5 mg/kg) (sponsor's table.)

Tissue	ng Equivalents ^{14}C -MK-4618/g							
	Animal Number (Sacrifice Time)							
	B24752 (2 Hours)	B24753 (8 Hours)	B24754 (12 Hours)	B24755 (24 Hours)	B24756 (48 Hours)	B24757 (168 Hours)	B24758 (336 Hours)	B24759 (840 Hours)
Adrenal gland	1560	837	517	371	69.2	ND	ND	ND
Arterial wall	1130	492	267	99.9	34.4	ND	ND	ND
Bile	11800	3310	2030	828	ND	ND	ND	ND
Blood	297	65.3	43.4	BLQ	BLQ	BLQ	ND	ND
Bone	115	43.6	44.2	54.0	BLQ	ND	ND	ND
Bone marrow	1060	740	422	123	BLQ	ND	ND	ND
Brain cerebellum	BLQ	BLQ	ND	ND	ND	ND	ND	ND
Brain cerebrum	BLQ	BLQ	ND	ND	ND	ND	ND	ND
Brain choroid plexus	1050	2430	1740	1480	287	ND	ND	ND
Brain medulla	BLQ	BLQ	ND	ND	ND	ND	ND	ND
Brain olfactory lobe	BLQ	BLQ	ND	ND	ND	ND	ND	ND
Bulbo-urethral gland	1490	1130	501	211	49.6	ND	ND	ND
Cecum	868	1460	694	94.2	33.4	ND	ND	ND
Diaphragm	1090	419	189	76.0	BLQ	ND	ND	ND
Epididymis	405	380	422	409	334	30.4	BLQ	ND
Esophagus	834	404	193	111	38.8	ND	ND	ND
Exorbital lacrimal gland	1430	2620	2440	1350	196	44.4	BLQ	ND
Eye	182	274	253	491	399	367	329	307
Eye lens	BLQ	BLQ	BLQ	BLQ	BLQ	ND	ND	ND
Eye uveal tract	1170	1710	1960	3240	2320	2180	2030	1980
Fat (abdominal)	205	77.3	61.3	BLQ	BLQ	ND	ND	ND
Fat (brown)	3000	1150	477	199	70.3	BLQ	ND	ND
Harderian gland	790	1080	954	480	132	BLQ	ND	ND
Intra-orbital lacrimal gland	1420	1830	1750	1320	323	48.5	BLQ	ND
Kidney	2630	1000	510	357	147	BLQ	ND	ND
Kidney cortex	2970	882	410	218	69.1	BLQ	ND	ND
Kidney medulla	2510	1090	655	430	208	BLQ	ND	ND
Large intestine	799	1200	353	266	58.4	BLQ	ND	ND
Liver	8010	2110	842	286	99.3	BLQ	ND	ND
Lung	970	532	369	142	37.7	ND	ND	ND
Lymph nodes	844	761	449	395	187	BLQ	ND	ND
Meninges	361	161	162	220	176	141	116	79.2
Muscle	440	209	112	43.0	BLQ	BLQ	ND	ND
Myocardium	1180	538	270	99.3	BLQ	BLQ	ND	ND
Nasal turbinates	328	238	195	168	42.3	ND	ND	ND
Pancreas	2220	1660	589	192	33.0	BLQ	ND	ND
Periosteum	743	523	305	137	64.1	ND	ND	ND
Pituitary gland	2720	2250	1980	1780	960	435	ND	ND
Preputial gland	1100	1200	874 ^a	1060	466 ^a	462 ^a	223 ^a	71.6 ^a
Prostate gland	473	835	364	103	BLQ	ND	ND	ND
Salivary gland	1840	1600	795	483	479	117	BLQ	ND
Seminal vesicle	505	668	453	230	39.0	ND	ND	ND
Skin (nonpigmented)	460	364	244	144	29.8	33.6	ND	ND
Skin (pigmented)	551	373	272	209	144	33.4	ND	ND
Small intestine	3130	966	444	122	32.8	ND	ND	ND
Spinal cord	BLQ	BLQ	BLQ	BLQ	ND	ND	ND	ND
Spleen	1840	787	494	275	106	BLQ	ND	ND
Stomach	1600	1270	855	313	58.6	ND	ND	ND
Stomach mucosa	3230	1750	1180	284	83.6	ND	ND	ND
Testis	153	194	182	257	218	120	81.8	37.6
Thymus	441	391	264	107	BLQ	ND	ND	ND
Thyroid	2510	2370	1510	652	126	52.6	ND	ND
Trachea	586	853	524	352	159	ND	ND	ND
Urinary bladder	884	1970	354	135	32.5	ND	ND	ND
Urine	14300	6590	683	329	BLQ	ND	ND	ND

BLQ Below limit of quantitation (<29.0 ng equivalents ^{14}C -MK-4618/g).

Estimated pharmacokinetic parameters for blood and selected tissues in male Long Evans rats following a single oral dose of ^{14}C -MK-4618 (5 mg/kg) (sponsor's table.)

Matrix	AUC _{0-t} (ng-eq·hr/g)	AUC _{0-∞} (ng-eq·hr/g)	C _{max} (ng-eq/g)	T _{max} (hours)	t _{1/2} (hours)
Adrenal gland(s)	22069	23232	1560	2.00	11.6
Arterial wall	11327	11951	1130	2.00	12.6
Bile	84958	94831	11800	2.00	8.26
Blood	1601	2026	297	2.00	6.79
Bone	1356	NC	115	2.00	NC
Bone marrow	12054	13172	1060	2.00	6.30
Brain cerebellum	NC	NC	NC	NC	NC
Brain cerebrum	NC	NC	NC	NC	NC
Brain choroid plexus	60354	65803	2430	8.00	13.2
Brain medulla	NC	NC	NC	NC	NC
Brain olfactory lobe	NC	NC	NC	NC	NC
Bulbo urethral gland	20011	20790	1490	2.00	10.9
Cecum	18420	19194	1460	8.00	16.0
Diaphragm	8423	9186	1090	2.00	6.96
Epididymis	40130	41758	422	12.0	37.1
Esophagus	9364	10236	834	2.00	15.6
Exorbital lacrimal gland	79416	83004	2620	8.00	56.0
Eye(s)	282444	NC	491	24.0	NC
Eye lens	NC	NC	NC	NC	NC
Eye uveal tract	1749230	NC	3240	24.0	NC
Fat (abdominal)	1329	2386	205	2.00	12.0
Fat (brown)	25992	27349	3000	2.00	13.4
Harderian gland	26416	28826	1080	8.00	12.7
Intra-orbital lacrimal gland	78756	81825	1830	8.00	43.9
Kidney(s)	27790	32002	2630	2.00	19.9
Kidney cortex	24323	25727	2970	2.00	14.1
Kidney medulla	30966	37541	2510	2.00	21.9
Large intestine	17509	18635	1200	8.00	13.4
Liver	55666	57402	8010	2.00	12.1
Lung(s)	12500	13106	970	2.00	11.1
Lymph node(s)	20127	27517	844	2.00	27.4
Meninges	99415	182406	361	2.00	726
Muscle	3959	4414	440	2.00	7.34
Myocardium	10166	11154	1180	2.00	6.90
Nasal turbinates	7594	8588	328	2.00	16.3
Pancreas	25744	26161	2220	2.00	8.76
Periosteum	11262	12801	743	2.00	16.6
Pituitary gland	165230	209318	2720	2.00	70.3
Preputial gland	229523	258174	1200	8.00	277
Prostate gland	9597	10576	835	8.00	6.59
Salivary gland(s)	71922	83109	1840	2.00	66.3

Seminal vesicle(s)	13592	14158	668	8.00	10.1
Skin (nonpigmented)	12366	NC	460	2.00	NC
Skin (pigmented)	22379	25039	551	2.00	55.2
Small intestine	23492	23961	3130	2.00	9.92
Spinal cord	NC	NC	NC	NC	NC
Spleen	21469	23974	1840	2.00	16.4
Stomach	25927	26721	1600	2.00	9.39
Stomach mucosa	37225	38331	3230	2.00	9.16
Testis(es)	77600	99924	257	24.0	412
Thymus	6473	7816	441	2.00	8.70
Thyroid	57934	65160	2510	2.00	95.2
Trachea	19045	23845	853	8.00	20.9
Urinary bladder	19038	19535	1970	8.00	10.6
Urine	97588	102993	14300	2.00	11.4

Study title: Consideration of rat placental permeability following administration of [³H] KRP-114V (Kyorin, Study No. AE-7499-G, 2015)

[³H] KRP-114V was administered to rats on Day 18 of gestation at a single oral dose of 10 mg/kg under fasting conditions.

The concentration of radioactivity in maternal tissue had a C_{max} of 1 to 4 hours. The concentrations in amniotic fluid, fetuses and fetal tissue were lower than the concentration in maternal plasma. At 1 hour, radioactivity in the maternal liver and kidneys was 26.10 to 10.57 times that in maternal plasma. In the maternal cerebrum, it was 0.42 to 0.06 times that in maternal plasma.

In fetuses, time dependent increases in tissue concentrations were observed. At 1 hour, radioactivity in the kidneys, liver, heart, gastrointestinal tract, lungs, whole body and blood was 0.33 to 0.16 times that in maternal plasma, while in the fetal brain, it was 0.03 times. At 4 hours, radioactivity in the fetal liver, kidneys and gastrointestinal tract was comparable to that in maternal plasma, while radioactivity in fetal heart, lungs, whole body, blood and brain was 0.66 to 0.10 times that in maternal plasma. At 24 hours, radioactivity in the fetal lungs, gastrointestinal tract, kidneys, liver, whole body and heart was 2.83 to 1.75 times that in maternal plasma, while radioactivity in the fetal brain was comparable to that in maternal plasma. Radioactivity in the fetal blood at 24 hours was 0.69 times that of maternal plasma.

Radioactivity in tissues after a single oral administration (sponsor's table.)

Tissue	Radioactivity concentration (ng eq. of KRP-114V/g or mL)		
	1 h	4 h	24 h
Plasma	669.78 ± 100.69	575.39 ± 46.71	57.75 ± 21.26
Blood	492.86 ± 56.41	439.13 ± 25.22	48.74 ± 13.46
Cerebrum	37.17 ± 4.84	59.37 ± 9.75	23.99 ± 4.05
Heart	2528.14 ± 614.61	1914.04 ± 256.35	417.88 ± 182.47
Lung	2937.58 ± 144.03	4368.58 ± 1063.15	1107.08 ± 274.10
Liver	14548.53 ± 906.75	13077.59 ± 1314.62	1437.06 ± 261.95
Kidney	7081.46 ± 1110.34	8087.46 ± 2031.71	1507.41 ± 384.32
Adrenal gland	4225.29 ± 1072.38	4775.09 ± 1322.83	2641.37 ± 856.39
Uterus	1413.52 ± 237.27	1778.12 ± 561.84	660.62 ± 269.43
Ovary	1115.66 ± 65.54	1737.95 ± 500.17	641.04 ± 137.03
Mammary gland	1484.94 ± 297.75	4618.87 ± 2211.87	1434.36 ± 349.90
Placenta	2765.11 ± 294.29	2581.19 ± 771.45	938.99 ± 359.82
Fetal membrane	1290.82 ± 542.30	4069.12 ± 2112.25	4515.30 ± 707.07
Amniotic fluid	8.40 ± 0.90	36.23 ± 28.59	29.34 ± 4.62
Fetus	112.83 ± 17.32	300.22 ± 143.63	102.10 ± 21.42
Fetal blood	104.59 ± 14.10	130.80 ± 65.94	39.75 ± 9.69
Fetal brain	16.85 ± 3.19	59.06 ± 35.66	53.03 ± 6.08
Fetal heart	180.34 ± 38.21	380.59 ± 149.94	101.32 ± 9.86
Fetal lung	133.94 ± 8.44	365.01 ± 168.12	163.59 ± 25.43
Fetal liver	209.29 ± 53.13	483.86 ± 269.82	147.74 ± 14.20
Fetal kidney	219.96 ± 56.57	467.53 ± 219.48	153.34 ± 18.63
Fetal digestive tract	172.82 ± 25.41	442.10 ± 241.57	158.82 ± 17.25

Radioactivity in tissues relative to plasma after a single oral administration (sponsor's table.)

Tissue	Ratio to the radioactivity concentration in plasma		
	1 h	4 h	24 h
Plasma	1.00	1.00	1.00
Blood	0.74	0.76	0.84
Cerebrum	0.06	0.10	0.42
Heart	3.77	3.33	7.24
Lung	4.39	7.59	19.17
Liver	21.72	22.73	24.88
Kidney	10.57	14.06	26.10
Adrenal gland	6.31	8.30	45.74
Uterus	2.11	3.09	11.44
Ovary	1.67	3.02	11.10
Mammary gland	2.22	8.03	24.84
Placenta	4.13	4.49	16.26
Fetal membrane	1.93	7.07	78.19
Amniotic fluid	0.01	0.06	0.51
Fetus	0.17	0.52	1.77
Fetal blood	0.16	0.23	0.69
Fetal brain	0.03	0.10	0.92
Fetal heart	0.27	0.66	1.75
Fetal lung	0.20	0.63	2.83
Fetal liver	0.31	0.84	2.56
Fetal kidney	0.33	0.81	2.66
Fetal digestive tract	0.26	0.77	2.75

Distribution of radioactivity in blood cells following a single oral administration (sponsor's table.)

Time (h)	Hematocrit value (%)	Distribution of radioactivity in blood cells (%)
1	36 ± 1	13.7 ± 3.2
4	33 ± 2	12.7 ± 3.5
24	34 ± 1	23.0 ± 10.5

Data are expressed as the mean ± S.D. of three animals.

Study title: In Vivo Metabolism of MK-4618 in Rats and P-glycoprotein Activity in Mice (Merck study no. PK003, 2010)

Male Sprague-Dawley rats (N=2) were administered intravenous [³H]MK-4618 at 5 mg/kg or oral [³H]MK-4618 at 10 mg/kg in bile duct-cannulated (BDC) animals. Bile, urine, and feces were collected up to 48 hours post-dose, with results tabulated below.

Recovery of Radioactivity (% of Dose) Following Single IV & Oral Administration of [³H]MK-4618 to BDC Male Sprague-Dawley Rats (sponsor's table.)

Species	Recovery of Radioactivity (% of Dose)			
	Urine	Bile	Feces	Total
Male Rat IV (5 mg/kg)				
1	35.7	34.5	12.6	82.8
2	38.4	31.0	12.9	82.3
Average	37.1	32.8	12.8	82.6
Male Rat Oral (10 mg/kg)				
3	36	32.5	21.6	90.1
4	33.6	34.0	18.6	86.2
5	26.2	42.5	16.8	85.5
Mean	31.9	36.3	19.0	87.3
SD ^b	5.1	5.4	2.4	2.5

Intact wild type and P-gP null mice (N=3) were administered oral MK-4618 at 2 mg/kg. Plasma and brain were collected at 2, 4, and 8 hours post-dose, and MK-4618 concentrations were determined by LC-MS/MS.

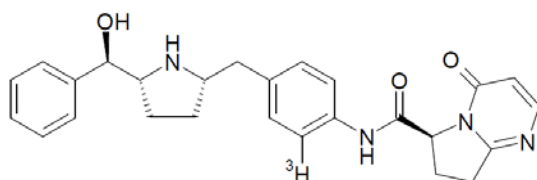
The higher plasma levels of MK-4618 levels in P-gp null mice, with no Pgp transport, indicate that MK-4618 may be a P-gp substrate in mice.

Concentrations of MK-4618 in Plasma and Brain and Brain to Plasma Ratio Following a Single Oral Administration of MK-4618 to Intact CF-1 Male Mice (sponsor's table.)

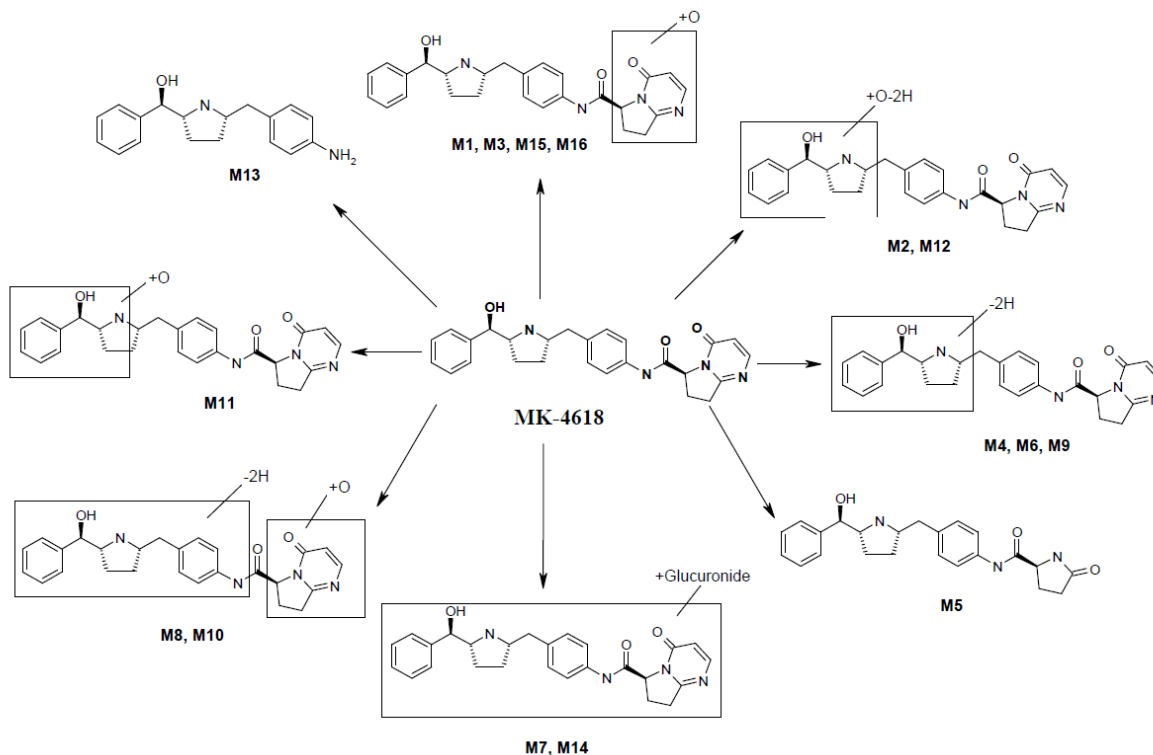
	Time (hrs)	Mean Plasma Conc. (nM)	Mean Brain Conc. (nM)	Brain:Plasma Ratio
Wild Type Mice	2	37.2	BLQ ^b	-
	4	10.9	BLQ	-
	8	7.9	BLQ	-
P-gp Null Mice	2	179.5	42.5	0.2
	4	91.8	66.2	0.7
	8	58.6	53.9	0.9

BLQ = Below the limit of quantitation (LQ in brain homogenate 15.9 nM)

Chemical Structure of [³H]MK-4618 (sponsor's figure.)



Structures of MK-4618 and its Metabolites Detected in Rat Plasma and Excreta Based on LC-MS/MS Analysis (sponsor's figure.)



Study title: Study of enterohepatic circulation in rats following administration of [³H] KRP-114V (Kyorin study no. AE-7498-G, 2015)

Male rats were bile duct cannulated and administered [³H] KRP-114V (oral, 10 mg/kg) under fasting conditions. The bile obtained (0.044 MBq in 1 mL, intraduodenal) was administered to male rats subjected to jugular vein cannulation, under fasting conditions.

At 8, 24 and 48 hours, 5.1%, 7.2% and 7.5% respectively of the administered radioactivity was excreted in bile. At 8, 24 and 48 hours, 4.0%, 6.1% and 7.3% respectively, was excreted in urine. At 24 and 48 hours, 40.3% and 79.9% respectively was excreted in feces (wet method.) At 24 and 48 hours, 39.6% and 71.9% respectively, was excreted in feces (dry method.) At 48 hours, 1.6% was found in gastrointestinal contents. In total, 98.4% of the administered radioactivity was excreted by 48 hours.

Radioactivity in plasma at 1, 4 and 6 hours was 130.96 ng eq./mL, 304.00 ng eq./mL and 142.01 ng eq./mL respectively, and below the limit of detection after that. The AUC_{0-last} was 3990 ng eq. •h/mL; t_{1/2} and AUC_{0-∞} could not be calculated. Approximately 15% of the administered radioactivity was absorbed and available to enterohepatic circulation in rats.

Cumulative excretion of radioactivity in bile, urine and feces after a single intraduodenal injection of bile sample to bile-duct cannulated fasting male rats (0.044 MBq in 1 mL) (sponsor's table.)

Time (h)	Cumulative excretion of radioactivity (% of radioactivity injected)		
	Bile	Urine	Feces
0- 8	5.1 ± 0.9	4.0 ± 1.7	—
24	7.2 ± 1.5	6.1 ± 2.4	40.3 (39.6) ± 15.1 (12.7)
48	7.5 ± 2.0	7.3 ± 2.6	79.7 (71.9) ± 4.0 (8.0)
Gastro-intestinal contents (48 h)			1.6 ± 1.3
Cage washing (48 h)			0.0 ± 0.0
Carcass (48 h)			2.3 ± 2.1
Total recovery			98.4 ± 0.2

Radioactivity concentration in plasma after a single intraduodenal injection of bile sample to bile-ducted cannulated fasting male rats (0.044MBq in 1 mL)

Time	Radioactivity concentration (ng eq. of KRP-114V/mL)		
	Plasma		
1 h	130.96	±	128.29
4	304.00	±	178.20
6	142.01	±	123.11
24	N.D.		
48	N.D.		
AUC _{0-last} (ng eq.·h/mL)	3990	±	5380
AUC _{0-∞} (ng eq.·h/mL)	N.C.		
t _{1/2} (h)	N.C.		

Study title: Consideration of milk transfer in rats following administration of [³H] KRP-114V (Kyorin study no. AE-7500-G, 2015)

[³H] KRP-114V (vibegron)(oral, 10 mg/kg) was administered to lactating rats (N=3) on Day 10 postpartum. Radioactivity was measured in milk and plasma at 1, 4, 12, and 24 postdose. In milk, C_{max} was 175.41 ng eq.·h/mL at t_{max} of 9 hours. In maternal plasma, C_{max} (236.35 ng eq.·h/mL) was achieved at t_{max} of 2 hours. The greatest milk-to-plasma ratio (about 2.2-fold) was observed at 12 hours. Concentrations in milk were reduced to about 25% of C_{max} by 24 hours after administration.

Radioactivity concentrations in milk and plasma after a single oral administration of [³H] KRP-114V to non-fasting lactating rats (sponsor's table.)

Time (h)	Radioactivity concentration (ng eq. of KRP-114V/mL)		
	Milk		Plasma
1	77.53 ± 29.57	[0.38]	203.99 ± 93.35
4	127.51 ± 73.73	[0.64]	200.15 ± 157.01
12	174.75 ± 134.60	[2.20]	79.57 ± 43.03
24	44.91 ± 33.16	[1.89]	23.75 ± 5.42
C _{max} (ng eq.·h/mL)	175.41 ± 134.02		236.35 ± 135.47
t _{max} (h)	9 ± 5		2 ± 2
AUC _{0-t} (ng eq.·h/mL)	2870 ± 1990		2450 ± 1480
AUC _{0-∞} (ng eq.·h/mL)	N.C.		1940*
t _{1/2} (h)	N.C.		9.5*
			(4-24 h)

[] = milk/plasma ratio

Study title: Metabolism, Excretion and Circulating Metabolites of [¹⁴C]MK-4618 Following a Single Oral and Intravenous Dose of MK-4618 in Sprague Dawley Rats and Cynomolgus Monkeys (Study no. PK014, 2014)

A single oral administration of [¹⁴C]MK-4618 was administered to three bile duct cannulated (BDC) rats (10 mg/kg) and three BDC Cynomolgus monkeys (25 mg/kg).

In rats, six oxidative metabolites (M1, M3, M6, M16, and M17) and one conjugated oxidative metabolite were identified. MK-4618 (66 to 89%) and metabolite M7 (O-glucuronide conjugate of MK-4618 (8 to 30%)) were the predominant circulating species in plasma from both orally and intravenously dosed rats following a single dose of MK-4618. Two other minor metabolites M6 (2%, oral) and M22 (5-7%, intravenous) were also detected in plasma.

In monkeys, four oxidative metabolites ((M3, M6, M17, and M29) and six conjugated oxidative metabolites (M26, M27, M28, M30, M33, and M34) were identified. MK-4618 (31-41%) metabolite M7 (O-glucuronide conjugate of MK-4618)(18-20%) and oxidative metabolite M17 (10-14%) were the predominant circulating species in plasma following a single oral dose. Four other metabolites M3 (<1-4%), M4 (1-3%), M22 (5-6%) and M31 (2-6%) were also detected. In intravenously dosed monkeys, MK-4618 (42-50%) was the predominant species. Four other metabolites M3 (5%), M7 (5-8%), M17 (7-8%) and M31 (5-9%) were also detected.

