CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207865Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION
(Addendum to the Pharmacology/Toxicology Review, dated July 21, 2015)

Application number:	207865
Supporting document/s:	0001, 0038
Applicant's letter date:	0001 July 25, 2014; 0038 October 29, 2015
CDER stamp date:	July 25, 2014/October 29, 2015
Product:	EMEND (aprepitant) powder for suspension (125 mg)
Indication:	For the prevention of nausea and vomiting associated with moderately and highly emetogenic chemotherapy.
Applicant:	Merck Sharp & Dohme Corp.
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Sushanta Chakder, Ph.D.
Supervisor:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, MD
Project Manager:	Mary Chung, Pharm.D.

Except when specifically identified, all data and information discussed below are necessary for approval of NDA 207865, and are owned by Merck Sharp & Dohme Corporation or are data for which Merck Sharp & Dohme Corporation has obtained a written right of reference. Any information or data necessary for approval of NDA 207865 that Merck Sharp & Dohme Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Merck Sharp & Dohme Corporation does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 207865.

Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, an approval of NDA 207865 is recommended.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The draft labeling of Emend conforms to the format specified under 21CFR 201.57(c)(14) Requirements for PLLR Prescription Drug Labeling. No changes in the nonclinical sections (Sections 8 and 13) of the proposed label are recommended.

1.2 Brief Discussion of Nonclinical Findings

In support of the pediatric indication of aprepitant capsules and aprepitant oral suspension, an oral toxicity study of aprepitant was conducted in juvenile rats. In addition, a 4-week IV toxicity study was conducted in juvenile dogs. The studies were reviewed previously (dated July 21, 2015) under the original submission of NDA 207865.

In the current Amendment, the safety of the excipients, degradants, and the leachables/extractables from the primary (b) (4) container for the Emend Oral Suspension formulation was assessed. There are no novel excipients in the Emend Suspension drug product, and there are no safety concerns for any excipient at the levels used. The Applicant's proposed acceptance criteria for any degradation products at not more than (NMT) (b) (4) % for a single unspecified degradant and NMT (b) (4) % for total degradation products, are the same as those for the approved Emend Capsule product, and are acceptable. The extractable study conducted on the primary (b) (4) container identified three Class 3 solvents at levels much lower ((b) (4) ppm) than the acceptable level of 5000 ppm as per ICH Q3C, and there are no safety concerns for these extractables.

Drug Information

2.1 Drug: EMEND Powder for Oral Suspension

2.1.1 CAS Registry Number: 170729-80-3

2.1.2 Generic Name

Aprepitant

2.1.3 Code Name

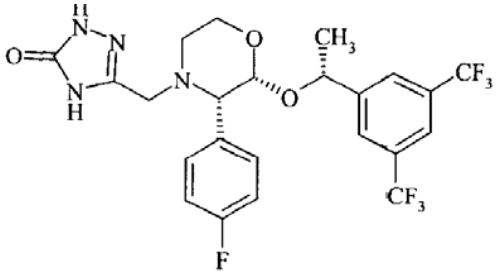
MK-0869/L-754030

2.1.4 Chemical Name

Chemical name: 5-[[(2R,3S)-2-[(1R)-1-[3, 5-bis(trifluoromethyl) phenyl] ethoxy]-1-(4-fluorophenyl)-4-morpholinyl] methyl]-1, 2-dihydro-3H-1,2,4-triazol-3-one.

2.1.5 Molecular Formula/Molecular Weight: $C_{23}H_{21}F_7N_4O_3$/534.43

2.1.6 Structure



2.1.7 Pharmacologic class

Neurokinin 1 (NK1) receptor antagonist

2.2 Relevant IND/s, NDA/s, and DMF/s

N/A

2.3 Clinical Formulation

2.3.1 Drug Formulation

Emend Oral Suspension is a pink to light pink powder containing 125 mg of (b) (4) aprepitant as the active ingredient. In addition, it contains hydroxypropyl cellulose (b) (4), sodium lauryl sulfate, sucrose, lactose (b) (4) red ferric oxide, sodium stearyl fumerate, (b) (4) with the total (b) (4) filled-weight of about (b) (4) mg. The componets of the drug formulation are listed in the Applicant's Table below.

Table 1 EMEND® for Oral Suspension Product Composition

Components	Function	Theoretical Quantity per (b) (4) (mg)
(b) (4)		
Aprepitant	Active Ingredient	125.0
Hydroxypropyl Cellulose (b) (4)	(b) (4)	(b) (4)
Sodium Lauryl Sulfate		
Sucrose		
(b) (4)		
(b) (4)		
Lactose (b) (4)		
Red Ferric Oxide		
Sodium Stearyl Fumarate		
Total Theoretical (b) (4) Fill Weight		
(b) (4)		

2.3.2 Comments on Novel Excipients

There are no novel excipients used in the Emend Suspension formulation, and there are no safety concerns for the excipients.

2.3.3 Comments on Impurities/Degradants of Concern

The Applicant set the acceptance criteria for any degradation products for Emend oral suspension at not more than (NMT) (b) (4) % for a single unspecified degradant and NMT

(b) (4)% for total degradation products. These specifications are the same as those for the approved Emend Capsule product, and are acceptable.

Table 1. Specification Established for EMEND® for Oral Suspension

Tests	Acceptance Criteria	Test Methods
Description	**Release and Shelf-Life** Pink to light pink (b) (4) powder	Visual observation.
Identity by HPLC-DAD	**Release** The wavelengths of maximum absorbance in the UV spectrum taken at the apex of the Aprepitant peak in the sample chromatogram are within (b) (4) of the wavelengths of maximum absorbance in the corresponding UV spectrum taken for the standard.	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec. 3.2.P.5.2.1
Identity by HPLC*	The retention times of the Aprepitant peak in the sample and standard chromatograms are essentially the same (within ± 2.5%).	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec. 3.2.P.5.2.1
Assay	**Release and Shelf-Life** 90.0 – 110.0% of Label Claim (b) (4)	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec. 3.2.P.5.2.1
Degradation Products	**Release and Shelf-Life** Any Unspecified: NMT (b) (4)% Total Degradation Products: NMT (b) (4)%	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec. 3.2.P.5.2.1
Uniformity of Dosage Units	**Release** Complies with the requirements of the USP <905>	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec. 3.2.P.5.2.1
Time for Constitution	**Release and Shelf-Life** Average Constitution Time (b) (4) seconds	Time for Constitution Sec.3.2.P.5.2.2
Microbial Quality	**Release** Total Aerobic Microbial Count: NMT (b) (4) cfu/g Total Combined Yeasts and Molds Count: NMT (b) (4) cfu/g Absence of *Escherichia coli* in (b) (4)	As per Ph. Eur. 2.6.12 and 2.6.13 and USP <61> and <62>
*Identification test performed after initial release of the product such as testing by an importation site and/or, packaging site.		

Container Closure System:

Each market packet contains one unit dose sachet containing EMEND for oral suspension, one mixing cup, one 5 mL oral dispenser, one Instructions for Use (IFU) and literature approved by the regulatory agencies. The sachet laminate is currently used with CDER approved products.

Primary Container Extractable Assessment: The primary (b) (4) container contains a (b) (4). The surfaces that are in contact with the product are the (b) (4). An extractable study was conducted to identify and qualify the extractables profile. (b) (4) were detected at levels of (b) (4) µg/g, respectively. These compounds are listed as Class 3 solvents in ICH Q3C Guidance, which states that the levels of these solvents at or lower than 5000 ppm (µg/g) would be

acceptable without further justification. Thus, there are no safety concerns for the extractables form the primary (b) (4) container.

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/s/

SUSHANTA K CHAKDER
12/01/2015

Addendum to Pharmacology/Toxicology Review Dated July 21, 2015 of NDA 21549 (S-025)/NDA 207865

Sponsor and Address: Merck Sharp & Dohme Corp.

Reviewer: Sushanta Chakder, Ph. D.
Supervisory Pharmacologist, DGIEP

Drug: Aprepitant (Emend) Capsules/Powder for suspension

Category: Neurokinin 1 (Substance P) Receptor Antagonist

In the finalized review dated 7/21/2015 of NDA 21549 (S-025) and NDA 207865, under Section 1.2 Brief Discussion of Nonclinical Findings, the systemic exposures ($AUC_{0\text{-}24hr}$) values for aprepitant in juvenile animals and pediatric patients were expressed as g.hr/ml. The systemic exposures should be micrograms.hr/ml (µg.hr/ml), and not g.hr/ml.

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/s/

SUSHANTA K CHAKDER
08/19/2015

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	207865
	21549 S-025
Supporting document/s:	000/025
Applicant's letter date:	NDA 207865- July 25, 2014
	NDA 21549 S-025- July 28, 2014
CDER stamp date:	July 25, 2014/July 28, 2014
Product:	EMEND (aprepitant) powder for suspension
	(125 mg)
	EMEND Capsules (80 mg, 125 mg)
Indication:	For the prevention of nausea and vomiting associated with moderately and highly emetogenic chemotherapy.
Applicant:	Merck Sharp & Dohme Corp.
Review Division:	Division of Gastroenterology and Inborn Errors
	Products (DGIEP)
Reviewer:	Sushanta Chakder, Ph.D.
Supervisor:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, MD
Project Manager:	Mary Chung, Pharm.D.

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Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, an approval of the NDA 207865 and NDA 21549-S025 is recommended.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The draft labeling of Emend generally conforms to the format specified under 21CFR 201.57(c)(14) Requirements for PLR (Physician's Labeling Rule) Prescription Drug Labeling. The following language is recommended for the nonclinical sections (Sections 8 and 13) of the label.

