CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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 REVIEW AND EVALUATION

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Applicant's letter date:	SDN 01 - September 5, 2014
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	SDN 14 – March 13, 2015
Product:	Rolapitant tablets
Indication:	Prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy
Applicant:	Tesaro, Inc.
Review Division:	Division of Gastroenterology and Inborn Errors Products
Reviewer:	Tracy Behrsing, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Mary Chung, PharmD

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application is for descriptive purposes only and is not relied upon for approval of NDA 206500.

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1 Executive Summary

1.1 Introduction

Tesaro, Inc. seeks to market rolapitant, a neurokinin-1 (NK-1) receptor antagonist, for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy in adult patients. Rolapitant is a new molecular entity (NME).

1.2 Brief Discussion of Nonclinical Findings

In support of the NDA, the Applicant conducted pharmacology, pharmacokinetics/ADME/toxicokinetics, general toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicology, and special toxicology studies with rolapitant.

Comparison of rolapitant exposures in animals relative to humans is complicated in this case because of differences in half-lives. The half-lives of rolapitant and its major metabolite (SCH 720881) are markedly longer in humans (169-183 h for rolapitant) than in Cynomolgus monkeys and rats (6-8 h for rolapitant). Although AUC data are available, comparison of steady-state AUC_{0-24h} values in animals to the $AUC_{0-\infty}$ value produced by a single dose in humans per treatment cycle does not reflect the cumulative total exposure in animals relative to exposure in humans over the same timeframe. Given these complexities, exposure multiples estimated on a body surface area basis will be used for exposure comparison in the label.

In repeat-dose oral toxicology studies in rodents with rolapitant hydrochloride, the liver and thyroid were identified as target organs. While a no observed adverse effect level (NOAEL) was not established in the 26-week oral toxicology study in rats, findings in the liver (e.g., hepatocellular hypertrophy) and secondary effects on the thyroid (e.g. follicular cell hypertrophy) appear to be related to the induction of hepatic enzymes by the drug and may not be relevant to humans. While incidences of convulsions were observed after acute and/or subchronic administration of rolapitant hydrochloride, convulsions did not occur in the chronic oral toxicity studies in rats and monkeys at doses that are several fold higher than the clinical dose. In the 26-week oral toxicity study in rats there were no incidences of convulsions at the highest dose tested (100 mg/kg/day rolapitant hydrochloride; equivalent to 90 mg/kg/day rolapitant free base). This dose (90 mg/kg/day) is 4.9-times the recommended human dose (180 mg rolapitant, 3 mg/kg for a 60 kg adult) on a body surface area basis. In the 39-week oral toxicity study in monkeys, the NOAEL was the highest dose tested (30 mg/kg/day rolapitant hydrochloride; equivalent to 27 mg/kg/day rolapitant free base). This dose is approximately 2.9 times the recommended human dose on a body surface area basis.

Rolapitant hydrochloride was negative in the Ames test, chromosome aberration assay, and mouse bone marrow micronucleus test. Metabolite SCH 720881 was also negative in the Ames test and chromosome aberration test. In 2-year oral carcinogenicity studies

in mice and rats, there were no statistically significant, treatment-related neoplastic findings at rolapitant hydrochloride doses up to 150 and 100 mg/kg/day, respectively (equivalent to 135 and 90 mg/kg/day rolapitant free base, respectively).

In an oral fertility and early embryonic development study in female rats, there was a transient decrease in body weight gain in maternal animals and increases in pre- and post-implantation losses at a rolapitant hydrochloride dose of 10 mg/kg/day (equivalent to 9 mg/kg/day rolapitant free base). At rolapitant hydrochloride doses ≥5 mg/kg/day (equivalent to ≥4.5 mg/kg/day rolapitant free base), there was a slight decrease in the number of corpora lutea and implantation sites. In an oral fertility and early embryonic development study, male mating and fertility indices and early embryonic development were not affected at up to 100 mg/kg/day rolapitant hydrochloride (equivalent to 90 mg/kg/day rolapitant free base). In embryofetal development studies of rolapitant hydrochloride administered by oral gavage to rats and rabbits, there were no significant treatment-related effects on reproductive parameters or fetal external, visceral, or skeletal malformations at doses up to 25 and 30 mg/kg/day, respectively (equivalent to up to 22.5 and 27 mg/kg/day rolapitant free base, respectively). In an oral pre- and postnatal development study in rats, the NOAEL for F0 maternal toxicity was 10 mg/kg/day rolapitant hydrochloride (equivalent to 9 mg/kg/day rolapitant free base) based on mortality/moribund condition, total litter loss, prolonged parturition, decreased gestation length, increased number of unaccounted-for implantation sites and effects on body weights and food consumption at 25 mg/kg/day. The NOAEL for offspring (F1) effects was 2.5 mg/kg/day rolapitant hydrochloride (equivalent to 2.25 mg/kg/day rolapitant free base) based on decreased postnatal survival and body weight gain at 25 mg/kg/day, decreased pup body weights at 10 and 25 mg/kg/day, and effects on memory at 10 mg/kg/day. The NOAEL for the F2 generation was ≥10 mg/kg/day rolapitant hydrochloride (equivalent to ≥9 mg/kg/day rolapitant free base).

1.3 Recommendations

1.3.1 Approvability: From a nonclinical perspective, the NDA is approvable.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling

In a February 25, 2015 Information Request, the Applicant was encouraged to revise the originally proposed text for sections 8.1 (b) (4) in the Use in Specific Populations section of the prescribing information per the Pregnancy and Lactation Rule (PLLR). In response to the Information Request, the Applicant submitted proposed revised text for sections 8.1 and 8.2 on March 13, 2015. In addition, proposed revised text for section 13 was also submitted on March 13, 2015.

Applicant's Proposed Version:

8.1 Pregnancy

Risk Summary

(b) (4)

Data

Animal Data

The potential embryo-fetal toxicity of rolapitant hydrochloride was assessed in pregnant rats administered oral doses of up to (b) (4) mg/kg/day throughout organogenesis. Rats administered (b) (4) mg/kg/day exhibited evidence of maternal toxicity including decreased body weight gain and/or body weight loss and a concomitant decrease in food consumption during the first week of dosing. No teratogenic or embryo-fetal effects were observed at up to (b) (4) mg/kg/day (b) (4) In rabbits administered rolapitant hydrochloride throughout the period of organogenesis, oral doses up to (b) (4) mg/kg/day (b) (4) were without effects on the developing fetus.

The pre- and post-natal developmental effects of rolapitant hydrochloride were assessed in rats administered oral doses (b) (4) mg/kg/day during the periods

of organogenesis and lactation. Maternal toxicity was evident based on prolonged parturition, decreased (b) (4)

(b) (4)

(b) (4)

Recommended Version:

8.1 Pregnancy

Risk Summary

(b) (4)

(b) (4)

Data

Animal Data

The potential embryo-fetal toxicity of rolapitant hydrochloride was assessed in pregnant rats administered oral doses equivalent to up to 22.5 mg/kg/day rolapitant free base throughout organogenesis. Rats administered doses equivalent to 13.5 or 22.5 mg/kg/day rolapitant free base exhibited evidence of maternal toxicity including decreased body weight gain and/or body weight loss and a concomitant decrease in food consumption during the first week of dosing. No teratogenic or embryo-fetal effects were observed at doses equivalent to up to 22.5 mg/kg/day rolapitant free base (approximately 1.2 times the recommended human dose on a body surface area basis). In rabbits administered rolapitant hydrochloride throughout the period of organogenesis, oral doses equivalent to up to 27 mg/kg/day rolapitant free base (approximately 2.9 times the recommended human dose on a body surface area basis) were without effects on the developing fetus.

The pre- and postnatal developmental effects of rolapitant hydrochloride were assessed in rats administered oral doses equivalent to 2.25, 9 or 22.5 mg/kg/day rolapitant free base during the periods of organogenesis and lactation. Maternal toxicity was evident based on mortality/moribund condition, decreased body weight and food consumption, total litter loss, prolonged parturition, decreased length of gestation, and increased number of unaccounted for implantation sites at a dose equivalent to 22.5 mg/kg/day free base (approximately 1.2 times the recommended human dose on a body surface area basis). Effects on offspring at this dose included decreased postnatal survival, and decreased body weights and body weight gain, and may be related to the maternal toxicity observed. At a maternal dose equivalent to 9 mg/kg/day rolapitant free base (approximately 0.5 times the recommended human dose on a body surface area basis), there was a decrease in memory in female pups in a maze test and a decrease in pup body weight.

Applicant's Proposed Version:

8.2 Lactation

Risk Summary

(b) (4)

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRAND NAME and any potential adverse effects on the breastfed (b) (4) from BRAND NAME or from the underlying maternal condition or the use of concomitant chemotherapy.

Data

(b) (4)

Radioactivity from labeled [^{14}C] rolapitant hydrochloride was transferred into milk of lactating rats following a single oral dose of (b) (4) mg/kg. Maximum radioactivity in milk was observed at 12 hr post-dose.

Based on average daily consumption of milk (2 mL/day) and the maximum milk radioactivity determined, pup exposure is expected to be 0.32% of the orally administered dose. (b) (4)

(b) (4)

(b) (4)

Recommended Version:

8.2 Lactation

Risk Summary

(b) (4)

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRAND NAME and any potential adverse effects on

the breastfed (b) (4) from BRAND NAME or from the underlying maternal condition or the use of concomitant chemotherapy.

Data

Animal Data

Radioactivity from labeled [^{14}C] rolapitant hydrochloride was transferred into milk of lactating rats following a single oral dose equivalent to 22.5 mg/kg rolapitant free base, and the maximum radioactivity in milk was observed at 12 hr post-dose. The mean milk (b) (4) plasma radioactivity concentration ratios in dams at 1 to 48 hr post-dose ranged from 1.24 to 3.25.

Based on average daily consumption of milk (2 mL/day) and the maximum milk radioactivity determined, pup exposure is expected to be 0.32% of the orally administered dose.

Applicant's Proposed Version

10. Overdosage

There are no data on overdose with BRAND NAME. (b) (4)

There is no antidote for BRAND NAME overdose (b) (4)

Evaluation

The Division commented in the 74 Day letter to the Applicant that the Overdosage section must be based on human overdosage data. If human data are unavailable, appropriate animal data and in vitro data regarding overdosage may be included. In the absence of human overdose data, acute toxicity findings in rats, mice and monkeys should be included in this section.