In humans, MK-4618 and its O-glucuronide conjugate metabolite M7 (12 to 14%) were the predominant circulating species. Two additional minor oxidative metabolites M4 (4-6%) and M17 (6-7%) were also detected in human plasma.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: Six-Month Oral Toxicity Study in Rats

Study no.: TT #10-60

Study report location: Merck archives

Conducting laboratory and location: Laboratoires Merck Sharp & Dohme-Chibret,
Riom, France

Date of study initiation: 13 January 2010

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: MK-4618 (L-002206358)

Lot Numbers	Purity area percent by HPLC
L-002206358-000L018	98.4
L-002206358-000L021	99.6

Key Study Findings: A No-Adverse-Effect Level (NOAEL) was observed at 30 mg/kg/day (about 21.3-fold the MRHD of 75 mg). Some brown fat accumulation, a pharmacologic effect in rats, was observed at this level in male rats. At 180 mg/kg/day (about 102-fold), one male was found dead in Study Week 12, and very slight or slight increases in alkaline phosphatase were observed. Decreased body weight gain was also observed at 180 mg/kg/day (-30% in males and -20% in females) and at 30 mg/kg/day in males only (-16%).

Methods

Doses: 0, 10, 30, and 180 mg/kg/day

Frequency of dosing: Once daily

Route of administration: Oral, by gavage

Dose volume: 5 ml/kg

Formulation/Vehicle: 20%(v/v) polyethylene glycol 400 in deionized
water

Species/Strain: Rat, Sprague-Dawley, Crl:CD(SD)

Number/Sex/Group: 15

Age: 38 or 39 days

Weight: Females: 109.6 to 133.9 g

Males: 137.6 to 170.9 g

Observations and Results**Mortality**

One male in the high dose group was found dead in Study Week 12, with findings consistent with urinary obstruction.

Clinical Signs

Salivation was observed at 180 mg/kg/day in most animals throughout the study.

Body Weights

Decreased body weight gain was observed at 180 mg/kg/day (-30% in males and -20% in females) and at 30 mg/kg/day in males only (-16%).

Feed Consumption:

No treatment related effects were observed.

Ophthalmoscopy:

No treatment related effects were observed.

Hematology

Very slight increases in erythrocytes, hemoglobin, and hematocrit were observed at 180 mg/kg/day in both sexes.

Clinical Chemistry

Very slight or slight increases in alkaline phosphatase and very slight decreases in triglycerides in males were observed at 180 mg/kg/day.

Urinalysis

Very slight increases in urine volume were observed at 30 mg/kg/day, in males only, and in both sexes at 180 mg/kg/day.

Gross Pathology:

No treatment related effects were observed.

Organ Weights:

No treatment related effects were observed.

Histopathology**Adequate Battery: yes****Peer Review: yes****Histological Findings:**

Accumulation of brown fat was observed throughout white adipose tissue at 180 mg/kg/day and 30 mg/kg/day (males only).

	Males (mg/kg/day)			Females (mg/kg/day)		
	10	30	180	10	30	180
Brown fat accumulation		5	15			15

Toxicokinetics: At the NOAEL of 30 mg/kg/day in rats, multiples of the clinical exposure following administration of a 75 mg dose were 21.3-fold, and at the high dose of 180 mg/kg/day, they were 102-fold.

(sponsor's table)

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Rats Following Dosing of MK-4618 : Study Week 13				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
10	Female	10.2 $\pm$ 1.76	1.82 $\pm$ 0.918	2.0 $\pm$ NC
	Male	7.62 $\pm$ 0.995	1.49 $\pm$ 0.139	2.0 $\pm$ NC
	All	8.89 $\pm$ 0.990	1.65 $\pm$ 0.421	2.0 $\pm$ NC
30	Female	81.5 $\pm$ 12.4	12.7 $\pm$ 3.39	4.0 $\pm$ NC
	Male	57.6 $\pm$ 3.98	11.4 $\pm$ 3.42	0.50 $\pm$ NC
	All	69.5 $\pm$ 6.53	11.0 $\pm$ 1.73	4.0 $\pm$ NC
180	Female	383 $\pm$ 36.5	52.4 $\pm$ 6.93	4.0 $\pm$ NC
	Male	280 $\pm$ 14.9	39.3 $\pm$ 2.10	4.0 $\pm$ NC
	All	332 $\pm$ 22.0	45.9 $\pm$ 4.37	4.0 $\pm$ NC

^a MK-4618 concentrations from all control animals at 1 hour postdose were below the lower limit of quantitation.

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

Study no.: TT #09-6050

Study report location: Merck archives

Conducting laboratory and location: Laboratoires Merck Sharp & Dohme-Chibret,
Merck Research Laboratories, Route de
Marsat, Riom, 63963 Clermont-Ferrand
Cedex 9, France

Date of study initiation: 17 December 2009

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: MK-4618 (L-002206358), 98.4% pure by
HPLC, stable for duration of study

Lot Numbers	Study Weeks Used
L-002206358-000L018	1 to 13
L-002206358-000L021	14 to 39

Key Study Findings

At 300 mg/kg/day (75-fold the AUC of the MRHD of 75 mg, 114-fold the C_{max}), transient electrocardiographic findings (increases in QRS duration consistent with a ventricular conduction defect and P wave partially or fully hidden in the T wave of the preceding complex) were observed at approximately 2 hours post dose (generally resolved by 24 hours post dose). In animals where PR and QT intervals could be evaluated (1 female and 1 male on 1 or 2 occasions) no prolongation in QT interval was observed. In these animals, there were marked increases in QRS duration and notable changes in QRS configuration, including "coving" of the S wave. Heart rates were slightly increased at 2 hours post dose but normalized by 24 hours. At 100 mg/kg/day (34-fold C_{max}, 17-fold AUC), heart rates were slightly increased at 2 hours post dose but normalized by 24 hours. A no effect level (NOEL) was 25 mg/kg/day (6.4-fold C_{max}, 2.1-fold AUC).

After nine months of treatment, no indication of cardiac histopathology was observed in males or females.

Methods

Doses:	0, 25, 100, and 300 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Oral, by nasogastric gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	20%(v/v) polyethylene glycol in deionized water
Species/Strain:	Monkey, cynomolgus
Number/Sex/Group:	4
Age:	Approximately 2 to 3 years
Weight:	Females: 2.3 to 3.1 kg Males: 2.5 to 4.0 kg

Observations and Results

Mortality

One control female and one high dose female were sacrificed in Weeks 37 and 26, respectively, due to distended abdomen, absence of stools, inappetence and decreased activity.

Clinical Signs

At 300 mg/kg/day, abdominal distension was observed in 3 females, but was also observed in 1 control animal, and was considered possibly due to the vehicle polyethylene glycol.

Body Weights: No drug related effects were observed.

Feed Consumption: No drug related effects were observed.

Ophthalmoscopy: No drug related effects were observed.

ECG:

Electrocardiograms were recorded pretest and, at approximately 2 hours and 24 hours postdose, in Study Weeks 4, 8, 12, 18, 25, 32, and 37 from all monkeys in dorsal recumbency. Recordings were made from leads I, II, III, aVR, aVL, aVF, and V2 (V3). The PR, QRS, and QT intervals were measured. An additional 1-minute recording was made from lead II, pretest, and at the same time points and Study Weeks as mentioned above, on all monkeys, for heart rate measurement only.

At 300 mg/kg/day (75-fold the C_{max} of the MRHD of 75 mg, 114-fold the AUC), transient electrocardiographic findings (increases in QRS duration consistent with a ventricular conduction defect and P wave partially or fully hidden in the T wave of the preceding complex) were observed at approximately 2 hours post dose (generally resolved by 24 hours post dose). In animals where PR and QT intervals could be evaluated (1 female and 1 male on 1 or 2 occasions) no prolongation in QT interval was observed. In these animals, there were marked increases in QRS duration and notable changes in QRS configuration, including "coving" of the S wave. After nine months of treatment, no indication of cardiac histopathology was observed. Heart rates were slightly increased at 2 hours post dose but normalized by 24 hours.

At 100 mg/kg/day (34-fold C_{max}, 17-fold AUC), heart rates were slightly increased at 2 hours post dose but normalized by 24 hours.

A NOEL was 25 mg/kg/day (6.4-fold C_{max}, 2.1-fold AUC).

Heart rates: (sponsor's tables)

ECG Summary Table

TT #	09-6050				Test Article:		MK-4618									
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys															
CONTROL	Heart Rate (beats/min)															
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0027	205	207	190	192	194	190	198	207	204	204	187	187	208	197	182	
09-0047	231	215	232	221	236	225	226	235	252	223	229	216	240	223	219	
09-0059	236	223	245	242	235	240	244	229	227	248	239	235	241	239	232	
09-0063	249	237	247	239	239	229	255	231	243	244	263	258	261	ES	ES	
Average	230	221	229	224	226	221	231	226	232	230	230	224	238	220	211	
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0026	237	222	235	226	242	232	243	228	225	221	225	215	220	228	222	
09-0042	177	216	213	195	203	198	210	193	199	187	189	196	185	194	187	
09-0044	256	213	191	182	216	207	211	195	214	225	198	211	203	210	203	
09-0064	244	234	220	231	230	245	241	241	237	237	232	250	245	247	245	
Average	229	221	215	209	223	221	226	214	219	218	211	218	213	220	214	

ES = Early Sacrifice min = minutes PRE = Pretest hr = Hour
PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:		MK-4618									
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys															
25 mg/kg/day	Heart Rate (beats/min)															
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0037	242	244	244	242	245	243	254	238	249	236	235	236	239	229	246	
09-0039	251	244	237	238	228	238	234	244	216	242	239	239	220	238	229	
09-0061	223	225	229	213	226	227	227	227	216	229	231	227	230	221	224	
09-0065	225	223	225	231	226	229	239	230	239	236	232	238	250	236	241	
Average	235	234	234	231	231	234	239	235	230	236	234	235	235	231	235	
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0038	227	219	198	214	214	214	212	216	190	210	198	203	197	206	190	
09-0046	222	206	218	213	214	210	213	213	211	206	227	217	227	212	205	
09-0048	228	228	241	218	228	217	213	219	200	222	228	242	230	220	220	
09-0062	233	250	236	251	244	243	240	234	231	224	236	233	240	223	238	
Average	228	226	223	224	225	221	220	221	208	216	222	224	224	215	213	

min = minutes PRE = Pretest hr = Hour
PD = Post Dose

ECG Summary Table

TT #	09-6050			Test Article:				MK-4618							
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys														
100 mg/kg/day	Heart Rate (beats/min)														
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0021	227	244	223	243	227	241	223	233	223	235	223	244	227	245	223
09-0041	228	243	229	239	228	246	242	245	236	238	227	247	233	232	208
09-0045	256	239	217	243	228	241	255	256	244	255	255	236	247	255	246
09-0067	248	263	239	257	232	261	251	250	231	257	240	243	247	247	238
Average	240	247	227	246	229	247	243	246	234	246	236	243	239	245	229
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0036	229	225	196	248	230	233	197	213	193	198	173	224	185	216	163
09-0052	211	242	204	235	237	247	242	243	251	229	226	242	232	255	232
09-0056	228	225	223	216	211	230	230	228	222	229	201	242	232	237	198
09-0060	208	242	205	239	227	247	225	241	212	244	208	244	212	242	209
Average	219	234	207	235	226	239	224	231	220	225	202	238	215	238	201

min = minutes PRE = Pretest hr = Hour
PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:				MK-4618							
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys															
300 mg/kg/day	Heart Rate (beats/min)															
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0043	226	214	191	214	226	222	236	245	232	237	242	230	220	227	231	
09-0049	226	224	196	225	197	229	162	222	199	220	180	217	174	215	184	
09-0053	234	226	199	233	203	239	186	218	178	221	199	227	188	216	182	
09-0057	202	194	177	209	174	199	176	204	179	196	182	ES	ES	ES	ES	
Average	222	215	191	220	200	222	190	222	197	219	201	225	194	219	199	
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0022	208	216	177	219	195	231	201	229	231	240	219	233	187	221	199	
09-0034	229	294	171	223	186	226	205	221	197	228	209	225	188	224	189	
09-0040	178	208	163	210	174	208	165	211	171	213	188	215	154	185	154	
09-0050	167	219	162	224	166	216	157	216	163	218	166	210	139	223	160	
Average	196	234	168	219	180	220	182	219	191	225	196	221	167	213	176	

ES = Early Sacrifice min = minutes PRE = Pretest hr = Hour

PD = Post Dose

PR interval (sponsor's tables)

ECG Summary Table

TT #	09-6050			Test Article:		MK-4618									
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys														
CONTROL	PR Interval (sec)														
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0027	0.06	0.07	0.06	0.08	0.07	0.07	0.07	0.07	0.07	0.07	0.08	0.08	0.07	0.08	0.08
09-0047	0.05	0.05	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.05	0.05	0.06	0.05	0.05	0.04
09-0059	0.06	0.07	0.06	0.06	0.06	0.07	0.06	0.06	0.06	0.06	0.07	0.07	0.06	0.07	0.07
09-0063	0.07	0.06	0.05	0.06	0.05	0.05	0.06	0.07	0.06	0.06	0.05	0.06	0.06	ES	ES
Average	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.07	0.06	0.07	0.06
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0026	0.07	0.08	0.06	0.07	0.07	0.07	0.07	0.07	0.07	0.08	0.07	0.08	0.08	0.08	0.08
09-0042	0.08	0.07	0.06	0.07	0.07	0.07	0.07	0.08	0.07	0.10	0.10	0.08	0.09	0.07	0.08
09-0044	0.06	0.06	0.06	0.06	0.07	0.07	0.07	0.08	0.06	0.06	0.07	0.07	0.06	0.06	0.08
09-0064	0.06	0.05	0.06	0.05	0.05	0.06	0.06	0.05	0.05	0.06	0.05	0.05	0.06	0.06	0.05
Average	0.07	0.07	0.06	0.06	0.07	0.07	0.07	0.07	0.06	0.08	0.07	0.07	0.07	0.07	0.07

ES = Early Sacrifice PRE = Pretest hr = Hour

sec = Seconds PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:		MK-4618									
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys															
25 mg/kg/day	PR Interval (sec)															
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0037	0.05	0.05	0.06	0.06	0.05	0.05	0.06	0.06	0.06	0.07	0.06	0.06	0.06	0.06	0.06	
09-0039	0.06	0.06	0.06	0.06	0.06	0.07	0.06	0.07	0.07	0.06	0.06	0.07	0.06	0.07	0.08	
09-0061	0.05	0.06	0.06	0.06	0.06	0.05	0.05	0.06	0.06	0.06	0.05	0.06	0.05	0.06	0.06	
09-0065	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.06	0.05	0.05	0.06	0.05	0.05	0.06	
Average	0.05	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.05	0.06	0.06	0.06	0.07	
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0038	0.04	0.06	0.06	0.05	0.05	0.06	0.06	0.06	0.07	0.06	0.08	0.06	0.06	0.06	0.07	
09-0046	0.07	0.07	0.06	0.07	0.06	0.07	0.07	0.07	0.07	0.06	0.06	0.07	0.06	0.07	0.07	
09-0048	0.05	0.05	0.05	0.06	0.05	0.07	0.07	0.06	0.05	0.06	0.08	0.05	0.07	0.06	0.05	
09-0062	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.05	0.05	0.05	0.04	0.05	0.06	
Average	0.05	0.06	0.06	0.06	0.05	0.06	0.06	0.06	0.06	0.06	0.07	0.06	0.06	0.06	0.06	

PRE = Pretest hr = Hour

sec = Seconds PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:				MK-4618						
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys														
100 mg/kg/day	PR Interval (sec)														
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0021	0.06	0.06	0.06	0.07	0.06	0.07	0.06	0.06	0.07	0.06	0.06	0.06	0.05	0.06	0.06
09-0041	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.07	0.06	0.06	0.08
09-0045	0.05	0.07	0.06	0.06	0.06	0.06	0.05	0.07	0.05	0.06	0.05	0.06	0.06	0.08	0.05
09-0067	0.06	0.07	0.05	0.06	0.05	0.06	0.05	0.06	0.06	0.06	0.05	0.06	0.06	0.07	0.06
Average	0.06	0.07	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.07	0.06
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0036	0.07	0.06	0.08	0.07	0.06	0.07	0.08	0.07	0.08	0.08	0.08	0.08	0.06	0.08	0.08
09-0052	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.05	0.06	0.06	0.06	0.07
09-0056	0.07	0.07	0.07	0.08	0.07	0.07	0.06	0.06	0.07	0.07	0.07	0.07	0.05	0.07	0.06
09-0060	0.06	0.06	0.07	0.06	0.05	0.07	0.06	0.06	0.06	0.06	0.07	0.06	0.06	0.07	0.07
Average	0.07	0.06	0.07	0.07	0.06	0.07	0.07	0.06	0.07	0.07	0.07	0.07	0.06	0.07	0.07

PRE = Pretest hr = Hour
sec = Seconds PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:				MK-4618						
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys														
300 mg/kg/day	PR Interval (sec)														
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0043	0.05	ND	0.06	ND	0.05	0.07	0.05	0.05	0.04	0.06	0.05	0.06	0.05	0.06	0.05
09-0049	0.06	ND	0.06	ND	0.08	ND	0.08	ND	0.09	0.08	0.06	0.08	0.09	ND	0.07
09-0053	0.06	ND	0.06	0.08	0.08	0.07	0.08	ND	0.09	0.08	0.07	0.08	0.07	0.08	0.09
09-0057	0.06	ND	0.07	0.08	0.08	ND	0.08	ND	0.07	0.05	0.07	ES	ES	ES	ES
Average	0.06	N/A	0.06	N/A	0.07	N/A	0.07	N/A	0.07	0.07	0.06	0.07	0.07	0.07	0.07
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0022	0.07	ND	0.07	0.08	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.06	0.08	0.08
09-0034	0.07	ND	0.07	ND	0.07	ND	0.07	ND	0.07	ND	0.06	ND	0.06	ND	0.07
09-0040	0.07	ND	0.06	0.07	0.06	0.05	0.06	0.06	0.05	0.08	0.04	0.08	0.07	0.09	0.08
09-0050	0.06	0.08	0.06	0.08	0.07	ND	0.07	0.08	0.07	ND	0.07	0.08	0.07	0.08	0.07
Average	0.07	N/A	0.07	N/A	0.07	N/A	0.07	0.07	0.07	NA	0.06	0.08	0.07	0.08	0.08

ES = Early Sacrifice PRE = Pretest ND = Not Determined (P wave was partially or fully hidden in the T wave at the precedent beat)
sec = Seconds PD = Post Dose N/A = Not Applicable hr = Hour

QRS and QT interval (sponsor's tables)

ECG Summary Table

TT #	09-6050				Test Article:				MK-4618							
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys															
CONTROL	QRS Interval (sec)															
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0027	0.05	0.04	0.04	0.04	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.04	0.04	0.05	0.04	
09-0047	0.04	0.04	0.04	0.04	0.05	0.04	0.04	0.05	0.05	0.04	0.04	0.04	0.04	0.05	0.05	
09-0059	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.05	0.04	0.04	0.04	0.04	0.04	0.04	
09-0063	0.04	0.05	0.05	0.06	0.06	0.05	0.05	0.04	0.06	0.05	0.05	0.04	0.05	ES	ES	
Average	0.04	0.04	0.04	0.05	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.04	0.04	0.05	0.04	
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0026	0.05	0.04	0.04	0.04	0.05	0.05	0.05	0.05	0.05	0.04	0.04	0.05	0.04	0.05	0.05	
09-0042	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.05	0.05	0.04	0.04	0.05	0.04	0.05	0.05	
09-0044	0.04	0.04	0.05	0.04	0.04	0.04	0.04	0.04	0.06	0.04	0.04	0.04	0.05	0.05	0.04	
09-0064	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.05	0.05	0.04	0.04	0.05	0.05	0.05	0.05	
Average	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.04	0.05	0.05	0.05	0.05	

ES = Early Sacrifice PRE = Pretest hr = Hour
sec = Seconds PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:				MK-4618						
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys														
25 mg/kg/day	QRS Interval (sec)														
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0037	0.05	0.05	0.04	0.04	0.04	0.05	0.04	0.04	0.05	0.05	0.04	0.04	0.05	0.05	0.06
09-0039	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.04	0.05	0.05	0.04	0.04	0.05	0.05	0.04
09-0061	0.04	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.04	0.05	0.05	0.05
09-0065	0.06	0.06	0.05	0.06	0.06	0.06	0.05	0.06	0.05	0.06	0.05	0.05	0.06	0.06	0.06
Average	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.04	0.05	0.05	0.05
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0038	0.05	0.04	0.04	0.05	0.04	0.05	0.04	0.04	0.04	0.04	0.03	0.04	0.05	0.05	0.04
09-0046	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.05	0.05	0.05	0.04	0.05	0.06	0.05	0.05
09-0048	0.05	0.05	0.04	0.05	0.04	0.05	0.04	0.04	0.04	0.04	0.03	0.05	0.04	0.05	0.06
09-0062	0.04	0.04	0.04	0.05	0.05	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.06	0.04	0.06
Average	0.05	0.05	0.04	0.05	0.05	0.05	0.05	0.04	0.04	0.04	0.04	0.05	0.05	0.05	0.05
PRE = Pretest hr = Hour															
sec = Seconds PD = Post Dose															

ECG Summary Table

TT #	09-6050				Test Article:				MK-4618						
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys														
100 mg/kg/day	QRS Interval (sec)														
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0021	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.06	0.05	0.05	0.05	0.05	0.05
09-0041	0.04	0.05	0.05	0.05	0.04	0.04	0.04	0.05	0.04	0.05	0.04	0.05	0.05	0.04	0.05
09-0045	0.04	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.04	0.05	0.04	0.05
09-0067	0.04	0.05	0.05	0.06	0.04	0.04	0.04	0.04	0.05	0.04	0.04	0.05	0.04	0.04	0.04
Average	0.04	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.05	0.05	0.04	0.05
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0036	0.04	0.04	0.04	0.04	0.05	0.05	0.04	0.05	0.04	0.04	0.04	0.05	0.05	0.04	0.05
09-0052	0.04	0.06	0.06	0.07	0.05	0.05	0.04	0.06	0.06	0.05	0.04	0.06	0.04	0.05	0.04
09-0056	0.05	0.04	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.05
09-0060	0.04	0.06	0.05	0.04	0.05	0.05	0.04	0.05	0.05	0.04	0.05	0.04	0.05	0.04	0.05
Average	0.04	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

PRE = Pretest hr = Hour
sec = Seconds PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:		MK-4618									
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys															
300 mg/kg/day	QRS Interval (sec)															
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0043	0.04	0.08	0.05	0.07	0.05	0.06	0.05	0.05	0.04	0.05	0.04	0.05	0.06	0.04	0.04	
09-0049	0.05	0.09	0.05	0.08	0.05	0.08	0.05	0.09	0.04	0.05	0.04	0.05	0.04	0.07	0.04	
09-0053	0.04	0.07	0.04	0.06	0.04	0.06	0.05	0.08	0.05	0.06	0.04	0.08	0.05	0.05	0.05	
09-0057	0.05	0.12	0.05	0.05	0.05	0.09	0.05	0.10	0.04	0.05	0.04	ES	ES	ES	ES	
Average	0.05	0.09	0.05	0.07	0.05	0.07	0.05	0.08	0.04	0.05	0.04	0.06	0.05	0.05	0.04	
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0022	0.05	0.08	0.04	0.04	0.04	0.06	0.05	0.05	0.05	0.04	0.04	0.05	0.05	0.05	0.04	
09-0034	0.05	0.11	0.05	0.09	0.05	0.10	0.05	0.12	0.05	0.10	0.04	0.12	0.06	0.11	0.04	
09-0040	0.04	0.10	0.04	0.07	0.05	0.07	0.04	0.05	0.05	0.05	0.04	0.05	0.04	0.04	0.04	
09-0050	0.04	0.05	0.04	0.05	0.04	0.12	0.05	0.05	0.05	0.08	0.04	0.05	0.05	0.04	0.04	
Average	0.05	0.09	0.04	0.07/0.06	0.05	0.09	0.05	0.07	0.05	0.07	0.04	0.07	0.05	0.06	0.04	