8.1 Pregnancy

8.1 Pregnancy

Risk Summary
There are no available data on EMEND use in pregnant women to inform the drug associated risk. In animal reproduction studies, no evidence of teratogenicity was seen in rats and rabbits with oral administration of aprepitant during organogenesis at exposures 1.6 and 1.4 times the adult human exposure at the recommended dose, respectively [see Data]. Consider the benefits and risks of EMEND when prescribing to a pregnant woman.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2- to 4% and 15- to 20%, respectively.

Data
Animal Data
Aprepitant crosses the placenta in rats and rabbits. Reproduction studies have been performed in rats at oral doses up to 1000 mg/kg twice daily (plasma AUC 0-24hr of 31.3 mcg•hr/mL, about 1.6 times the adult human exposure at the recommended dose) and in rabbits at oral doses up to 25 mg/kg/day (plasma AUC 0-24hr of 26.9 mcg•hr/mL, about 1.4 times the adult human exposure at the recommended dose) and have revealed no evidence of impaired fertility or harm to the fetus due to aprepitant. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers Lactation

Risk Summary
Lactation studies have not been conducted to assess the presence of aprepitant in human milk, the effects on the breastfed infant, or the effects on milk production. Aprepitant is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for EMEND and any potential adverse effects on the breastfed infant from EMEND or from the underlying maternal condition

Aprepitant is excreted in the milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for possible serious adverse reactions in nursing infants from aprepitant and because of the potential for tumorigenicity shown for aprepitant in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Juvenile Animal Study

A study was conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and sexual development. Rats were treated at oral doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended pediatric human dose and exposure in female rats equivalent to the pediatric human exposure) from the early postnatal period (Postnatal Day 10) through Postnatal Day 58. Slight changes in the onset of sexual maturation were observed in female and male rats (accelerated vaginal patency and delayed preputial separation up to 4 days compared to control); however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenicity studies were conducted in Sprague-Dawley rats and in CD-1 mice for 2 years. In the rat carcinogenicity studies, animals were treated with oral doses ranging from 0.05 to 1000 mg/kg twice daily. The highest dose produced a systemic exposure to aprepitant (plasma AUC 0-24hr) of 0.7 to 1.6 times the adult human exposure (AUC0-24hr = 19.6 mcg•hr/mL) at the recommended dose of 125 mg/day. Treatment with aprepitant at doses of 5 to 1000 mg/kg twice daily caused an increase in the incidences of thyroid follicular cell adenomas and carcinomas in male rats. In female rats, it produced hepatocellular adenomas at 5 to 1000 mg/kg twice daily and hepatocellular carcinomas and thyroid follicular cell adenomas at 125 to 1000 mg/kg twice daily. In the mouse carcinogenicity studies, the animals were treated with oral doses ranging from 2.5 to 2000 mg/kg/day. The highest dose produced a systemic exposure of about 2.8 to 3.6 times the adult human exposure at the recommended dose. Treatment with aprepitant produced skin fibrosarcomas at 125 and 500 mg/kg/day doses in male mice.

Mutagenesis
Aprepitant was not genotoxic in the Ames test, the human lymphoblastoid cell (TK6) mutagenesis test, the rat hepatocyte DNA strand break test, the Chinese hamster ovary (CHO) cell chromosome aberration test and the mouse micronucleus test.

Impairment of Fertility
Aprepitant did not affect the fertility or general reproductive performance of male or female rats at doses up to the maximum feasible dose of 1000 mg/kg twice daily (providing exposure in male rats lower than the exposure at the recommended adult human dose and exposure in female rats at about 1.6 times the adult human exposure).

1.2 Brief Discussion of Nonclinical Findings

Aprepitant is a selective antagonist of human substance P/neurokinin 1 (NK1) receptors. EMEND (aprepitant) capsule is currently approved as a triple therapy regimen, including a 5-HT3 receptor antagonist and a corticosteroid, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy in adult patients. In support of the original and subsequent supplemental marketing application, a comprehensive nonclinical pharmacology, pharmacokinetics, general toxicology, genotoxicity, reproductive toxicity and carcinogenicity evaluations of aprepitant and fosaprepitant were conducted. In support of the pediatric indication of aprepitant capsules and aprepitant oral suspension, an oral toxicity study of aprepitant was conducted in juvenile rats. In addition, a 4-week IV toxicity study was conducted in juvenile dogs.

In the juvenile rat toxicity study, the potential effects of aprepitant on development, growth, behavior, and reproductive performance were assessed following oral administration from Postnatal Day (PND) 10 through Postnatal Week (PNW) 9 at doses of 0, 10, 250, or 1000 mg/kg b.i.d. (0, 20, 500, and 2000 mg/kg/day) followed by a treatment-free interval through PNW 17. The high dose was the maximum feasible dose. Dose levels for the juvenile rat study were based on results from a range-finding study in which aprepitant was well tolerated at dose levels up to 1000 mg/kg b.i.d. following administration to rats from PND 10 through PNW 9 (TT #08-7605) The age of the rats at the start of the study correlates to a human age of approximately 1 month. Thus, this study provides an assessment of potential toxicities of aprepitant that supports the youngest pediatric age (6 months). Treatment-related findings included transient decreases in mean body weight gain in all drug-treated groups and slight changes in clinical pathology parameters in all groups; similar findings were also observed in the adult animal studies. There were no treatment-related effects on neurobehavioral assessments of sensory and motor functions, and learning and memory. In addition, significantly early vaginal opening in mid and high dose group females and significantly delayed preputial separation in all male groups were noted. These findings in male and female pups may not have any clinical significance. There were no treatment-related effects on mating performance, fertility, or embryonic/fetal survival and no treatment-related gross or histpathological changes in the ovaries, testes, prostate, pituitary, or adrenal glands at any time. Therefore, these findings were not considered to be adverse. Test article-related changes in the liver (increased organ weight and hepatocellular hypertrophy) and thyroid (increased organ weight and follicular cell hypertrophy) were similar to findings observed in adult rats and were considered to be secondary to hepatic enzyme induction and to be of minimal toxicological significance. Thus, the highest dose tested in the study (1000 mg/kg b.i.d.) was a well-tolerated dose in juvenile rats. Systemic exposures (AUC0-24hr) at this dose were equivalent to (female rats; 21.3 g.hr/mL) and less than (11.5 g.hr/mL; male rats) the exposure in pediatric patients (20.9 g.hr/mL; 6 months to <12 years of age) at the recommended dose.

A 4-week intravenous injection study was conducted in juvenile beagle dogs to assess

potential effects of EDTA present in the clinical formulation (TT #10-9017). Dogs (PND 14) were administered 2, 4, or 6 mg/kg/day of fosaprepitant solution containing 0.125 mg/mL EDTA once daily by intravenous injection for 4 weeks. The high dose was the maximum feasible dose. The age of the dogs corresponds to a human age of less than 1 month based on overall CNS and reproductive development. There were no treatment-related effects on electrocardiography, heart rate, blood pressure, or clinical pathology parameters. Treatment-related histopathologic changes were observed in the testes in male dogs at 6 mg/kg/day (reduced size of Leydig cells) and in the reproductive tract of female dogs at 4 mg/kg/day and 6 mg/kg/day (endometrial and myometrial hypertrophy of the uterine horns and body, hypertrophy of the cervical muscularis, and edema of the lamina propria and submucosa of the vagina). The morphology of the seminiferous epithelium and ovaries of the treated dogs was similar to control. These changes were considered to be reversible, to have no impact on further development, and to be of minimal toxicological significance. Decreased relative heart weight (approximately 23%) noted at 6 mg/kg/day was not associated with any histopathological or electrocardiographic changes. Dogs in all drug-treated groups had microscopic findings at the injection sites related to the intravenous fosaprepitant formulation. There were no findings attributable to EDTA. The 4 mg/kg dose was the NOAEL, and the 6 mg/kg/day dose was a well-tolerated in this study. Systemic exposure to aprepitant at this dose level was approximately 6-fold the exposure in pediatric patients at the recommended dose.

Aprepitant was shown to be neither mutagenic nor genotoxic in standard genotoxicity assays. In 2-year carcinogenicity studies, neoplastic changes were observed in several organs which are included in the existing label of aprepitant. However, for the CINV indication, the drug will be used intermittently only for short periods. Aprepitant had no effects on female or male fertility in rats. Aprepitant was not teratogenic nor did it cause any embryo-fetal toxicity in rats or rabbits at doses in which transplacental exposures were demonstrated. Maternal systemic exposures were approximately 1.3-fold the exposure at the recommended pediatric dose. It had no effects on pre- and post-natal development in rats. In rats, a significant lactational transfer of aprepitant was demonstrated. Thus, the toxicological profile of oral aprepitant has been studied adequately in adult and juvenile animals, and does not raise any significant safety concerns.

Drug Information

2.1 Drug: EMEND Capsules/Powder for Oral Suspension

2.1.1 CAS Registry Number: 170729-80-3

2.1.2 Generic Name

Aprepitant

2.1.3 Code Name

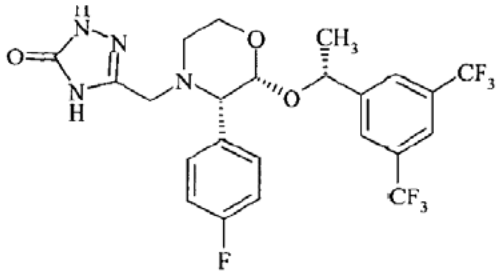
MK-0869/L-754030

2.1.4 Chemical Name

Chemical name: 5-[[(2R,3S)-2-[(1R)-1-[3, 5-bis(trifluoromethyl) phenyl] ethoxy]-1-(4-fluorophenyl)-4-morpholinyl] methyl]-1, 2-dihydro-3H-1,2,4-triazol-3-one.