Recommended Version:

There are no data on overdose with BRAND NAME. Single oral doses of rolapitant hydrochloride equivalent to 450 mg/kg rolapitant free base in rats, 270 mg/kg rolapitant free base in mice, and 90 mg/kg rolapitant free base in monkeys (about 24, 7, and 10 times the recommended human dose, respectively, based on body surface area) were lethal or produced moribund condition. Primary clinical signs of acute toxicity in rats were hunched appearance, hypoactivity, tremors, ataxia, abnormal stool, and dehydration. Tremors, convulsions, and pale extremities were observed in mice. In monkeys, primary clinical signs of acute toxicity were hunched appearance, hypoactivity, loose or soft stool, emesis, and convulsions.

There is no antidote for BRAND NAME overdose. Discontinue BRAND NAME in the event of overdose, and institute general supportive measures and close observation.

Applicant's Proposed Version

12.1 Mechanism of Action

Rolapitant is a (b) (4) selective and competitive (b) (4) antagonist. Rolapitant does not have significant affinity for the NK2 or NK3 receptors or for a battery of other receptors, transporters, enzymes and ion channels.

Rolapitant is also active in animal models of chemotherapy-induced emesis. (b) (4)
(b) (4)

(b) (4)

Evaluation:

Detailed information on efficacy in animals should not be included in Section 12.1.

Recommended Version:

Rolapitant is a selective and competitive (b) (4) Rolapitant does not have significant affinity for the NK2 or NK3 receptors or for a battery of other receptors, transporters, enzymes and ion channels. Rolapitant is also active in animal models of chemotherapy-induced emesis.

(b) (4)

Applicant's Proposed Version

13. Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Rolapitant hydrochloride was not genotoxic in an Ames test, a human peripheral blood lymphocyte chromosome aberration test, and a mouse micronucleus test.

(b) (4)

(b) (4) Rolapitant hydrochloride did not affect the fertility or general reproductive performance of male rats at doses up to (b) (4) mg/kg/day (b) (4)

Evaluation:

Exposure multiples estimated on a body surface area basis should be used for exposure comparison, and doses should be expressed as rolapitant free base for consistency with other sections of the label. In addition, per the ECAC conclusions (ECAC meeting minutes dated May 2, 2012), there were no significant drug-related neoplastic findings in mice or rats. Thus, incidences of thyroid follicular cell adenomas, thyroid follicular cell carcinomas, and benign pheochromocytomas of the adrenal gland in rats do not need to be included in the label. Finally, decreases in corpora lutea and implantation sites observed in the fertility and early embryonic development study in females should be included.

Recommended Version:

13. Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential of rolapitant hydrochloride was assessed in 2-year carcinogenicity studies in CD-1 mice and Sprague-Dawley rats. In mice, there were no drug-related neoplastic findings at doses equivalent to up to 135 mg/kg/day rolapitant free base (approximately 3.6 times the recommended human dose on a body surface area basis). In rats, there were no drug-related neoplastic findings at doses equivalent to up to 90 mg/kg/day rolapitant free base (approximately 4.9 times the recommended human dose on a body surface area basis).

Rolapitant hydrochloride was not genotoxic in an Ames test, a human peripheral blood lymphocyte chromosome aberration test, and a mouse micronucleus test.

In a fertility and early embryonic development study in female rats, rolapitant hydrochloride at an oral dose equivalent to 9 mg/kg/day free base (approximately 0.5 times the recommended human dose on a body surface area basis) (b) (4)

At a dose equivalent to 4.5 mg/kg/day free base (approximately 0.2 times the recommended human dose on a body surface area basis), there were slight decreases

in the number of corpora lutea and implantation sites. Rolapitant hydrochloride did not affect the fertility or general reproductive performance of male rats at doses equivalent to up to 90 mg/kg/day rolapitant free base (approximately 4.9 times the recommended human dose on a body surface area basis).

2 Drug Information

2.1 Drug

Rolapitant

CAS Registry Number

Rolapitant hydrochloride monohydrate: 914462-92-3
Rolapitant free base: 552292-08-7

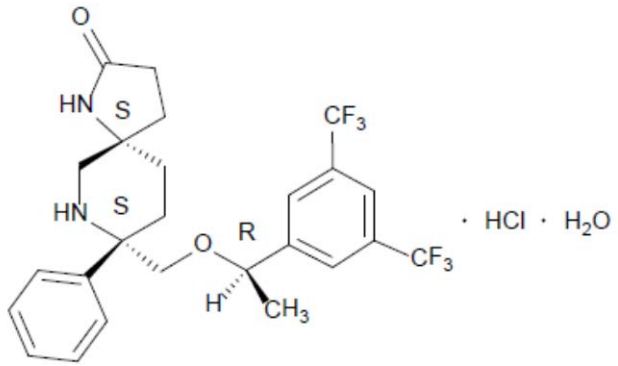
Generic Name
Rolapitant hydrochloride

Code Name
SCH 619734, (b) (4)

Chemical Name
(5S,8S)-8-[[(1R)-1-[3,5 Bis(trifluoromethyl phenyl]ethoxy]methyl]-8-phenyl-1,7-diazaspiro[4.5]decan-2-one monohydrochloride monohydrate

Molecular Formula/Molecular Weight
$C_{25}H_{29}ClF_6N_2O_3$ or $C_{25}H_{26}F6N_2O_2 \cdot HCl \cdot H_2O$ / 554.95

Structure or Biochemical Description:
Rolapitant hydrochloride monohydrate contains a spirolactam ring structure with three chiral centers in S,S,R configuration. The Applicant's figure below shows the chemical structure.



Pharmacologic Class
Substance P/Neurokinin-1 Receptor Antagonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 72,754
IND (b) (4)
DMF (b) (4)
DMF
DMF

2.3 Drug Formulation

The drug product is an immediate release, film-coated blue tablet containing 90 mg of rolapitant (equivalent to 100 mg rolapitant hydrochloride) (b) (4) The following tables from the Applicant's submission show the composition of the drug product and film coatings.

Table 1: Composition of Rolapitant 100 mg Coated Tablets

Component	Quality Grade	Function	Unit Formula (mg/unit)
			(b) (4)
Drug Substance (b) (4)	Internal specifications	Active	100.0[a]
Lactose Monohydrate	USP/NF, Ph Eur		(b) (4)
Pregelatinized Starch	USP/NF, Ph Eur		
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur		
Povidone (b) (4)	USP, Ph Eur		
Croscarmellose Sodium	USP/NF, Ph Eur		
			(b) (4)
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur		(b) (4)
Croscarmellose Sodium	USP/NF, Ph Eur		
Colloidal silicon dioxide	USP/NF, Ph Eur		
Magnesium Stearate	USP/NF, Ph Eur		
Film Coating			
(b) (4) Blue	USP/NF, Ph Eur[d]		(b) (4)
Clear	USP/NF, Ph Eur		
Total Tablet Weight			520.0

(b) (4)

2.4 Comments on Novel Excipients

All [redacted] excipients meet current United States Pharmacopeia/National Formulary (USP/NF) and Pharmacopeia Europa (Ph Eur) standards. The only non-compendial excipients used in the drug formulation are [redacted] Blue [redacted] Clear [redacted] A letter of authorization to refer to the [redacted] was provided.

Each of the excipients [with the exception of [redacted] Clear [redacted] Blue [redacted], are listed in the FDA Inactive Ingredients Database (IID) and are used [redacted]

Although [redacted] Blue [redacted] is not listed in the database, several other [redacted] Blue coatings are listed. Furthermore, the components of the [redacted] Blue coating are very commonly used in pharmaceuticals and the drug product reviewer indicated there is no concern for [redacted] Blue from a CMC perspective. The list of ingredients in the Opadry coating materials is shown in the Applicant's table below.

Table 2: List of Ingredients in [redacted] Blue and [redacted] Clear Coating Systems

Coating Material	Components
[redacted] Blue	Polyvinyl Alcohol (USP/NF, Ph. Eur.) Titanium Dioxide (USP/NF, Ph. Eur.) Polyethylene Glycol (USP/NF, Ph. Eur.) Talc (USP/NF, Ph. Eur.) FD&C Blue #2/Indigo Carmine Lake (complies with CFR title 21 part 74.102 and EC directive 2008/128/EC)
[redacted] Clear	Polyvinyl Alcohol [redacted] (USP/NF, Ph. Eur.) Talc (USP/NF, Ph. Eur.) Polyethylene Glycol (USP/NF, Ph. Eur.) Polysorbate 80 (USP/NF, Ph. Eur.).

2.5 Comments on Impurities/Degradants of Concern

Drug Substance

During development of the drug substance, [redacted] manufacturing processes have been used: [redacted] The proposed specifications are shown in the Applicant's table below.

Table 1: Specifications for Rolapitant Hydrochloride Monohydrate

Test	Type	Analytical Method	Acceptance Criteria
Description	Visual	AA.TG018	White to off-white powder
Identification	IR	USP <197K> AA.001832	Conforms to reference standard spectrum
	HPLC	CR.LC4265	Mean retention time of the main peak is within (b) (4)% of the mean retention time for the reference standard.
Chloride Identity	Visual Precipitation	AA.001838	Conforms
Chloride Assay	Titration	AA.TM4184	(b) (4)% of the theoretical content
Assay	HPLC	CR.LC4265	(b) (4)
Individual Unspecified Related Impurities			NMT (b) (4)% w/w
Total Impurities			NMT (b) (4)% w/w
(b) (4) Impurities	HPLC	(b) (4)	(b) (4) Impurity / NMT (%w/w)
		CR.LC4500	(b) (4)
		CR.LC4500	
		CR.LC4500	
		CR.LC4500	
		CR.LC4501	
		CR.LC4501	
		CR.LC4501	
Residual Solvents	HS-GC	CR.GC4205	
Solid Form Confirmation	(b) (4)	USP <941>, AA.RX4063	
Heavy Metals	(b) (4)	USP <231> Method II AA.001935	

Table 1: Specifications for Rolapitant Hydrochloride Monohydrate (Continued)

Test	Type	Analytical Method	Acceptance Criteria
Residue on Ignition	(b) (4)	USP <281> AA.001830	NMT (b) (4)% w/w
Particle Size	(b) (4)	AA.PS4167	D_{50}: (b) (4)µm D_{90}: NMT (b) (4)µm
Water Content	Titration	AA.TM4184	(b) (4)% w/w to (b) (4)% w/w

Unspecified and Specified Impurities. The proposed specifications for individual unspecified impurities (NMT (b) (4)%) and chiral impurities (NMT (b) (4)%) meet the ICH Q3A Impurities in New Drug Substances identification and qualification thresholds,

respectively, for drug substances with a maximum daily dose ≤ (b) (4) g/day. Thus, the proposed specifications are acceptable.