ES = Early Sacrifice PRE = Pretest hr = Hour

sec = Seconds PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:		MK-4618								
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys														
CONTROL	QT Interval (sec)														
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0027	0.19	0.18	0.18	0.20	0.16	0.16	0.16	0.15	0.16	0.14	0.17	0.16	0.18	0.15	0.17
09-0047	0.16	0.18	0.18	0.18	0.18	0.16	0.18	0.16	0.16	0.18	0.17	0.18	0.18	0.18	0.16
09-0059	0.11	0.17	0.16	0.14	0.16	0.18	0.16	0.16	0.16	0.16	0.15	0.16	0.16	0.16	0.16
09-0063	0.16	0.16	0.16	0.17	0.16	0.17	0.16	0.14	0.16	0.16	0.18	0.13	0.14	ES	ES
Average	0.16	0.17	0.17	0.17	0.17	0.17	0.17	0.15	0.16	0.16	0.17	0.16	0.17	0.16	0.16
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0026	0.15	0.17	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.18	0.16	0.14
09-0042	0.16	0.17	0.16	0.16	0.18	0.18	0.17	0.17	0.18	0.18	0.18	0.18	0.18	0.16	0.18
09-0044	0.16	0.17	0.15	0.14	0.16	0.16	0.18	0.17	0.15	0.15	0.18	0.16	0.16	0.15	0.15
09-0064	0.17	0.18	0.18	0.18	0.17	0.18	0.18	0.17	0.16	0.16	0.17	0.17	0.18	0.18	0.17
Average	0.16	0.17	0.16	0.16	0.17	0.17	0.17	0.17	0.16	0.16	0.17	0.17	0.18	0.16	0.16

ES = Early Sacrifice PRE = Pretest hr = Hour
sec = Seconds PD = Post Dose

ECG Summary Table

TT #	09-6050			Test Article:		MK-4618									
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys														
25 mg/kg/day	QT Interval (sec)														
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0037	0.16	0.16	0.16	0.16	0.16	0.16	0.17	0.17	0.18	0.17	0.17	0.16	0.16	0.17	0.16
09-0039	0.17	0.16	0.14	0.17	0.14	0.18	0.17	0.14	0.16	0.13	0.14	0.17	0.16	0.16	0.14
09-0061	0.18	0.19	0.20	0.18	0.14	0.16	0.20	0.17	0.18	0.17	0.18	0.20	0.18	0.18	0.16
09-0065	0.19	0.18	0.18	0.18	0.18	0.17	0.18	0.18	0.18	0.18	0.17	0.17	0.18	0.17	0.18
Average	0.18	0.17	0.17	0.17	0.16	0.17	0.18	0.17	0.18	0.16	0.17	0.18	0.17	0.17	0.16
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0038	0.16	0.16	0.16	0.16	0.16	0.14	0.18	0.16	0.18	0.16	0.17	0.16	0.18	0.15	0.16
09-0046	0.18	0.14	0.18	0.15	0.18	0.18	0.19	0.15	0.15	0.17	0.16	0.15	0.16	0.14	0.18
09-0048	0.16	0.16	0.16	0.18	0.17	0.19	0.18	0.18	0.17	0.18	0.18	0.17	0.18	0.18	0.18
09-0062	0.15	0.16	0.16	0.16	0.16	0.16	0.16	0.13	0.14	0.16	0.16	0.14	0.14	0.14	0.14
Average	0.16	0.16	0.17	0.16	0.17	0.17	0.18	0.16	0.16	0.17	0.17	0.16	0.17	0.15	0.17

PRE = Pretest hr = Hour
sec = Seconds PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:		MK-4618								
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys														
100 mg/kg/day	QT Interval (sec)														
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0021	0.17	0.20	0.17	0.16	0.18	0.16	0.18	0.17	0.18	0.16	0.17	0.16	0.17	0.16	0.17
09-0041	0.14	0.14	0.15	0.16	0.16	0.16	0.14	0.17	0.16	0.16	0.17	0.16	0.20	0.14	0.15
09-0045	0.18	0.16	0.16	0.16	0.17	0.16	0.14	0.16	0.18	0.15	0.16	0.16	0.18	0.14	0.14
09-0067	0.17	0.20	0.17	0.16	0.16	0.14	0.16	0.14	0.16	0.14	0.16	0.14	0.16	0.14	0.16
Average	0.17	0.18	0.16	0.16	0.17	0.16	0.16	0.16	0.17	0.15	0.17	0.16	0.18	0.15	0.16
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0036	0.17	0.16	0.19	0.16	0.17	0.16	0.19	0.18	0.20	0.18	0.20	0.18	0.20	0.17	0.21
09-0052	0.14	0.20	0.18	0.14	0.17	0.14	0.16	0.14	0.13	0.14	0.16	0.14	0.20	0.14	0.13
09-0056	0.18	0.18	0.19	0.18	0.19	0.17	0.18	0.18	0.19	0.17	0.20	0.18	0.18	0.16	0.20
09-0060	0.16	0.16	0.18	0.16	0.16	0.16	0.17	0.16	0.14	0.15	0.17	0.15	0.16	0.13	0.16
Average	0.16	0.18	0.19	0.16	0.17	0.16	0.18	0.17	0.17	0.16	0.18	0.16	0.19	0.15	0.18

PRE = Pretest hr = Hour
sec = Seconds PD = Post Dose

ECG Summary Table

TT #	09-6050				Test Article:		MK-4618									
Study Title:	Nine-Month Oral Toxicity Study in Cynomolgus Monkeys															
300 mg/kg/day	QT Interval (sec)															
Female #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0043	0.18	ND	0.16	ND	0.17	0.18	0.17	0.15	0.16	0.17	0.17	0.17	0.16	0.14	0.16	
09-0049	0.17	ND	0.18	ND	0.18	ND	0.18	ND	0.18	0.18	0.20	0.18	0.20	ND	0.19	
09-0053	0.16	ND	0.18	ND	0.18	0.18	0.20	ND	0.20	0.17	0.18	0.18	0.20	0.18	0.19	
09-0057	0.19	ND	0.16	0.14	0.18	ND	0.18	ND	0.17	0.14	0.16	ES	ES	ES	ES	
Average	0.18	N/A	0.17	N/A	0.18	N/A	0.18	N/A	0.18	0.17	0.18	0.18	0.19	0.16	0.18	
Male #	PRE	Study Week 4		Study Week 8		Study Week 12		Study Week 18		Study Week 25		Study Week 32		Study Week 37		
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0022	0.18	ND	0.19	0.18	0.19	0.17	0.18	0.18	0.16	0.17	0.18	0.18	0.18	0.18	0.19	
09-0034	0.18	ND	0.18	ND	0.20	ND	0.18	ND	0.19	ND	0.18	ND	0.20	ND	0.18	
09-0040	0.20	ND	0.18	ND	0.20	0.20	0.19	0.17	0.20	0.18	0.18	0.18	0.22	0.20	0.20	
09-0050	0.21	0.18	0.19	0.18	0.20	ND	0.22	0.16	0.22	ND	0.20	0.20	0.23	0.18	0.22	
Average	0.19	N/A	0.19	N/A	0.20	N/A	0.19	0.17	0.19	NA	0.19	0.19	0.21	0.19	0.20	

ES = Early Sacrifice PRE = Pretest ND = Not Determined (P wave was partially or fully hidden in the T wave at the precedent beat)
sec = Seconds PD = Post Dose N/A = Not Applicable hr = Hour

Hematology: No drug related effects were observed.

Clinical Chemistry: No drug related effects were observed.

Urinalysis: No drug related effects were observed.

Gross Pathology: No drug related effects were observed.

Organ Weights

No dose related effects were observed; however, heart weights outside of the historical range for size based on overall body weight were observed in all dose groups, including the control group. There were no histopathologic correlates.

Histopathology

Adequate Battery: yes

Peer Review: yes

Histological Findings:

At 300 mg/kg/day, very slight cellular infiltration was observed in the liver (females). Very slightly increased brown fat in the white adipose tissue was observed at all doses in both sexes.

Test Article-Related Postmortem Findings
MK-4618, Sexes Combined

Dose, mg/kg/day	25	100	300
Number of Animals	8	8	8 ^a
Histomorphology (Incidence)			
Liver	NE		
Cellular infiltration		-	2 ^b
White adipose tissue			
Brown fat accumulation	2	2	8 ^a
^a 8 animals examined including 1-early sacrificed female in Study Week 26. ^b change seen in females only. - = No test article-related change. NE = Group not examined.			

*Sponsor's table

Toxicokinetics:

At a clinical dose of 75 mg/day vibegron, a C_{max} of 123 ng/mL (0.277 uM) and an AUC_{0-24h} of 1450 ng·h/mL (3.26 uM·hr) were observed in Study RVT-901-1002. (sponsor's table.)

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618 : Study Day 1				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
25	Female	13.1 $\pm$ 2.12	2.44 $\pm$ 0.495	2.8 $\pm$ 0.75
	Male	5.96 $\pm$ 1.95	1.03 $\pm$ 0.229	1.3 $\pm$ 0.25
	All	9.53 $\pm$ 1.90	1.74 $\pm$ 0.368	2.0 $\pm$ 0.46
100	Female	83.8 $\pm$ 7.43	17.4 $\pm$ 3.81	2.5 $\pm$ 0.50
	Male	74.4 $\pm$ 7.83	11.0 $\pm$ 1.86	2.1 $\pm$ 0.72
	All	79.1 $\pm$ 5.30	14.2 $\pm$ 2.31	2.3 $\pm$ 0.41
300	Female	196 $\pm$ 98.2	35.6 $\pm$ 12.1	1.8 $\pm$ 0.83
	Male	276 $\pm$ 37.0	45.7 $\pm$ 5.52	2.8 $\pm$ 0.75
	All	236 $\pm$ 50.8	40.6 $\pm$ 6.46	2.3 $\pm$ 0.55

^a MK-4618 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.023 μ M).

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618 : Study Week 13				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
25	Female	7.25 $\pm$ 1.54	2.25 $\pm$ 0.783	0.88 $\pm$ 0.13
	Male	6.39 $\pm$ 2.66	1.28 $\pm$ 0.675	1.3 $\pm$ 0.25
	All	6.82 $\pm$ 1.43	1.77 $\pm$ 0.512	1.1 $\pm$ 0.15
100	Female	55.1 $\pm$ 9.11	9.42 $\pm$ 1.38	2.5 $\pm$ 0.50
	Male	55.0 $\pm$ 11.6	9.62 $\pm$ 1.56	2.1 $\pm$ 0.72
	All	55.0 $\pm$ 6.81	9.52 $\pm$ 0.963	2.3 $\pm$ 0.41
300	Female	236 $\pm$ 13.4	31.1 $\pm$ 4.64	2.5 $\pm$ 0.50
	Male	254 $\pm$ 43.2	32.1 $\pm$ 4.28	2.8 $\pm$ 0.75
	All	245 $\pm$ 21.2	31.6 $\pm$ 2.93	2.6 $\pm$ 0.42

^a MK-4618 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.023 μ M).

Study title: Three-Month Oral Toxicity Study in Rats

Study no.: **TT #09-6012**

Conducting laboratory and location: Laboratoires Merck Sharp & Dohme-
Chibret Merck Research Laboratories
Route de Marsat, Riom, 63963 Clermont-
Ferrand Cedex 9, France

Date of study initiation: 14 April 2009

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: Lot Number L-002206358-000L018, 98.4 area percent pure by HPLC

Key Study Findings

The NOEL level was 12 mg/kg/day (4.6-fold the MRHD). At 300 mg/kg/day (248-fold), decreases in body weight gain were observed, along with atrophy of the ovaries, uterus, and cervix, decreased uterus and ovary weights, decreased kidney and pituitary weights, and decreased spleen, liver, and prostate weights.

Methods

Doses: 0, 3, 12, and 300 mg/kg/day of MK-4618 (as base compound)
Dosing: Once daily via oral gavage
Formulation/Vehicle: 20% (v/v) polyethylene glycol 400, 5 mL/kg
Species/Strain: Crl:CD(SD) rats
Number/Sex/Group: 10
Age: 5 weeks
Weight: Females: 114.0 to 146.2 g
Males: 151.6 to 184.9 g

Observations and Results

Clinical Signs, Body Weights, Food Consumption

At 300 mg/kg/day, slight to moderate decreases in body weight gain, transient postdosing salivation, slight increases in erythrocytes, hemoglobin, and hematocrit (females only), very slight and slight increases in serum alanine aminotransferase and alkaline phosphatase, and slight decreases in serum triglycerides were observed.

Histopathology

At 300 mg/kg/day, atrophy of the ovaries, uterus, and cervix, correlating with decreased ovary weight and with decreased size of the uterus and ovaries were observed. Decreases in kidney and pituitary weights and decreases in spleen, liver, and prostate weights in males only were observed.

Toxicokinetics**(sponsor's table)**

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Rats Following Dosing of MK-4618 : Study Week 13				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
3	Female	2.07 $\pm$ 0.262	0.301 $\pm$ 0.0884	2.0 $\pm$ NC
	Male	2.35 $\pm$ 0.641	0.589 $\pm$ ID	2.0 $\pm$ NC
	All	2.16 $\pm$ 0.265	0.416 $\pm$ 0.158	2.0 $\pm$ NC
12	Female	14.4 $\pm$ 1.49	2.24 $\pm$ 0.908	1.0 $\pm$ NC
	Male	15.7 $\pm$ 2.16	2.64 $\pm$ 0.744	2.0 $\pm$ NC
	All	15.0 $\pm$ 1.30	2.26 $\pm$ 0.634	1.0 $\pm$ NC
300	Female	725 $\pm$ 86.0	108 $\pm$ 29.5	2.0 $\pm$ NC
	Male	893 $\pm$ 69.6	114 $\pm$ 10.0	2.0 $\pm$ NC
	All	809 $\pm$ 56.9	111 $\pm$ 14.0	2.0 $\pm$ NC

NC = Not Calculated

ID = Insufficient Data

^a MK-4618 concentrations in plasma from all control group animals at 1 hour post-dose were below the lower limit of quantitation of the bioanalytical method.

Study title: Three-Month Oral Toxicity Study in Cynomolgus MonkeysStudy no.: **TT #09-6013**

Conducting laboratory and location: Laboratoires Merck Sharp & Dohme-Chibret, Merck Research Laboratories
Route de Marsat, Riom, 63963 Clermont-Ferrand Cedex 9, France

Date of study initiation: 22 April 2009

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: Lot Number L-002206358-000L018, 98.4 area percent pure by HPLC

Key Study Findings

Two females were found dead at 1000 mg/kg/day (181-fold the C_{max} of the MRHD of 75 mg, 255-fold AUC). ECG changes were observed in all surviving males at this dose and it should be considered that these deaths may have been due to cardiac arrhythmias. A NOAEL for ECG changes was 120 mg/kg/day (43-fold the C_{max} of the MRHD of 75 mg, 20.7-fold AUC). ECG changes were observed in males after approximately 3 weeks of dosing at 1000 mg/kg/day at approximately 1 hour and/or 24 hours postdosing, and after approximately 1 month and 2 months of dosing at 360

mg/kg/day (2/3 males) at approximately 1 hour post dose. They consisted of QRS distortion (consistent with ventricular conduction effects) at both dosages. In 1 animal at 1000 mg/kg/day, absence of P waves and PR prolongation were also observed (consistent with atrioventricular conduction defects). After approximately 2 months of dosing at 360 mg/kg/day (about 104-fold C_{max}, 58-fold AUC), ECG changes were limited to QRS distortion. There were no test article-related histomorphological changes in the heart that correlated with these conduction defects.

At 1000/360 mg/kg/day, very slight to slight cellular infiltration was observed in the liver along with increases in serum liver enzyme activities. At 120 mg/kg/day and above, increased brown fat was observed.

Methods

Doses:	0, 12, 36, 120, and 1000/360 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Oral by nasogastric gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	20% (v/v) polyethylene glycol 400 in deionized water acidified with 1.0N HCl to reach a pH of 2.5 +/- 0.5; pH was adjusted with couple of drops of NaOH when necessary
Species/Strain:	Monkey, cynomolgus
Number/Sex/Group:	3
Age:	Approximately 3 years
Weight:	Females: 2.4 to 3.1 kg Males: 2.5 to 4.9 kg

Observations and Results

Mortality

There were 2 unscheduled deaths of females at 1000 mg/kg/day, prior to lowering the dose to 360 mg/kg/day in Study Week 3. On the day of or preceding death, decreased activity, decreased skin turgor, and/or coldness to the touch, and/or inappetence were observed. Although the cause of death was not evident at the histomorphological examination, ECG changes were observed in all surviving males at this dose and it should be considered that these deaths may have been due to cardiac arrhythmias.

Clinical Signs

At 1000 mg/kg/day postdose vomiting and decreased skin turgor (males) were observed.

Body Weights

No treatment related effects were observed.

Ophthalmoscopy

No treatment related effects were observed.

ECG

ECG changes were observed in males after approximately 3 weeks of dosing at 1000 mg/kg/day (3/3 males) at approximately 1 hour and/or 24 hours postdosing, and after approximately 1 month and 2 months of dosing at 360 mg/kg/day (2/3 males) at approximately 1 hour postdosing. Changes consisted of QRS distortion at both dosages. In 1 animal at 1000 mg/kg/day, absence of P waves and PR prolongation were also observed. After approximately 2 months of dosing at 360 mg/kg/day, ECG changes were limited to QRS distortion. No effects on ECG morphology were observed at 120 mg/kg/day.

Hematology/ Clinical Chemistry

At 1000 mg/kg/day, very slight increases in serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) activities, and very slight decreases in serum cholesterol and proteins were observed. Decreased reticulocytes (moderate), lymphocytes (slight), hemoglobin (very slight), and hematocrit (slight) were observed in a single male at 360 mg/kg/day, very slight increases in serum AST and ALT were observed in males only. No effects were observed at 120 mg/kg/day.

Histopathology

Very slight to slight cellular infiltration was observed in the liver in the 1000/360-mg/kg/day group along with increases in serum liver enzyme activities. At 120 mg/kg/day and above, increased brown fat was observed in both sexes.

Toxicokinetics

(sponsor's table)

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618: Study Day 1				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
12	Female	2.58 $\pm$ 0.837	0.461 $\pm$ 0.174	1.7 $\pm$ 0.33
	Male	1.65 $\pm$ 0.498	0.353 $\pm$ 0.121	1.7 $\pm$ 0.33
	All	2.11 $\pm$ 0.482	0.407 $\pm$ 0.0979	1.7 $\pm$ 0.21
36	Female	13.4 $\pm$ 0.780	2.35 $\pm$ 0.364	2.3 $\pm$ 0.88
	Male	13.9 $\pm$ 4.70	2.68 $\pm$ 0.938	2.0 $\pm$ 0.0
	All	13.7 $\pm$ 2.13	2.52 $\pm$ 0.456	2.2 $\pm$ 0.40
120	Female	68.8 $\pm$ 15.0	11.0 $\pm$ 1.54	2.7 $\pm$ 0.67
	Male	91.1 $\pm$ 20.0	14.6 $\pm$ 2.88	1.8 $\pm$ 1.1
	All	80.0 $\pm$ 12.2	12.8 $\pm$ 1.66	2.3 $\pm$ 0.60
1000	Female	221 $\pm$ 78.1	37.0 $\pm$ 14.5	2.8 $\pm$ 1.2
	Male	324 $\pm$ 179	53.9 $\pm$ 29.4	2.8 $\pm$ 1.2
	All	273 $\pm$ 90.4	45.5 $\pm$ 15.1	2.8 $\pm$ 0.74

^a MK-4618 concentrations in plasma from all control group animals were below the lower limit of quantitation.

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618: Study Week 3/4				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
12 ^b	Female	1.85 $\pm$ 0.842	0.377 $\pm$ 0.180	1.3 $\pm$ 0.33
	Male	1.83 $\pm$ 0.485	0.399 $\pm$ 0.142	1.2 $\pm$ 0.44
	All	1.84 $\pm$ 0.435	0.388 $\pm$ 0.103	1.3 $\pm$ 0.25
36 ^b	Female	12.8 $\pm$ 3.91	3.52 $\pm$ 0.556	1.2 $\pm$ 0.44
	Male	14.9 $\pm$ 3.52	3.46 $\pm$ 0.690	1.5 $\pm$ 0.50
	All	13.8 $\pm$ 2.40	3.49 $\pm$ 0.397	1.3 $\pm$ 0.31
120 ^b	Female	50.9 $\pm$ 0.378	10.4 $\pm$ 0.645	1.7 $\pm$ 0.33
	Male	84.1 $\pm$ 18.4	13.1 $\pm$ 2.35	3.3 $\pm$ 0.67
	All	67.5 $\pm$ 11.1	11.8 $\pm$ 1.25	2.5 $\pm$ 0.50
1000 ^c	Female ^d	327 $\pm$ ID	26.8 $\pm$ ID	2.0 $\pm$ ID
	Male	1000 $\pm$ 247	57.7 $\pm$ 8.25	3.3 $\pm$ 0.67
	All	833 $\pm$ 243	50.0 $\pm$ 9.69	3.0 $\pm$ 0.58

ID = Insufficient Data

^a MK-4618 concentrations in plasma from all control group animals were below the lower limit of quantitation in Study Week 4.^b Study Week 4^c Study Week 3 before dose lowering. Timepoints were limited to 2, 4, and 24 hours.^d Data obtained from 1 female only.

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618: Study Week 7				
Dose (mg/kg/day)	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
1000/360 ^a	Female ^b	195 $\pm$ ID	23.7 $\pm$ ID	4.0 $\pm$ ID
	Male	188 $\pm$ 12.0	30.3 $\pm$ 8.04	1.2 $\pm$ 0.44
	All	190 $\pm$ 8.60	28.7 $\pm$ 5.92	1.9 $\pm$ 0.77

ID = Insufficient Data

^a Dose was lowered from 1000 mg/kg/day to 360 mg/kg/day in Study Week 3 (after toxicokinetic sampling) due to mortality.^b Data obtained from 1 female only.

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618: Study Week 13				
Dose (mg/kg/day) ^c	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
12	Female	2.53 $\pm$ 1.36	0.467 $\pm$ 0.215	1.7 $\pm$ 0.33
	Male	1.84 $\pm$ 0.544	0.437 $\pm$ 0.165	0.67 $\pm$ 0.17
	All	2.18 $\pm$ 0.671	0.452 $\pm$ 0.121	1.2 $\pm$ 0.28
36	Female	11.0 $\pm$ 1.83	3.63 $\pm$ 0.369	0.50 $\pm$ 0.0
	Male	12.8 $\pm$ 2.92	3.10 $\pm$ 0.970	1.7 $\pm$ 0.33
	All	11.9 $\pm$ 1.59	3.36 $\pm$ 0.479	1.1 $\pm$ 0.30
120	Female	54.9 $\pm$ 9.67	13.5 $\pm$ 2.50	0.83 $\pm$ 0.17
	Male	85.7 $\pm$ 9.21	14.6 $\pm$ 0.425	2.3 $\pm$ 0.88
	All	70.3 $\pm$ 9.11	14.0 $\pm$ 1.16	1.6 $\pm$ 0.52
1000/360 ^a	Female ^b	194 $\pm$ ID	29.2 $\pm$ ID	4.0 $\pm$ ID
	Male	337 $\pm$ 46.5	41.5 $\pm$ 5.10	2.8 $\pm$ 1.2
	All	302 $\pm$ 48.6	38.4 $\pm$ 4.74	3.1 $\pm$ 0.88

ID = Insufficient Data

^a Dose was lowered from 1000 mg/kg/day to 360 mg/kg/day in Study Week 3 (after toxicokinetic sampling) due to mortality.

^b Data obtained from 1 female only.

^c MK-4618 concentrations in plasma from all control group animals were below the lower limit of quantitation in Study Week 13.

Study title: MK-4618/L-000753555: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

Study no.: TT #10-6038

Study report location: Safety Assessment, Laboratoires Merck Sharp & Dohme-Chibret, Riom, France.

Conducting laboratory and location: Laboratoires Merck Sharp & Dohme-Chibret, Merck Research Laboratories. Route de Marsat, Riom, 63963 Clermont-Ferrand Cedex 9, France

Date of study initiation: 26 October 2010 (additional male group initiated on 1 December 2010)

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: MK-4618 (lot # L-002206358-000L021, base compound): 99.6 area percent by HPLC, and L-000753555 (lot # L-000753555-001J012, tartrate salt): 99.8 area percent by HPLC

Key Study Findings:

A dose level for MK-4618 was 100 mg/kg/day (approximately 23 times the MRHD of 75 mg by C_{max}, 13 times by AUC) with tolterodine doses of 1 and 5 mg/kg/day (approximately 1.5 to 4 times the clinical exposure of poor tolterodine metabolizers following a 4 mg dose and 5 or more times the clinical exposure of the active tolterodine metabolite in extensive tolterodine metabolizers following a MRHD of 4 mg). Tolterodine was tested alone and in combination with MK-4618. An additional group of males were dosed with MK-4618 and 3 mg/kg/day of tolterodine following the death of one 5 mg/kg/day male.

At a combination dose of 100/5 (MK-4618/tolterodine) mg/kg/day, one male was found dead following observations of distended abdomen, signs of stomach content aspiration, decreased heart rate at 2 hours (27%) and 24 hours post dose (42%), increased PR interval at 2 hours post dose (50%), and increased QT and QTc intervals 2 hours (20% and 13%, respectively) and 24 hours post dose (56% and 30%, respectively).

Effects on heart rate were observed in all dose groups.