2.1.5 Molecular Formula/Molecular Weight: $C_{23}H_{21}F_7N_4O_3$/534.43

2.1.6 Structure



2.1.7 Pharmacologic class

Neurokinin 1 (NK1) receptor antagonist

2.2 Relevant IND/s, NDA/s, and DMF/s

None

2.3 Clinical Formulation

2.3.1 Drug Formulation

Each capsule of Emend contains 80 or 125 mg aprepitant. In addition to the active drug, each capsule contains the following inactive ingredients: sucrose (b) (4), microcrystalline cellulose (b) (4), hydroxypropyl cellulose (b) (4), sodium lauryl sulfate (b) (4). The 125 mg capsule also contains red ferric oxide and yellow ferric oxide.

2.3.2 Comments on Novel Excipients

None

2.3.3 Comments on Impurities/Degradants of Concern

None

2.4 Proposed Clinical Population and Dosing Regimen

The applicant is seeking approval of aprepitant capsules for pediatric patients 12 years and older. For patients aged 6 months to 12 years, a powder for oral suspension formulation has been developed. Both dosage forms will be used as a triple therapy regimen, including a 5-HT3 receptor antagonist and a corticosteroid, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy in pediatric patients

2.5 Regulatory Background: The pediatric studies in patients 2 to 17 years of age for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy were deferred previously. Several meetings were held between Merck and the agency, and Merck proposed pharmacokinetic studies in 6 months to 12 year-old pediatric patients, in addition to efficacy and safety data in pediatric CINV patients 6 months to 17 years of age. In a subsequent communication, an extension of the deferral was granted until October 31, 2013.

Studies Submitted

- MK-0869: Exploratory Oral Range-Finding and Toxicokinetic Study in Juvenile Rats, Study no: TT #08-7605
- MK-0869: Oral Juvenile Toxicity Study in Rats, Study no: TT#09-7200
- A 4-week Intravenous Injection Toxicity Study of MK-0517 in the juvenile Beagle Dog, Study No. TT#10-9017

Toxicology Studies:

Study title: MK-0869: Exploratory Oral Range-Finding and Toxicokinetic Study in Juvenile Rats.

Key study findings: In this dose range finding study, the effects of MK-0869 (aprepitant) were evaluated in juvenile rats (post-natal day 10 (PND 10) to post-natal day 56 (PND 56)) following oral (gavage) administration of 5, 125, 500 or 1000 mg/kg twice daily (6 hr. apart) doses. A control group received the vehicle consisting of 20% sucrose/4% hydroxypropyl cellulose-super low/0.19% sodium lauryl sulfate). There were no treatment-related mortalities or clinical signs at any dose level. Dose-related decreases in mean body weight gains were observed between PND 10 and 14 in groups treated with 125 mg/kg b.i.d. and higher doses. No changes in body weight gains were observed during the remaining study period. Exposure to MK-0869 was not dose related, and the Cmax and AUC plateaued between 125 and 1000 mg/kg b.i.d. doses. The 1000 mg/kg b.i.d. dose was tolerated well in juvenile rats.

Study no: TT #08-7605
Volume #, and page #: Electronic submission.
Conducting laboratory and location: Merck Research Laboratories, West Point, Pennsylvania.
Date of study initiation: November 03, 2008
GLP compliance: A statement of GLP compliance was not provided.
QA report: yes ( ) no (X)
Drug, lot #, radiolabel, and % purity: MK-0869 (Aprepitant) (b) (4) Lot No. L-000754030-018W010. The batch (b) (4) was prepared with MK-0869 (Lot No. L-000754030-004H076); purity, 99.9%.

Formulation/vehicle: MK-0869 was suspended in deionized water containing 20% (w/v) sucrose, 4% (w/v) hydroxypropyl cellulose-super low and 0.19% (w/v) sodium lauryl sulfate.

Methods:
Dosing:
Species/strain: Crl: CD (SD) Sprague-Dawley rats
#/sex/group or time point (main study): A total of 15 litters (3/group) were selected for the study. On PND 0, 5 pups per sex per litter were randomly selected and foot tattooed. On PND 1, each litter was reduced to 5 pups/sex, and the pups were fostered between litters, each litter being comprised of pups originating from at least 5 different litters, with no litter-mates of the same sex. Each dosage group comprised of 15 male and 15 female pups.

Satellite groups used for toxicokinetics or recovery: None
Age: 10 days old
Weight: 20.3-30.9 g for males, 19.2-28.9 g for females.

Doses in administered units: The doses of MK-0869 used were 0, 5, 125, 500 and 1000 mg/kg b.i.d. (5 mL/kg) or 10, 250, 1000 and 2000 mg/kg/day. The sponsor stated that the doses were based on results from oral toxicity studies in adult rats, in which dose levels of 125 mg/kg/day and greater resulted in a plateau in systemic exposure of MK-0869 and its circulating drug-related substances.
Route, form, volume, and infusion rate: The doses were administered by oral gavage twice daily (at a dosing volume of 5 ml/kg) from PND 10 through 56. The second dose was administered approximately 6 hours after the first dose.

Observations and times:

Clinical signs: The animals were observed daily for clinical signs and mortality.
Body weights: The animals were weighed daily form PND 10 through 34, and twice per week thereafter.

Termination: All surviving animals were euthanized on PND 56 or 57 and discarded without further examination.

Toxicokinetic Blood Collection: Blood samples for TK analysis were collected from all surviving animals on PNW 4 and 9 at 2, 4, 6, 8, 10 and 24 hours after the first daily dose. Four rats/sex/group were bled at each time point.

Results:

Mortality: There were 11 deaths during the study as described in the Table below. The deaths were not considered treatment-related because the incidences were not dose-related. However, there was only one animal death in the control group, and all 10 mortalities observed were in treatment groups.

Missing, Found Dead, and Early Sacrifice Animals

Dose Group	Animal Number*	Postnatal Week of Death	Missing (M), Found Dead (FD), or Early Sacrifice (ES)
Control	08-5455F	5	FD
5 mg/kg b.i.d.	08-5495F	3	FD
5 mg/kg b.i.d.	08-5484M[a]	4	FD
5 mg/kg b.i.d.	08-5490M[a]	4	FD
125 mg/kg b.i.d.	08-5529F[b]	4	FD
125 mg/kg b.i.d.	08-5526M[b]	4	FD
500 mg/kg b.i.d.	08-5542M[c]	4	FD
500 mg/kg b.i.d.	08-5550M[c]	4	FD
500 mg/kg b.i.d.	08-5556M	4	FD
1000 mg/kg b.i.d.	08-5574M[d]	4	FD
1000 mg/kg b.i.d.	08-5580M[d]	9	FD

* Animals with the same superscript were fostered to the same F_0 female.

Clinical signs: No treatment-related clinical signs were observed in any group.

Body weights: There were dose and treatment-related decreases in mean body weight gain between PND 10 and 14 in groups treated with 125 mg/kg b.i.d. and higher doses, compared to the control (female/male: 22%/25%, 52%/48%, and 52%/55% at 125, 500 and 1000 mg/kg b.i.d. groups, respectively). Mean body weights were similar in all groups during the remainder of the study.

Toxicokinetics: Exposure to MK-0869 was not dose related, and the Cmax and AUC plateaued between 125 and 1000 mg/kg b.i.d. doses. The toxicokinetic findings for male and female pups are summarized in the sponsor's Table below.

Mean Plasma MK-0869 Toxicokinetic Parameters
Postnatal Week 4

	MK-0869 (mg/kg b.i.d.)			
	Females			
	5	125	500	1000
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	5.61	27.5	32.1	31.3
C_{max} (µg/mL)	0.453	2.09	2.65	2.33
T_{max} (hr)	8.0	10	8.0	8.0
	Males			
	5	125	500	1000
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	5.01	25.0	27.3	31.4
C_{max} (µg/mL)	0.402	2.29	2.30	2.44
T_{max} (hr)	10	8.0	8.0	8.0

Mean Plasma MK-0869 Toxicokinetic Parameters
Postnatal Week 9

	MK-0869 (mg/kg b.i.d.)			
	Females			
	5	125	500	1000
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	6.95	26.9	46.0	37.8
C_{max} (µg/mL)	0.572	1.50	2.48	2.22
T_{max} (hr)	8.0	10	10	10
	Males			
	5	125	500	1000
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	2.71	10.3	11.1	8.44
C_{max} (µg/mL)	0.265	0.689	0.561	0.505
T_{max} (hr)	2.0	10	10	8.0

In conclusion, in the dose-ranging study in juvenile rats, MK-0869, at doses up to 1000 mg/kg b.i.d. was tolerated well.

Study title: MK-0869: Oral Juvenile Toxicity Study in Rats.

Key study findings:

MK-0869 was administered to juvenile rats at doses of 10, 250 or 1000 mg/kg b.i.d. doses from PND 10 to PND 57. Treatment-related changes included, transient decreases in mean body weight gain between PND 10 and PND 12 (all groups), significantly early vaginal opening (mid and high dose groups), significantly delayed preputial separation (all groups), hematological changes (decreased hemoglobin, hematocrit, MCV, MCH and MCHC and increased platelet levels in mid and high dose groups), and serum chemistry changes. There were no treatment-related effects on mortality, physical signs, food consumptions, ophthalmologic evaluation, behavioral assessment (motor activity, startle habituation and passive avoidance), and reproductive performance including embryonic/fetal survival. Increased liver and thyroid weights, and dose-related hepatocellular hypertrophy and thyroid follicular cell hypertrophy were observed in males and females, related to drug metabolizing enzyme inductions, and were reversible at the end of the recovery period. Thyroid follicular cell hypertrophy and hepatocellular hypertrophy were also observed in previous toxicology studies with MK-0869 in adult rats. Based on the results of the study, the oral NOAL dose was <10 mg/kg b.i.d in juvenile rats. The 1000 mg/kg b.i.d. dose was well-tolerated in juvenile rats.