Elemental Impurities. (b) (4)

The proposed specification for heavy metals in the drug substance is NMT (b) (4) ppm. (b) (4)

The ICH Q3D (*Current Step 4 Version,* December 2014) oral permitted daily exposures (PDEs) for (b) (4) µg/day. The lowest oral PDE among the 24 elemental impurities addressed in ICH Q3D is 5 µg/day (for cadmium and lead). Thus, the proposed specification is acceptable.

Residual Solvents. The proposed specification for (b) (4) is within the concentration limit in ICH Q3C Impurities: Residual Solvents, and thus is acceptable.

Potential Genotoxic Impurities. The Applicant developed an assessment and control strategy following ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals. The threshold of toxicological concern (TTC) for potential genotoxic impurities (PGIs) was calculated by the Applicant as (b) (4) ppm based upon a series of assumptions. Rolapitant is administered as a single dose of 200 mg rolapitant hydrochloride (equivalent to 180 mg rolapitant free base) per chemotherapy cycle. Complete chemotherapy treatment may require up to 6 cycles, spaced 2 to 4 weeks apart, resulting in up to 6 doses of rolapitant over a 3 to 6 month period. It was considered unlikely that a patient would require more than 5 complete cancer treatments of 6 cycles each over their lifetime (i.e., a total of 30 days or doses). In accordance with Table 3 of ICH M7, the acceptable total daily intake for multiple impurities is 120 µg/day for treatment durations ≤1 month. Thus, the TTC was calculated as (b) (4) ppm (120 µg/day / (b) (4) g = (b) (4) µg/g).

Using two complementary computational toxicology quantitative structure activity relationship (QSAR) methods [DEREK (expert rule-based) and Leadscope Genotox Database (statistical- and expert rule-based)], the Applicant identified (b) (4)

Table 5: Summary of Identified (b) (4) and Proposed Control Strategy

Category	Name	Structure	Step of Origin	Proposed Control Strategy
(b) (4)				

The Applicant identified (b) (4) Levels of these PGIs were controlled through process controls, development of analytical methods for batch analysis, and a spiking study to (b) (4) Batch analysis data for the (b) (4) were all below the level of quantitation (b) (4) pm). The drug substance reviewer indicated that there are no concerns with respect to potential genotoxic impurities.

Drug Product:
The proposed drug product specification for individual unspecified impurities is NMT (b) (4)% w/w, which meets the ICH Q3B(R2) Impurities in New Drug Products identification threshold for products with maximum daily doses >10 mg to 2 g. The specification for total impurities is NMT (b) (4)%.

2.6 Proposed Clinical Population and Dosing Regimen

Rolapitant is indicated for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of (b) (4) emetogenic cancer chemotherapy (b) (4)

(b) (4)

The recommended dosage is 180 mg rolapitant (equivalent to 200 mg rolapitant hydrochloride) given orally 1-2 h prior to the initiation of chemotherapy. Rolapitant should be administered in conjunction with a corticosteroid (Dexamethasone) and a 5-HT_3 receptor antagonist. Rolapitant can be administered prior to the initiation of each chemotherapy cycle, but at no less than 2 week intervals.

2.7 Regulatory Background

- A Type B meeting (End of Phase 2; IND 72,754) was held on April 5, 2010. A Type C meeting (End of Phase 2 meeting follow-up) was held on July 5, 2011. A separate CMC EOP2 meeting was held on January 28, 2013.
- A Type B (Pre-NDA) meeting was held on July 2, 2014 under IND 72,754. The Division concurred that the nonclinical program appeared to be adequate to support the NDA for the proposed indication.

3 Studies Submitted

3.1 Studies Reviewed

STUDY	REPORT NUMBER	REVIEW PAGE
PHARMACOLOGY		
Primary Pharmacology		
Summary of Studies to Assess the Antiemetic Activity of SCH 619734 (Compound B) in the Ferret	D-46833	26
In Vitro and In Vivo Pharmacological Characterization of SCH 619734	D-46896	26
Secondary Pharmacology		
In Vitro Pharmacology Study of SCH 619734 and SCH 720881	100000503	28
In Vitro and In Vivo Pharmacological Characterization of SCH 619734	D-46896	26, 28
In Vitro Pharmacology: SPCORP Panel: Option I (Human Assays) – Study of Compounds 119577 and 119579	D-46458	28
In Vitro Pharmacology: SPCORP Panel: Option II (non-human assays) – Study of Compound 119577	D-46459	28
In Vitro Pharmacology: Binding Assays – Study of SCH 619734	21202	28
In Vitro Pharmacology: High-Throughput Profile and Bindings Assays – Study of SCH 720881	21203	28
In Vitro Pharmacology: Binding Assays – Study of 619734	21204	28
In Vitro Pharmacology Study of SCH 619734 and SCH 720881	100017372	28
Safety Pharmacology		
Single Oral (Gavage) Dose Respiratory Safety Pharmacology Study of SCH 619734 in the Rat	03123	30
Acute Central Nervous System Pharmacological Profile of SCH 619734 Following Oral Administration in Rats	03124	31
Single Oral (Gavage) Dose Cardiovascular Safety	03125	31

Pharmacology Study of SCH 619734 in Male Cynomolgus Monkeys		
Effects of SCH 619734 on Action Potential Parameters in Isolated Canine Cardiac Purkinje Fibers	05255	31
Effects of SCH 720881 on Cloned HERG Potassium Channels Expressed in Mouse L-929 Cells	08107	33
In Vitro Effects on hERG Current, Cardiovascular Effects in Conscious Cynomolgus Monkeys and Effects on CNS, Respiratory, Renal and Gastrointestinal Function in Rats	46553	35
PHARMACOKINETICS/ADME/TOXICOKINETICS		
Absorption		
Exploratory Nonclinical Pharmacokinetics and Metabolism of SCH 619734	04917; Studies NKC-302, -312, -314, -327, -295, -328, -338, -359, -342, -343, -401, and -404 are raw data source files referenced in Study No. 04917.	36
Bi-Directional Caco-2 Permeability	DM27365	37
Determination of Permeability and Effect of SCH 720881 on PGP Using Human CACO-2 Cells	KB-0046-DV-PB	41
Distribution		
Exploratory Nonclinical Pharmacokinetics and Metabolism of SCH 619734	04917	36
In Vitro Binding of SCH 619734 to Mouse, Rat, Rabbit, Dog, Monkey, and Human Plasma Proteins Using Equilibrium Dialysis	DM27248	42
Tissue Distribution and Excretion Pattern of ^{14}C- SCH 619734-Derived Radiocarbon after a Single Oral Dose to Male and Female Albino and Pigmented Rats	DM27343	43
Formulation Excipient Effects on Plasma Pharmacokinetics and Brain Uptake of SCH 619734 in Rats	DM27349	52
SCH 720881 Binding to Human, Rat and Monkey Plasma Proteins	KB-0046-DV-EB	53
SCH 619734 and SCH 720881 Binding to Rat Brain Proteins	KB-0048-DV-EB	54
Brain Exposure of SCH 720881 in Male Sprague-Dawley Rats Following Oral Administration of Rolapitant	KB-0043-DA-RI	54
Metabolism		
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3.2 Studies Not Reviewed

- Study reports for nonclinical studies conducted in monkeys to evaluate the abuse liability of rolapitant (2013-001 and 2013-002) are not reviewed. These studies will be evaluated by Controlled Substances Staff (CSS).
- The following analytical methods and method validation reports are not reviewed: 04021, 04065, 04945, 04946, DM27161, DM27320, DM27321, DM27322, PR-10-5008-N, XBL11070, XBL11070 Amend 1, and XBL13005.
- Study XBL 11073 (UV Analysis and Certification of SCH 619734 and SCH 720881) was not reviewed. Rolapitant and metabolite SCH 720881 were reported to not absorb UVB, UVA or visible radiation; and thus, no phototoxicity studies were conducted.

3.3 Previous Reviews Referenced

- Pharmacology review of IND 72,754 dated December 29, 2005
- Pharmacology review of IND 72,754 dated March 10, 2006
- Pharmacology review of IND 72,754 dated November 24, 2010
- Pharmacology review of IND 72,754 dated May 9, 2012
- Pharmacology review of IND 72,754 dated December 5, 2012
- Pharmacology review of IND (b) (4) dated August 14, 2013

Above reviews of INDs 72,754 and (b) (4) were cited and incorporated into this review as appropriate. On Form 356h, the Applicant cross-referenced IND 72,754.

4 Pharmacology

4.1 Primary Pharmacology

Reviews of Study Nos. D-46833 and D-46896 are incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

Antiemetic Activity of SCH 619734 (Compound B) in the Ferret (Study No. D-46833)

This study was conducted to examine the effect of SCH 619734 against acute and delayed apomorphine (0.125 mg/kg, SC) or cisplatin-induced (5-10 mg/kg, IP) emesis in male ferrets (n = 4-6/dose). SCH 619734 was tested at oral (gavage) doses of 0.03, 0.1 and 0.3 and 1 mg/kg. Control group received 0.4% carboxymethylcellulose. SCH 619734 was administered either as a 4 hour single pretreatment or daily dosing for 3 days at 1.0 mg/kg. The animals were observed for 72 hours and the number of retches/vomits were recorded every two hours interval for 72 hours.

SCH 619734 produced dose-related inhibition of emesis induced by apomorphine and cisplatin with ED_{50} values of 0.03 and 0.07 mg/kg, respectively. Both daily pretreatment, as well as a single pretreatment of SCH 619734 at 1 mg/kg prior to cisplatin inhibited both the acute phase (0-24 h) and delayed phase (24-72 h) emesis by 90-95%.