Methods

Doses:	0/1, 0/5, 100/1, and 100/5 mg/kg/day MK-4618 (base compound) / in combination with the tartrate salt form of L-000753555 (tolterodine), with an added dose group of 100/3 mg/kg/day in males (see protocol deviation below)
Frequency of dosing:	daily
Route of administration:	Oral, gavage
Species/Strain:	Monkey, cynomolgus
Age:	Approximately 2 to 3 years
Weight:	Females: 2.5 to 3.2 kg, Males: 2.8 to 4.1 kg
Deviation from study protocol:	To further determine the potential toxicity and toxicokinetic profile of MK-4618, L-000753555 and L-000753555 metabolite (L-002391826, 5-hydroxymethyl tolterodine metabolite), a group of 4 males was added to the study about 1 month after the initial study start date. The dosing level was 100 mg/kg/day of MK-4618 immediately followed by L-000753555 at 3 mg/kg/day. This group followed the same study design as the remaining groups regarding antemortem, postmortem, and toxicokinetic parameters.

Number/Sex/Group:

	Females	Males
Control (vehicles) ^a	3	3
<u>MK-4618/L-000753555^b</u>		
0 mg/kg/day/1 mg/kg/day	3	3
0 mg/kg/day/5 mg/kg/day	3	3
100 mg/kg/day/1 mg/kg/day	3	3
100 mg/kg/day/3 mg/kg/day ^c	0	4
100 mg/kg/day/5 mg/kg/day	3	3
^a 1 mL/kg of 0.5% (w/v) methylcellulose in deionized water administered immediately after 5 mL/kg of 20% (v/v) polyethylene glycol 400 in deionized water. ^b L-000753555 administered immediately after 5 mL/kg of 20% (v/v) polyethylene glycol 400 in deionized water or MK-4618. ^c Group added 5 weeks after the initial study start date.		

Observations and Results**Mortality**

At 100/5 mg/kg/day, one male was found dead on Study Day 10 prior to dosing, exhibiting discharge from the nose and mouth, consistent with regurgitation and aspiration of gastric contents.

Clinical Signs

At 100/5 mg/kg/day, dilated pupils, increase in urine volume, distended abdomen (2 males), transient decreases in heart rate (females), and a decrease in mean albumin (males, very slight) were observed. In the male that died, decreased food consumption, distended abdomen, and scant feces were observed.

At 100/3 mg/kg/day, distended abdomen (1 male), dilated pupils, and increased urine volume were observed.

At 100/1 mg/kg/day, transient decreases in heart rate and increases in urine volume were observed.

At 0/5 mg/kg/day, transient decreases in heart rate and dilated pupils (females), and increased urine volume (males) were observed.

At 0/1 mg/kg/day, occasional transient decreases in heart rate were observed in males only. No effect was observed in 0/1 mg/kg/day females.

Body Weights: No treatment related effects were observed.

Feed Consumption: No treatment related effects were observed.

Ophthalmoscopy: No treatment related effects were observed.

ECG

At 100/5 mg/kg/day, in the male that died (Study Week 2), decreased heart rate at 2 hours (27%) and 24 hours post dose (42%), increased PR interval at 2 hours post dose (50%), and increased QT and QTc intervals at 2 hours (20% and 13%, respectively) and 24 hours post dose (56% and 30%, respectively), were observed. Additionally, transient decreases in heart rate were observed (Study Week 8) in 2 males at 0/1 mg/kg/day 2 hours (14% and 15%) and/or 24 hours post dose (16%), and in 1 female at 0/5 mg/kg/day 2 hours post dose (19%). In Study Weeks 2 and/or 4, 8, and 13, transient decreases in heart rate were observed at 24 hours post dose only, in 1 female and 2 males at 100/1 mg/kg/day (13% to 20%) and in 2 females at 100/5 mg/kg/day (11% and 16%).

Test Article-Related Changes in Heart Rate: Absolute Values in Beats/min (Percent Difference Relative to Pretest) 2 Hours and 24 Hours Post Dose (sponsor's table.)

Group (mg/kg/day) Animal #	Pretest	MK-4618/L-000753555							
		Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		+2 hrs	+24 hrs	+2 hrs	+24 hrs	+2 hrs	+24 hrs	+2 hrs	+24 hrs
0/1:									
10-0038M	231	-	-	-	-	197 (-15%)	-	-	-
10-0048M	264	-	-	-	-	228 (-14%)	221 (-16%)	-	-
0/5:									
10-0035F	242	-	-	-	-	196 (-19%)	-	-	-
100/1:									
10-0015F	240	-	201 (-16%)	-	207 (-14%)	-	193 (-20%)	-	194 (-19%)
09-0116M	216	-	-	-	189 (-13%)	-	193 (-20%)	-	179 (-17%)
10-0050M	231	-	-	-	-	-	202 (-13%)	-	-
100/5:									
10-0039F	238	-	208 (-13%)	-	-	-	-	-	-
10-0043F	255	-	-	-	-	-	213 (-16%)	-	227 (-11%)
10-0022Ma	267	195 (-27%)	154 (-42%)	N/A	N/A	N/A	N/A	N/A	N/A

a Animal found dead on Study Day 10.

- = No test article-related change.

Heart rate (sponsor's table.)

TT # 10-6038

Test Article: MK-4618/L-000753555

Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

CONTROL		Heart Rate (beats/min)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0025	205	210	228	208	238	243	240	217	225
10-0027	258	251	250	253	258	241	247	250	260
10-0029	226	223	225	227	230	213	236	227	226
Average	230	228	234	229	242	232	241	231	237

Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0066	242	231	244	232	241	230	236	232	244
10-0006	242	232	245	225	241	205	226	211	237
10-0030	250	231	244	242	238	233	240	235	234
Average	245	231	244	233	240	223	234	226	238

TT # 10-6038

Test Article: MK-4618/L-000753555

Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

20% Peg 400 L-000753555 1mg/kg/day		Heart Rate (beats/min)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0017	242	236	238	241	238	239	245	252	239
10-0019	231	220	220	225	216	216	222	218	222
10-0037	258	253	250	255	240	241	231	258	246
Average	244	236	236	240	231	232	233	243	236

Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0034	220	228	222	215	223	216	207	217	219
10-0038	231	207	217	207	220	197	229	218	225
10-0048	264	252	255	240	250	228	221	252	238
Average	238	229	231	221	231	214	219	229	227

PRE = Pretest hr = hour min = minutes

PD = postdose

TT # 10-6038

Test Article: MK-4618/L-000753555

Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

20% Peg 400 L-000753555 5mg/kg/day		Heart Rate (beats/min)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0117	247	233	229	241	233	242	227	230	235
10-0035	242	232	235	246	237	196	232	241	246
10-0047	240	242	242	239	239	243	235	241	244
Average	243	236	235	242	236	227	231	237	242

Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0020	250	239	234	224	237	227	227	228	226
10-0026	231	233	224	236	222	232	224	224	226
10-0028	229	230	235	218	214	240	218	230	229
Average	237	234	231	226	224	233	223	227	227

PRE = Pretest hr = hour min = minutes

PD = postdose

TT # 10-6038
Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

Test Article: MK-4618/L-000753555

MK-4618 100 mg/kg/day L-000753555 1 mg/kg/day		Heart Rate (beats/min)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0015	240	220	201	225	207	225	193	216	194
10-0049	233	237	232	234	225	238	224	231	221
10-0051	261	251	243	253	242	253	246	257	246
Average	245	236	225	237	225	239	221	235	220

Male #		Study Week 2		Study Week 4		Study Week 8		Study Week 13	
	PRE	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0116	216	216	204	220	189	213	183	220	179
10-0018	226	234	226	224	220	239	229	227	217
10-0050	231	239	221	232	221	214	202	225	211
Average	224	230	217	225	210	222	205	224	202

PRE = Pretest hr = hour min = minutes

PD = postdose

TT # 10-6038
Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

Test Article: MK-4618/L-000753555

MK-4618 100 mg/kg/day L-000753555 3 mg/kg/day		Heart Rate (beats/min)							
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0054	226	226	234	215	221	245	245	228	239
10-0056	245	244	246	246	244	254	241	253	239
10-0058	240	227	224	236	243	240	241	231	230
10-0060	253	240	232	243	236	249	255	245	238
Average	241	234	234	235	236	247	246	239	237

TT # 10-6038
Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

Test Article: MK-4618/L-000753555

MK-4618 100 mg/kg/day L-000753555 5 mg/kg/day		Heart Rate (beats/min)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0023	238	247	238	247	244	240	235	231	234
10-0039	238	239	208	238	217	230	226	234	230
10-0043	255	229	231	240	228	231	213	233	227
Average	244	238	226	242	230	234	225	233	230

Male #		Study Week 2		Study Week 4		Study Week 8		Study Week 13	
	PRE	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0008	233	230	211	235	214	237	230	236	203
10-0022	267	195	154	FD	FD	FD	FD	FD	FD
10-0046	240	236	217	247	226	239	238	231	217
Average	247	221	194	241	220	238	234	234	210

PRE = Pretest hr = hour min = minutes

PD = postdose FD = Found Dead

QT interval (sponsor's table.)

CONTROL		QT Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0025	0.16	0.16	0.16	0.15	0.15	0.14	0.16	0.16	0.16
10-0027	0.16	0.15	0.14	0.14	0.14	0.14	0.14	0.14	0.14
10-0029	0.17	0.18	0.18	0.16	0.17	0.16	0.16	0.17	0.18
Average	0.16	0.16	0.16	0.15	0.15	0.15	0.15	0.16	0.16

Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0066	0.16	0.14	0.16	0.15	0.16	0.15	0.14	0.14	0.17
10-0006	0.17	0.17	0.16	0.17	0.16	0.18	0.18	0.18	0.18
10-0030	0.16	0.17	0.17	0.13	0.16	0.16	0.14	0.14	0.13
Average	0.16	0.16	0.16	0.15	0.16	0.16	0.15	0.15	0.16

PRE = Pretest hr = hour
sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

20% Peg 400 L-000753555 1mg/kg/day		QT Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0017	0.18	0.18	0.17	0.16	0.18	0.18	0.18	0.18	0.19
10-0019	0.18	0.18	0.18	0.18	0.19	0.18	0.18	0.18	0.18
10-0037	0.16	0.13	0.16	0.15	0.14	0.17	0.16	0.14	0.16
Average	0.17	0.16	0.17	0.16	0.17	0.18	0.17	0.17	0.18

Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0034	0.16	0.17	0.16	0.16	0.17	0.16	0.18	0.17	0.18
10-0038	0.18	0.20	0.20	0.19	0.19	0.20	0.18	0.19	0.19
10-0048	0.16	0.16	0.18	0.17	0.18	0.18	0.17	0.17	0.18
Average	0.17	0.18	0.18	0.17	0.18	0.18	0.18	0.18	0.18

PRE = Pretest hr = hour
sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

20% Peg 400 L-000753555 5mg/kg/day		QT Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0117	0.16	0.17	0.16	0.17	0.16	0.13	0.16	0.14	0.16
10-0035	0.17	0.16	0.16	0.17	0.17	0.18	0.16	0.17	0.17
10-0047	0.16	0.17	0.17	0.16	0.16	0.18	0.16	0.17	0.18
Average	0.16	0.17	0.16	0.17	0.16	0.16	0.16	0.16	0.17

Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0020	0.18	0.18	0.18	0.19	0.19	0.20	0.18	0.19	0.18
10-0026	0.16	0.18	0.16	0.14	0.15	0.14	0.14	0.14	0.15
10-0028	0.16	0.17	0.18	0.17	0.18	0.16	0.16	0.17	0.18
Average	0.17	0.18	0.17	0.17	0.17	0.17	0.16	0.17	0.17

PRE = Pretest hr = hour
sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day L-000753555 1mg/kg/day		QT Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0015	0.16	0.15	0.18	0.15	0.18	0.17	0.17	0.15	0.18
10-0049	0.16	0.16	0.16	0.16	0.15	0.16	0.17	0.17	0.16
10-0051	0.16	0.18	0.17	0.18	0.17	0.17	0.17	0.17	0.18
Average	0.16	0.16	0.17	0.16	0.17	0.17	0.17	0.16	0.17

Male #		Study Week 2		Study Week 4		Study Week 8		Study Week 13	
	PRE	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0116	0.18	0.17	0.18	0.18	0.19	0.18	0.19	0.17	0.20
10-0018	0.18	0.17	0.17	0.18	0.18	0.17	0.17	0.17	0.17
10-0050	0.17	0.18	0.18	0.17	0.19	0.20	0.20	0.18	0.19
Average	0.18	0.17	0.18	0.18	0.19	0.18	0.19	0.17	0.19

PRE = Pretest hr = hour
 sec = Seconds PD = postdose

MK-4618 100 mg/kg/day L-000753555 3 mg/kg/day		QT Interval (sec)							
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0054	0.16	0.16	0.16	0.16	0.16	0.15	0.16	0.17	0.17
10-0056	0.16	0.16	0.16	0.17	0.16	0.16	0.18	0.16	0.16
10-0058	0.16	0.14	0.18	0.14	0.15	0.14	0.14	0.15	0.15
10-0060	0.16	0.16	0.16	0.16	0.17	0.16	0.17	0.16	0.17
Average	0.16	0.16	0.17	0.16	0.16	0.15	0.16	0.16	0.16

PRE = Pretest hr = hour
 sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day L-000753555 5mg/kg/day		QT Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0023	0.18	0.16	0.16	0.16	0.18	0.17	0.15	0.14	0.16
10-0039	0.16	0.17	0.18	0.16	0.18	0.18	0.16	0.17	0.17
10-0043	0.17	0.17	0.18	0.17	0.18	0.18	0.18	0.17	0.18
Average	0.17	0.17	0.17	0.16	0.18	0.18	0.16	0.16	0.17

Male #		Study Week 2		Study Week 4		Study Week 8		Study Week 13	
	PRE	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0008	0.16	0.18	0.18	0.16	0.18	0.17	0.17	0.17	0.18
10-0022	0.16	0.20	0.25	FD	FD	FD	FD	FD	FD
10-0046	0.18	0.18	0.18	0.16	0.18	0.18	0.18	0.18	0.18
Average	0.17	0.19	0.20	0.16	0.18	0.18	0.18	0.18	0.18

PRE = Pretest hr = Hour
 sec = Seconds PD = postdose FD = Found Dead

Corrected QT interval (sponsor's table.)

TT #

10-6038

Test Article:

MK-4618/L-000753555

Study Title:

Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

CONTROL		QTcf ~ QT/RR ^{1/3}							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0025	0.241	0.243	0.250	0.227	0.237	0.223	0.254	0.246	0.248
10-0027	0.260	0.242	0.225	0.226	0.228	0.223	0.224	0.225	0.228
10-0029	0.265	0.279	0.280	0.249	0.266	0.244	0.253	0.265	0.280
Average	0.255	0.255	0.252	0.234	0.244	0.230	0.244	0.245	0.252
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0066	0.255	0.219	0.255	0.235	0.254	0.235	0.221	0.220	0.271
10-0006	0.271	0.267	0.256	0.264	0.254	0.271	0.280	0.274	0.285
10-0030	0.258	0.266	0.271	0.207	0.253	0.251	0.222	0.221	0.205
Average	0.261	0.251	0.261	0.235	0.254	0.252	0.241	0.238	0.254

PRE = Pretest PD = posidose hr = hour

PRE = Pretest PD = postdose hr = hour

TT #10-6038

Study Title:Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

Test Article:

MK-4618/L-000753555

20% Peg 400 L-000753555 1mg/kg/day	QTcf = QT/RR ^{1/3}								
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
	0.287	0.284	0.269	0.254	0.285	0.288	0.290	0.301	
	0.282	0.277	0.277	0.280	0.291	0.276	0.279	0.277	0.279
	0.260	0.210	0.258	0.243	0.222	0.270	0.251	0.228	0.256
	Average	0.276	0.257	0.268	0.259	0.266	0.277	0.273	0.265
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
	0.247	0.265	0.248	0.245	0.263	0.245	0.272	0.261	0.277
	0.282	0.302	0.307	0.287	0.293	0.297	0.281	0.292	0.295
	0.262	0.258	0.292	0.270	0.290	0.281	0.262	0.274	0.285
	Average	0.264	0.275	0.282	0.267	0.282	0.274	0.272	0.276

PRE = Pretest PD = postdose hr = hour

TT #		10-6038				Test Article:		MK-4618/L-000753555			
Study Title:		Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys									
20% Peg 400 L-000753555 5mg/kg/day		QTcf = QT/RR ^{1/3}									
Female #		PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13		
			2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
09-0117		0.256	0.267	0.250	0.270	0.251	0.207	0.249	0.219	0.252	
10-0035		0.271	0.251	0.252	0.272	0.269	0.267	0.251	0.270	0.272	
10-0047		0.254	0.271	0.271	0.254	0.254	0.287	0.252	0.270	0.287	
Average		0.260	0.263	0.258	0.265	0.258	0.254	0.251	0.253	0.270	
Male #		PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13		
			2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	
10-0020		0.290	0.285	0.283	0.295	0.301	0.312	0.280	0.296	0.280	
10-0026		0.251	0.283	0.248	0.221	0.232	0.220	0.217	0.217	0.234	
10-0028		0.250	0.266	0.284	0.262	0.275	0.254	0.246	0.266	0.281	
Average		0.264	0.278	0.272	0.259	0.269	0.262	0.248	0.260	0.265	

PRE = Pretest PD = postdose hr = hour

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day L-000753555 1mg/kg/day		QTcf = QT/RR ^{1/3}							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0015	0.254	0.231	0.269	0.233	0.272	0.264	0.251	0.230	0.266
10-0049	0.251	0.253	0.251	0.252	0.233	0.253	0.264	0.266	0.247
10-0051	0.261	0.290	0.271	0.291	0.271	0.275	0.272	0.276	0.288
Average	0.255	0.258	0.264	0.259	0.259	0.264	0.262	0.257	0.267

Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0116	0.276	0.260	0.271	0.277	0.279	0.274	0.275	0.262	0.288
10-0018	0.280	0.268	0.265	0.279	0.277	0.269	0.266	0.265	0.261
10-0050	0.266	0.285	0.278	0.267	0.293	0.306	0.300	0.280	0.289
Average	0.274	0.271	0.271	0.274	0.283	0.283	0.280	0.269	0.279

PRE = Pretest PD = postdose hr = hour

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day L-000753555 3mg/kg/day		QTcf = QT/RR ^{1/3}							
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0054	0.249	0.249	0.252	0.245	0.247	0.240	0.256	0.265	0.269
10-0056	0.256	0.255	0.256	0.272	0.255	0.259	0.286	0.258	0.254
10-0058	0.254	0.218	0.279	0.221	0.239	0.222	0.223	0.235	0.235
10-0060	0.258	0.254	0.251	0.255	0.269	0.257	0.276	0.256	0.269
Average	0.254	0.244	0.260	0.248	0.253	0.245	0.260	0.254	0.257

PRE = Pretest PD = postdose
hr = hour

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day / L-000753555 5mg/kg/day		QTcf = QT/RR ^{1/3}							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0023	0.285	0.256	0.253	0.256	0.287	0.270	0.237	0.219	0.252
10-0039	0.253	0.269	0.273	0.253	0.276	0.282	0.249	0.268	0.266
10-0043	0.276	0.266	0.282	0.270	0.281	0.282	0.274	0.267	0.280
Average	0.271	0.264	0.269	0.260	0.281	0.278	0.253	0.251	0.266

Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0008	0.251	0.282	0.274	0.252	0.275	0.269	0.266	0.269	0.270
10-0022	0.263	0.296	0.342	FD	FD	FD	FD	FD	FD
10-0046	0.286	0.284	0.276	0.256	0.280	0.285	0.285	0.282	0.276
Average	0.267	0.287	0.297	0.254	0.278	0.277	0.276	0.276	0.273

Pre = Pretest PD = postdose hr = hour
FD = Found Dead

PR interval (sponsor's table.)

CONTROL		PR Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0025	0.08	0.07	0.07	0.08	0.06	0.06	0.06	0.06	0.07
10-0027	0.06	0.05	0.06	0.06	0.05	0.07	0.05	0.05	0.06
10-0029	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Average	0.06	0.06	0.06	0.06	0.05	0.06	0.05	0.05	0.06
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0066	0.06	0.06	0.06	0.07	0.06	0.07	0.07	0.07	0.06
10-0006	0.07	0.06	0.06	0.07	0.07	0.07	0.07	0.07	0.07
10-0030	0.06	0.06	0.06	0.07	0.07	0.07	0.07	0.07	0.08
Average	0.06	0.06	0.06	0.07	0.07	0.07	0.07	0.07	0.07

PRE = Pretest hr = hour min = minutes
sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

20% Peg 400 L-000753555 1mg/kg/day		PR Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0017	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
10-0019	0.07	0.07	0.06	0.06	0.06	0.06	0.06	0.07	0.06
10-0037	0.05	0.06	0.05	0.05	0.06	0.06	0.06	0.06	0.06
Average	0.06	0.06	0.05	0.05	0.06	0.06	0.06	0.06	0.06
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0034	0.06	0.05	0.06	0.06	0.06	0.06	0.06	0.07	0.07
10-0038	0.06	0.07	0.07	0.07	0.06	0.07	0.06	0.06	0.06
10-0048	0.06	0.07	0.06	0.07	0.06	0.06	0.06	0.06	0.06
Average	0.06	0.06	0.06	0.07	0.06	0.06	0.06	0.06	0.06

PRE = Pretest hr = hour
sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

20% Peg 400 L-000753555 5mg/kg/day		PR Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0117	0.06	0.06	0.06	0.06	0.06	0.06	0.07	0.07	0.06
10-0035	0.06	0.06	0.05	0.05	0.06	0.06	0.06	0.05	0.05
10-0047	0.05	0.06	0.06	0.06	0.07	0.05	0.06	0.06	0.06
Average	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0020	0.05	0.06	0.06	0.06	0.06	0.06	0.05	0.06	0.06
10-0026	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
10-0028	0.06	0.07	0.07	0.07	0.06	0.05	0.06	0.06	0.07
Average	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06

PRE = Pretest hr = hour
sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day L-000753555 1mg/kg/day		PR Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0015	0.06	0.07	0.08	0.07	0.07	0.07	0.06	0.08	0.08
10-0049	0.05	0.06	0.05	0.07	0.06	0.06	0.06	0.07	0.06
10-0051	0.04	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.06
Average	0.05	0.06	0.06	0.06	0.06	0.06	0.06	0.07	0.07

Male #		PR Interval (sec)							
	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0116	0.07	0.06	0.07	0.07	0.07	0.06	0.07	0.07	0.06
10-0018	0.06	0.06	0.06	0.06	0.05	0.06	0.06	0.06	0.06
10-0050	0.06	0.06	0.07	0.07	0.07	0.06	0.07	0.07	0.07
Average	0.06	0.06	0.07	0.07	0.06	0.06	0.07	0.07	0.06

PRE = Pretest hr = hour
 sec = Seconds PD = postdose

MK-4618 100 mg/kg/day L-000753555 3 mg/kg/day		PR Interval (sec)							
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0054	0.05	0.06	0.05	0.06	0.06	0.06	0.06	0.06	0.06
10-0056	0.06	0.06	0.06	0.06	0.06	0.07	0.06	0.06	0.06
10-0058	0.06	0.05	0.06	0.07	0.06	0.07	0.07	0.07	0.07
10-0060	0.06	0.07	0.06	0.07	0.06	0.08	0.06	0.07	0.06
Average	0.06	0.06	0.06	0.07	0.06	0.07	0.06	0.07	0.06

PRE = Pretest hr = hour min = minutes
 sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day L-000753555 5mg/kg/day		PR Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0023	0.06	0.06	0.06	0.06	0.06	0.06	0.05	0.06	0.06
10-0039	0.05	0.07	0.06	0.07	0.06	0.07	0.05	0.07	0.07
10-0043	0.05	0.06	0.05	0.07	0.06	0.07	0.06	0.07	0.06
Average	0.05	0.06	0.06	0.07	0.06	0.07	0.05	0.07	0.06

Male #		PR Interval (sec)							
	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0008	0.06	0.07	0.07	0.07	0.07	0.06	0.07	0.08	0.07
10-0022	0.06	0.09	0.07	FD	FD	FD	FD	FD	FD
10-0046	0.06	0.07	0.06	0.06	0.06	0.07	0.07	0.07	0.07
Average	0.06	0.08	0.07	0.07	0.07	0.07	0.07	0.08	0.07

PRE = Pretest hr = hour
 sec = Seconds PD = postdose FD = Found Dead

QRS interval (sponsor's table.)