Study no: TT #09-7200
Volume #, and page #: Electronic submission.
Conducting laboratory and location: Merck Research Laboratories, West Point, Pennsylvania.
Date of study initiation: Jun 17, 2009
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: MK-0869 (Aprepitant) (b) (4) Lot No. L-000754030-018W010. The batch (b) (4) was prepared with MK-0869 (Lot No. L-000754030-004H076); purity, 99.9%.

Formulation/vehicle: MK-0869 was suspended in deionized water containing (b) (4) % (w/v) sucrose, 4% (w/v) hydroxypropyl cellulose-super low and 0.19% (w/v) sodium lauryl sulfate.

Methods:
Dosing:
Species/strain: Crl: CD (SD) Sprague-Dawley rats
#/sex/group or time point (main study): Each group consisted of 10 litters, and each litter contained 4 pups/sex. Each litter was comprised of pups from different litters.
Satellite groups used for toxicokinetics or recovery: None
Age: 10 days old
Weight: 22-32 g for males, 21-31 g for females.
Doses in administered units: The doses of MK-0869 used were 0, 10, 250 and 1000 mg/kg b.i.d. or 20, 500 and 2000 mg/kg/day. The doses were selected based on the results of an oral dose range-finding study, in which there were decreases in mean body

weight gain at 125 mg/kg b.i.d. and higher doses. A plateau in systemic exposures and Cmax values was observed between 125 and 1000 mg/kg b.i.d. doses.
Route, form, volume, and infusion rate: The doses were administered by oral gavage twice daily (at a dosing volume of 5 ml/kg) from PND 10 through 57 or 58. The second dose was administered approximately 6 hours after the first dose.

Observations and times:

Clinical signs and mortality: The animals were observed daily for clinical signs and mortality, with additional observation 1 to 5 hours after each dose.

No treatment-related clinical signs were observed in any group. There was no treatment related mortality in any group.

Body weights: The animals were weighed daily form PND 10 through 34, twice per week from SW 5 through 8, and once per week from Study Week 9 (SW 9) until study termination.
There were transient (between PND 10 and 12), treatment-related decreases in mean body weight gain in all treatment groups compared to the control (female/male: 26%/20%, 66%/64%, and 78%/77% lower than control at 10, 250 and 1000 mg/kg b.i.d. doses, respectively). The mean body weight gains from PND 12 to 34 were similar for all groups.

Food consumption: Food consumptions were measured twice weekly from SW (study week) 6 until study termination.
No treatment-related changes in food consumption were observed in any group during the study period.

Developmental Tests/Landmarks: Beginning on PND 28, vaginal opening in females was assessed every other day until developmental criterion was achieved or until PND 38. Beginning on PND 30, preputial separation in males was assessed every other day until the developmental criterion was achieved or until PND 54.

In females, there was a significant test article-related earlier appearance of vaginal opening in the 250 and 1000 mg/kg b.i.d. groups. On the first day of observation (PND 28), all females in these two groups displayed vaginal opening. No significant effects on vaginal opening were observed at the 10 mg/kg b.i.d. group, when compared to control.

In males, there were significant dose-related delays in the appearance of preputial separation in all MK-0869-treated groups (mean day of occurrence was 2, 3.2, and 4 days delayed in 10, 250 and 1000 mg/kg b.i.d. doses, respectively, compared to controls).

Ophthalmologic Examination: During SW 7 (study week 7; PNW 8), ophthalmic examinations (indirect ophthalmoscopy) were performed on 20 animals/sex in the control and high dose groups.
No treatment-related ophthalmologic changes were observed in any group.

Hematology: Blood samples for hematological examinations were collected from 7 to 10 rats/sex/group during SW 7 and again during SW 13.

There were significant treatment-related hematological changes in the 250 and 1000 mg/kg b.i.d. dose groups at the end of the treatment (SW 7) and following recovery period (SW 13). Slightly decreased hemoglobin, hematocrit, MCV, MCH and MCHC and increased platelet counts were observed in both males and females at these two dose levels. In addition, decreased leucocyte and decreased lymphocyte levels were observed in the high dose females and mid- and low dose males. Hematological changes for female and male rats are shown in the sponsor's Table below.

Test Article-Related Hematological Changes
(Percent Difference in Mean Values From Control)

		MK-0869 (mg/kg b.i.d.)					
	Study	Females			Males		
Parameter	Week	10	250	1000	10	250	1000
Hemoglobin	7	–	-6*	-9*	–	-4*	-6*
Hematocrit	7	–	-4*	-5*	–	–	–
MCV	7	–	-3*	-6*	–	-4*	-6*
	13	–	–	-6*	–	–	-5*
MCH	7	–	-6*	-9*	–	-6*	-9*
	13	–	-3*	-7*	–	–	-6*
MCHC	7	–	-2*	-3*	–	-2*	-3*
Platelets	7	–	+43*	+43*	–	+19*	+35*
Leukocytes	13	–	–	-21	–	-26*	-27*
Lymphocytes	13	–	–	-24	–	-27*	-29*
Anisocytosis	13	–	–	I	–	–	I

– = No treatment-related change.
* Statistically significant (P≤0.05).
I = Increased based on incidence and/or severity.

Clinical chemistry: Blood samples for clinical chemistry examinations were collected from 7 to 10 rats during SW 7 and during SW 13 (recovery animals).

Significant treatment-related changes in several clinical chemistry parameters were observed in both males and females at the end of treatment (SW 7) and were completely or partially reversible following the recovery period (SW 13). In females, there were dose-related increases in total protein, globulin, potassium and cholesterol levels, and decreased A/G ratio, and alkaline phosphatase levels. Similar changes were also observed in males; however, the changes were less prominent, and mostly not dose-dependent. The significant clinical chemistry changes observed in female and male rats are shown in the sponsor's Table below.

Test Article-Related Serum Biochemical Changes
(Percent Difference in Mean Values From Control)

Parameter	Study Week	MK-0869 (mg/kg b.i.d.) Females 10	Females 250	Females 1000	Males 10	Males 250	Males 1000
Glucose	7	–	–	+27*	–	–	–
Protein	7	+5*	+13*	+15*	–	+8*	+6*
Globulin	7	+20*	+35*	+40*	–	+20*	+20*
	13	–	+14*	+14*	–	–	–
A/G Ratio	7	-17*	-28*	-28*	–	-13*	-19*
	13	–	–	-12*	–	–	–
Alk. Phos.	7	-33*	-40*	-44*	-17	-23*	-29*
Potassium	7	+9	+11*	+13*	–	+10*	+10*
Calcium	7	–	I*	I*	–	I*	I*
Cholesterol	7	+32*	+119*	+133*	–	–	–
	13	+20	+29*	+35*	–	–	–
Triglycerides	7	–	–	-33*	–	-53*	-56*

– = No treatment-related change.
* Statistically significant (P≤0.05).
I = Increased based on incidence and/or severity.

Behavioral Assessment: Twenty rats/sex/group were tested sequentially in all behavioral tests as indicated below.

a. Passive Avoidance
b. Open-Field Motor Activity
c. Auditory Startle Harbituation

There were no treatment-related effects on tests of passive avoidance, auditory startle habituation, or open field motor activity.

Reproductive Assessment: Beginning in SW 11 (PNW 11/12), 20 pairs of rats from each treatment group were cohabitated to assess the effects on mating and fertility. Each female was placed in the cage of one non-sibling male from the same dose group for a maximum of 20 nights, except Female #09-3183 and #09-3171 from 250 mg/kg b.i.d group were inadvertently paired with sibling male. Two pairs in the control group, 3 pairs in the 10 mg/kg b.i.d. group, 6 pairs in the 250 mg/kg b.i.d. group and 8 pairs in the 1000 mg/kg b.i.d. group did not mate within the first 10 nights, and the male was replaced with another male of the group that had previously mated. Mated females were euthanized on GD 15, 16 or 17 and the uteri removed and pregnancy status recorded. Corpora lutea and implants were counted, and each classified as live fetus, dead fetus or resorption. If there was no evidence of pregnancy, the uterus was examined for any early implantation sites.

No significant treatment-related effects on mating performance and fertility parameters were observed in any group. The average time to mating was slightly longer for the MK-0869 treatment groups (not significant). Mean maternal body weights were comparable across groups.

Embryonic/Fetal Survival: There were no treatment-related effects of MK-0869 on embryonic/fetal survival. Mean numbers of corpora lutea, implantations, live fetuses per pregnant female, and the derived peri- and post-implantation loss values were similar to that seen in the untreated dams in the conducting laboratory.

Necropsy: Unscheduled deaths up to PND 20 were discarded without examination. Animals sacrificed after PND 20 or at study termination were anesthetized and subsequently euthanized. Routine complete necropsies were performed on up to 10 rats/sex/group at scheduled sacrifice.

There were no gross pathological changes observed at any doses.

Organ Weights: Organ weights of the following organs were recorded at necropsy.

adrenals	liver
brain	pituitary
heart	prostate
ovaries	spleen
kidneys	testes
thyroids	thymus

Treatment- and dose-related increases in the liver and thyroid weights are observed in both males and females (shown in the Table below). At final necropsy after the 5-week recovery period, slightly increased liver weight was observed in mid- and high- dose females (23% and 17% higher than controls, respectively).

Test Article-Related Postmortem Findings - Interim Necropsy

	Females			Males		
Dose, mg/kg b.i.d.	10	250	1000	10	250	1000
Number of Animals:	10	10	10	10	10	10
Organ Weights[a,b]						
Liver	+29*	+107*	+123*	+30*	+76*	+67*
Thyroid	+18	+52*	+72*	+14*	+44*	+40*
Histomorphology (Incidence)						
Liver						
Hepatocellular hypertrophy	7	10	10	7	10	10
Thyroid						
Follicular cell hypertrophy	7	10	10	7	10	10

[a] Values are the mean percent change from concurrent controls of organ weight relative to brain weight.
[b] Statistics performed by trend assessment by sexes separate; * = P≤0.05

Treatment-related increases in liver weights correlated with the increased liver size, and slight to moderate hepatocellular hypertrophy in treatment group male and female animals. Increased thyroid weight correlated with increased thyroid size and follicular cell hypertrophy in the treated animals.