***In Vitro* and *In Vivo* Pharmacological Characterization of SCH 619734 (Study No. D-46896)**

In vitro binding assays were conducted in Chinese hamster ovary (CHO) cells stably transfected with NK1, NK2 and NK3 receptors using different radiolabeled substrates e.g., ^{3}H-substance-P (^{3}H-SP), ^{3}H-SR48968, ^{125}I-neurokinin B (^{125}I-NKB) and ^{3}H-paroxetine. For NK1 receptor binding studies, ^{3}H-SP or ^{125}I-BHSP were used for NK1 binding assays. NK2 receptor affinity was determined using ^{3}H-SR48968. For NK3 receptor binding studies, ^{125}I-NKB was used. Calcium channel affinity was determined using ^{3}H-desmethoxyverapamil (D888). ^{3}H-Paroxetine was utilized for the serotonin transporter binding studies. For norepinephrine transporter binding, membranes were incubated with ^{3}H-nisoxetine. Membranes expressing the dopamine transporter were incubated with ^{3}H-GBR12935. *In vivo* behavioral studies (reversal of NK1-agonist-induced foot-thumping, anxiolytic profile using elevated plus-maze) were conducted in female Mongolian gerbils. In addition, antitussive profile of SCH 619734 was also tested in Guinea pigs and dogs (capsaicin-induced cough in the Guinea pig and mechanically-induced cough in dogs).

The affinity constants (Ki) of SCH 619734 for the NK1, NK2 and NK3 receptors are shown in the table below (from page 27 of the report). SCH 619734 was found to bind with high affinity (Ki = 0.66 nM) at the NK1 receptor. SCH 619734 also displayed high selectivity (>1000 fold) for the NK1 receptor compared with the NK2 and NK3 receptor subtypes.

Table 1 Receptor binding profile of SCH 619734.

	hNK1	hNK2	hNK3
K_i (nM)	0.66	>1200[a]	4050
Ratio: NKx/NK1	1	>1500	>6000

a: 10% displacement of specific binding at 3 μM

The Ki values of SCH 619734 for the NK1 receptor of the gerbil, guinea pig and monkey were 0.13 nM, 0.72 nM , and 2.5 nM, respectively. . However, SCH 619734 showed lower affinity for the rabbit (Ki = 31.7 nM), mouse (Ki = 60.4 nM) and rat (Ki = 78.6) NK1 receptors. This was attributed to a difference in an amino acid in the seventh transmembrane domain of the NK1 receptor in these species (McLean, S. 1996. Nonpeptide Antagonists of the NK1 Tachykinin Receptor. Med Res Rev, 16: 297-317). These results are summarized in the following table (from page 27 of the report).

Table 2 NK1 receptor binding profile of SCH 619734 in different species.

Species	Gerbil	Guinea Pig	Monkey	Rabbit	Rat	Mouse
Ki (nM)	0.13	0.72	2.5	31.7	78.6	60.4

The results of the binding studies suggested that SCH 619734 binds competitively and reversibly to the NK1 receptor. SCH 619734 has low affinity for both L-type calcium channels and the active transporters of dopamine (DA), norepinephrine (NE) and serotonin (HT). SCH 619734 produced about 3% inhibition at 10 μM at the verapamil-sensitive L type calcium channel and produced 5% inhibition at the 5HT transporter at 10 μM, while the Ki values at the DA and NE transporters were 7.0 μM and 4.2 μM, respectively. In the gerbil foot-thumping pharmacodynamic (PD) assay, SCH 619734 inhibited NK1-agonist-induced foot thumping behavior with an ID90 of 0.3 mg/kg PO for up to 24 hr. In the gerbil elevated plus-maze, SCH 619734 produced anxiolytic-like activity at doses of 1 and 3 mg/kg.

4.2 Secondary Pharmacology

Reviews of Study Nos. 100000503, D-46896, D-46458, D-46459, 21202, 21203, and 21204 are incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

***In Vitro* Pharmacology of SCH 619734 and SCH 720881 (Study Nos. 100000503, D-46896, D-46458, D-46459, 21202, 21203, 21204)**

SCH 619734 and SCH 720881 (metabolite) were evaluated for binding to ion channels, transporters and other G-protein coupled receptors (GPCR). SCH 619734 showed > 1000-fold lower affinity for a panel of 115 other receptors, transporters, enzymes, or channels, and > 200-fold lower affinity for glucocorticoid receptor (IC50 = 290 nM, Ki = 150 nM), than for the NK1 receptor. The sponsor commented that patients receiving HEC and MEC are frequently administered dexamethasone. In three Phase 3 studies (HEC and MEC), SCH 619734 was administered in combination with dexamethasone, a known agonist of the glucocorticoid receptor with a Ki = 2.0 nM. SCH 619734 and SCH 720881 showed ≥ 75-fold lower affinity for the glucocorticoid receptor than dexamethasone. The estimated highest free fraction of SCH 619734 in the human brain (≤ 14 nM at a 200 mg oral dose, plasma Cmax = 977 ng/ml or 1.8 µM) based on brain exposure in rats (SN-DM27349) was significantly lower than the estimated free fraction of dexamethasone in the human brain (150 nM at a 200 mg dose). Based on this, the sponsor contended that SCH 619734 is not expected to affect glucocorticoid signaling or to effectively compete with dexamethasone for glucocorticoid binding. The metabolite SCH 720881 has > 1000-fold lower affinity for a panel of 86 other receptors, transporters, enzymes, or channels tested (report Nos. D 46896, D-46458, D-46459, 21202, 21203, 21204, and 100000503). SCH 619734 and SCH 720881 had more than 1000-fold lower affinity for receptors in neurotransmitter systems associated with abuse potential than for the NK1 receptor.

In Vitro Pharmacology Study of SCH 619734 and SCH 720881 (Study No. 100017372)

Methods: SCH 619734 and metabolite SCH 720881 were tested in binding assays for the CB1and sigma (non-selective) receptors, Cl^- channel (GABA gated), and norepinephrine and dopamine transporters in the presence or absence of 10% human serum. Compound binding was calculated as percent inhibition of the binding of a radiolabeled ligand specific for each target, and IC50 values were calculated.

Results: As shown in the Applicant's tables below, IC50 values for SCH 619734 ranged from 2.6E-6 to 1.6E-5 M in the absence of human serum, and 1.6E-5 to 3.9E-5 M in the presence of serum. IC50 values for metabolite SCH 720881 ranged from 5.6E-6 to 1.7E-5 M in the absence of human serum, versus 2.4E-5 to 4.1E-5 M in the presence of serum. Similarly, Ki values were increased in the assays conducted in the presence of human serum, suggesting that there is plasma protein binding and only free drug is available to interact with the receptors.

5.3.1. Compound SCH 619734

Assay	IC_{50}	K_I	K_B	EC_{50}	nH
CB_1*(h)* (agonist radioligand)	1.6E-05 M	1.4E-05 M			1.5
Cl^- channel (GABA-gated) (antagonist radioligand)	2.6E-06 M	2.2E-06 M			1.4
dopamine transporter*(h)* (antagonist radioligand)	8.7E-06 M	4.6E-06 M			2.4
norepinephrine transporter*(h)* (antagonist radioligand)	5.6E-06 M	4.2E-06 M			1.8
sigma (non-selective) (h) (agonist radioligand)	5.2E-06 M	4.2E-06 M			1.1

5.3.3. Compound SCH 619734 + 10% Human Serum

Assay	IC_{50}	K_I	K_B	EC_{50}	nH
Cl^- channel (GABA-gated) (antagonist radioligand)	1.7E-05 M	1.4E-05 M			1.2
dopamine transporter*(h)* (antagonist radioligand)	3.9E-05 M	2.0E-05 M			2.3
norepinephrine transporter*(h)* (antagonist radioligand)	2.6E-05 M	1.9E-05 M			1.2
sigma (non-selective) (h) (agonist radioligand)	1.6E-05 M	1.3E-05 M			1

5.3.2. Compound SCH 720881

Assay	IC_{50}	K_I	K_B	EC_{50}	nH
CB_1*(h)* (agonist radioligand)	1.7E-05 M	1.5E-05 M			1.5
Cl^- channel (GABA-gated) (antagonist radioligand)	5.6E-06 M	4.6E-06 M			1.6
dopamine transporter*(h)* (antagonist radioligand)	1.0E-05 M	5.5E-06 M			1.6
norepinephrine transporter*(h)* (antagonist radioligand)	9.6E-06 M	7.1E-06 M			1.5
sigma (non-selective) (h) (agonist radioligand)	1.0E-05 M	8.0E-06 M			1.3

5.3.4. Compound SCH 720881 + 10% Human Serum

Assay	IC_{50}	K_I	K_B	EC_{50}	nH
Cl^- channel (GABA-gated) (antagonist radioligand)	2.7E-05 M	2.2E-05 M			1.5
dopamine transporter*(h)* (antagonist radioligand)	3.1E-05 M	1.7E-05 M			>3
norepinephrine transporter*(h)* (antagonist radioligand)	4.1E-05 M	3.0E-05 M			2.2
sigma (non-selective) (h) (agonist radioligand)	2.4E-05 M	2.0E-05 M			1.1

4.3 Safety Pharmacology

Reviews of Study Nos. 03123, 03124, 03125, 05255, 08107, and 46553 are incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

A Single Oral (Gavage) Dose Respiratory Safety Pharmacology Study of SCH 619734 in the Rat (Study No. 03123)

Methods: This study evaluated the potential respiratory effects of SCH 619734 when administered as single oral (gavage) doses of 5, 25, or 100 mg/kg (5 mL/kg) to male rats (n = 2/dose) and 1, 5, or 25 mg/kg (5 mL/kg) to female rats (n = 2/dose). The following respiratory parameters were recorded: respiratory rate, tidal volume and minute volume. Control animals received 0.4% (w/v) aqueous hydroxypropyl methylcellulose (HPMC), pH 4.0.

Results: There was no treatment-related mortality or clinical signs. Respiratory rates for male rats at 25 or 100 mg/kg were significantly lower than the vehicle control at several time points from approximately 2.5 to 5.75 hours post-dose. However, tidal volume or minute volume was not affected. Respiratory rate changes in male rats were not considered to be treatment-related as the magnitude of these changes were similar to or less than that of the historical control values for this parameter in rats and the absence of a dose response. The following table (from page 31 of the report) shows the results.