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

CONTROL		QRS Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0025	0.04	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.04
10-0027	0.04	0.05	0.05	0.04	0.05	0.05	0.04	0.05	0.04
10-0029	0.04	0.05	0.04	0.04	0.05	0.05	0.04	0.05	0.04
Average	0.04	0.05	0.04	0.04	0.05	0.05	0.04	0.05	0.04
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0066	0.05	0.05	0.04	0.05	0.05	0.05	0.04	0.05	0.04
10-0006	0.04	0.05	0.04	0.04	0.05	0.05	0.05	0.05	0.04
10-0030	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.04
Average	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.04

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

20% Peg 400 L-000753555 1mg/kg/day		QRS Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0017	0.04	0.05	0.04	0.04	0.05	0.04	0.04	0.05	0.04
10-0019	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
10-0037	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Average	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0034	0.05	0.05	0.04	0.05	0.05	0.04	0.04	0.04	0.04
10-0038	0.05	0.04	0.04	0.06	0.06	0.04	0.04	0.05	0.04
10-0048	0.05	0.04	0.05	0.05	0.05	0.05	0.05	0.04	0.05
Average	0.05	0.04	0.04	0.05	0.05	0.04	0.04	0.04	0.04

PRE = Pretest hr = hour
 sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

20% Peg 400 L-000753555 5mg/kg/day		QRS Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0117	0.05	0.05	0.04	0.05	0.05	0.04	0.04	0.04	0.05
10-0035	0.04	0.04	0.04	0.04	0.05	0.04	0.04	0.05	0.06
10-0047	0.05	0.04	0.04	0.04	0.04	0.04	0.05	0.05	0.05
Average	0.05	0.04	0.04	0.04	0.05	0.04	0.04	0.05	0.05
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0020	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
10-0026	0.05	0.04	0.04	0.04	0.05	0.04	0.04	0.05	0.04
10-0028	0.05	0.05	0.04	0.05	0.05	0.04	0.05	0.05	0.04
Average	0.05	0.05	0.04	0.05	0.05	0.04	0.05	0.05	0.04

PRE = Pretest hr = hour
 sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day L-000753555 1mg/kg/day		QRS Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0015	0.04	0.05	0.04	0.05	0.05	0.04	0.04	0.05	0.05
10-0049	0.05	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.05
10-0051	0.05	0.05	0.04	0.04	0.05	0.04	0.05	0.04	0.05
Average	0.05	0.05	0.04	0.04	0.05	0.04	0.04	0.04	0.05

Male #		Study Week 2		Study Week 4		Study Week 8		Study Week 13	
	PRE	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
09-0116	0.05	0.04	0.04	0.04	0.05	0.04	0.05	0.05	0.05
10-0018	0.04	0.05	0.04	0.04	0.05	0.05	0.05	0.04	0.04
10-0050	0.05	0.05	0.04	0.05	0.05	0.05	0.05	0.05	0.04
Average	0.05	0.05	0.04	0.04	0.05	0.05	0.05	0.05	0.04

PRE = Pretest hr = hour
 sec = Seconds PD = postdose

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day L-000753555 3 mg/kg/day		QRS Interval (sec)							
Male #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0054	0.04	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.04
10-0056	0.06	0.06	0.05	0.05	0.05	0.06	0.05	0.05	0.04
10-0058	0.06	0.05	0.05	0.05	0.05	0.05	0.04	0.04	0.04
10-0060	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.05
Average	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.05	0.04

TT # 10-6038 Test Article: MK-4618/L-000753555
 Study Title: Three-Month Oral Combination Toxicity Study in Cynomolgus Monkeys

MK-4618 100 mg/kg/day L-000753555 5mg/kg/day		QRS Interval (sec)							
Female #	PRE	Study Week 2		Study Week 4		Study Week 8		Study Week 13	
		2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0023	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.04	0.05
10-0039	0.06	0.05	0.04	0.04	0.05	0.05	0.05	0.04	0.04
10-0043	0.05	0.05	0.04	0.05	0.06	0.04	0.05	0.06	0.05
Average	0.05	0.05	0.04	0.05	0.05	0.05	0.05	0.05	0.05

Male #		Study Week 2		Study Week 4		Study Week 8		Study Week 13	
	PRE	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD	2-hr PD	24-hr PD
10-0008	0.05	0.04	0.05	0.05	0.05	0.05	0.05	0.06	0.04
10-0022	0.05	0.05	0.05	FD	FD	FD	FD	FD	FD
10-0046	0.05	0.06	0.05	0.06	0.05	0.04	0.04	0.05	0.05
Average	0.05	0.05	0.05	0.06	0.05	0.05	0.05	0.06	0.05

PRE = Pretest hr = Hour
 sec = Seconds PD = postdose FD = Found Dead

Urinalysis

Increased urine volume was observed at 100/5 mg/kg/day and 100/1 mg/kg/day in both sexes, and at 100/3 mg/kg/day and 0/5 mg/kg/day in males. Decreased specific gravity was observed in males only.

Test Article-Related Changes in Urinalysis (Percent Difference in Mean or Individual Values From Concurrent Control Mean Values) (sponsor's table.)

Parameter	Study Week	MK-4618/L-000753555 (mg/kg/day)									
		Females					Males				
		0/1	0/5	100/1	100/3	100/5	0/1	0/5	100/1	100/3	100/5
Urine volume	4	-	-	+63	N/A	+66	-	-	+161 ^a	+346%	+147 ^a
	8	-	-	-	N/A	-	-	+132	+335 ^a	+166%	+652 ^a
	12	-	-	+59	N/A	-	-	+63	+69	+104%	+77

^a Change observed in a single individual.

- = No treatment-related change.

N/A = Not Applicable.

Gross Pathology: No treatment related effects were observed.

Organ Weights: No treatment related effects were observed.

Histopathology: No treatment related effects were observed.

Adequate Battery: yes

Histological Findings

Test article-related histomorphological findings were limited to very slight accumulation of brown fat in white adipose tissue of 1 male at 100/5 mg/kg/day, an expected pharmacologic effect of the beta-3 selective adrenergic agonists in animals.

Toxicokinetics

At a clinical dose of 75 mg/day vibegron, a C_{max} of 123 ng/mL (0.277 uM) and an AUC_{0-24h} of 1450 ng•h/mL (3.26 uM•hr) were observed in Study RVT-901-1002.

Vibegron (MK-4618): (sponsor's tables)

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618/L-000753555 : Study Day 1				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
100/1	Female	74.8 $\pm$ 7.90	16.3 $\pm$ 2.12	2.2 $\pm$ 1.0
	Male	54.4 $\pm$ 3.76	8.97 $\pm$ 1.22	2.0 $\pm$ 1.0
100/3	Male	42.9 $\pm$ 4.13	6.34 $\pm$ 1.37	1.8 $\pm$ 0.25
100/5	Female	67.7 $\pm$ 8.75	13.6 $\pm$ 2.37	2.0 $\pm$ 0.0
	Male	59.8 $\pm$ 11.9	9.50 $\pm$ 2.72	2.3 $\pm$ 0.88

^a MK-4618 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.011 μ M).

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618/L-000753555 : Study Week 2				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
100/1	Female	108 $\pm$ 14.7	15.7 $\pm$ 0.903	2.3 $\pm$ 0.88
	Male	35.1 $\pm$ 4.12	7.32 $\pm$ 0.625	1.3 $\pm$ 0.33
100/3	Male	37.9 $\pm$ 3.12	6.67 $\pm$ 0.871	0.88 $\pm$ 0.38
100/5	Female	41.5 $\pm$ 5.34	9.42 $\pm$ 1.88	1.5 $\pm$ 0.50
	Male	66.3 $\pm$ ID	11.5 $\pm$ ID	1.0 $\pm$ ID

ID = Insufficient Data

^a MK-4618 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 0.011 μ M).

Tolterodine (L-000753555) (sponsor's tables):

Summary Mean ($\pm$ SE) Plasma L-000753555 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618/L-000753555 : Study Day 1				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (ng•hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
0/1	Female ^b	71.7	9.85	0.50
	Male ^b	139	11.5	0.50
0/5	Female	399 $\pm$ 133	31.6 $\pm$ 10.9	6.7 $\pm$ 1.3
	Male	170 $\pm$ ID	17.3 $\pm$ ID	6.0 $\pm$ ID
100/1	Female	75.7 $\pm$ 36.8	15.8 $\pm$ 2.28	2.2 $\pm$ 1.0
	Male ^b	43.2	15.1	0.50
100/3	Male ^b	209	12.0	24
100/5	Female	386 $\pm$ ID	27.3 $\pm$ ID	5.0 $\pm$ ID
	Male	375 $\pm$ 97.7	42.9 $\pm$ 22.5	2.2 $\pm$ 1.0

ID = Insufficient Data

^a L-000753555 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 5 ng/mL).

^b Data obtained from one animal only, other animals had no or less than 3 levels above LLQ (5 ng/mL).

Summary Mean ($\pm$ SE) Plasma L-000753555 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618/L-000753555 : Study Week 2				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (ng•hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
0/1	Female ^b	330	87.8	0.50
	Male	132 $\pm$ ID	12.8 $\pm$ ID	2.3 $\pm$ ID
0/5	Female	982 $\pm$ 346	98.8 $\pm$ 43.5	3.0 $\pm$ 2.5
	Male	577 $\pm$ 22.8	41.5 $\pm$ 2.45	8.0 $\pm$ 0.0
100/1	Female	205 $\pm$ 103	36.4 $\pm$ 6.81	1.2 $\pm$ 0.44
	Male ^b	225	27.8	0.50
100/3	Male	881 $\pm$ 305	81.3 $\pm$ 32.7	3.3 $\pm$ 1.8
100/5	Female	690 $\pm$ 225	38.2 $\pm$ 10.8	4.2 $\pm$ 2.2
	Male	1800 $\pm$ ID	348 $\pm$ ID	0.75 $\pm$ ID

ID = Insufficient Data

^a L-000753555 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 5 ng/mL).

^b Data obtained from one animal only, other animals had no or less than 3 levels above LLQ (5 ng/mL).

Summary Mean ($\pm$ SE) Plasma L-000753555 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618/L-000753555 : Study Week 13				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (ng•hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
0/1	Female	249 $\pm$ ID	23.6 $\pm$ ID	0.50 $\pm$ ID
	Male ^b	179	13.4	2.0
0/5	Female	1210 $\pm$ 374	115 $\pm$ 40.8	3.0 $\pm$ 2.5
	Male	561 $\pm$ 281	45.1 $\pm$ 23.9	8.0 $\pm$ 0.0
100/1	Female	643 $\pm$ ID	77.5 $\pm$ ID	2.3 $\pm$ ID
	Male ^b	119	8.38	8.0
100/3	Male	896 $\pm$ 245	68.6 $\pm$ 12.3	3.0 $\pm$ 2.5
100/5	Female	476 $\pm$ 108	29.8 $\pm$ 4.25	8.0 $\pm$ 0.0
	Male	1380 $\pm$ ID	122 $\pm$ ID	0.75 $\pm$ ID

ID = Insufficient Data

^a L-000753555 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 5 ng/mL).^b Data obtained from one animal only, other animals had no or less than 3 levels above LLQ (5 ng/mL).

Tolterodine metabolite (L-002391826) (sponsor's tables):

Summary Mean ($\pm$ SE) Plasma L-002391826 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618/L-000753555 : Study Day 1				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (ng•hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
0/1	Female	ID	ID	ID
	Male	ID	ID	ID
0/5	Female	ID	ID	ID
	Male	ID	ID	ID
100/1	Female	ID	ID	ID
	Male	ID	ID	ID
100/3	Male	ID	ID	ID
100/5	Female	186 $\pm$ ID	24.9 $\pm$ ID	2.0 $\pm$ ID
	Male ^b	130	13.2	0.50

ID = Insufficient Data

^a L-002391826 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 5 ng/mL).^b Data obtained from one animal only, other animals had no or less than 3 levels above LLQ (5 ng/mL).

Summary Mean ($\pm$ SE) Plasma L-002391826 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618/L-000753555 : Study Week 2				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (ng•hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
0/1	Female ^b	16.5	7.08	0.50
	Male	ID	ID	ID
0/5	Female	176 $\pm$ ID	21.0 $\pm$ ID	0.50 $\pm$ ID
	Male ^b	74.3	6.03	0.50
100/1	Female	ID	ID	ID
	Male	ID	ID	ID
100/3	Male ^b	327	21.1	0.50
100/5	Female	191 $\pm$ 89.9	11.7 $\pm$ 2.32	4.7 $\pm$ 1.8
	Male	438 $\pm$ ID	47.9 $\pm$ ID	0.75 $\pm$ ID

ID = Insufficient Data

^a L-002391826 concentrations in plasma from all control group animals were below the lower limit of quantitation (LLQ = 5 ng/mL).^b Data obtained from one animal only, other animals had no or less than 3 consecutive levels above LLQ (5 ng/mL).

Summary Mean ($\pm$ SE) Plasma L-002391826 Toxicokinetic Parameters in Monkeys Following Dosing of MK-4618/L-000753555 : Study Week 13				
Dose (mg/kg/day) ^a	Sex	AUC _{0-24 hr} (ng•hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
0/1	Female	ID	ID	ID
	Male	ID	ID	ID
0/5	Female	175 $\pm$ ID	15.7 $\pm$ ID	4.3 $\pm$ ID
	Male	ID	ID	ID
100/1	Female ^b	56.4	14.1	1.0
	Male	ID	ID	ID
100/3	Male	138 $\pm$ 14.5	14.7 $\pm$ 3.17	3.5 $\pm$ 2.3
100/5	Female	165 $\pm$ ID	9.70 $\pm$ ID	8.0 $\pm$ ID
	Male	287 $\pm$ ID	26.2 $\pm$ ID	2.0 $\pm$ ID

ID = Insufficient Data

^a L-002391826 concentrations in plasma from all control group animals were below LLQ (5 ng/mL).^b Data obtained from one animal only, other animals had no or less than 3 levels above LLQ (5 ng/mL).

Human Steady-State Exposures to Tolterodine (Detrol LA 4 mg QD) and 5-HMT (metabolite) at Therapeutic Doses

	Tolterodine		5-HMT	
	C _{max}	AUC	C _{max}	AUC
	(ng/mL)	(ng•h/mL)	(ng/mL)	(ng•h/mL)
CYP2D6 EMs	3.4	40.8	2.7	33.6
CYP2D6 PMs	19	312	-	-

EM = Extensive metabolizer

PM = Poor metabolizer

Dosing Solution Analysis

All assay results were within the acceptable concentration range ($\pm 10\%$) and shown to be stable under the conditions of the study.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Microbial Mutagenesis Assay

Study no.: TT #09-8033
 Conducting laboratory and location: Merck Research Laboratories, West Point, Pennsylvania, 19486 U.S.A
 Date of study initiation: 07 May 2009
 GLP compliance: yes
 QA statement: yes
 Drug, lot #, and % purity: Lot # L-002206358-000L018, 98.5 area percent by LCAP

Key Study Findings: MK-4618 was not mutagenic under the conditions of this assay.

Methods

Strains: *Salmonella typhimurium* (TA1535, TA97a, TA98, and TA100) and *Escherichia coli* (WP2 uvrA pKM101)
 Concentrations in definitive study: 30, 100, 300, 1000, 3000, and 5000 $\mu\text{g}/\text{plate}$ with and without S-9 metabolic activation
 Negative control: vehicle

Positive control: *Salmonella* strains and *E. coli* strain WP2
uvrA pKM101: 2-aminoanthracene, 1
µg/plate and 2 µg/plate or 2 µg/plate and 5
µg/plate, with and without S-9 metabolic
activation

Formulation/Vehicle: ethanol

Incubation & sampling time: The test article was incubated for 48 hours
with and without a liver microsomal
enzyme activation S-9 prepared from rats
treated with phenobarbital and beta-
naphthoflavone. The test article was
tested using triplicate plates with and/or
without metabolic activation for each strain
tested.

Study Validity: The positive controls showed appropriate S-9- and strain-dependent increases in revertants. No precipitate was seen on the plates at any concentration tested. No inhibition of bacterial lawn or revertant growth was noted at any concentration tested.

Results: MK-4618 did not produce any 2-fold or greater increases in histidine revertants relative to control.

Study title: Microbial Mutagenesis Assay

Study no.: TT #09-8147

Conducting laboratory and location: Merck Research Laboratories, West
Point, Pennsylvania, 19486 U.S.A.

Date of study initiation: 23-Oct-2009

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: Lot # L-002206358-000L018, 98.4 area
percent by LCAP

Key Study Findings: MK-4618 was not mutagenic under the conditions of this assay.

Methods

Strains: *Salmonella typhimurium* (TA1535, TA97a,
TA98, and TA100) and *Escherichia coli*
(WP2 uvrA pKM101)

Concentrations in definitive study: 0, 100, 300, 1000, 3000, and 5000
µg/plate

Negative control: vehicle

Positive control: *Salmonella* strains and *E. coli* strain WP2 uvrA pKM101: 2-aminoanthracene (2AA), 1 µg/plate and 2 µg/plate or 2 µg/plate and 5 µg/plate, with and without S-9 metabolic activation

Formulation/Vehicle: ethanol

Incubation & sampling time: The test article was incubated for 48 hours with and without a liver microsomal enzyme activation S-9 prepared from rats treated with phenobarbital and beta-naphthoflavone. The test article was tested using triplicate plates with and/or without metabolic activation for each strain tested.

Study Validity: The positive control showed appropriate S-9- and strain-dependent increases in revertants. No precipitate was seen on the plates at any concentration tested. No inhibition of bacterial lawn or revertant growth was noted at any concentration tested.

Results: MK-4618 did not produce any 2-fold or greater increases in histidine revertants relative to control.

Study title: L-004965547: Exploratory Microbial Mutagenesis Assay

Study no.: TT #10-8111 and TT #10-8118

Conducting laboratory and location: Merck Research Laboratories, West Point, Pennsylvania, 19486 U.S.A.

Date of study initiation: 23 November 2010

Drug, lot #, and % purity: L-004965547 (dihydrochloride salt), a production intermediate of MK-4618

Key Study Findings

L-004965547 (vibegron dihydrochloride salt; a production intermediate of MK-4618) was judged to be negative for mutagenesis under the conditions tested.

Methods

Strains: *Salmonella typhimurium* test strains TA1535, TA97a, TA98, and TA100 and *Escherichia coli* test strain WP2 uvrA pKM101

Concentrations in definitive study: 0, 1, 3, 10, 30, and 100 µg/plate

Basis of concentration selection: L-004965547 was tested over a concentration range of 100 to 5000 µg/plate in TT #10-8111 and was not scored due to severe toxicity of the test article at all dose levels tested. In TT #10-8118, L-004965547 was tested over a concentration range of 1.0 to 100 µg/plate

Negative control: DMSO

Positive control: 2-aminoanthracene (2AA)

Formulation/Vehicle: DMSO

Study Validity

Positive and negative controls produced the expected results. No precipitate was seen at any concentration tested. Inhibition of bacterial lawn growth was observed at 10 µg/plate or higher and interfered with the scoring of some of plates. Some inhibition of background lawn was also noted at 3.0 µg/plate in *E. coli* without metabolic activation. Inhibition of revertant growth was noted at 10 µg/plate or higher.

Results

There was no increase in revertants of 2-fold or greater at any dose tested, with or without metabolic activation, and L-004965547 was judged to be negative for mutagenesis under the conditions tested.

Study title: L-004965550: Exploratory Microbial Mutagenesis Assay.

Study no.: TT #10-8112 and TT #10-8119
Conducting laboratory and location: Merck Research Laboratories, West Point, Pennsylvania, 19486 U.S.A.
Date of study initiation: 22 November 2010
Drug, lot #, and % purity: L-004965550 (dihydrochloride salt), a production intermediate of MK-4618

Key Study Findings

L-004965550 (vibegron dihydrochloride salt; a production intermediate of MK-4618) was judged to be negative for mutagenesis under the conditions tested.

Methods

Strains: *Salmonella typhimurium* test strains TA1535, TA97a, TA98, and TA100 and *Escherichia coli* test strain WP2 uvrA pKM101

Concentrations in definitive study: 0, 1, 3, 10, 30, and 100 µg/plate

Basis of concentration selection: L-004965550 was tested over a concentration range of 100 to 5000 µg/plate in TT #10-8112 was not scored due to severe toxicity of the test article at all dose levels tested. L-004965550 was tested over a concentration range of 1.0 to 100 µg/plate in TT #10-8119).

Negative control: DMSO

Positive control: 2-aminoanthracene (2AA)

Formulation/Vehicle: DMSO

Study Validity

Positive and negative controls produced the expected results. No precipitate was seen at any concentration tested. Inhibition of bacterial lawn growth was observed at 30 µg/plate or higher in most test strains and at 10 µg/plate in *E. coli* without metabolic activation. Inhibition of revertant growth was noted at 10 or 30 µg/plate in all test strains.

Results

There was no increase in revertants of 2-fold or greater at any dose tested, with or without metabolic activation, and L-004965550 was judged to be negative for mutagenesis under the conditions tested.

Study title: L-004973245: Exploratory Microbial Mutagenesis Assay

Study no.: TT #10-8122

Conducting laboratory and location: Merck Research Laboratories, West Point, Pennsylvania, 19486 U.S.A.

Date of study initiation: 15 December 2010

Drug, lot #, and % purity: L-004973245 (a base compound) a production intermediate of MK-4618

Key Study Findings

L-004973245 (production intermediate; impurity) was judged to be positive for mutagenesis under the conditions tested.

Methods

Strains: *Salmonella typhimurium* test strains TA1535, TA97a, TA98, and TA100 and *Escherichia coli* test strain WP2 uvrA pKM101

Concentrations in definitive study: 0, 30, 100, 300, 1000, 3000 and 5000
µg/plate

Negative control: DMSO

Positive control: 2-aminoanthracene (2AA)

Formulation/Vehicle: DMSO

Study Validity

Positive and negative controls produced the expected results. Precipitate was seen at 5000 µg/plate, but did not interfere with scoring of the plates. Inhibition of bacterial lawn growth was observed at 300 µg/plate or higher in all test strains and interfered with scoring of the plates at 1000 µg/plate and higher. The top doses that could be evaluated were limited by toxicity at 300 to 1000 µg/plate.

Results

Microbial Mutagenesis Assay for L-004973245 (*Salmonella* his+ or *Escherichia coli* trp+ Revertants per Plate) (sponsor's table.)

Conc./Plate	TA100 15-DEC-2010				TA1535 15-DEC-2010				TA97a 15-DEC-2010			
	Without S-9		With S-9		Without S-9		With S-9		Without S-9		With S-9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 µg	194.7	23.0	196.2	21.8	11.9	3.4	10.6	1.9	119.4	13.3	164.2	19.3
30 µg	224.7	21.8	326.3	48.1	12.3	3.5	22.0 ^P	5.6	157.0	14.9	180.0	30.1
100 µg	426.7 ^P	9.1	480.0 ^P	27.5	22.0	3.5	44.7 ^P	5.1	232.0	17.3	204.3	8.6
300 µg	909.7 ^P	56.0	1036.7 ^P	27.5	54.3 ^P	4.6	109.3 ^P	15.5	241.7 ^P	42.7	366.7 ^P	11.9
1000 µg	I		I		I		91.3 ^A	9.5	I		I	
3000 µg	I		I		I		I		I		I	
5000 µg	I		I		I		I		I		I	
DMSO 100 µL	194.7	23.0	196.2	21.8	11.9	3.4	10.6	1.9	119.4	13.3	164.2	19.3
2AA 1.0 µg	201.7	14.6	501.3	25.0	10.7	2.5	81.7	16.9	129.7	7.6	336.7	29.8
2AA 2.0 µg	201.7	19.0	936.0	35.9	13.7	3.8	116.3	5.5	125.3	8.4	676.3	27.8

Conc./Plate	TA98 15-DEC-2010				WP2 uvrA pKM101 15-DEC-2010							
	Without S-9		With S-9		Without S-9		With S-9		Without S-9		With S-9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 µg	47.7	7.4	59.9	7.8	118.9	21.0	129.2	21.4				
30 µg	57.7	10.3	69.3	11.6	130.7	5.1	148.7	20.6				
100 µg	95.7 ^P	13.8	84.0	4.0	138.3	1.2	134.3	30.0				
300 µg	187.3 ^P	32.6	201.3 ^P	14.6	114.7	20.1	155.7	35.5				
1000 µg	I		I		I		I					
3000 µg	I		I		I		I					
5000 µg	I		I		I		I					
DMSO 100 µL	47.7	7.4	59.9	7.8	118.9	21.0	129.2	21.4				
2AA 1.0 µg	55.3	10.6	335.7	49.0								
2AA 2.0 µg	69.3	6.0	730.3	52.8	141.0	15.1	282.3	54.2				
2AA 5.0 µg					143.0	15.0	667.0	24.0				

Salmonella typhimurium/E. coli genotypes:
 TA100 his G46 (base substitution) ΔuvrB rfa pKM101 (R factor).
 TA1535 his G46 (base substitution) ΔuvrB rfa.
 TA97a his D6610 (frameshift) ΔuvrB rfa pKM101 (R factor).
 TA98 his D3052 (frameshift) ΔuvrB rfa pKM101 (R factor).
 WP2 uvrA pKM101 (trp-) ΔuvrA pKM101 (R factor).
 S-9 = Metabolic activation.
 SD = Standard deviation.
 ^ = Slight inhibition of background lawn.
 I = Inhibition of background lawn on minimal plate.
 P = Positive dose (2.0-fold or greater increase over solvent control).
 2AA = 2-Aminoanthracene DMSO = Dimethyl sulfoxide

L-004973245 caused 2-fold or greater increases in revertants, relative to control, in all of the *Salmonella* strains tested, both in the presence and absence of

metabolic activation, and was judged to be positive for mutagenesis under the conditions of this assay.