Histopathology: The following tissues from the control and high dose animals at interim necropsy and from found dead rats were prepared, stained and examined microscopically. Tissues from the control and high dose groups were examined histopathologically.

Organs examined histopathologically:

brain (including cerebral cortex, subcortical white matter, basal ganglia, thalamus, hippocampus, midbrain, cerebellum, and medulla oblongata)

spinal cord (cervical)

peripheral nerve (sciatic)

eye

optic nerve

pituitary

adrenals

thyroids

parathyroids

Harderian gland

salivary gland (submandibular/sublingual)

heart

aorta

skeletal muscle (quadriceps)

small intestine (duodenum, jejunum, and ileum)

Peyer's patches

esophagus

large intestine (colon and cecum)

urinary bladder

skin (from inguinal mammary region)

mammary gland

liver

lungs

trachea

spleen

thymus

prostate

seminal vesicles

lymph nodes (mesenteric and cervical)

pancreas

testes

epididymides

uterus

cervix

ovaries

vagina

bone (femur, tibia, and femorotibial joint)

stomach (glandular and nonglandular portions)

bone marrow (in bone section)

kidneys

Parathyroids, optic nerve, trachea, Payer's patches, aorta, lymph nodes, and mammary gland (males) were evaluated when present in section. Additionally, liver and thyroids were evaluated histologically from all rats at the end of the dosing phase, and from rats in the control and the high dose groups approximately 5 weeks after cessation of dosing.
Treatment-related hepatocellular hypertrophy and thyroid follicular cell hypertrophy were observed in treated males (0/10, 7/10, 10/10 and 10/10 in control, 10 mg b.i.d, 250 mg b.i.d and 1000 mg b.i.d groups, respectively, for both organs) and females (0/10, 7/10, 10/10 and 10/10 in control, 10 mg b.i.d, 250 mg b.i.d and 1000 mg b.i.d groups, respectively, for both organs).

The severity of findings was dose-related. Hepatocellular hypertrophy was very slight in females at 10 mg/kg b.i.d., very slight to slight in males at 10 mg/kg b.i.d., and slight to moderate in males and females at 250 and 1000 mg/kg b.i.d. doses. Thyroid follicular cell hypertrophy was very slight to slight at 10 mg/kg b.i.d., and slight to moderate at 250 and 1000 mg/kg b.i.d. doses in both males and females. There were no histopathologic changes observed in any group at the end of the 5-week recovery period, indicating a reversibility of the findings after cessation of dosing..

Toxicokinetics: Blood samples for TK analysis were collected from 3 animals/sex/time point in SW 5 (PNW 6) at 2, 4, 6, 8, 10 and 24 hours after the first daily dose. The 6 hour time point was collected prior to the second dose of the day.

During SW 6, blood samples were collected from 3 rats/sex/group/time point at 2, 4, 6, 8, 10 and 24 hours after dosing. Mean systemic exposure (AUC0-24 hr) values of MK-0869 were approximately 1.9 to 2-fold higher in females than males in SW6. Mean Cmax values were approximately 1.6 to 2.7-fold higher in females when compared to males. Mean systemic exposure and mean Cmax values of MK-0869 were less than dose proportional across the dose range studied in both males and females. A plateau in mean systemic exposure and Cmax values were observed between 250 mg/kg b.i.d. and 1000 mg/kg b.i.d. in both males and females.

The toxicokinetic parameters for male and female animals are shown in the sponsor's Table below.

Mean (± SE) Plasma MK-0869 Toxicokinetic Parameters – PNW 6

	MK-0869 (mg/kg b.i.d.)[a]		
	Females		
	10	250	1000
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	13.8 ± 0.238	29.9 ± 2.53	21.3 ± 4.86
C_{max} (µg/mL)	1.16 ± 0.0752	2.74 ± 0.600	1.90 ± 0.595
T_{max} (hr)	8.0 ± NC	8.0 ± NC	8.0 ± NC
	Males		
	10	250	1000
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	7.33 ± 1.27	15.3 ± 1.97	11.5 ± 1.99
C_{max} (µg/mL)	0.742 ± 0.0373	1.02 ± 0.0928	0.854 ± 0.126
T_{max} (hr)	8.0 ± NC	8.0 ± NC	8.0 ± NC

[a] Drug concentrations in plasma from all control animals were below the LLQ of the bioanalytical method (LLQ = 0.005 µg/mL).
NC = Not Calculated.

In summary, daily oral administration of MK-0869 to juvenile rats at dose levels of 10, 250 or 1000 mg/kg b.i.d. from PND 10 to PND 57 was associated with transient decreases in mean body weight gain between PND 10 and PND 12 (all groups), significantly early vaginal opening (mid and high dose groups), significantly delayed preputial separation (all groups), hematological changes (decreased hemoglobin, hematocrit, MCV, MCH and MCHC and increased platelet levels in mid and high dose groups), and serum chemistry changes. There were no treatment-related effects on mortality, physical signs, food consumptions, ophthalmologic evaluation, behavioral assessment (motor activity, startle habituation and passive avoidance), and reproductive performance including embryonic/fetal survival. Increased liver and thyroid weights, and dose-related hepatocellular hypertrophy and thyroid follicular cell hypertrophy were observed in males and females which were reversible at the end of the recovery period. Thyroid follicular cell hypertrophy and hepatocellular hypertrophy were also observed in previous toxicology studies with MK-0869 in adult rats. Based on the results of the study, the oral NOAL dose was <10 mg/kg b.i.d in juvenile rats.

Study title: A 4-Week Intravenous Toxicity Study of MK-0517 in the Juvenile Beagle Dog

Study no.:	901958
Study report location:	Electronic Submission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 12, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Fosaprepitant dimeglumide (MK-0517/L-000758298)

Key Study Findings: Intravenous administration of fosaprepitant (MK-0517) to juvenile dogs (4 animals/sex/group) for 28 days (Day 14 pp to Day 41 pp) at dose levels of 2, 4 and 6 mg/kg/day was associated with lower body weight gains in males at 6 mg/kg/day and in females at ≥ 4 mg/kg/day. Treatment-related changes were observed in male and female reproductive organs which include reduced size of interstitial cells in testes associated with lower testicular weights at 6 mg/kg/day, and hypertrophy of the endometrium and myometrium of the uterine horns and body associated with increased uterine weights at 4 and 6 mg/kg/day. In addition, hypertrophy of the cervix and edema of the lamina propria and submucosa of the vagina were noted at these doses. At the injection sites, intimal proliferation of the cephalic veins with an increased incidence and severity of inflammation was noted at ≥ 2 mg/kg/day. The NOAEL was 4 mg/kg/day for males and 2 mg/kg/day for females. The 6 mg/kg/day dose was tolerated well in this study. It is to be noted that the control animals received the same amount of EDTA that was received by the high dose Fosaprepitant group.

Methods

Doses:	0, 2.0, 4.0 and 6.0 mg/kg/day. The sponsor stated that the 6 mL/kg (6 mg/kg) was the maximum feasible dosing volume for this age of animals and route of administration.
Frequency of dosing:	Once a day for 4 weeks (Day 14 pp until Day 41 pp)
Route of administration:	Intravenous injection into jugular and/or cephalic vein
Dose volume:	Control 6 mL/kg; 2, 4 and 6 mL/kg for 2, 4 and 6 mg/kg groups, respectively.
Formulation/Vehicle:	0.125 mg/mL EDTA (disodium EDTA dehydrate) in 0.9% Sodium Chloride Injection, USP
Species/Strain:	Beagle dog pups
Number/Sex/Group:	4 pups/sex/group
Age:	Two weeks old at the start of dosing
Weight:	717-1374 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	No major deviations

The doses for the 4-week toxicology study were based on a one week dose ranging study in juvenile beagle dogs (Study # 902280). In the one week study, four groups of pups (4 animals/group) were intravenously administered 0, 2, 4 and 6 mg/kg/day doses of MK-0517 for 1 week commencing on Day 14 post partum (pp). There was no mortality or treatment related clinical observations during the course of the study. No treatment related changes in body weight, ECG, blood pressure, clinical pathology (hematology and clinical chemistry), or macroscopic observations were observed in any group in this 1-week toxicity study. Thus, MK-0517 was well tolerated in beagle pups at IV doses up to 6 mg/kg/day for 1 week. The sponsor stated that the 6 ml/kg is the highest feasible dosing volume at this age and route of administration, and thus, 6 mg/kg/day was the highest feasible dose.

Observations and Results

Mortality:

The animals were observed twice a day for mortality and moribundity.
There was no mortality during the study.

Clinical Signs:

The animals were observed twice daily for clinical signs. More frequent observations were undertaken if considered appropriate.

There were no treatment related clinical signs at any MK-0517 doses. Blue skin at forelimbs and/or ventral cervical region and/or swollen forelimbs, ventral thoracic and/or abdominal regions were observed in all groups including the control. These effects were related to the dosing procedure, and not considered to be treatment related. Clinical observations for different groups are summarized in the sponsor's Table below.