Table 3 Means (Standard Errors) of Baseline Averages for Pulmonary Parameters by Sex

Sex	Dose Group (SCH 619734)	Mean (Standard Error) (N=6)		
		Respiratory Rate (breaths/min)	Tidal Volume (mL/breath)	Minute Volume (mL/min)
Male	Control (0 mg/kg)	141.4 (4.7)	0.939 (0.052)	127.4 (4.5)
	Low Dose (5 mg/kg)	135.0 (7.8)	0.916 (0.045)	119.1 (8.5)
	Mid-Dose (25 mg/kg)	153.2 (8.2)	1.076 (0.032)	156.8 (12.5)
	High-Dose (100 mg/kg)	150.1 (4.9)	1.070 (0.061)	154.5 (7.6)
	Sig. Diff. Among Dose Groups[a]			Yes (Low vs. Mid)
Female	Control (0 mg/kg)	121.1 (5.4)	0.973 (0.085)	111.0 (6.8)
	Low-Dose (1 mg/kg)	148.9 (7.3)	0.737 (0.050)	101.4 (3.9)
	Mid-Dose (5 mg/kg)	127.5 (10.0)	0.926 (0.049)	110.1 (7.8)
	High-Dose (25 mg/kg)	143.0 (3.7)	0.845 (0.035)	115.4 (5.8)
	Sig. Diff. Among Dose Groups[a]	Yes	Yes	

[a] Yes indicates that the ANOVA found significant differences in baseline averages existed among dose groups at p=0.05. When pairs of dose groups differed, based on the post hoc t-test comparisons at p=0.05/6=0.0083, these are specified within parentheses.

The Acute Central Nervous System Pharmacological Profile of SCH 619734 Following Oral Administration in Rats (Study No. 03124)

Methods: In this study, neuropharmacological activity of SCH 619734 was characterized following a single oral (gavage) dose of 0, 5, 25 or 100 mg/kg (5 mL/kg) to male rats (n = 6/dose) and 0, 1, 5 or 25 mg/kg (5 mL/kg) to female rats (n = 6/dose) using a functional observational battery (FOB: home cage, handling, open field, sensory, neuromuscular and physiological observations) and spontaneous locomotor activity at predose and 240 minutes post-dose. Control animals received 0.4% (w/v) aqueous HPMC, pH 4.0.

Results: There were no treatment-related differences in the FOB for males or females. There were no SCH 619734-related differences in motor activity counts in either sex.

A Single Oral (Gavage) Dose Cardiovascular Safety Pharmacology Study of SCH 619734 in Male Cynomolgus Monkeys (03125)

Methods: In this study, six male Cynomolgus monkeys were instrumented with radiotelemetry transmitters for the measurement of blood pressure, heart rate and electrocardiographic (ECG) intervals and ECG morphology. Each animal received either the vehicle (0.4% (w/v) aqueous HPMC or SCH 619734 at 5 or 15 mg/kg (5 mL/kg) once on Days 1, 8 and 15.

Results: There were no SCH 619734-related changes in the heart rate, blood pressure, ECG intervals (RR, QT, PR and QRS) and ECG morphology at either 5 or 15 mg/kg. Mean plasma concentrations after a single oral dose of 5 or 15 mg/kg SCH 619734 reached 731 and 2830 ng/mL, respectively, at eight hours post-dose.

Effects of SCH 619734 on Action Potential Parameters in Isolated Canine Cardiac Purkinje Fibers (Study No. 05255)

Methods: The *in vitro* effects of SCH 619734 on cardiac action potentials in isolated, canine Purkinje fibers were measured at concentrations of 0.1, 1 and 10 µM using six fiber preparations at three frequencies (0.5, 1 and 2 Hz). Positive control was d-sotalol (100 µM). The following parameters were examined: resting membrane potential (RMP), upstroke amplitude (UA), maximum rate of depolarization (MRD), action potential duration at 60% repolarization (APD60), action potential duration at 90% repolarization (APD90).

Results: There were no significant treatment-related effects on RMP, UA, and MRD. At 10 µM, SCH 619734 shortened APD60 by up to maximum of 14% (1 Hz) vs. an increase of 0.8% in fibers exposed to the vehicle. At 10 µM, SCH 619734 shortened APD90 by up to maximum of 9.5% (1 Hz) vs. an increase of 0.3% in fibers exposed to the vehicle.. Positive control, d-sotalol, increased the APD60 and APD90. The following tables (from page 30, 32 and 34 of the report) show the summary results for SCH 619734 and vehicle control.

Table 1. Summary of the Effects of SCH 619734

0.5 Hz					
SCH 619734	APD_{60}	APD_{90}	RMP	UA	MRD
μM[a]	(Δ%)	(Δ%)	(ΔmV)	(ΔmV)	(Δ%)
0.1	-7.0 ± 3.4	-5.8 ± 2.6	-0.4 ± 0.7	-1.0 ± 1.2	1.4 ± 7 6
1	-8.9 ± 6.7	-5.6 ± 4.2	1.5 ± 1.2	-5.7 ± 4.0	-8.7 ± 11.9
10	-13.0 ± 4.2*	-8 7 ± 2.1*	0 4 ± 0.4	-0.6 ± 0.6	1.7 ± 6.6
1 Hz					
SCH 619734	APD_{60}	APD_{90}	RMP	UA	MRD
μM[a]	(Δ%)	(Δ%)	(ΔmV)	(ΔmV)	(Δ%)
0.1	-6.5 ± 3.8	-5.6 ± 3.1	-0.2 ± 0.7	-1.3 ± 1.6	-2.8 ± 6 8
1	-9.4 ± 5.0	-5.6 ± 2.4	1.6 ± 1.2	-5.5 ± 3.1	-8.3 ± 11.3
10	-14.0 ± 3.5*	-9.5 ± 2.2*	1.1 ± 0.6	-1.7 ± 1 1	-2.4 ± 4.5
2 Hz					
SCH 619734	APD_{60}	APD_{90}	RMP	UA	MRD
μM[a]	(Δ%)	(Δ%)	(ΔmV)	(ΔmV)	(Δ%)
0.1	-4.3 ± 2.6	-3.9 ± 2.2	-0.8 ± 0.6	-1.4 ± 1.5	-2.6 ± 7.3
1	-5.7 ± 3.1	-3.1 ± 1.7	0.9 ± 1.2	-4.7 ± 2.8	-9.0 ± 12.1
10	-12.3 ± 2.4*	-7.4 ± 1.7*	0.4 ± 0.6	-2.2 ± 0.8	-4.9 ± 5.4

Values represent means ± SEM, n = 6 fibers

* Denotes statistical significance (p <0 05) when compared to time-matched vehicle control sequence

a: Target concentrations are indicated. Actual tissue bath concentrations were below the lower limit of quantitation, 1 19 and 8 04 μM, respectively

Table 2. Summary of the Effects of Vehicle Control

0.5 Hz					
Vehicle	APD_{60}	APD_{90}	RMP	UA	MRD
	(Δ%)	(Δ%)	(ΔmV)	(ΔmV)	(Δ%)
V1	-1.0 ± 1.0	-0.9 ± 1.0	0.7 ± 0.5	-0.3 ± 1.5	-4.8 ± 2.9
V2	-1.7 ± 2.3	-1.7 ± 2.0	0.0 ± 0.8	-2.8 ± 3.1	-4.3 ± 5.8
V3	1 4 ± 1 1	0 9 ± 1.2	-0.8 ± 0.7	-1.3 ± 2 8	-5 3 ± 6 6
1 Hz					
Vehicle	APD_{60}	APD_{90}	RMP	UA	MRD
	(Δ%)	(Δ%)	(ΔmV)	(ΔmV)	(Δ%)
V1	-1.0 ± 1.0	-0.7 ± 1.0	0.5 ± 0.6	-0.5 ± 1.3	0.0 ± 3.0
V2	-1.8 ± 1.2	-1.3 ± 0.9	-0.7 ± 1.0	-4.2 ± 3.4	-6.9 ± 6.8
V3	0.8 ± 1.0	0.3 ± 1.2	-1.9 ± 1.0	-2.5 ± 2.5	-4.5 ± 6.3
2 Hz					
Vehicle	APD_{60}	APD_{90}	RMP	UA	MRD
	(Δ%)	(Δ%)	(ΔmV)	(ΔmV)	(Δ%)
V1	0.5 ± 0.9	0.5 ± 0.5	0.6 ± 0.8	-1.2 ± 1.1	-1.0 ± 2.3
V2	-0.6 ± 1.4	-0.7 ± 1.2	-2.3 ± 0.7	-3.4 ± 2.6	-3.5 ± 8.3
V3	0.8 ± 0.7	0.6 ± 0.6	-1.5 ± 1.2	-2.6 ± 2.4	-4.0 ± 7.2

Values represent means ± SEM, n = 6 fibers

Table 3. Summary of the Effects of 100 µM *dl*-Sotalol

Sotalol	APD_{60}	APD_{90}	RMP	UA	MRD
	(Δ%)	(Δ%)	(ΔmV)	(ΔmV)	(Δ%)
0.5 Hz	35 7 ± 6 5*	36 6 ± 5 2*	1.6 ± 1.5	-5.5 ± 4 8	-12.5 ± 5.3
1.0 Hz	34.0 ± 5.7*	33 5 ± 4 5*	0.0 ± 1.5	-5.1 ± 5 4	-13.1 ± 6.5
2.0 Hz	25 3 ± 3 7*	24 9 ± 3 2*	0.0 ± 1.5	-5.8 ± 4 7	-12.1 ± 5.2

Values represent means ± sem , n=6 fibers

*APD_{60} and APD_{90} were statistically (p <0.05) more prolonged when compared to vehicle control sequence 3

Effects of SCH 720881 on Cloned HERG Potassium Channels Expressed in Mouse L-929 Cells (Study No. 08107)

Methods: This study was conducted to examine the effects of SCH 720881, metabolite of SCH 619734, on cloned human hERG encoded potassium (K^+) channel current expressed in mouse L-929 cells using voltage-clamp assay. SCH 720881 was used at concentrations of 0.3, 1.0, 3.0, 10, and 20 µM. The positive control group received 30

nM cisapride. The control group received buffer solution containing 0.1% dimethylsulfoxide (DMSO).

Results: SCH 720881 inhibited hERG potassium channel currents in a concentration-dependent manner with an IC50 of 5.8 µM. The positive control article, cisapride, inhibited hERG potassium channel currents by 90% at 30 nM, as expected. The following table (from page 18 of the report) shows the results.

Statistical Summary: Ratio of hERG Tail Current Amplitudes at Post-exposure vs. Pre-exposure of Mouse L-929 Cells to SCH 720881				
Concentration of SCH 720881 (µM)	Mean Ratio (Mean)	Standard Deviation (SD)	Standard Error of the Mean (SEM)	Number of Cells (N)
0 (Control)	0.96	0.04	0.02	4
0.3	0.77	0.03	0.02	3
1.0	0.74	0.05	0.03	3
3.0	0.57	0.11	0.06	3
10	0.26	0.03	0.02	3
20	0.09	0.04	0.02	3

The following figure (from page 24 of the report) shows the concentration-response relationship of SCH 720881 on hERG tail current in mouse L-929 cells.