Study title: L-002187113: Exploratory Microbial Mutagenesis Assay

Study no.: TT #12-8031
Conducting laboratory and location: Merck Research Laboratories, West Point, Pennsylvania, 19486 U.S.A.
Date of study initiation: 17 February 2012
Drug, lot #, and % purity: L-002187113 (a hydrochloride salt), a production intermediate of MK-4618

Key Study Findings

L-002187113 (production intermediate; impurity) was considered positive for mutagenesis under the conditions of this assay.

Methods

Strains: *Salmonella typhimurium* test strains TA1535, TA97a, TA98, and TA100 and *Escherichia coli* test strain WP2 uvrA pKM101 with and without rat liver S-9
Concentrations in definitive study: 0, 100, 300, 1000, 3000, and 5000 mg/kg/day
Basis of concentration selection: L-002187113 was tested over a concentration range of 100 to 5000 µg/plate. The top dose was limited to 1000 µg/plate due to toxicity.
Negative control: DMSO
Positive control: 2-aminoanthracene (2AA)
Formulation/Vehicle: DMSO

Study Validity

Positive and negative controls produced the expected results. Suppression of bacterial lawn growth limited the top dose to 1000 µg/plate. Precipitate was seen at 5000 µg/plate without metabolic activation, but did not interfere with scoring.

Results

L-002187113 (*Salmonella* his+ or *Escherichia coli* trp+ Revertants per Plate)
(sponsor's table.)

Conc./Plate	TA100 17-FEB-2012				TA1535 17-FEB-2012				TA97a 17-FEB-2012			
	Without S-9		With S-9		Without S-9		With S-9		Without S-9		With S-9	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 µg	162.9	20.1	145.9	22.4	14.4	4.3	17.3	5.0	137.8	27.2	186.7	18.3
100 µg	158.0	32.2	151.7	43.4	16.0	3.6	20.7	10.8	147.0	21.0	203.3	23.4
300 µg	167.0	18.7	207.0	17.4	12.3	1.2	33.3	9.3	151.3	15.5	189.3	3.1
1000 µg	164.0	25.1	220.7	15.9	19.7	0.6	62.3 ^P	12.2	156.3	42.2	220.7	16.3
3000 µg	I		I		I		I		I		I	
5000 µg	I*		I		I*		I		I*		I	
DMSO 100 µL	162.9	20.1	145.9	22.4	14.4	4.3	17.3	5.0	137.8	27.2	186.7	18.3
2AA 1.0 µg	167.0	27.7	444.7	19.6	12.3	6.4	79.7	22.2	133.0	21.1	412.3	11.7
2AA 2.0 µg	163.7	15.5	865.7	67.1	19.0	10.4	135.0	22.6	147.0	23.4	705.0	25.0

Conc./Plate	TA98 17-FEB-2012				WP2 uvrA pKM101 17-FEB-2012							
	Without S-9		With S-9		Without S-9		With S-9					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
0 µg	41.2	7.4	47.0	4.8	147.8	18.7	144.8	23.9				
100 µg	43.0	10.6	43.3	11.0	134.3	2.9	149.3	35.4				
300 µg	54.3	9.0	43.7	6.4	134.3	15.3	142.7	20.8				
1000 µg	71.0	12.3	69.0	9.5	70.7 [^]	2.3	88.3	26.9				
3000 µg	I		I		I		I					
5000 µg	I*		I		I*		I					
DMSO 100 µL	41.2	7.4	47.0	4.8	147.8	18.7	144.8	23.9				
2AA 1.0 µg	40.0	7.8	244.0	7.9								
2AA 2.0 µg	45.7	7.0	527.7	9.8	146.0	12.2	274.3	32.2				
2AA 5.0 µg					145.3	10.0	557.3	14.3				

Salmonella typhimurium/E. coli genotypes:
 TA100 his G46 (base substitution) ΔuvrB rfa pKM101 (R factor)
 TA1535 his G46 (base substitution) ΔuvrB rfa.
 TA97a his D6610 (frameshift) ΔuvrB rfa pKM101 (R factor).
 TA98 his D3052 (frameshift) ΔuvrB rfa pKM101 (R factor).
 WP2 uvrA pKM101 (trp-) ΔuvrA pKM101 (R factor).

S-9 = Metabolic activation.
 SD = Standard deviation.
 I = Inhibition of background lawn on minimal plate.
 * = Precipitate; did not interfere with scoring.
 ^ = Slight inhibition of background lawn.
 P = Positive dose (2-fold or greater increase over solvent control).

2AA = 2-Aminoanthracene DMSO = Dimethyl sulfoxide

L-002187113 caused a 3.6-fold increase in revertants at 1000 µg/plate in TA1535 with metabolic activation and was therefore considered positive for mutagenesis under the conditions of this assay. Weak dose related increases were also seen in other strains with and without metabolic activation up to 1.7-fold but did not meet the 2-fold criterion for a positive result, in the presence of toxicity at the higher doses.

Study title: L-002124860: Exploratory Microbial Mutagenesis Assay

Study no.: TT #07-8119
 Conducting laboratory and location: Merck Research Laboratories, West Point, Pennsylvania, 19486 U.S.A.
 Date of study initiation: 15 November 2007
 Drug, lot #, and % purity: L-002124860 (base compound)

Key Study Findings

L-002124860 (vibegron impurity) was judged to be negative for mutagenesis under the conditions of this assay.

Methods

Strains: *Salmonella typhimurium* test strains TA1535, TA97a, TA98, and TA100 and *Escherichia coli* test strain WP2 uvrA pKM101 with and without rat liver S9

Concentrations in definitive study: 0, 30, 100, 300, 1000, 3000, and 6000 µg/plate

Negative control: DMSO

Positive control: 2-aminoanthracene (2AA)

Formulation/Vehicle: DMSO

Study Validity

Positive and negative controls produced the expected results. No precipitate was observed at any concentration tested. No inhibition of bacterial lawn or revertant growth was observed at any concentration tested.

Results

L-002124860 did not cause any 2-fold or greater increases in revertants at any concentration tested in the presence or absence of metabolic activation, and was therefore judged to be negative for mutagenesis under the conditions of this assay.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: Chromosome Aberration Test in Human Blood Lymphocytes

Study no.:	TT #09-9028
Conducting laboratory and location:	(b) (4)
Date of study initiation:	15 October 2009
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	Lot # L-002206358-000L018, 98.4% pure by LCAP

Key Study Findings: MK-4618 was not genotoxic under the conditions of this assay.

Methods

Cell line:	Human peripheral blood lymphocytes
Concentrations in definitive study:	0, 0.4, 0.8, 1.6, 3.2, 6.4, 12.8, 25.6, 51.2, 102.4, and 225 μ M
Basis of concentration selection:	test article solubility
Negative control:	vehicle
Positive control:	Mitomycin C in the absence of S-9 and Cyclophosphamide monohydrate in the presence of S-9
Formulation/Vehicle:	ethanol
Incubation & sampling time:	4 hours in the absence and presence of rat S-9 mix and for 21 hours in the absence of rat S-9

Study Validity: The test system was in accordance with regulatory guidelines. Positive and negative controls responded as expected.

Results: At doses up to 225 μ M (the maximum soluble dose level), which did not result in marked toxicity, cultures treated with MK-4618 did not show any statistically significant increases in the incidence of aberrant metaphases when examined microscopically.

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

Study title: Assay for Micronucleus Induction in Rat Bone Marrow From a 14-Day Oral Toxicity Study

Study no: TT #09-8729

Conducting laboratory and location: Merck Research Laboratories, Merck & Co., Inc., West Point, Pennsylvania 19486 U.S.A.

Date of study initiation: 2 April 2009

GLP compliance: yes

QA statement: yes

Key Study Findings: MK-4618 was not genotoxic under the conditions of this assay.

Methods

Doses in definitive study: 0, 2, 20, and 1000 mg/kg/day

Frequency of dosing: Daily, for 14 days, sacrificed after dosing Day 14

Route of administration: oral gavage

Dose volume: 5 mL/kg/day

Formulation/Vehicle: 20% Polyethylene Glycol (PEG) 400 in deionized Water acidified with hydrochloric acid to a pH of 2.5 ± 0.2 (20% PEG 400),

Species/Strain: Crl:CD(SD) rats, male and female, 8 weeks old

Number/Sex/Group: 10/sex/group. Two thousand polychromatic erythrocytes (PCE) per rat were scored for micronuclei (MN-PCE) from coded slides from each of 10 vehicle-treated rats per sex, each of 4 low- and high dose positive control male rats, and from each of 5 MK-4618-treated rats per group per sex. The frequencies of PCE and of mature, normochromatic erythrocytes (NCE) were also recorded among 1000 erythrocytes per rat.

Negative control: vehicle

Positive control: mitomycin C

Study Validity: The test system was in accordance with regulatory guidelines. Positive and negative controls responded as expected.

Results: The frequencies of micronucleated PCE (MN-PCE) for each MK-4618-treatment group were within the typical range for historical vehicle controls (0.6 to 3.4 MN-PCE). There was no apparent effect of MK-4618 on bone marrow PCE.

8 Carcinogenicity

Study title: Two-Year Oral Carcinogenicity Study in CD1 Mice

Study no.:	TT #12-6031
Conducting laboratory and location:	Safety Assessment and Laboratory Animal Resources (SALAR), Laboratoires Merck Sharp & Dohme-Chibret, Riom, France
Date of study initiation:	16 May 2012
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	MK-4618 (L-002206358)base compound, Lot Number L-002206358-000L023
CAC concurrence:	Protocol concurrence 30 August 2011;

Key Study Findings

Oral administration of vibegron at 0, 10, 30, or 90 mg/kg/day in males and 0, 15, 50, or 150 mg/kg/day in females did not show treatment-related malignancies. Survival was comparable among groups. NOELs for carcinogenicity were 90 and 150 mg/kg/day in males and females, respectively, with systemic exposures (AUC_{0-24}) of 68.6 and 178 $\mu\text{M}\cdot\text{hr}$ (30495 and 79128 $\text{ng}\cdot\text{h/mL}$), respectively (exposure margins 21.0 and 54.6-fold the clinical exposure at the proposed dose of 75 mg/day (mean value of 1140 $\text{ng}\cdot\text{h/mL}$). Non-neoplastic test article-related changes were limited to increased incidence of brown fat accumulation, at the high dose in males and females.

Adequacy of Carcinogenicity Study

Dose levels were selected based on maximum tolerated doses from sub-chronic and chronic toxicity studies in mice and Executive CAC recommendation. Adequate controls were provided.

Appropriateness of Test Models

CD-1 mouse is a commonly used model for the 2-year assay.

Evaluation of Tumor Findings

No treatment related neoplastic changes were observed. FDA statistical review was provided.

Methods

Doses:	0, 15, 50, or 150 mg/kg/day for females and 0, 10, 30, or 90 mg/kg/day for males (given as a free base)
Frequency of dosing:	daily
Dose volume:	10 ml/kg
Route of administration:	Oral, gavage

Formulation/Vehicle: polyethylene glycol 400 in deionized water (10:90 w/w)

Basis of dose selection: Dose levels were selected based on toxicity data from a 3-month oral range-finding and toxicokinetic study in mice and Executive CAC recommendation.

Species/Strain: CRL:CD1(ICR) mice

Number/Sex/Group: 50/sex/group

Age: 5 weeks

Animal housing: animals were socially housed

Paradigm for dietary restriction: NA

Controls employed: Control group 1: water acidified to pH of 2.5.
Control group 2 and 3: polyethylene glycol 400 in deionized water (10:90 w/w)

Interim sacrifice: NA

Satellite groups: 3 PK/TK MK-4618-treated groups in each arm that received 15, 50, or 150 mg/kg/day for females and 10, 30, or 90 mg/kg/day for males (6/sex/group)

Deviation from study protocol: Males were treated for 104 weeks and females for 99 weeks based on the survival rate in this gender (eCAC approval was obtained.)

Observations and Results

Mortality

There was no test article-related increase in mortality in either females or males.

Total Unscheduled Deaths (Incidence and Percentage of Animals Found Dead or Unscheduled Sacrificed; n=50/sex/group)(sponsor's table)

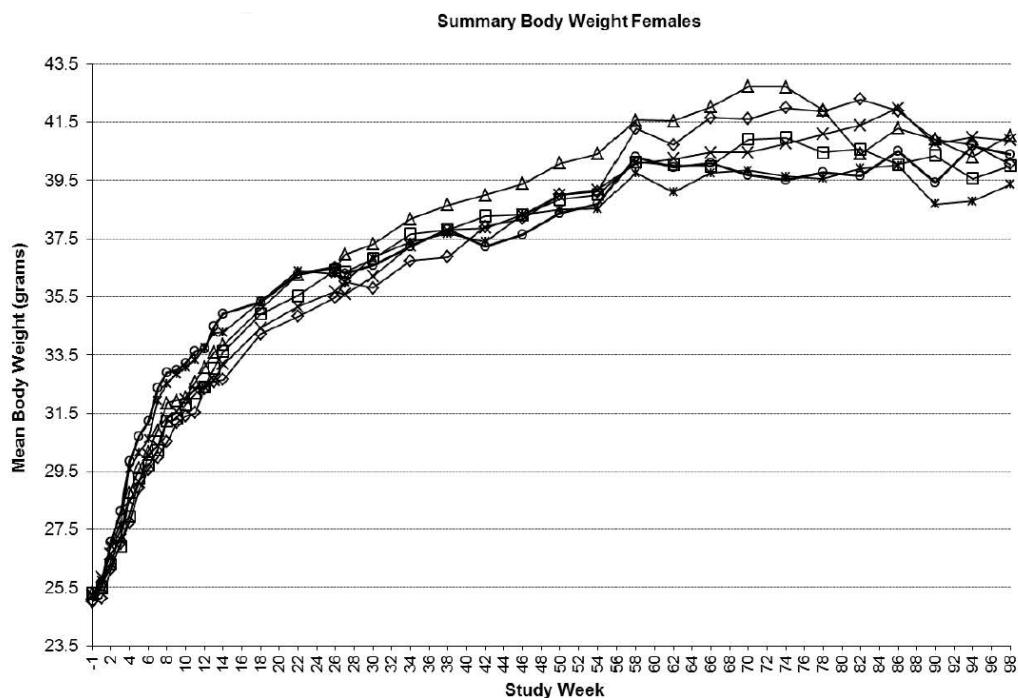
Dose Group	Number Dead (Percent)	
	Females ^a	Males
Control 1 (0 mg/kg/day)	27 (54%)	22 (44%)
Control 2 (0 mg/kg/day)	29 (58%)	28 (56%)
Control 3 (0 mg/kg/day)	30 (60%)	26 (52%)
<u>MK-4618</u>		
10 mg/kg/day	-	27 (54%)
15 mg/kg/day	29 (58%)	-
30 mg/kg/day	-	27 (54%)
50 mg/kg/day	29 (58%)	-
90 mg/kg/day	-	27 (54%)
150 mg/kg/day	24 (48%)	-

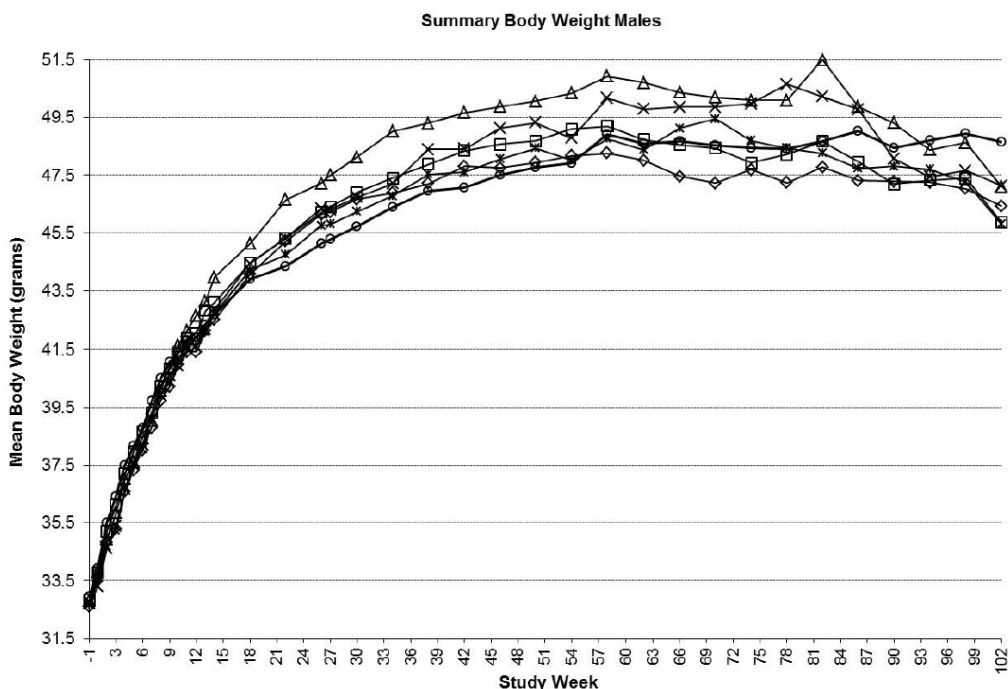
^a Based on survival rate in females, final necropsy in all female groups was performed in Study Week 100.

- Not Applicable.

Clinical Signs/ Body Weights

No treatment related effects were observed.
(sponsor's figure.)





Gross Pathology

Non-neoplastic test article-related changes were limited to increased incidence of brown fat accumulation, at the high-dose in males and females.

Histopathology

Neoplastic

No treatment related neoplasms were observed.

Non Neoplastic

There was a test article-related increased incidence of brown fat accumulation at the high dose in males and females.

Test Article-Related Postmortem Findings MK-4618 (sponsor's table.)

Dose, mg/kg/day	Females			Males		
	15	50	150	10	30	90
Number of Animals	50	50	50	50	50	50
Histomorphology (Incidence)						
White Adipose Tissue, Brown Fat Accumulation	-	-	21	-	-	18
- = No test article-related change.						

Toxicokinetics

Summary Mean ($\pm$ SE) Plasma MK-4618 Concentrations (μ M) in Mice Following Dosing of MK-4618: Study Week 5 (sponsor's table.)

			Time (hr)	
Week	Dose (mg/kg/day)	Sex	0.5	24
5	10	Male	0.864 $\pm$ 0.133	0.00 $\pm$ 0.00
	15	Female	1.15 $\pm$ 0.124	0.00 $\pm$ 0.00
	30	Male	8.11 $\pm$ 3.52	0.00 $\pm$ 0.00
	50	Female	15.9 $\pm$ 5.31	0.00 $\pm$ 0.00
	90	Male	32.5 $\pm$ 3.66	0.0178 $\pm$ 0.0178
	150	Female	45.9 $\pm$ 2.19	0.0354 $\pm$ 0.00459

MK-4618 concentrations in plasma from all control group animals at 0.5 hour postdose were below the lower limit of quantitation (LLQ = 0.0227 μ M) of the bioanalytical method.

Summary Mean ($\pm$ SE) Plasma MK-4618 Concentrations (μ M) in Mice Following Dosing of MK-4618: Study Week 27 (sponsor's table)

			Time (hr)	
Week	Dose (mg/kg/day)	Sex	0.5	24
27	10	Male	1.01 $\pm$ 0.0837	0.00 $\pm$ 0.00
	15	Female	1.88 $\pm$ 0.340	0.00 $\pm$ 0.00
	30	Male	6.08 $\pm$ 1.89	0.00756 $\pm$ 0.00756
	50	Female	6.95 $\pm$ 0.742	0.00857 $\pm$ 0.00857
	90	Male	32.5 $\pm$ 4.39	0.0352 $\pm$ 0.00932
	150	Female	51.2 $\pm$ 6.71	0.0467 $\pm$ 0.00908

MK-4618 concentrations in plasma from all control group animals at 0.5 hour postdose were below the lower limit of quantitation (LLQ = 0.0225 μ M) of the bioanalytical method.

Dosing Solution Analysis

Samples of all dosing formulations were collected for analysis of concentration in Study Day 1 and Study Weeks 5, 18, 27, 40, 53, 66, 79, 92, 99, 100, and 104. All assay results were within the acceptable concentration range ($\pm$ 10% of claim for a solution).

Study title: MK-4618: Two-Year Oral Carcinogenicity Study in Rats with Six-Month Toxicokinetic Evaluation.

Study no.: TT #11-6036
Study report location: SALAR, Laboratoires Merck Sharp & Dohme-Chibret, Riom, France
Conducting laboratory and location: Safety Assessment and Laboratory Animal Resources (SALAR), Laboratoires Merck Sharp & Dohme-Chibret, Riom, France
Date of study initiation: 25 November 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: MK-4618, Lot Number L-002206358-000L023, 99.9% pure
CAC concurrence: Protocol concurrence 30 August 2011;

Key Study Findings

Oral administration of vibegron at 0, 3, 10, 20, or 30 mg/kg/day in males and 0, 20, 60, or 180 mg/kg/day in females did not show treatment-related malignancies. Survival was comparable among groups. NOELs for carcinogenicity were 30 and 180 mg/kg/day in males and females, respectively, with systemic exposures (AUCs) of 57.6 and 383 $\mu\text{M}\cdot\text{hr}$ (25605 and 170258 $\text{ng}\cdot\text{h/mL}$) in male and female rats (exposure margins of 17.7 and 117-fold clinical exposures at the proposed dose of 75 mg/day (mean value of 1140 $\text{ng}\cdot\text{h/mL}$). Non-neoplastic test article-related changes were limited to increased incidence of brown fat accumulation and vacuolation of the adrenal zona glomerulosa at ≥ 10 mg/kg/day in males and at > 20 mg/kg/day in females.

Adequacy of Carcinogenicity Study

Dose levels were selected based on maximum tolerated doses from sub-chronic and chronic toxicity studies in rats and Executive CAC recommendation. Adequate controls were provided.

Appropriateness of Test Models

Sprague-Dawley rat is a commonly used model for the 2-year assay.

Evaluation of Tumor Findings

No treatment related neoplastic changes were observed. FDA statistical review was provided.

Methods

Doses: 0, 20, 60, or 180 mg/kg/day for females and 0, 3, 10, 20, or 30 mg/kg/day for males
Frequency of dosing: Daily
Dose volume: 5 ml/kg
Route of administration: Oral, gavage

Formulation/Vehicle: 20% (v/v) polyethylene glycol 400 in deionized water

Basis of dose selection: Dose levels were selected based on toxicity data from sub-chronic and chronic toxicity studies in rats and Executive CAC recommendation.

Species/Strain: Rat, Sprague-Dawley, Crl:CD(SD)

Number/Sex/Group: 50

Age: 4 to 5 weeks Females: 86.2 to 128.7 g Males: 92.2 to 166.4 g

Animal housing: Individual

Paradigm for dietary restriction: NA

Dual control employed: Water (acidified daily with 1.0N HCl to reach a pH of 2.5±0.2) and vehicle controls employed

Satellite groups: 4/sex/group for toxicokinetics

Observations and Results

Mortality

No treatment related effect was observed.

Total Unscheduled Deaths (Incidence and Percentage of Animals Found Dead or Sacrificed Early; n=50/sex/group) (sponsor's table.)