Table 1 Summary of Clinical Observations

F1 Generation Pups
Detailed Examination

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

	Number of Animals Exhibiting Clinical Observations								
	Males				Sex	Females			
Observations	1	2	3	4	Group	1	2	3	4
Number of animals per group	4	4	4	4		4	4	4	4
Fur Staining Yellow/Abdominal	1	.	.	.		1	.	.	.
Fur Staining Yellow/Hindlimb Left	2	.	1	.		2	.	2	.
Fur Staining Yellow/Hindlimb Right	2	.	1	.		2	.	2	.
Fur Staining Yellow/Ventral Aspect Generalized	2	.	1	.		2	.	1	.
Fur Wet/ Ventral Aspect Generalized	.	.	1	.		.	.	1	.
Skin Blue/Forelimb Left	1	1	2	4		.	.	2	2
Skin Blue/Forelimb Right	.	1	2	4		.	.	2	1
Skin Blue/Ventral Cervical	4	3	2	3		3	3	3	4
Skin Scab/Ventral Cervical	.	1	.	.		.	.	.	.
Swollen Soft/Abdominal	.	.	.	.		1	.	.	.
Swollen Soft/Forelimb Left	.	.	3	2		.	2	4	2
Swollen Soft/Forelimb Right	.	.	3	2		.	2	3	2
Swollen Soft/Inguinal Left	.	.	.	.		.	2	.	.
Terminal Euthanasia	4	4	4	4		4	4	4	4

Body Weights:

Body weights of individual animals were measured daily until Day 21 pp, then twice weekly from Days 22 to 41 pp.

Decreased body weight gains were observed in males at 6 mg/kg/day and in females at 4 and 6 mg/kg/day, generally between Days 31 and 42 pp. The overall body weight gain during pp Days 14 to 42 was decreased by 18% for males at 6 mg/kg/day and by

32% and 15% for females at 4 and 6 mg/kg/day, respectively as compared with the control. The body weights of male and female pups on Days 1, 14 and 42 pp and body weight gains on Day 14 and Day 42 pp are shown in the Table below.

Table: Body weights (g) and body weight gains for male and female pups.

	Male					**Female**				
Group	Day 1	Day 14	Wt. gain Day 14	Day 42	Wt. gain Day 41	Day 1	Day 14	Wt. gain Day 14	Day 42	Wt. gain Day 41
Control	333.5	1141.8	**808.3**	2761.3	**2427.8**	315.3	1005.3	**690.0**	2635.3	**2320.0**
2 mg/kg	346.8	1253.3	**906.5**	2806.3	**2459.5**	355.3	1255.0	**899.7**	2706.5	**2351.2**
4 mg/kg	288.3	1003.0	**714.7**	2438.3	**2150.0**	290.8	899.8	**609.0**	2009.3	**1718.5**
6 mg/kg	340.0	1114.5	**774.5**	2448.5	**2108.5**	332.3	1047.3	**715.0**	2440.3	**2108.0**

Feed Consumption: Not measured.

Ophthalmoscopy: Not done

ECG and Blood Pressure:

Indirect blood pressure and ECG recordings were obtained from all treated animals during the pre-treatment period and on Days 14, 21, 28, 35 and 40 pp. Blood pressure (from tails) and ECG recordings were done immediately after dosing, and completed within 30 minutes post-dose. ECG tracings and blood pressure data were analyzed by a veterinary cardiologist.

No treatment related effects on ECG or arterial blood pressure were observed in any treatment group. Mean arterial blood pressures for different groups on Days 14, 21, 28, 35 and 40 are shown in the Tables below.

Table 4 Summary of Mean Arterial Blood Pressure (mmHg)

0 - 30 Minutes Post Dose
Females

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	Pretreatment	Day Post Partum 14	21	28	35	40
1	Mean	56.0	65.0	62.5	75.0	72.0	85.3
	SD	9.8	10.2	6.6	8.0	4.7	10.8
	N	4	4	4	4	4	4
2	Mean	63.5	60.5	65.0	85.0	80.8	78.3
	SD	7.9	2.4	5.4	5.9	6.8	9.6
	N	4	4	4	4	4	4
3	Mean	50.8	56.0	60.5	62.5 A	64.5	71.3
	SD	7.1	7.3	3.3	1.7	2.1	8.7
	N	4	4	4	4	4	4
4	Mean	54.5	56.5	74.0 A	79.8	80.0	75.0
	SD	6.4	9.5	2.9	5.4	11.5	8.3
	N	4	4	4	4	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 4 Summary of Mean Arterial Blood Pressure (mmHg)

0 - 30 Minutes Post Dose
Males

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	Pretreatment	Day Post Partum 14	21	28	35	40
1	Mean	52.3	59.0	67.0	76.8	74.0	79.8
	SD	8.5	5.5	5.2	5.9	10.1	6.6
	N	4	4	4	4	4	4
2	Mean	61.8	71.0	70.8	72.8	77.8	81.5
	SD	7.7	7.2	8.1	16.9	7.0	12.0
	N	4	4	4	4	4	4
3	Mean	49.5	60.0	59.8	66.5	58.8 A	77.3
	SD	11.1	3.4	11.0	3.9	2.9	7.0
	N	4	4	4	4	4	4
4	Mean	52.5	56.5	74.0	76.3	80.5	81.0
	SD	6.6	2.6	13.8	8.3	8.1	2.8
	N	4	4	4	4	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

The heart rate and ECG parameters for different groups of males and females at pre-treatment, Day 14 and Day 40 pp are summarized in the Tables below.

Table 5 Summary of Electrocardiography Values

Pretreatment Period
Males

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	HR bpm	PR msec	QRS msec	QT msec	QTcΨ msec
1	Mean	265.0	82.5	42.5	152.5	219.8
	SD	12.9	5.0	1.0	5.0	4.2
	N	4	4	4	4	4
2	Mean	227.5	80.0	41.0	162.5	226.3
	SD	18.9	0.0	2.0	12.6	13.0
	N	4	4	4	4	4
3	Mean	257.5	80.0	38.5	147.5	214.0
	SD	26.3	0.0	1.9	5.0	4.5
	N	4	4	4	4	4
4	Mean	227.5	80.0	39.5	160.0	223.8
	SD	22.2	0.0	3.4	0.0	2.2
	N	4	4	4	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 5 Summary of Electrocardiography Values

Pretreatment Period
Females

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	HR bpm	PR msec	QRS msec	QT msec	QTcΨ msec
1	Mean	272.5	80.0	40.0	145.0	212.8
	SD	34.0	0.0	0.0	5.8	3.4
	N	4	4	4	4	4
2	Mean	227.5	77.5	42.0	152.5	216.3
	SD	22.2	5.0	1.6	5.0	3.4
	N	4	4	4	4	4
3	Mean	255.0	77.5	41.5	150.0	216.0
	SD	37.0	5.0	3.0	8.2	6.4
	N	4	4	4	4	4
4	Mean	275.0	80.0	42.0	150.0	217.8
	SD	31.1	0.0	1.6	8.2	6.3
	N	4	4	4	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 5 Summary of Electrocardiography Values

Day 14 Post Partum - 0-30 Minutes Post Dose
Males

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	HR bpm	PR msec	QRS msec	QT msec	QTcΨ msec
1	Mean	260.0	77.5	41.0	152.5	220.0
	SD	16.3	5.0	2.0	9.6	9.1
	N	4	4	4	4	4
2	Mean	227.5	77.5	40.0	147.5	211.0
	SD	38.6	5.0	0.0	5.0	2.6
	N	4	4	4	4	4
3	Mean	242.5	80.0	40.0	157.5	222.8
	SD	15.0	0.0	3.3	5.0	4.7
	N	4	4	4	4	4
4	Mean	222.5	77.5	40.0	160.0	223.0
	SD	44.3	5.0	0.0	11.5	7.0
	N	4	4	4	4	4

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)
D - P ≤ 0.05 E - P ≤ 0.01 F - P ≤ 0.001 (Dunn)

Table 5 Summary of Electrocardiography Values

Day 14 Post Partum - 0-30 Minutes Post Dose
Females

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	HR bpm	PR msec	QRS msec	QT msec	QTcΨ msec
1	Mean	280.0	80.0	39.0	140.0	208.3
	SD	31.6	0.0	2.0	14.1	11.8
	N	4	4	4	4	4
2	Mean	237.5	75.0	39.0	150.0	214.8
	SD	15.0	5.8	2.0	0.0	1.5
	N	4	4	4	4	4
3	Mean	212.5 B	80.0	41.5	157.5	219.8
	SD	25.0	0.0	1.9	5.0	2.5
	N	4	4	4	4	4
4	Mean	242.5	80.0	40.0	147.5	212.8
	SD	25.0	0.0	0.0	5.0	3.6
	N	4	4	4	4	4

Significantly different from control group (Group 1) value: A - P ≤ 0.05 B - P ≤ 0.01 C - P ≤ 0.001 (Dunnett)

Table 5 Summary of Electrocardiography Values

Day 40 Post Partum - 0-30 Minutes Post Dose
Males

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	HR bpm	PR msec	QRS msec	QT msec	QTcΨ msec
1	Mean	212.5	80.0	41.5	152.5	214.8
	SD	22.2	0.0	1.0	5.0	5.9
	N	4	4	4	4	4
2	Mean	192.5	75.0	41.0	160.0	220.0
	SD	9.6	5.8	2.0	8.2	7.0
	N	4	4	4	4	4
3	Mean	202.5	80.0	39.5	157.5	218.5
	SD	22.2	0.0	1.9	5.0	5.0
	N	4	4	4	4	4
4	Mean	197.5	75.0	43.5	162.5	223.0
	SD	17.1	5.8	2.5	9.6	8.1
	N	4	4	4	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Table 5 Summary of Electrocardiography Values

Day 40 Post Partum - 0-30 Minutes Post Dose
Females

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	HR bpm	PR msec	QRS msec	QT msec	QTcΨ msec
1	Mean	225.0	80.0	42.0	155.0	218.5
	SD	17.3	0.0	1.6	5.8	6.6
	N	4	4	4	4	4
2	Mean	182.5	77.5	42.5	162.5	220.8
	SD	26.3	5.0	3.0	5.0	4.6
	N	4	4	4	4	4
3	Mean	197.5	77.5	40.5	165.0	223.8
	SD	55.6	5.0	1.0	20.8	12.6
	N	4	4	4	4	4
4	Mean	187.5	77.5	40.5	162.5	221.3
	SD	22.2	5.0	1.0	9.6	7.9
	N	4	4	4	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Hematology:

Blood samples for hematology, coagulation and clinical chemistry were collected via a jugular vein during the treatment period on Days 35 and 42 pp. Blood samples were analyzed for the following hematological parameters.