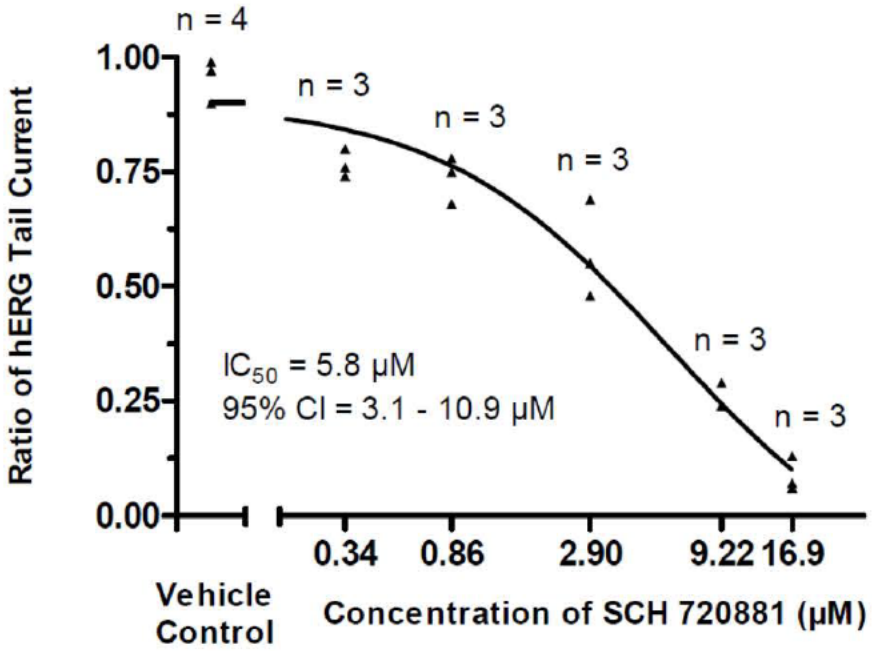


Figure 2 Concentration-Response Relationship of SCH 720881 on hERG Tail Current in Mouse L-929 Cells

Note: The effects were expressed as the ratio of the post-exposure value relative to the pre-exposure value of the tail current amplitude. Pre-exposure values were measured at least 5 min after patch rupture was established, as the average amplitude of 6 tail currents prior to initiation of perfusion of SCH 720881 or control article. Post-exposure values were collected as the average of 6 tail currents at approximately 15 minutes after switching to the superfusion line of SCH 720881 when a steady-state effect was observed. Post-exposure values for control were recorded at approximately 12-15 minutes after collection of pre-exposure control values.

***In Vitro* Effects on hERG Current, Cardiovascular Effects in Conscious Cynomolgus Monkeys and Effects on CNS, Respiratory, Renal and Gastrointestinal function in rats (Study No. 46553)**

Methods: In this study, SCH 619734 was tested in a series of non-GLP safety pharmacology studies in male rats for effects on the CNS, respiratory, renal and gastrointestinal (GI) functions (gastric emptying, intestinal transit,) following single oral doses of 5 and 10 mg/kg. Telemetry studies in freely roaming male Cynomolgus monkeys examined potential effects of SCH 619734 on blood pressure, heart rate, morphology of the ECG and ECG intervals at oral doses of 2 and 5 mg/kg. A second primate telemetry study examined blood pressure and heart rate only following oral doses of 1, 2 and 5 mg/kg SCH 619734. The effect of SCH 619734 on hERG current was assessed at 1, 3 and 10 µM concentrations using patch clamp technique in mouse L-929 cells stably transfected with the human ether-a-go-go-related gene (hERG).

Results:

Cardiovascular: SCH 619734 produced a concentration-dependent inhibition of hERG tail current with an IC50 of 1.05 µM. These findings indicated that SCH 619734 possesses the ability to inhibit IKr and may have potential to prolong ventricular repolarization *in vivo*. The sponsor commented that based on the low plasma exposure required for efficacy (46.3 ng/mL or 93 nM), coupled with high (>99%) protein binding, the possibility that SCH 619734 would prolong ventricular repolarization *in vivo* seems unlikely since a concentration 3,763-fold greater than that needed for the efficacy would need to be achieved in order to reach a free drug level of 1.05 µM.

In telemetry studies in conscious, male Cynomolgus monkeys at 2 and 5 mg/kg PO, there were no significant treatment-related effects on blood pressure, EGG morphology or EGG intervals at 2 or 5 mg/kg of SCH 619734. Heart rate was also not affected by the treatment at 5 mg/kg. However, there was a small (about 20 beats/min) increase in heart rate at 2 mg/kg. Plasma levels at 6 hr post-dose at 2 and 5 mg/kg were 290 ng/mL and 820 ng/mL, respectively. A repeat telemetry study in Cynomolgus monkeys at oral doses of 1, 2 and 5 mg/kg did not demonstrate any significant effect on heart rate. The small rise in the heart rate at 2 mg/kg in the initial study was not considered treatment-related in the absence of any dose response. Mean plasma levels at 6 hr post-dose at 1, 2 and 5 mg/kg were 102, 250 and 717 ng/mL, respectively. Higher doses could have been tested.

CNS Findings: In rats given a single oral dose of 5 mg/kg of SCH 619734, there were no treatment-related effects on behavioral, neurological or autonomic measures. The 10 mg/kg dose of SCH 619734 produced a slow-walking gait, reduced palpebral opening (squinted eyes) and staring. However, these effects were not considered biologically significant as these changes were mild in nature.

Respiratory, Renal and Gastrointestinal Effects: There were no SCH 619734-related effects on respiratory rate, tidal volume, minute volume, arterial pH, blood gas levels, urine output, urinary electrolyte excretion, creatinine clearance, gastric emptying or intestinal motility in rats at any of the tested oral doses of 5 or 10 mg/kg.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption

Reviews of Study Nos. 04917 and DM27365 are copied below verbatim from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP). It is noted that the review of Study No. 04917 also addresses Study Nos. NKC-302, -312, -314, -327, -295, -328, -338, -359, -342, -343, -401, and -404, as the NKC studies are raw data source files referenced in Study No. 04917.

Exploratory Nonclinical Pharmacokinetics and Metabolism of SCH 619734 (Study No. 04917)

Methods: Exploratory absorption, distribution, metabolism, excretion (ADME) and pharmacokinetic studies of SCH 619734 (amorphous form) or ^{3}H-SCH 619734 (specific activity = 156-365 µCi/mg) were performed in male mice, male Sprague Dawley rats, male Cynomolgus monkeys, and female gerbils following PO and/or IV administration. Serial blood samples were collected after treatment at selected time points (up to 48 hr). The total radioactivity in the plasma was determined by liquid scintillation spectrometry (LSS). In addition, the concentrations of SCH 619734 were determined by LC-MS/MS using non-validated assays.

Brain uptake was assessed after oral administration of SCH 619734 at 5, 10, 30, and 100 mg/kg in rats in single dose studies. Plasma and brain (cerebellum and brain stem) samples were collected at 24 or 48 hr post-dose. In gerbils, plasma and brain samples were collected at 1, 2, 4, 6, 8, 24, and 48 hr post-dose. In addition, brain-to-plasma (B/P) ratios were calculated. The extent of binding of SCH 619734 to mouse, gerbil, rat, dog, Cynomolgus monkey, and human plasma proteins was determined by equilibrium dialysis at an initial plasma concentration of 10 µM.

A single dose of ^{3}H-SCH 619734 was administered orally to two SD rats (15.6 mg/kg) and two Cynomolgus monkeys (10 mg/kg). Bile and urine samples were collected for the analysis of metabolites after treatment over the intervals of 0-24 hr for rats and 0-48 hr for monkeys. The metabolism of SCH 619734 was evaluated *in vitro* using rat, monkey and human hepatocytes.

Bile duct-cannulated animals were administered oral (15.6 mg/kg to one rat and 10 mg/kg to one monkey) and intravenous (5 mg/kg to one rat and 2 mg/kg to one monkey) doses of ^{3}H-SCH 619734. Bile and urine were collected at intervals up to 24 hr for rats and 48 hr for monkeys.

Results: SCH 619734 was well absorbed following oral administration. SCH 619734 was highly protein bound in the mouse, rat, gerbil, dog, monkey and human plasma. The extent of protein binding was 99.9% in mice, 99.9% in gerbils, 99.7% in rats,

99.9% in dogs and monkeys, and 99.8% in humans. In single dose studies, plasma AUC and Cmax values increased with dose.

The extent of brain penetration by SCH 619734 was evaluated after oral administration of SCH 619734 (amorphous hydrochloride salt form) to gerbils (0.3 mg/kg, free base) and rats (5, 10, 30, and 100 mg/kg, free base). Based on $AUC_{0\text{-}48hr}$ values in the brain (4473 ng.hr/g) and plasma (1168 ng.hr/mL) of gerbils, SCH 619734 exhibited extensive brain penetration with a brain to plasma AUC ratio of 3.8. The brain to plasma ratios in gerbils at the 24 hr and 48 hr time points post-dose ranged from 2.6 to 3.3. In rats, brain concentrations of SCH 619734 were only determined at a single time point (24 hr or 48 hr) after dosing. Across the doses of 10 to 100 mg/kg, the brain to plasma concentration ratio at 48 hr post dose ranged from 0.2 to 2.5; and at a dose of 5 mg/kg, this ratio ranged from 2.4 to 5.0 at 24 hr after post-dose. The results indicated that SCH 619734 was distributed into the brain of rats and gerbils.

In rats and monkeys, after oral administration of ^{3}H-SCH 619734, SCH 619734 undergoes extensive metabolism. In addition to the parent compound, the bile contained M+16, M+14, M+30, M+32 oxidative metabolites; M-224 and M-240 oxidative cleavage products; and various glucuronide conjugates. Parent compound was not detected in the rat or monkey urine. In rats and monkeys, plasma concentrations of total radioactivity were greater than those of parent drug, indicating the presence of circulating metabolites. The M+16 metabolite isolated in the rat bile, subsequently identified as SCH 720881, was found to have affinity for the human NK_1 receptor (Ki = 0.42 nM). The following figures (from page 31-33 of the report) show the metabolites characterized in the rat and monkey bile and urine.