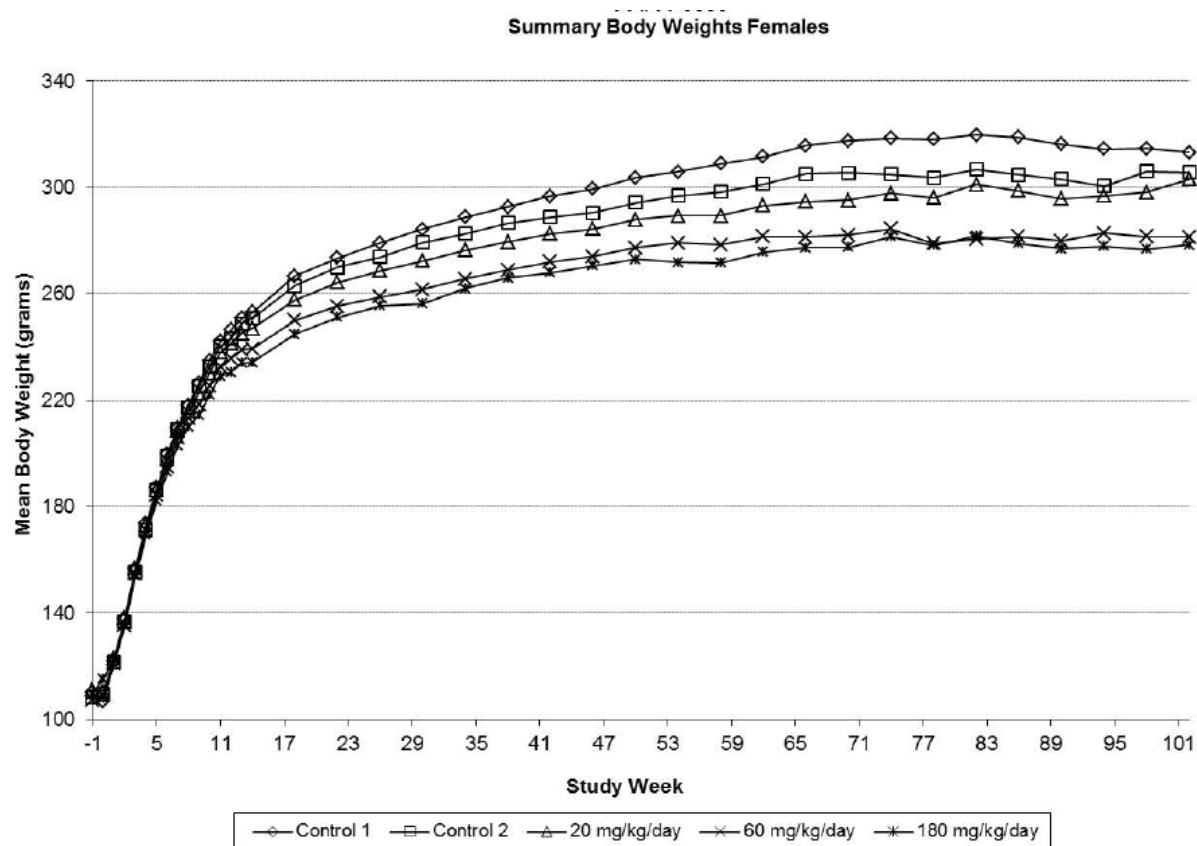
Dose Group	Number Dead (Percent)	
	Females	Males
Control 1	19 (38%)	16 (32%)
Control 2	24 (48%)	20 (40%)
<u>MK-4618</u>		
3 mg/kg/day	-	20 (40%)
10 mg/kg/day	-	19 (38%)
20 mg/kg/day	15 (30%)	12 (24%)
30 mg/kg/day	-	11 (22%)
60 mg/kg/day	21 (42%)	-
180 mg/kg/day	12 (24%)	-
- = Not Applicable.		

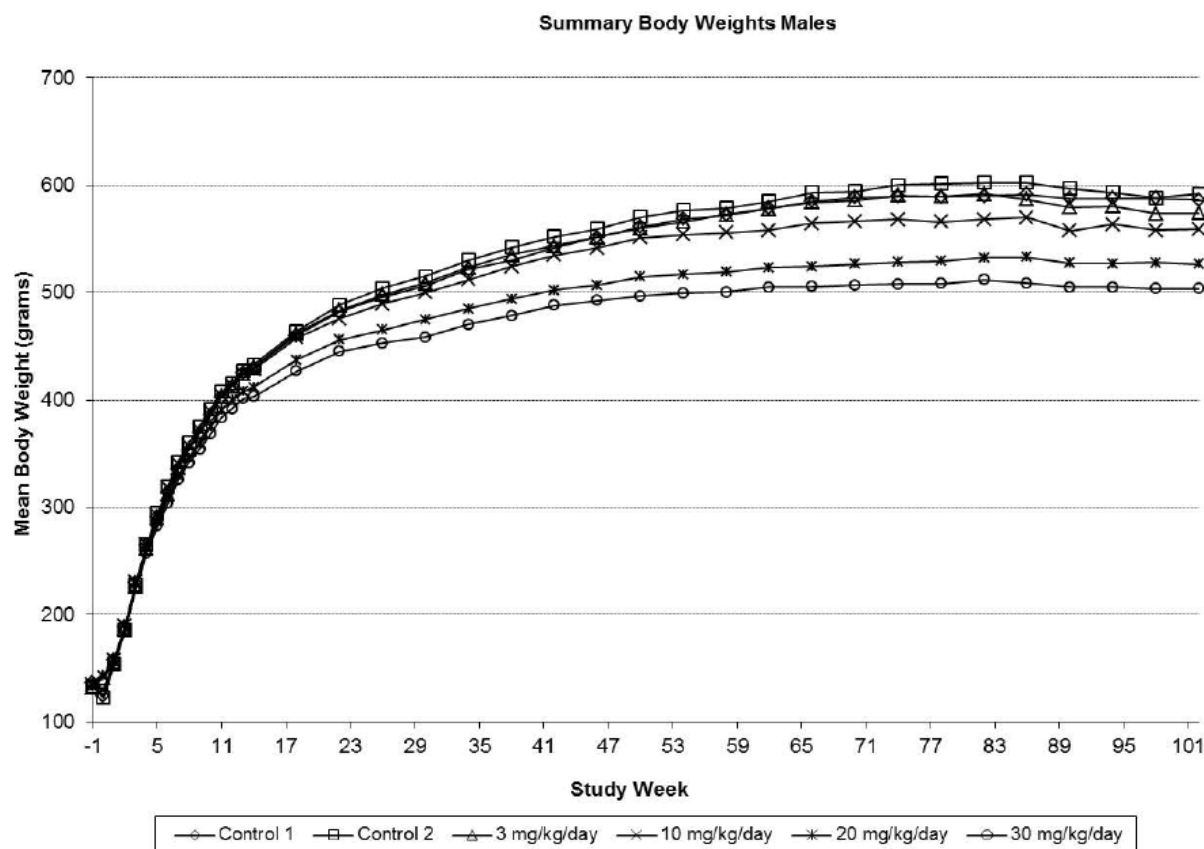
Clinical Signs

Salivation was observed at ≥60 mg/kg/day in females only. Dose dependent transient clinical signs were occasionally observed (lateral, sternal or supine recumbency, consistent with hyperthermia) in females at ≥20 mg/kg/day and in males at ≥3 mg/kg/day.

Body Weights

Decreased body weight gain was observed at ≥ 60 mg/kg/day in females (-12% at 60 mg/kg/day and -15% at 180 mg/kg/day) and at ≥ 20 mg/kg/day in males (-15% at 20 mg/kg/day and -19% at 30 mg/kg/day).
(sponsor's figure)





Gross Pathology

No treatment related effects were observed.

Histopathology

Peer Review: yes

Neoplastic

No treatment related effects were observed.

Non-neoplastic

Non-neoplastic test article-related changes were limited to increased incidence of brown fat accumulation and vacuolation of the adrenal zona glomerulosa at ≥ 10 mg/kg/day in males and at >20 mg/kg/day in females.

Non-neoplastic changes

	Males (mg/kg/day)						Females (mg/kg/day)				
	0	0	3	10	20	30	0	0	20	60	180
*Adrenal, vac. zona glomer.		1		2	16	20			4	14	21
**White adipose, brown fat accu.		1		4	17	19			1	3	4

*All changes were very slight or slight.

**Brown fat accumulation is animal specific pharmacology.

Toxicokinetics

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Rats Following Dosing of MK-4618: Study Week 14 (sponsor's table.)

Week	Dose (mg/kg/day)	Sex	AUC _{0-24 hr} (μ M*hr)	C _{max} (μ M)	T _{max} (hr)
14	60	Female	83.5 $\pm$ 17.9	13.6 $\pm$ 3.44	4.0 $\pm$ 0.0

Summary Mean ($\pm$ SE) Plasma MK-4618 Concentrations (μ M) in Rats Following Dosing of MK-4618: Study Week 14 (sponsor's table)

			Time (hr)	
Week	Dose (mg/kg/day)	Sex	2	24
14	Vehicle	F+M	0.00 $\pm$ 0.00	NC
	3	M	0.162 $\pm$ 0.0153	0.00 $\pm$ 0.00
	10	M	1.06 $\pm$ 0.221	0.0473 $\pm$ 0.0106
	20	F+M	8.80 $\pm$ 1.47	0.142 $\pm$ 0.0115
	30	M	5.52 $\pm$ 1.90	0.151 $\pm$ 0.0104
	60	F	7.05 $\pm$ 0.586	0.223 $\pm$ 0.0139
	180	F	39.8 $\pm$ 12.6	0.915 $\pm$ 0.189

NC = Not Calculated.

F = Female, M = Male.

MK-4618 concentrations in plasma from all control group animals at 2 hours postdose were below the lower limit of quantitation (LLQ = 0.0227 $\square$ M) of the bioanalytical method.

Summary Mean (+SE) Plasma MK-4618 Concentrations (µM) in Rats Following Dosing of MK-4618: Study Week 27 (sponsor's table)

Week	Dose (mg/kg/day)	Sex	Time (hr)	
			2	24
27	Vehicle	F+M	0.00 ± 0.00	NC
	3	M	0.129 ± 0.0112	0.00 ± 0.00
	10	M	0.778 ± 0.104	0.0569 ± 0.00830
	20	F+M	7.02 ± 1.64	0.132 ± 0.0160
	30	M	6.35 ± 2.40	0.149 ± 0.0273
	60	F	10.2 ± 2.55	0.291 ± 0.0209
	180	F	24.5 ± 9.71	1.28 ± 0.415

NC = Not Calculated.

F = Female, M = Male.

MK-4618 concentrations in plasma from all control group animals at 2 hours postdose were below the lower limit of quantitation (LLQ = 0.0227 µM) of the bioanalytical method.

Dosing Solution Analysis

Samples of all dosing formulations were collected for analysis of concentration on Study Day 1 and in Study Weeks 14, 27, 40, 53, 66, 79, 92, and 104. All assay results were within the acceptable concentration range (±10% of claim for a solution). The vehicle and the compound in this vehicle were shown to be stable under the conditions of this study.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Oral Fertility Study in Male Rats

Study no.: **TT #11-7110**
Study report location: Safety Assessment & Laboratory Animal Resources, Merck Research Laboratories, West Point, Pennsylvania, U.S.A.
Conducting laboratory and location: Merck Research Laboratories
Merck & Co., Inc.
West Point, Pennsylvania 19486 U.S.A.
Date of study initiation: 10 February 2011
GLP compliance: yes
QA statement: yes
Drug, lot #, and % purity: Base form of MK-4618, Lot number L-002206358-000L021, 99.6 % pure

Key Study Findings

The NOEL for male fertility parameters in rats was > 300 mg/kg/day.

The NOEL for general toxicity parameters in male rats was 10 mg/kg/day, based on transient decreases in mean body weight gain at 30 and 300 mg/kg/day.

Methods

Doses: 0, 10, 30, and 300 mg/kg/day
Frequency of dosing: daily
Dose volume: 5 ml/kg
Route of administration: Oral, gavage
Formulation/Vehicle: polyethylene glycol 400 in deionized water (20:80 w/w)
Species/Strain: Crl:CD(SD) rats
Number/Sex/Group: 20 males per group
Study design: Male rats were dosed for 15 days prior to cohabitation, during cohabitation, and until the day prior to scheduled sacrifice (approximately 6 weeks total). Males were housed with untreated females in a 1:1 ratio following 2 weeks of treatment. On GD 15 to 17 all females were euthanized, uterine contents examined for embryonic/fetal viability, and corpora lutea counted. Sperm Motility Analysis: At necropsy a sperm suspension was prepared from the mid region of the left vas deferens of each male.

Epididymal Sperm Head Quantitation: The frozen left cauda epididymis from each male in the high dose and control group was thawed, minced, and homogenized. An aliquot of the sperm suspension was stained with bis benzimide trihydrochloride fluorescent dye and subsequently analyzed for sperm number. Epididymal sperm head counts were expressed as the number of sperm/cauda epididymis and the number of sperm/g cauda epididymis.

Observations and Results

Mortality: There were no unscheduled deaths during the study.

Clinical Signs: Intermittent pre- and/or post-dose salivation was observed in 13 of 20 males in the 300 mg/kg/day group.

Body Weight/ Food Consumption: Decreases in mean body weight gain were observed during the 2-week pre-mating period in the 30 and 300 mg/kg/day groups (22% and 78% below control, respectively) and continued after the mating period (Study Weeks 3 to 6). There were no test article-related effects at 10 mg/kg/day. No treatment related effects on food consumption were observed.

Necropsy: No test article-related effects on terminal body weights or testes weights were observed.

Fertility Parameters: There were no test article-related effects on mating, fertility, sperm parameters, or embryonic/fetal viability at any dose level.

Study title: Oral Fertility Study in Female Rats

Study no.:	TT #11-7320
Study report location:	Safety Assessment, Merck Research Laboratories, West Point, Pennsylvania, U.S.A.
Conducting laboratory and location:	Merck Research Laboratories, West Point, Pennsylvania, U.S.A.
Date of study initiation:	11 September 2011
GLP compliance:	yes
QA statement:	yes
Drug, lot #, and % purity:	Base form of MK-4618, lot number L-002206358-000L021, 99.6 % pure by LCAP

Key Study Findings

The NOEL for fertility parameters and for general toxicity in female rats was 300 mg/kg/day.

Methods

Doses:	0, 30, 100, 300, and 1000 mg/kg/day
Frequency of dosing:	daily
Dose volume:	5 ml/kg
Route of administration:	Oral, gavage
Formulation/Vehicle:	20% polyethylene glycol 400 in deionized water (20:80 w/w)(all dosing formulations were acidified daily to a pH of 2.5)
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	20 females per group
Study design:	Female rats were dosed for 14 days prior to cohabitation, during cohabitation, and through Gestation Day (GD) 7. Females were housed with untreated male rats at a 1:1 ratio following 14 days of treatment for a maximum of 20 nights. The day of confirmed mating was considered GD 0. On GD 15 to 17, all surviving females were euthanized, uterine contents examined for embryonic/fetal viability, and corpora lutea counted.

Observations and Results

Mortality: There were 2 deaths at 1000 mg/kg/day. One female was euthanized on Premating Day (PMD) 10 due to adverse physical signs and body weight loss, and the other female was found dead on PMD 11.

Clinical Signs: At 1000 mg/kg/day, decreased activity was observed prior to the 2 unscheduled deaths (premating). The premature sacrifice female was also cool to the touch. Urine stained fur in 10 of 20 females, no feces in the cage pan of 3 females, and red nasal discharge in 6 females were also observed premating. Physical signs during gestation included urine-stained or discolored fur in 6 of 18 females, and blood-like substance on the tail and/or tip of ears in 2 females.

Body Weight: Increases in mean maternal body weight gain were observed at 1000 mg/kg/day between PMD 8 to 14 (53% above control) and GD 0 to 8 (14% above control). Losses in premating body weights were observed in the females that were found dead or euthanized prematurely.

Feed Consumption: At 1000 mg/kg/day, there was a transient decrease in mean food consumption between PMD 1 and 5 (36% below control).

Necropsy

At termination, there were gross examination findings of distended colon in 6 females of the 1000 mg/kg/day group. This finding was also observed in one female in each of the 100-mg/kg/day and 300-mg/kg/day groups.

Fertility Parameters: No effect was observed on corpora lutea, implantations, resorptions, or live fetuses.

	Females (mg/kg/day)				
	0	30	100	300	1000
Mating Index (%)	100	100	100	100	100
Fecundity Index (%)	100	95	100	100	72
Fertility Index (%)	100	95	100	100	72

Mating Index = Mated females/females cohabited (excluding females found dead or sacrificed during cohabitation).

Fecundity Index = Pregnant females/mated females (excluding females with an undetermined pregnancy status).

Fertility Index = Pregnant females/females cohabited (excluding females found dead or sacrificed during cohabitation or with an undetermined pregnancy status).

9.2 Embryonic Fetal Development

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

Study no.: TT #11-7280
 Study report location: Archives of Merck Research Laboratories
 Conducting laboratory and location: Merck Research Laboratories, West Point, Pennsylvania, U.S.A., and Laboratoires Merck Sharp & Dohme-Chibret, Riom, France
 Date of study initiation: 10 September 2011
 GLP compliance: yes
 QA statement: yes
 Drug, lot #, and % purity: Base compound of MK-4618, lot number L-002206358-000L021, 99.6 area percent pure by liquid chromatography area percent

Key Study Findings

At 1000 mg/kg/day vibegron (1867-fold the MRHD), maternal body weight loss and lethality were observed.

At 300 mg/kg/day (267-fold the MRHD), no maternal or developmental toxicity or teratogenicity was observed.

Methods

Doses: 0, 30, 100, 300, and 1000 mg/kg/day
Frequency of dosing: daily
Dose volume: 5 ml/kg
Route of administration: Oral, gavage
Formulation/Vehicle: 20% polyethylene glycol 400 in deionized water (20:80 w/w)
Species/Strain: Crl:CD(SD) rats,
Number/Sex/Group: 28 females (24 controls)
Study design: In time-mated females, administration from GD 6 through 20; toxicokinetic profile on GD 15/16.

Observations and Results

Mortality

At 1000 mg/kg/day, 3 dams were euthanized on GD 10 or 13 due to body weight loss or recumbency. Two females were found dead on GD 14 or 16. All remaining females in this group were euthanized due to decreased body weight gain or decreased food consumption and physical signs.

Clinical signs:

At 1000 mg/kg/day, clinical signs included no feces, urine stained fur, red or brown nose discharge, red or brown vaginal discharge, blood-like substance in pan with no apparent source, food wastage, cool to touch, decreased motor activity, alopecia, and/or eye lacrimation. At 300 mg/kg/day, no treatment related effects were observed.

Body Weight

At 1000 mg/kg/day, progressive maternal body weight loss beginning on GD 8 was observed. Mean maternal body weight gain was decreased 62% compared to control from GD 6 – 14. At 300 mg/kg/day, no treatment related effects were observed.

Feed Consumption

At 1000 mg/kg/day, decreases in maternal food consumption were observed.

Toxicokinetics

Exposures of 30, 100, 300, and 1000 mg/kg/day represent multiples of the MRHD of 75 mg vibegron via AUC of 9-, 89-, 275-, and 1867-fold, respectively. MK-4618 concentrations in control group plasma at 1 hour postdose were below the lower limit of quantitation (0.023 µM).

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Rats Following Dosing of MK-4618: Gestation Day 15 (Sponsor's table)

Dose (mg/kg/day)	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
30	29.8 $\pm$ 8.07	2.66 $\pm$ 0.950	4.0 $\pm$ NC
100	289 $\pm$ 38.2	23.5 $\pm$ 5.52	4.0 $\pm$ NC
300	896 $\pm$ 95.5	63.8 $\pm$ 10.9	8.0 $\pm$ NC
1000	6090 $\pm$ 330	325 $\pm$ 9.92	1.0 $\pm$ NC

NC = Not Calculated

Necropsy

Cesarean Section Data

No treatment related effects were observed at 300 mg/kg/day or below.

Offspring

No treatment related effects were observed at 300 mg/kg/day or below.

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

Study no.: TT #11-7170
 Study report location: Archives of Merck Research Laboratories,
 Conducting laboratory and location: Merck Research Laboratories, West Point,
 Pennsylvania, U.S.A., and Laboratoires
 Merck Sharp & Dohme-Chibret, Riom,
 France
 Date of study initiation: 9 September 2011
 GLP compliance: yes
 QA statement: yes
 Drug, lot #, and % purity: MK-4618 (L-002206358), Lot Number L-
 002206358-000L021, 99.6 area percent
 pure by HPLC

Key Study Findings

At 300 mg/kg/day (898-fold the MRHD), decreased maternal food consumption, reduced fetal body weight, and increased incidence of delayed skeletal ossification were observed (skull, sternebra, metacarpal, and talus-calcaneus bones).

At 100 mg/kg/day (286-fold the MRHD), no maternal or developmental toxicity was observed.

Methods

Doses: 0, 30, 100, and 300 mg/kg/day
 Frequency of dosing: daily
 Dose volume: 2 ml/kg
 Route of administration: Oral, gavage
 Formulation/Vehicle: 20% polyethylene glycol 400 in deionized water (20:80 w/w)
 Species/Strain: Dutch belted rabbits
 Number/Sex/Group: 22 females/group
 Study design: Time-mated, oral administration from Gestation Days (GD) 7 - 20; toxicokinetics on GD 15.

Observations and Results**Mortality**

No unscheduled deaths occurred.

Clinical Signs

No treatment related effects were observed.

Body Weight

No treatment related effects were observed.

Feed Consumption

At 300 mg/kg/day, a transient decrease in mean maternal food consumption was observed on GD 8 and 13 (30% and 21% below the control group, respectively).

Toxicokinetics

Exposures of 30, 100, and 300 mg/kg/day represent multiples of the MRHD of 75 mg vibegron via AUC of 86-, 285-, and 898-fold, respectively.

Summary Mean ($\pm$ SE) Plasma MK-4618 Toxicokinetic Parameters in Rabbits Following Dosing of MK-4618: Gestation Day 15 (Sponsor's table)

Dose (mg/kg/day)	AUC _{0-24 hr} (μ M•hr)	C _{max} (μ M)	T _{max} (hr)
30	280 $\pm$ 75.6	79.0 $\pm$ 23.1	1.2 $\pm$ 0.44
100	929 $\pm$ 75.5	211 $\pm$ 21.1	0.83 $\pm$ 0.17
300	2930 $\pm$ 56.5	359 $\pm$ 28.0	1.2 $\pm$ 0.44

Necropsy**Cesarean Section Data**

In the 300-mg/kg/day group, there was a MK-4618-related decrease in mean live fetal weight (14% and 9% below the control group in females and males, respectively).

Mean fetal weights

Fetal Weights	Females (mg/kg/day)			
	0	30	100	300
Mated females	18	18	18	18
Total Litters Examined	15	18	18	18
Live Fetal Weight (g), Litter Mean $\pm$ SD				
Males	32.2+2.6	30.4+3.2	31.1+3.2	27.7+3.4
Females	31.3+2.9	31.7+3.4	31.5+4.1	28.6+2.1
Live Fetal Weight (%)				
Males		-5%	-3%	-14%
Females		--	--	-9%

Offspring

At 300 mg/kg/day, increased incidences of fetuses with sites of incomplete ossification (skull [primarily the hyoid], sternebra, metacarpal, and talus-calcaneus) were observed.

Summary of Examinations of Fetuses

Summary of Fetal Ossification Data (Alizarin Red Evaluation)

	Females (mg/kg/day)			
	0	30	100	300
Torso and Limb Examination				
Total Litters Examined	15	18	18	18
Live Fetuses/Litters Examined	94/15	126/18	119/18	124/18
Fetuses with Incomplete Ossification (%)	2	6	1	16
Litters with Incomplete Ossification (%)	2	5	1	10
Number of Ossified Sacrocaudal Vertebrae	19.4	19.3	19.2	19.3
Head Examination				
Total Litters Examined	15	18	18	18
Live Fetuses/Litters Examined	94/15	126/18	119/18	124/18
Fetuses with Incomplete Ossification (%)	1	2	1	11
Litters with Incomplete Ossification (%)	1	2	1	6
Site and Number of Fetuses with Incomplete Ossification (%L.M. $\pm$ SD)				
Incomp. Ossification of Cervical Vertebra	0	2	0	1
Incomp. Ossification of Skull Bone	1	2	1	11
Incomp. Ossification of Sternebra	2	1	0	6
Incomp. Ossification of Metacarpal	0	3	0	11
Incomp. Ossification of Pelvic Bone	0	0	1	0
Incomp. Ossification of Talus-Calcaneus	0	0	0	2

Summary of Fetal Ossification Data (micro-CT Evaluation)

	Females (mg/kg/day)			
	0	30	100	300
Torso and Limb Examination				
Total Litters Examined	15	18	18	18
Live Fetuses/Litters Examined	94/15	126/18	119/18	124/18
Fetuses with Incomplete Ossification (%)	17	33	35	51
Litters with Incomplete Ossification (%)	8	11	15	16
Number of Ossified Sacrocaudal Vertebrae ± SD	19.0	19.0	19.1	19.1
Head Examination				
Total Litters Examined	15	18	18	18
Live Fetuses/Litters Examined	94/15	126/18	119/18	124/18
Fetuses with Incomplete Ossification (%L.M.± SD)	10	13	9	26
Litters with Incomplete Ossification (%)	5	6	6	10
Site and Number of Fetuses with Incomplete Ossification (%L.M.± SD)				
Incomp. Ossification of Cervical Vertebra	0	1	0	0
Incomp. Ossification of Skull Bone	10	13	9	26
Incomp. Ossification of Sternebra	3	2	2	12
Incomp. Ossification of Metacarpal	15	30	34	44
Incomp. Ossification of Pelvic Bone	0	0	2	4
Incomp. Ossification of Talus-Calcaneus	0	0	1	4

Summary of Fetal Visceral Examinations

	Females (mg/kg/day)			
	0	30	100	300
Fetal Visceral Examinations				
Total Litters Examined	15	18	18	18
Live Fetuses/Litters Examined	94/15	126/18	119/18	124/18
Fetuses with Malformations (%)	3	6	7	14
Litters with Malformations (%)	2	3	5	8
___ Ventricular Septal Defect (%)	2 ^{a,b}	0	0	0
___ Right-Sided Aortic Arch (%)	1 ^b	0	0	0
___ Renal Artery Malformation (%)	0	0	1	0
___ Absent Kidney (%)	0	1	1	1
___ Absent Gallbladder (%)	1 ^a	0	0	3
___ Small Gallbladder (%)	1	4	2	3
___ Gallbladder Malformation (%)	0	0	1	1
___ Supernumerary Gallbladder (%)	0	1	2	6
Fetuses with Variations (%)	1	0	0	0
Litters with Variations (%)	1	0	0	0
___ Fluid-Filled Thoracic Cavity (%)	1 ^a	0	0	0

^a Multiple alterations observed for one litter, one fetus

^b Multiple alterations observed for one litter, one fetus

Effects showing a positive linear correlation, but within historical limits

	Females (mg/kg/day)			
	0	30	100	300
Malformations (p value <)				
Litters with malformations (0.0154)	2	3	5	8
Litters with gallbladder malformations (0.0187)	1	3	4	8
Litters with supernumerary gallbladder (0.0025)	0	1	2	6
Litters affected %		0.6%	11.1 %	33.3 %

(b) (4) Historical Control Data:

Effect	Av. %	Min %	Max %	High dose MK-4618 %
Absent gallbladder	1.38	0.00	7.69	16.7%
Reduced gallbladder	4.48	0.00	26.32	16.7%
Enlarged gallbladder	0.86	0.00	10.00	0.00 %
Supernumerary gallbladder	0.34	0.00	10.53	33.3 %

9.3 Prenatal and Postnatal Development

Study title: Study for Effects of KRP-114V on Pre- and Postnatal Development, including Maternal Function by Oral Administration in Rats

Study no.: P150044

Study report location: archives of the test facility

Conducting laboratory and location:

(b) (4)

Date of study initiation: 23 March 2015

GLP compliance: yes

QA statement: yes

Drug, lot #, and % purity: Lot # 000L037, 99.4% pure

Key Study Findings

At 500 mg/kg/day (458-fold the MRHD), decreased maternal body weight gain was observed during gestation (along with decreased food consumption) and during lactation. Developmental toxicity was observed in F1 offspring (increased stillborn index, lethality, reduced viability on Lactation Day 4, decreased weaning index, decreased body weight and body weight gains, low physical development differentiation indices [piliation, incisor eruption, eye opening, and/or preputial separation], and effects on sensory function and reflexes) at this dose.