Red blood cell count Hemoglobin concentration Hematocrit Mean corpuscular volume Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin Reticulocyte count (absolute and percent)	Platelet count Red cell distribution width Mean platelet volume White blood cell count (total, absolute and percent differential)

There were no treatment-related changes in hematology parameters.

Coagulation: Samples of plasma were prepared for determination of activated partial thromboplastin time (APTT) and prothrombin time (PT).

On Day 35 pp, a statistically significant decrease (9.8%) in prothrombin time (PT) was observed in females at 6 mg/kg/day when compared with controls. However, by Day 42 pp, all values for PT were comparable to control values. PT and APTT for different groups on Days 35 and 42 pp are summarized in the sponsor's Tables below.

Day 35 Post Partum
Males

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	PT seconds	APTT seconds
1	Mean	6.225	14.398
	SD	0.087	1.516
	N	4	4
2	Mean	6.075	13.665
	SD	0.210	0.511
	N	4	4
3	Mean	6.400	13.933
	SD	0.640	1.174
	N	4	4
4	Mean	6.138	12.518
	SD	0.333	3.256
	N	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Day 35 Post Partum
Females

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	PT seconds	APTT seconds
1	Mean	6.400	15.115
	SD	0.524	2.808
	N	4	4
2	Mean	5.988	14.363
	SD	0.118	0.879
	N	4	4
3	Mean	5.913	14.148
	SD	0.048	0.775
	N	4	4
4	Mean	5.775 D	13.045
	SD	0.144	1.249
	N	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Day 42 Post Partum
Males

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	PT seconds	APTT seconds
1	Mean	6.050	14.648
	SD	0.071	1.873
	N	4	4
2	Mean	6.350	13.248
	SD	0.392	1.548
	N	4	4
3	Mean	6.075	13.680
	SD	0.035	0.382
	N	2	2
4	Mean	6.038	12.665
	SD	0.193	0.484
	N	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Day 42 Post Partum
Females

Group 1 - Control
Group 2 - MK-0517 2 mg/kg/day
Group 3 - MK-0517 4 mg/kg/day
Group 4 - MK-0517 6 mg/kg/day

Group	Summary Information	PT seconds	APTT seconds
1	Mean	6.200	13.237
	SD	0.433	3.271
	N	3	3
2	Mean	6.063	14.283
	SD	0.250	0.993
	N	4	4
3	Mean	6.017	14.350
	SD	0.104	1.600
	N	3	3
4	Mean	5.963	12.930
	SD	0.103	0.994
	N	4	4

Significantly different from control group (Group 1) value: A - $P \leq 0.05$ B - $P \leq 0.01$ C - $P \leq 0.001$ (Dunnett)
D - $P \leq 0.05$ E - $P \leq 0.01$ F - $P \leq 0.001$ (Dunn)

Clinical Chemistry:

Serum samples were prepared from blood samples collected via a jugular vein during the treatment period on Days 35 and 42 pp, and analyzed for clinical chemistry parameters.

No treatment-related clinical chemistry parameters were observed in any group. No differences in the levels of electrolytes (calcium, sodium, potassium, chloride) were observed between control and different treatment groups on pp Days 35 and 42. Electrolyte levels on Days 35 and 42 pp for different groups are summarized in the Table below.

PP Day 35 (Males)

Group	Ca (mg/dL)	Na (mmol/L)	K (mmol/L)	CL (mmol/L)
Control	12.08±0.39	146.0±0.8	5.348±0.377	106.5±2.5
2 mg/kg/day	11.88±0.33	145.8±1.0	5.228±0.185	108.5±2.1
4 mg/kg/day	11.55±0.37	143.8±1.0	5.780±0.417	107.3±0.5
6 mg/kg/day	11.93±0.67	144.3±1.5	5.575±0.537	106.8±0.5

PP Day 35 (Females)

Group	Ca (mg/dL)	Na (mmol/L)	K (mmol/L)	CL (mmol/L)
Control	12.20±0.37	145.3±1.5	5.723±0.318	106.5±1.3
2 mg/kg/day	11.73±0.34	144.5±1.3	5.150±0.263	107.8±1.0
4 mg/kg/day	11.45±0.26	143.5±1.3	5.548±0.692	107.0±1.4
6 mg/kg/day	11.98±0.17	143.5±0.6	5.300±0.227	106.8±1.0

PP Day 42 (Males)

Group	Ca (mg/dL)	Na (mmol/L)	K (mmol/L)	CL (mmol/L)
Control	11.55±0.19	147.3±1.5	5.493±0.051	109.5±1.3
2 mg/kg/day	11.65±0.0.21	146.0±1.4	5.763±0.349	109.3±1.7
4 mg/kg/day	11.80±0.0.54	146.5±1.3	5.418±0.517	108.5±1.7
6 mg/kg/day	11.53±0.05	144.5±0.6	5.040±0.164	108.5±0.6

PP Day 42 (Females)

Group	Ca (mg/dL)	Na (mmol/L)	K (mmol/L)	CL (mmol/L)
Control	11.48±0.21	146.5±1.7	5.315±0.286	109.8±1.0

2 mg/kg/day	11.35±0.21	145.0±0.8	5.293±0.210	109.3±0.5
4 mg/kg/day	11.25±0.29	143.8±1.0	5.153±0.478	108.0±1.2
6 mg/kg/day	11.73±0.25	144.5±1.7	5.065±0.150	108.0±1.4

Gross Pathology:

All main study animals were subjected to complete necropsy examination which included evaluation of the carcass and musculoskeletal system, all external surfaces and orifices, cranial cavity and external surfaces of the brain, and thoracic, abdominal and pelvic cavities with their associated organs and tissues.

Treatment-related gross pathology findings were limited to the injection sites of the cephalic veins in some pups at 4 and 6 mg/kg/day doses. These findings, described either as firm or thickening, correlated with microscopic findings at the injection sites.

Organ Weights:

Organs identified in the Table below weighed at necropsy.

Decreased testes weights and increased uterus weights were observed at 6 mg/kg/day. One female (#354) at 4 mg/kg/day also had increased uterus weights. Decreased heart weights were observed in both male and female pups receiving the 6 mg/kg/day dose. Changes in the testes and uterus weights correlated with microscopic findings in these organs. However, no microscopic changes in the heart or electrocardiographic changes were observed in any treatment group. Organ weight changes for different groups are summarized in the Table below.

Summary of Organ Weight Data - Scheduled Euthanasia (Day 42 *pp*) [a]

	Males			Females		
Group	2	3	4	2	3	4
Dose (mg/kg/day)	2	4	6	2	4	6
No. Animals per Group	4	4	4	4	4	4
Body weight (Final)	2	-12	-11	3	-24	-7
Heart						
Absolute value	—	—	-20	—	-31	-25
% of body weight	—	—	-10	—	-10	-20
% of brain weight	—	—	-23	—	-30	-24
Testes						
Absolute value	—	—	-46			
% of body weight	—	—	-40			
% of brain weight	—	—	-48			
Uterus						

	Males			Females		
Group	2	3	4	2	3	4
Dose (mg/kg/day)	2	4	6	2	4	6
No. Animals per Group	4	4	4	4	4	4
Absolute value				—	+33	**+265**
% of body weight				—	+75	**+307**
% of brain weight				—	+37	**+273**

[a] All values expressed as percent difference of control group means.
Values highlighted in bold were statistically significant from control group – $P \leq 0.05$; refer to data tables for actual significance levels and tests used.

Histopathology:

Tissues listed in the Table were collected from all animals, and fixed in buffered formalin for histopathology examinations. Histopathology examinations were performed on tissues from the control and high dose animals. Tissues from the low and mid dose groups with findings potentially related to the test article were also evaluated. Testes, uterus, cervix, vagina, right cephalic, left cephalic and right jugular injection sites from the mid dose animals, and the injection sites from the low dose animals were examined. Female reproductive tract (vagina, cervix and uterus) were examined from all groups.