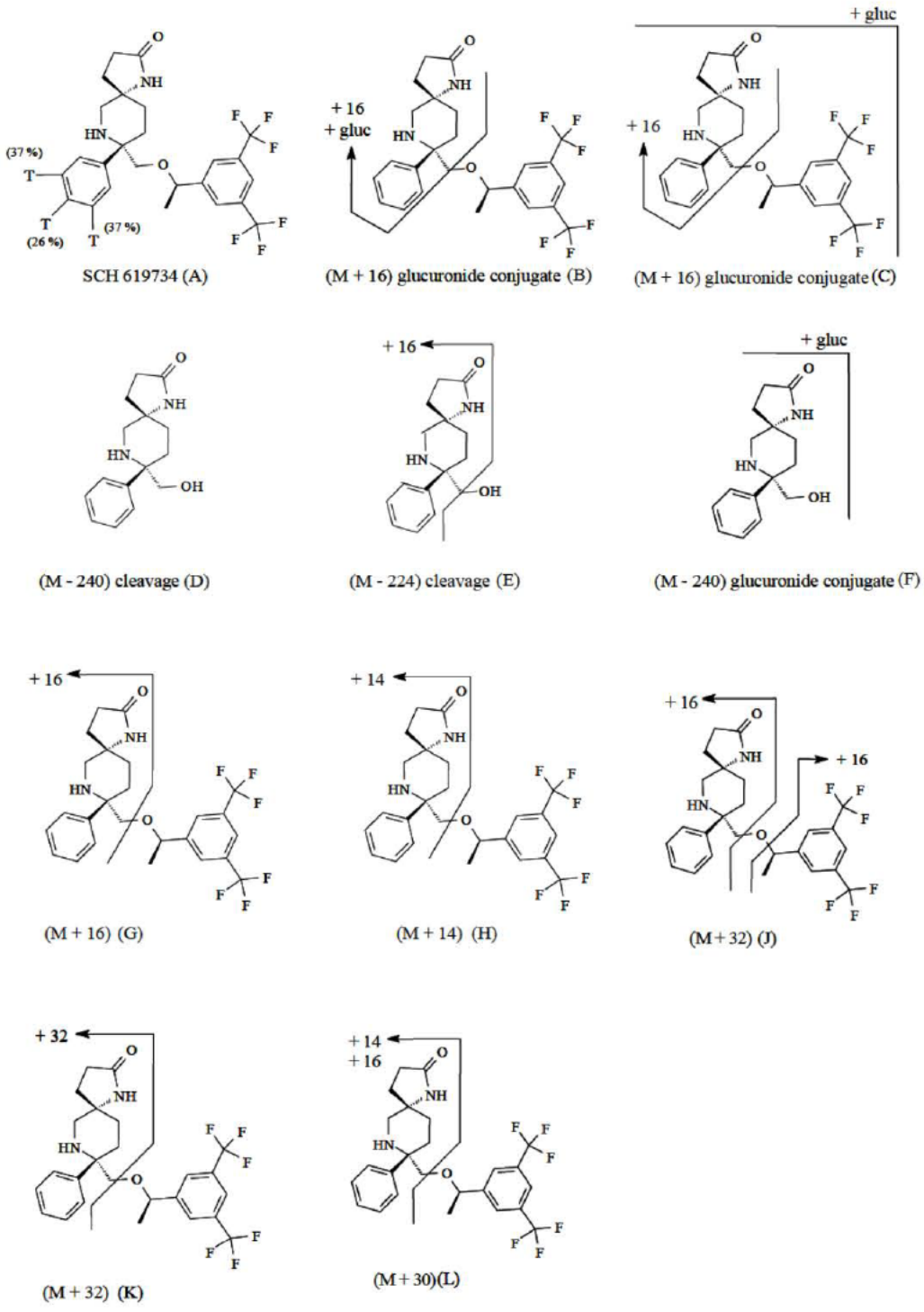


Figure 6 Metabolites of [3H]-SCH 619734 Characterized in Rat and Monkey Bile and Urine

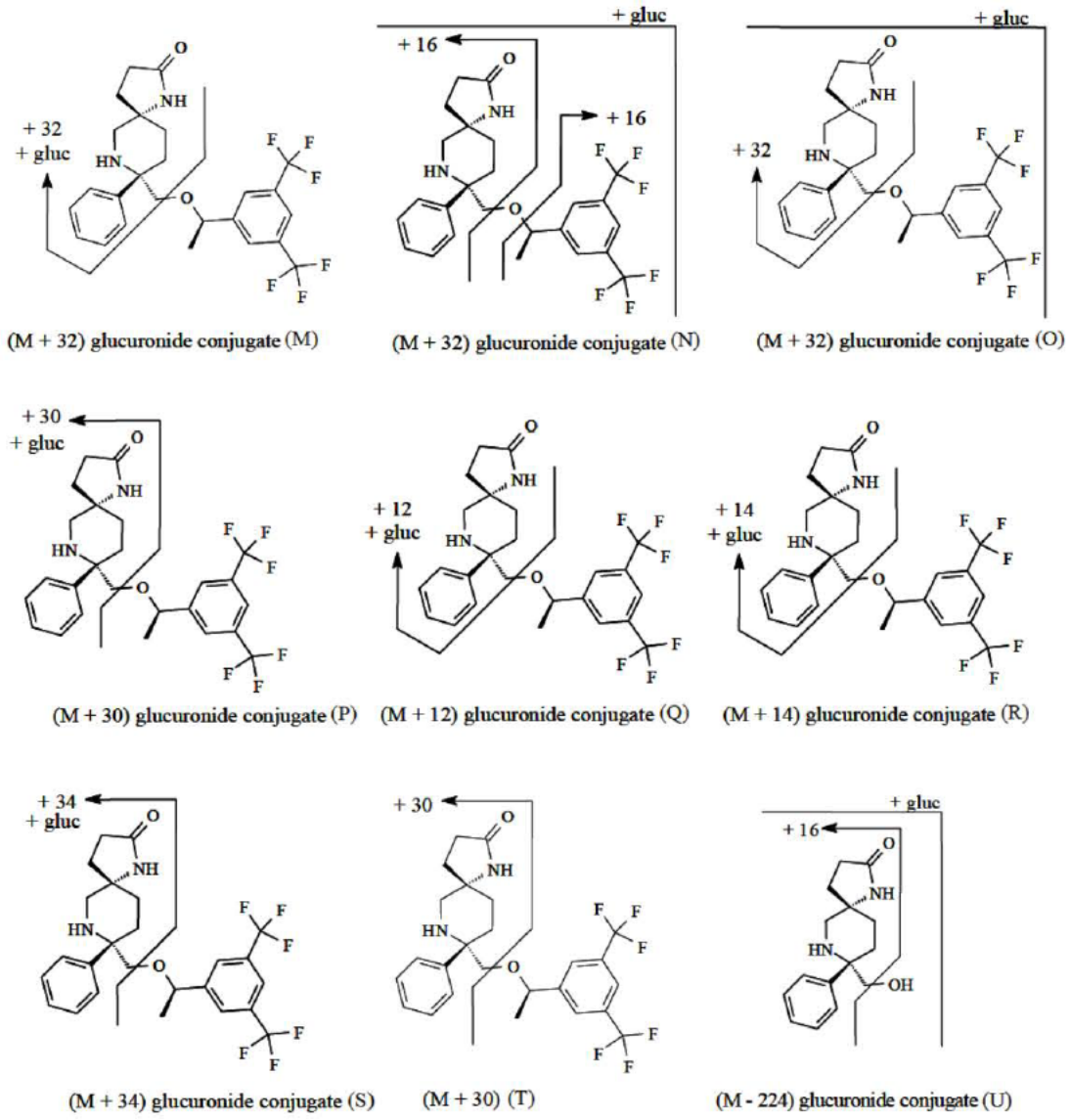
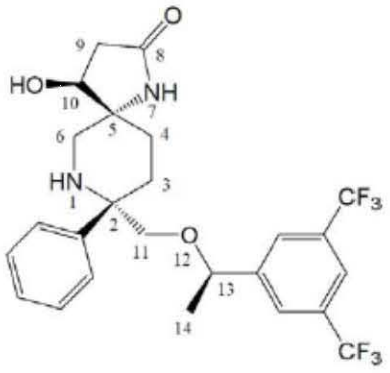
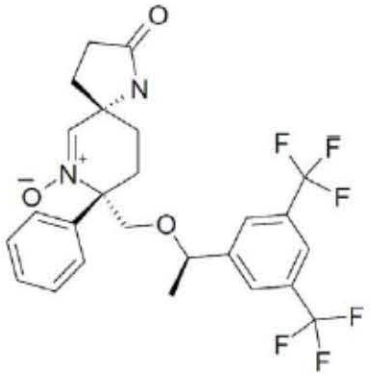


Figure 6 Continued. Metabolites of [3H]-SCH 619734 Characterized in Rat and Monkey Bile and Urine



SCH 720881



SCH 730742

Figure 7 Chemical Structures of the M + 16 (SCH 720881) and the M + 14 (SCH 730742) Metabolites of SCH 619734 Isolated from Rat Bile and Plasma as Determined by NMR and/or Mass Spectrometry

SCH 619734 was not a potent inducer of rat liver microsomal cytochrome P450 enzymes (CYP1A1, 1A2, 2B, 3A or 4A). Evaluation of CYP3A4 induction through the PXR pathway showed a 1.7, 2.4, 4.7 and 14.7-fold induction at concentrations of 0.3, 1, 3, and 10 µM, respectively. The sponsor stated that the expected therapeutic plasma concentrations in humans is <1 µM; therefore, CYP3A4 induction appears to be unlikely at the proposed human dose. SCH 619734 and its active metabolite SCH 720881 were not potent inhibitors of human CYP2C9, 2C19, 2D6 or 3A4. The primary routes of metabolism in the rat and monkey were oxidation followed by glucuronide conjugation. There were no glutathione or acyl glucuronide conjugates formed from SCH 619734 in rats and monkeys. The primary route of excretion was fecal in both rats and monkeys and the majority of the radioactivity was eliminated in 7 days in rats and in 10 days in monkeys. In rats, within 168 hr post-dose, fecal excretion of administered radioactivity was 54.6 % and urinary excretion was 34%. In bile-duct cannulated monkeys, within 48 hr (IV) post-dose, 48% of administered dose was excreted in the bile and 8% in the urine, while within 240 hr post-dose, 58% of dose was recovered in the feces and 18.6% in the urine in non-cannulated animals.