At 100 mg/kg/day (89-fold the MRHD), decreased maternal body weight gain was observed during lactation.

NOAELs were 30 mg/kg/day (9-fold the MRHD) for maternal toxicity, and 100 mg/kg/day for developmental toxicity.

Methods

Doses: 0, 30, 100, and 500 mg/kg/day
Frequency of dosing: daily
Dose volume: 5 ml/kg
Route of administration: Oral, gavage
Formulation/Vehicle: 20 w/w% polyethylene glycol (pH2.5)
Species/Strain: Rat, Crl:CD(SD)
Number/Sex/Group: 20
Study design: Administration from Gestation Day 6 to Lactation Day 20

Observations and Results

F₀ Dams

Survival: No treatment related effects were observed.
Clinical signs: No treatment related effects were observed.
Body weight/ Feed consumption: Decreased maternal body weight gain and food consumption were observed during gestation and during lactation at 500 mg/kg. Decreased body weight gain was observed during the lactation period at the 100 and 500 mg/kg.
Effects on dams: No effects on delivery, nursing behavior, gestation length, number of implantations, numbers of newborns, or gestation index were observed.

F₁ Generation

Survival: An increase in stillborn index was observed, and all offspring of 2 dams died at 500 mg/kg/day on Lactation Days 4 and 10. Low values in viability index were observed on Post Natal Day 4
Body weight: At 500 mg/kg/day, decreased body weights and body weight gains were observed.
Feed consumption: At 500 mg/kg/day, decreased food consumption was observed.
Physical development: At 500 mg/kg/day, piliation, incisor eruption, eye opening, and/or preputial separation were delayed.
Neurological assessment: At 500 mg/kg/day, righting reflex and visual placing response were delayed. No effects on motor activity, learning and memory, or emotional behavior were observed.
Reproduction: No treatment related effects on fertility were observed.
Other: At 500 mg/kg/day, low weaning index was observed.

Body weight gains in F0 dams from Gestation Days 6 to 20 (sponsor's table.)

Sex: Female		Control	30 mg/kg	100 mg/kg	500 mg/kg
Day(s) Relative to Mating Litter:					
9(6→9)	Mean	12.05	14.35	10.66	5.17 ^{ss1}
	SD	4.14	5.58	3.28	6.97
	N	20	19	19	20
12(6→12)	Mean	29.13	32.08	29.33	23.84
	SD	4.34	6.66	4.87	7.96
	N	20	19	19	20
15(6→15)	Mean	47.91	51.98	49.88	45.49
	SD	6.49	6.66	6.15	7.72
	N	20	19	19	20
18(6→18)	Mean	88.38	93.97	92.24	86.23
	SD	8.03	10.57	7.81	6.67
	N	20	19	19	20
20(6→20)	Mean	120.25	127.37	123.56	119.54
	SD	11.62	14.32	10.71	10.32
	N	20	19	19	20

1 [ss - Test: Steel 2 Sided p < 0.01]

Body weight gains in F0 dams from Lactation Days 0 to 21

Sex: Female		Control	30 mg/kg	100 mg/kg	500 mg/kg
Day(s) Relative to Littering					
4(0→4)	Mean	33.46	30.06	21.54 ^{dd1}	19.36 ^{dd1}
	SD	9.51	11.02	12.46	11.76
	N	20	19	19	20
7(0→7)	Mean	36.90	32.64	23.96 ^{dd1}	26.20 ^{d3}
	SD	10.76	11.09	15.43	9.84
	N	20	19	19	19
10(0→10)	Mean	43.58	35.52	26.66 ^{dd1}	30.74 ^{dd1}
	SD	12.38	11.56	16.39	12.45
	N	20	19	19	19
14(0→14)	Mean	43.11	35.02	24.35 ^{dd1}	27.74 ^{dd1}
	SD	11.24	14.69	16.50	12.61
	N	20	19	19	18
17(0→17)	Mean	36.98	30.13	21.72 ^{ss2}	25.25
	SD	8.88	19.66	17.43	16.44
	N	20	19	19	18
21(0→21)	Mean	18.11	13.19	9.09	17.27
	SD	12.98	16.20	15.83	15.24
	N	20	19	19	18

1 [dd - Test: Dunnett 2 Sided p < 0.01] ; 2 [ss - Test: Steel 2 Sided p < 0.01]; 3 [d - Test: Dunnett 2 Sided p < 0.05]

Body weights in male offspring during lactation period (postnatal Days 0 to 21)

Sex: Male			Control	30 mg/kg	100 mg/kg	500 mg/kg
Day(s) Relative to Littering						
Sum of Count of Pup BW	0		137	135	126	148
	4		135	135	125	141
	7		78	75	76	74
	14		78	75	76	70
	21		78	75	76	70
Mean Male Pup BW	0	Mean	6.972	6.834	6.910	6.484 d ¹
		SD	0.538	0.665	0.536	0.513
		N	20	19	19	20
	4	Mean	11.380	11.349	10.873	9.035 ss ²
		SD	0.796	1.668	1.238	1.269
		N	20	19	19	19
	7	Mean	18.936	19.063	18.186	14.480 ss ²
		SD	1.305	1.978	1.786	2.722
		N	20	19	19	19
	14	Mean	38.370	38.863	36.853	28.840 dd ³
		SD	2.212	2.457	3.270	3.447
		N	20	19	19	18
	21	Mean	61.978	63.154	59.684	46.808 dd ³
		SD	3.931	4.483	5.923	5.869
		N	20	19	19	18

1 [d - Test: Dunnett 2 Sided p < 0.05]; 2 [ss - Test: Steel 2 Sided p < 0.01]; 3 [dd - Test: Dunnett 2 Sided p < 0.01]

Body weights in female offspring during lactation period (postnatal Days 0 to 21)

Sex: Female			Control	30 mg/kg	100 mg/kg	500 mg/kg
Day(s) Relative to Littering						
Sum of Count of Pup BW	0		142	135	138	127
	4		139	133	135	115
	7		82	76	76	72
	14		82	76	76	71
	21		82	76	76	71
Mean Female Pup BW	0	Mean	6.555	6.493	6.555	6.131 d ¹
		SD	0.429	0.595	0.463	0.545
		N	20	19	19	20
	4	Mean	10.872	10.722	10.495	8.725 ss ²
		SD	0.773	1.526	1.124	1.328
		N	20	19	19	19
	7	Mean	18.149	18.240	17.370	13.541 ss ²
		SD	1.413	1.876	1.742	3.018
		N	20	19	19	19
	14	Mean	36.984	37.410	35.376	27.353 ss ²
		SD	2.068	2.188	3.029	4.057
		N	20	19	19	18
	21	Mean	60.342	60.735	57.339	45.273 dd ³
		SD	3.686	4.603	5.445	6.583
		N	20	19	19	18

1 [d - Test: Dunnett 2 Sided p < 0.05]; 2 [ss - Test: Steel 2 Sided p < 0.01]; 3 [dd - Test: Dunnett 2 Sided p < 0.01]

Effects on the F1 Generation

	Females (mg/kg/day)			
	0	30	100	500
Maternal multiples of MRHD via AUC		9	89	458
Total Litters Examined	20	19	19	20
Live Fetuses/Litters Examined	279/	270/	264/	275/
No. of stillborn	4	1	2	7
No. of dead from Days 1 to 4	1	2	3	12
Viability index Day 4 (%)	98.3	99.4	98.6	91.6
Weaning index (%)	100.0	100.0	100.0	92.8
Pilation (%), Day 8				
__ male	100.0	100.0	100.0	93.0
__ female	100.0	100.0	100.0	96.3
Incisor eruption (%), Day 11				
__ male	95.0	96.1	97.4	82.0*
__ female	96.3	92.1	89.5	76.4*
Eye opening (%), Day 15				
__ male	100.0	98.7	100.0	90.3
__ female	98.8	100.0	100.0	90.3
Preputial separation (%), Day 22	40.0	31.6	26.3	0.0*
Righting reflex (%), Day 7				
__ male	100.0	100.0	100.0	98.2
__ female	100.0	100.0	100.0	93.4

Visual placing response (%), Day 16				
— male	100.0	100.0	100.0	94.4
— female	100.0	100.0	100.0	94.4

F₂ Generation

No effects on the F₂ generation were observed.

11 Integrated Summary and Safety Evaluation

Vibegron (MK-4618, RVT-901) is a β_3 -adrenergic agonist being developed for overactive bladder. MK-4618 activated the human β_3 adrenergic receptor and increased cAMP levels, with an EC₅₀ of 1.1 nM and 84% activation relative to isoproterenol. MK-4618 exhibited >9000-fold selectivity for β_3 -AR over β_1 -AR or β_2 -AR in cell based in vitro functional assays.

Activation of the β_3 AR increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling. In a bladder strip assay, MK-4618 induced relaxation of bladder smooth muscle in a concentration-dependent manner, with an EC₅₀ of 3.0 μ M in rats and 0.087 μ M in humans.

Rhesus monkey was shown to be pharmacologically similar in response to β_3 -AR agonist as humans, while agonist activity at the rabbit and dog β_3 adrenergic receptors was approximately 10-fold less potent and activity at the rat receptor was 100-fold less potent than human. Metabolite profiles in toxicology species were similar to those observed in humans.

In a 6-month rat study, a NOAEL was observed at 30 mg/kg/day (about 21.3-fold). Some brown fat accumulation, a pharmacologic effect in rats, was observed at this level in male rats. At 180 mg/kg/day (about 102-fold), one male was found dead in study week 12, and very slight or slight increases in alkaline phosphatase were observed. Decreased body weight gain was observed at 180 mg/kg/day (-30% in males and -20% in females) and at 30 mg/kg/day in males only (-16%).

Vibegron was tested up to 9 months in Cynomolgus monkeys. At 300 mg/kg/day (approximately 75 times the expected clinical exposure at the MRHD of 75 mg dose of vibegron), abdominal distension was observed in female monkeys only, (3 high-dose and 1 control) and was considered possibly due to the vehicle. No histopathological effects were observed, except for slight accumulation of brown fat in white adipose tissue (a pharmacologic effect common to beta-3-adrenergic agonists in animals) and very slight cellular infiltration in the liver at 300 mg/kg/day (seen only in females previously exhibiting abdominal distension.) However, at 1000 (reduced to 360) mg/kg/day in a 3-month study, increases in serum liver enzyme activities were also observed.

Electrocardiograms were also recorded in this study at pretest and at approximately 2 hours and 24 hours postdose, in Study Weeks 4, 8, 12, 18, 25, 32, and 37 from all monkeys in dorsal recumbency.

At 300 mg/kg/day (75-fold the AUC of the MRHD of 75 mg, 114-fold the C_{max}), transient electrocardiographic findings (increases in QRS duration consistent with a ventricular conduction defect and P wave partially or fully hidden in the T wave of the preceding complex) were observed at approximately 2 hours post dose (generally resolved by 24 hours post dose). In animals where PR and QT intervals could be evaluated (1 female and 1 male on 1 or 2 occasions), no prolongation in QT interval was observed. In these animals, there were marked increases in QRS duration and notable changes in QRS configuration, including "coving" of the S wave. Heart rates were slightly increased at 2 hours post dose but normalized by 24 hours. At 100 mg/kg/day (34-fold C_{max}, 17-fold AUC), heart rates were slightly increased at 2 hours post dose but normalized by 24 hours. A NOEL was 25 mg/kg/day (6.4-fold C_{max}, 2.1-fold AUC). After nine months of treatment, no indication of cardiac histopathology was observed despite the ECG findings.

A cardiac safety pharmacology study was also conducted in rhesus monkeys (2 monkeys/sex/dose) using an escalating dose design, at doses of 2.5, 15 and 135 mg/kg MK-4618. At 2.5 mg/kg (0.22-fold the MRHD of 75 mg by C_{max}, 0.16-fold by AUC) and above, transient increased heart rate (an expected pharmacological effect of a β_3 -adrenergic receptor agonist), increased respiration rate, and increased body temperature (a metabolic effect of β_3 -adrenergic receptor agonists observed in animals) were observed. Increases in uncorrected QT interval were also observed at all doses. Corrected QT (QT_c) changes, to account for large changes in heart rate, did not reveal a dose relationship, which was interpreted to indicate that drug related increases in QT interval were an artifact of increased heart rate. At 15 mg/kg (2.7-fold C_{max}, 1.3-fold AUC) and above, decreased PR interval was also observed (10 to 19%). At 135 mg/kg (42-fold C_{max}, 31-fold AUC), increased diastolic blood pressure (13 mmHg, 19%), respiration depth (7 mmHg, 103%), and QRS interval (6 msec, 12%) were also observed in addition to effects observed at lower doses.

No NOEL for cardiac effects was observed in this study. However, at 2.5 mg/kg, no increase in PR interval was observed to coincide with the observed transient increase in heart rate.

In a three-month toxicology study in monkeys, 2 females were found dead at 1000 mg/kg/day (181-fold the C_{max} of the MRHD of 75 mg, 255-fold AUC). ECG changes were observed in all surviving males at this dose and it should be considered that these deaths may have been due to cardiac arrhythmias. A NOAEL for ECG changes was 120 mg/kg/day (43-fold the C_{max} of the MRHD of 75 mg, 20.7-fold AUC.) ECG changes were observed in males after approximately 3 weeks of dosing at 1000 mg/kg/day at approximately 1 hour and/or 24 hours postdosing, and after approximately 1 month and

2 months of dosing at 360 mg/kg/day (2/3 males) at approximately 1 hour post dose. They consisted of QRS distortion (consistent with ventricular conduction effects) at both dosages. In 1 animal at 1000 mg/kg/day, absence of P waves and PR prolongation were also observed (consistent with atrioventricular conduction defects). After approximately 2 months of dosing at 360 mg/kg/day (about 104-fold C_{max}, 58-fold AUC), ECG changes were limited to QRS distortion. There were no histomorphological changes in the heart that correlated with heart rate or ECG changes.

In non-GLP studies, vibegron was administered intravenously to mixed breed anesthetized and vagotomized dogs (N=2) at 0.3, 0.7, 1, 2, and 7 mg/kg (separated by 30 minutes). Heart rate, mean arterial pressure, and electrocardiographic parameters were monitored. Plasma concentrations were approximately 3, 8, 14, 26, and 116-fold C_{max} at the MRHD of 75 mg vibegron. Transient decreases in mean arterial pressure and increases in heart rate were observed at all doses. No effects on QT interval changes were observed. At doses > 1 mg/kg (about 14-fold), small (<10 %) increases in QRS interval were observed.

In a three-month oral combination toxicity study in cynomolgus monkeys (N=3/group), monkeys were administered vibegron, followed immediately by the tartrate salt of tolterodine, at 0/0, 0/1, 0/5, 100/1, and 100/5 mg/kg/day (vibegron/tolterodine). Following the death of one 100/5 male (approximately 23 times the MRHD of 75 mg vibegron by C_{max}, 13 times by AUC and 4 times the MRHD of 4 mg tolterodine), a 100/3 (vibegron/tolterodine) group was added.

At a combination dose of 100/5 (MK-4618/tolterodine) mg/kg/day, one male was found dead following observations of distended abdomen, signs of stomach content aspiration, decreased heart rate at 2 hours (27%) and 24 hours post dose (42%), increased PR interval at 2 hours post dose (50%), and increased QT and QTc intervals 2 hours (20% and 13%, respectively) and 24 hours post dose (56% and 30%, respectively). Effects on heart rate were observed in all dose groups. Vibegron did not appear to increase the exposure of tolterodine in this study, nor did tolterodine increase exposure to vibegron.

In CHO-K1 Chinese Hamster Ovary cells, at a concentration of 31 µM (112-fold the MRHD of 75 mg using C_{max})(N=5), MK-4618 had no statistically significant effect on hERG channel tail current, but at the maximum testable concentration of 101 µM (365-fold)(N=4), it inhibited hERG current by 21.4%

Mutagenesis

Vibegron was not mutagenic in in vitro microbial reverse mutation (Ames) assays, was not genotoxic activity in an in vitro human peripheral blood lymphocyte chromosomal aberration assay, and did not increase the frequency of micronucleated polychromatic erythrocytes in an in vivo rat bone marrow micronucleus assay.

Carcinogenesis

In CD-1 mice, oral administration of vibegron at 0, 10, 30, or 90 mg/kg/day in males and 0, 15, 50, or 150 mg/kg/day in females for two years did not cause treatment-related malignancies. Survival was comparable among groups. NOELs for carcinogenicity were 90 and 150 mg/kg/day in males and females, respectively, with systemic exposures (AUC_{0-24}) of 68.6 and 178 $\mu\text{M}\cdot\text{hr}$ (30495 and 79128 $\text{ng}\cdot\text{h/mL}$), respectively (exposure margins 21.0 and 54.6-fold the clinical exposure at the MRHD of 75 mg/day (mean value of 1140 $\text{ng}\cdot\text{h/mL}$). Non-neoplastic test article-related changes were limited to increased incidence of brown fat accumulation, at the high dose in males and females. Dose levels were selected based on maximum tolerated doses from sub-chronic and chronic toxicity studies in mice and Executive CAC recommendation. Adequate controls were provided. FDA statistical review was conducted.

In Sprague-Dawley rats, oral administration of vibegron at 0, 3, 10, 20, or 30 mg/kg/day in males and 0, 20, 60, or 180 mg/kg/day in females for two years did not cause treatment-related malignancies. Survival was comparable among groups. NOELs for carcinogenicity were 30 and 180 mg/kg/day in males and females, respectively, with systemic exposures ($AUCs$) of 57.6 and 383 $\mu\text{M}\cdot\text{hr}$ (25605 and 170258 $\text{ng}\cdot\text{h/mL}$) in male and female rats (exposure margins of 17.7 and 117-fold clinical exposures at the MRHD of 75 mg/day (mean value of 1140 $\text{ng}\cdot\text{h/mL}$). Non-neoplastic test article-related changes were limited to increased incidence of brown fat accumulation and vacuolation of the adrenal zona glomerulosa at ≥ 10 mg/kg/day in males and at >20 mg/kg/day in females.

Dose levels were selected based on maximum tolerated doses from sub-chronic and chronic toxicity studies in rats and Executive CAC recommendation. Adequate controls were provided. FDA statistical review was conducted.

Reproductive toxicity

In fertility/general reproductive toxicity studies conducted in rats, females were treated with daily oral doses of 0, 30, 100, 300, or 1000 mg/kg/day vibegron and males were treated with daily oral doses of 0, 10, 30, or 300 mg/kg/day vibegron. The NOEL for fertility parameters in female and male rats was 300 mg/kg/day (275-fold the systemic exposure at the MRHD of 75 mg by AUC. General toxicity (body weight loss) and decreased fertility parameters were observed in female rats at 1000 mg/kg/day (1867-fold the MRHD).

In an embryo-fetal developmental toxicity study in rats, pregnant rats were treated with daily oral doses of 0, 30, 100, 300, or 1000 mg/kg/day vibegron from days 6 to 20 of gestation. At 1000 mg/kg/day vibegron (1867-fold the MRHD), maternal body weight loss and lethality were observed. At 300 mg/kg/day (267-fold the MRHD), no maternal or developmental toxicity or teratogenicity was observed.

In an embryo-fetal developmental toxicity study in rabbits, pregnant rabbits were treated with daily oral doses of 0, 30, 100, or 300 mg/kg/day vibegron from days 7 to 20 of gestation. At 300 mg/kg/day (898-fold the MRHD), decreased maternal food consumption, reduced fetal body weight, and increased incidence of delayed skeletal ossification (skull, sternebra, metacarpal, and talus-calcaneus bones) were observed. At 100 mg/kg/day (286-fold the MRHD), no maternal or developmental toxicity was observed.

In a pre- and post-natal developmental toxicity study, pregnant or lactating rats were treated with daily oral doses of 0, 30, 100, or 500 mg/kg/day vibegron from day 6 of gestation through day 20 of lactation. At 500 mg/kg/day (458-fold the MRHD), decreased maternal body weight gain was observed during gestation (along with decreased food consumption) and during lactation. Developmental toxicity was observed in F1 offspring (increased stillborn index, lethality, reduced viability on Lactation Day 4, decreased weaning index, decreased body weight and body weight gains, low physical development differentiation indices [piliation, incisor eruption, eye opening, and/or preputial separation], and effects on sensory function and reflexes) at this dose. At 100 mg/kg/day (89-fold the MRHD), decreased maternal body weight gain was observed during lactation. NOAELs were 30 mg/kg/day (9-fold the MRHD) for maternal toxicity, and 100 mg/kg/day for developmental toxicity.

12 Appendix/Attachments

Executive CAC Final Study Minutes

Date of Meeting: July 2, 2019

Committee: Karen Davis Bruno, PhD, OND IO, Chair

Tim McGovern, PhD, OND IO Member

Ron Wange, PhD, OND IO, Member

Jane Sohn, PhD, DNDP, Alternate Member

Mukesh Summan, PhD, DBRUP, Pharm/Tox Team 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 106410

Drug Name: Vibegron [RVT-901 (MK-4618)] tablets

Sponsor: Urovant Sciences GMBH

Background

Vibegron (MK-4618) is beta-3 adrenergic receptor (β 3-AR) agonist that is being developed for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Mouse Carcinogenicity Study

Vibegron was administered to CRL:CD1(ICR) mice orally daily in polyethylene glycol 400 in deionized water (10:90 w/w) at 0, 10, 30, or 90 mg/kg/day in males and 0, 15, 50, or 150 mg/kg/day in females (50 mice/sex/dose, up to a maximally tolerated dose) for 104 weeks in males and 99 weeks in females (due to excessive mortality in females). Acidified water control groups were also included.

Rat Carcinogenicity Study

Vibegron was administered to Crl:CD(SD) (Sprague-Dawley) rats orally daily in 20% (v/v) polyethylene glycol 400 in deionized water at 0, 3, 10, 20, or 30 mg/kg/day in males and 0, 20, 60, or 180 mg/kg/day in females (50 rats/sex/dose, up to a maximally tolerated dose) for 104 weeks in males and females. Acidified water control groups were also included.

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 in the 2-year CD-1 mouse study in either males or females.

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 in the 2-year rat study in either males or females.

Karen Davis Bruno, PhD
Chair, Executive CAC

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
10/20/2020 02:42:01 PM

KIMBERLY P HATFIELD
10/20/2020 03:23:17 PM
I concur with the evaluation and conclusions of Dr. McLeod-Flynn.