Tissue Collection and Preservation

Tissue	Weight	Collect	Microscopic Evaluation	Comment
Animal identification	-	X	-	-
Artery, aorta	-	X	X	From thoracic segment
Bone marrow smear	-	X	X	Bone marrow smears (3) were collected and stained from the femur
Bone marrow, femur	-	X	X	Collected with bone, femur, decalcified before sectioning
Bone marrow, sternum	-	X	X	Collected with bone, sternum, decalcified before sectioning
Bone, femur	-	X	X	Collected distal end to include femoral tibial joint, decalcified before sectioning
Bone, sternum	-	X	X	Decalcified before sectioning
Brain	X	X#	X	Including cerebral cortex, subcortical white matter, basal ganglia, thalamus, hippocampus, midbrain, cerebellum, and medulla oblongata
Cervix	-	X	X	Collected with uterus.
Epididymis	-	X	X	Paired examination; Fixed in modified Davidson's fluid
Esophagus	-	X	X	-
Eye	-	X	X	Paired examination; Fixed in Davidson's fixative maintain left and right orientation
Gallbladder	-	X#	X	See liver
Gland, adrenal	X	X	X	Paired weight and examination
Gland, mammary	-	X	X	Collected with inguinal skin.; Examined only when present in the routine section of skin
Gland, parathyroid	-	X	X	Collected with thyroid; Examined only when present in the routine section of thyroid
Gland, pituitary	X	X	X	-
Gland, prostate	X	X	X	-
Gland, salivary	-	X	X	Mandibular; Only 1 required for examination
Gland, thyroid	X	X	X	Paired weight and examination; weight included parathyroid
Gross lesions/masses	-	X	X	-
Gut-associated lymphoid tissue	-	X	X	Collected with small intestine
Heart	X	X#	X	Collected with aorta
Injection sites	-	X	X	-
Kidney	X	X	X	Paired weight and examination, maintain left and right orientation
Large intestine, cecum	-	X	X	-
Large intestine, colon	-	X	X	-
Large intestine, rectum	-	X	-	-
Larynx	-	X	X	One level examined
Liver	X	X#	X	Weighed with drained gall bladder; Sample of 2 lobes collected and examined microscopically; right medial lobe and quadrate lobe (5 mm thick) left attached to gall bladder wall. Extra samples of left lateral, left medial, right medial and right lateral lobes collected for possible future use
Lung	X	X	X	Infused with 10% neutral buffered formalin after weighing; Sample of 2 lobes

Tissue	Weight	Collect	Microscopic Evaluation	Comment
Lymph node, retropharyngeal	-	X	X	Only 1 required for examination
Lymph node, mesenteric	-	X	X	-
Muscle, skeletal	-	X	X	From thigh (rectus femoris)
Nerves, optic	-	X	X	Fixed in Davidson's fixative
Nerve, sciatic	-	X	X	Only 1 required for examination
Ovary	X	X	X	Paired weight and examination
Pancreas	-	X	X	-
Skin	-	X	X	Inguinal; collected with mammary gland
Small intestine, duodenum	-	X	X	-
Small intestine, ileum	-	X	X	-
Small intestine, jejunum	-	X	X	-
Spinal cord	-	X	X	Cervical
Spleen	X	X	X	-
Stomach	-	X	X	Fundus and pylorus regions
Testis	X	X	X	Paired weight and examination; Fixed in Modified Davidson's fixative.
Thymus	X	X	X	-
Tongue	-	X	X	-
Trachea	-	X	X	-
Urinary bladder	-	X	X	-
Uterus	X	X	X	Horns and body
Vagina	-	X	X	-

X = Procedure conducted; = Not applicable.
* Collected as per Merck's specific requirements for collection and trimming of these organs.

Adequate Battery

Yes

Peer Review

Yes

Histological Findings

MK-0517-related microscopic findings were noted in the testes, female reproductive tract (uterus, cervix and vagina) and most injection sites (right and left cephalic vein and right jugular veins). Microscopic findings for the male and female reproductive tract and injection sites are summarized in the Tables below.

Summary of Microscopic Findings in the Reproductive System - Scheduled Euthanasia (Day 42 *pp*) [a]

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	2	4	6	0	2	4	6
No. Animals Examined	4	4	4	4	4	4	4	4
Testis (No. Examined)	4	0	4	4	—	—	—	—
Reduced size: interstitial cell	(0)	—	(0)	(4)	—	—	—	—
Cervix (No. Examined)	—	—	—	—	4	4	4	4
Hypertrophy: muscularis	—	—	—	—	(0)	(0)	(1)	(4)
Uterus (No. Examined)	—	—	—	—	4	4	4	4
Hypertrophy: endometrial and myometrial	—	—	—	—	(0)	(0)	(1)	(4)
Vagina(No. Examined)	—	—	—	—	4	4	4	4
Edema: lamina propria/submucosa	—	—	—	—	(0)	(0)	(1)	(4)

[a] Numbers in parentheses represent the number of animals with the finding.

Text Table 14

Summary of Microscopic Findings at the Injection Sites - Scheduled Euthanasia (Day 42 *pp*) [b]

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	2	4	6	0	2	4	6
No. Animals Examined	4	4	4	4	4	4	4	4
Cephalic Veins (No. Examined) [a]	8	8	8	8	8	8	8	8
Proliferation: intimal	(0)	(6)	(7)	(7)	(0)	(6)	(7)	(5)
Minimal	—	3	3	2	—	2	2	2
Slight	—	3	3	5	—	4	3	2
Moderate	—	—	1	—	—	—	2	1
Inflammation	(5)	(6)	(8)	(8)	(5)	(7)	(8)	(6)
Minimal	3	1	2	—	2	1	—	—
Slight	2	5	3	6	2	3	4	5
Moderate	—	—	3	2	1	3	4	1
Jugular vein, right (No. Examined)	4	4	4	4	4	4	4	4
Proliferation: intimal	(0)	(1)	(0)	(1)	(0)	(0)	(0)	(0)
Minimal	—	1	—	1	—	—	—	—

[a] Sum of observations made from right and left cephalic veins.
[b] Numbers in parentheses represent the number of animals with the finding.

In male pups treated with the 6 mg/kg/day dose, the interstitial (Leydig) cells had minimal to slight reduction in size with more compact connective tissue surrounding the seminiferous tubules when compared with controls. This finding correlated with decreased testicular weight observed at 6 mg/kg/day.

Changes in the female reproductive tract include slight to moderate hypertrophy of the endometrium (both stroma and endometrial glands) and of the myometrium within the horns and body of the uterus, observed in females at 6 mg/kg/day and in one female at 4 mg/kg/day. These observations were associated with slight to moderate hypertrophy of the muscularis of the cervix and with minimal to moderate edema of the lamina propria and submucosa of the vagina. These findings correlated with the increased uterine weights observed at ≥ 4 mg/kg/day.

Characteristic changes in the affected veins at the injection sites included minimal to moderate intimal proliferation within cephalic veins for a majority of pups treated at ≥ 2 mg/kg/day. There was no apparent dose response for the intimal change, based on bilateral evaluations. Inflammation was observed within and adjacent to the injected veins in all groups, but with an increased incidence and severity for the cephalic veins at ≥ 2 mg/kg/day. The inflammation generally involved the vascular intima and media with an infiltration of neutrophils and accumulation of mononuclear inflammatory cells admixed with scattered neutrophils, fibrin and/or fibrosis in the perivascular space.

Toxicokinetics:

Blood samples for toxicokinetic analysis were collected on Day 41 pp at 2, 5, 15, and 30 min, and 1, 4, 8 and 24 hours after dosing. Plasma samples were analyzed for concentrations of MK-0517 and MK-0869 (active metabolite) by LC MS/MS using a validated analytical procedure.

Plasma concentrations of MK-0517 declined rapidly after administration and were generally only quantifiable up to 5 minutes postdose, and therefore systemic exposure (AUC) could not be calculated except for two animals (Animal Nos. 352 and 452). The Cmax increased with increasing dose level in an approximately dose-proportional manner. The estimated $T_{1/2}$ for Animal No. 352 was 0.0501 h. The $T_{1/2}$ could not be calculated for Animal No. 452. No apparent gender differences in systemic exposure of MK-0517 were observed.

The formation of the active drug (MK-0869) was rapid, occurring at 2 – 5 minutes post-dose. The concentration of MK-0869 declined slowly and was detectable up to 24 hours after dosing. The exposure of MK-0869 was dose-proportional between 2 and 4 mg/kg/day dose, but was more than dose-proportional between 4 and 6 mg/kg/day. The estimated $T_{1/2}$ at 2 and 4 mg/kg/day ranged from 7.78 to 10.3 hours. No gender differences in the systemic exposure were observed at any dose level. Rapid conversion of MK-0517 to MK-0869 was observed, and the ratios of drug to pro-drug were 2.3 or greater. Plasma TK parameters for male and female animals on Day 41 pp are summarized in the sponsor's Table below.

Mean Plasma MK-0517 Concentrations (µg/mL) in Dogs
Following Intravenous Administration of MK-0517 - Day 41 (pp)

Time point postdose	MK-0517 (mg/kg/day)		
	Females		
	2	4	6
2 min (µg/mL)	0.958	1.23	3.51
5 min (µg/mL)	0.0224	0.0874	0.147
	Males		
	2	4	6
2 min (µg/mL)	1.16	1.96	2.83
5 min (µg/mL)	0.0507	0.0597	0.0619
Values are the mean			

Mean Plasma MK-0869 Toxicokinetic Parameters in Dogs
Following Intravenous Administration of MK-0517 - Day 41 (pp)

	MK-0517 (mg/kg/day)		
	Females		
	2	4	6
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	15.9	39.3	106
C_{max} (µg/mL)	2.23	5.30	10
T_{max} (hr)	0.0333	0.0333	0.0833
	Males		
	2	4	6
$AUC_{0\text{-}24\ hr}$ (µg•hr/mL)	19.7	35.8	132
C_{max} (µg/mL)	2.66	4.60	10.5
T_{max} (hr)	0.0333	0.0583	0.0833
Values are the mean			

In summary, Intravenous administration of fosaprepitant (MK-0517) to juvenile beagle dogs for 28 days (Day 14 pp to Day 41 pp) at 0, 2, 4 and 6 mg/kg/day doses resulted in lower body weight gains in males at 6 mg/kg/day and in females at ≥ 4 mg/kg/day. Treatment-related microscopic changes included reduced size of interstitial cells in testes associated with lower testicular weights at 6 mg/kg/day, and hypertrophy of the endometrium and myometrium of the uterine horns and body associated with increased uterine weights at 4 and 6 mg/kg/day. In addition, hypertrophy of the cervix and edema of the lamina propria and submucosa of the vagina were noted at these doses. At the injection sites, intimal proliferation of the cephalic veins with an increased incidence and severity of inflammation was noted at ≥ 2 mg/kg/day. Rapid conversion of MK-0517 to the active drug MK-0869 was observed at all dose levels. The NOAEL was 4 mg/kg/day for males and 2 mg/kg/day for females based on adverse effects on the reproductive organs. The 6 mg/kg IV dose was well-tolerated in juvenile dogs.

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07/21/2015