Bi-Directional Caco-2 Permeability (Study No. DM27365)

Methods: The objective of this non-GLP study was to determine the bi-directional Caco 2 permeability of SCH 619734 across Caco-2 cell monolayers. Caco-2 monolayers were treated with SCH 619734 on the apical side (A-to-B) or basolateral side (B-to-A) and then incubated at 37°C. Samples were taken from the receiver chamber at 2 hours and from the donor chamber at 0 and 2 hour time points. At the conclusion of the 2 hour incubation, the transepithelial electrical resistance (TEER) values of the cells were read and the cells were rinsed with the HBSS buffer.

Results: The results demonstrated a high absorption potential at concentrations from 5 to 20 µM, with A-to-B and B-to-A values consistently ranged between 10 and $20x10^{-6}$ cm/s.

Determination of Permeability and Effect of SCH 720881 on PGP Using Human CACO-2 Cells (Study No. KB-0046-DV-PB)

Methods: Metabolite SCH 720881 was evaluated to determine whether it is a Pgp substrate or inhibitor. In this study, the permeability and efflux of SCH 720881 was assayed in the presence and absence of Pgp inhibitors (verapamil [a non-selective inhibitor] and haloperidol [a specific inhibitor]). In addition, the efflux of a Pgp substrate (talinolol) was assessed in the presence and absence of either SCH 720881 or verapamil. The dosing solutions containing SCH 720881 (1 and 10 µM) were added to the apical side (A-to-B) or basolateral side (B-to-A) and incubated at 37ºC for 2 h.

Results: Apparent permeability (P_{app}) values for SCH 720881 in the A-to-B direction were 4.63E-06 cm/s (1 µM) and 7.29E-06 cm/s (10 µM). The efflux ratios (ratio of P_{app} in the A-B to B-A direction) were 0.955 and 0.583 at 1 and 10 µM, respectively. The presence of Pgp inhibitors did not affect efflux ratio values for the test compound, indicating that SCH 720881 is not a Pgp substrate. SCH 720881 also did not affect the efflux ratio of talinolol, indicating that the test compound is not an inhibitor of Pgp activity.

Distribution

Reviews of Study Nos. DM27248, DM27343 and DM27349 are incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

In vitro Binding of SCH 619734 to Mouse, Rat, Rabbit, Dog, Monkey, and Human Plasma Proteins using Equilibrium Dialysis (Study No. DM27248)

Methods: Plasma samples from each species (mouse, rat, rabbit, dog, monkey and human) were incubated for 24 hours with ^{3}H SCH 619734 (specific activity = 42.23 mCi/mg) at 15, 5, 0.5, 0.1, and 0.01 µg/mL concentrations and plasma protein binding was determined using equilibrium dialysis.

Results: The extent of SCH 619734 plasma protein binding in all species ranged from 99.5% to 99.9%. The following table (from page 26 of the report) shows the protein binding data.

Table 1 Mean Percent Binding of [3H]-SCH 619734 to Mouse, Rat, Rabbit, Dog, Monkey, and Human Plasma Proteins

Nominal ^{3}H-SCH 619734 (µg/mL)	Range of Measured ^{3}H-SCH 619734 Mean Concentration Post-Dialysis (µg/mL)	Mouse		Rat		Rabbit		Dog		Monkey		Human	
		%Bound[a]	CV[b]	%Bound[a]	CV[b]	%Bound[a]	CV[b]	%Bound[a]	CV[b]	%Bound[a]	CV[b]	%Bound[a]	CV[b]
0.01	0.00742 to 0.00911	99.8	0	99.8	0	99.6	0	99.7	0	99.8	0	99.8	0
0.1	0.0734 to 0.116	99.8	0	99.8	0	99.6	0	99.8	0	99.8	0	99.9	0
0.5	0.362 to 0.467	99.9	0	99.7	0	99.6	0	99.7	0	99.8	0	99.8	0
5	3.84 to 5.48	99.8	0	99.7	0	99.6	0	99.7	0	99.8	0	99.8	0
15	11.5 to 14.6	99.8	0	99.7	0	99.5	0	99.7	0	99.8	0	99.8	0

a: The %bound at each ^{3}H-SCH 619734 concentration is reported as a mean of 6 replicates, see Appendix 3 for details.
b: CV, coefficient of variation expressed as a percent.

Tissue Distribution and Excretion Pattern of ^{14}C-SCH 619734-Derived Radiocarbon after a Single Oral Dose to Male and Female Albino and Pigmented Rats (Study No. DM27343)

Methods: The objectives of this study was to assess the tissue distribution and excretion pattern of ^{14}C-SCH 619734 after a single oral (gavage) 25 mg/kg of ^{14}C SCH 619734 (specific activity = 115.4 µCi/mg or 100 µCi/kg, 5 mL/kg) dose to SD rats (groups 1-4, n = 15/sex; n = 2/time point/sex). The vehicle contains 0.4% (w/v) aqueous hydroxypropyl methylcellulose (HPMC). The following figure (from page 39 of the report) shows the position of the radiolabel.

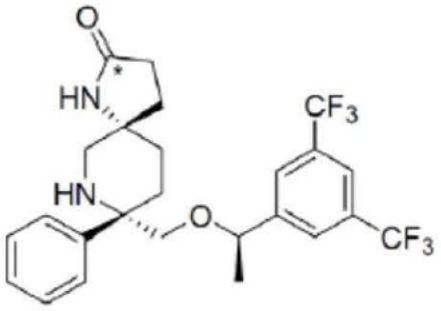


Figure 1 Chemical Structure of [14C]-SCH 619734
*Indicates position of ^{14}C-radiolabel

Animals were fasted overnight prior to dosing and until 4 hr post-dose. Carcass, urine, feces and cage wash were collected at specified time points for radioactivity. The following table (from page 14 of the report) shows the study designs.

Group	Test Article (^{14}C-SCH)	Nominal Dose[a]			Time Point/Interval (hr)		No. Rats[b]	
		mg/kg[e]	µCi/kg	mL/kg	Carcass	Urine, Feces, and Cage washes[c]	Gender	Strain[d]
1	619734	25	100	5	1, 2, 4, 8, 24, 48, and 168	0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168	14 Male	SD
2							14 Female	SD
3							14 Male	LE
4							14 Female	LE
5	Vehicle[f]	0	0		24	0-24	1 Male/1 Female	SD/LE

a: Single dose administered by oral gavage (PO).
b: n = 2/time point/gender, except for vehicle controls (Group 5) where n = 1/time point/gender/strain.
c: Rats that were scheduled to be euthanized at 168 hr post-dose (Groups 1 through 4) or at 24 hr (Group 5) were individually housed in plastic metabolism cages after dosing for collection of urine, feces, and cage wash samples over 24 hr intervals.
d: SD (Sprague Dawley; albino) and LE (Long-Evans; pigmented) rat strains
e: Doses are expressed as the hydrochloride monohydrate salt. When expressed as the free base the dose is 22.5 mg SCH 619734/kg body weight
f: 0.4% HPMC (pH 4)

Results: There was no apparent strain difference in the distribution pattern or tissue concentrations of SCH 619734-derived radioactivity. Female rats excreted a ten-fold smaller percentage (~2.4% of the administered dose) in the urine compared to male rats (~24%). Radioactivity was absorbed quickly into the blood and widely distributed to tissues. The peak radioactivity were typically observed at 8-hr post-dose although in several cases peak concentrations were also seen at 2 and 4 hr time points, particularly in the male albino rat. The highest amount of radioactivity were detected in tissues associated with metabolism and excretion (liver, stomach, bladder and intestine walls), various glandular tissues (adrenal gland, harderian gland, pituitary gland and salivary glands), and the lung, pancreas, spleen, skin and epididymis. The majority of tissues had concentrations that were higher (4-fold) than that in the blood except in the bone and the lens of the eye, where the radioactivity was lower than the blood concentration. The tissue concentrations declined over time. At the 168 hr post-dose, quantifiable residual radioactivity could still be detected in the majority of tissues in female pigmented rats, but only a limited number of tissues in male pigmented and albino male and female rats. The following tables (from page 27-28 of the report) show tissue radioactivity in male and female albino and pigmented rats.

Table 3 Mean (CV, %) Tissue Radiocarbon Concentrations After a Single Oral 25 mg [14C]-SCH 619734/kg Suspension Dose to Male Albino Rats (Group 1)

Tissue Group	Tissue Name	Radiocarbon Concentration [SCH 619734 ng equiv/g (CV, %)][3]													
		1-hr		2-hr		4-hr		8-hr		24-hr		48-hr		168-hr	
Vascular	Blood	1550	(14)	3660	(5)	3490	(14)	3230	(35)	1400	(17)	BQL	(NC)	BQL	(NC)
Lymphatic	Lymph Node	3970	(41)	8480	(34)	10300	(46)	8250	(10)	3840	(NC)	BQL	(NC)	BQL	(NC)
Metabolic/ Excretory	Bladder	4590	(NC)	12700	(NC)	10500	(NC)	13300	(NC)	3430	(NC)	1060	(NC)	BQL	(NC)
	Kidney	10100	(18)	19800	(NC)	17500	(6)	14400	(12)	7620	(17)	1140	(17)	BQL	(NC)
	Liver	23000	(9)	33700	(3)	31200	(3)	24700	(1)	11800	(6)	3200	(1)	491	(87)
Central Nervous System	Brain	1740	(13)	4500	(5)	4350	(7)	3430	(9)	1720	(14)	BQL	(NC)	BQL	(NC)
	Spinal Cord	1860	(14)	3960	(8)	3990	(27)	4210	(1)	1620	(NC)	BQL	(NC)	BQL	(NC)
Endocrine	Adrenal Gland	13400	(NC)	30300	(NC)	21500	(NC)	20400	(NC)	11800	(NC)	1550	(NC)	964	(24)
	Pituitary Gland	4700	(NC)	13900	(NC)	12000	(46)	17100	(NC)	7800	(NC)	686	(89)	BQL	(NC)
	Thymus	2380	(13)	8930	(4)	9560	(3)	9390	(7)	4870	(3)	BQL	(NC)	BQL	(NC)
	Thyroid Gland	2640	(NC)	13500	(28)	13800	(NC)	12500	(NC)	4640	(13)	1170	(NC)	BQL	(NC)
Secretory	Harderian Gland	3620	(NC)	18200	(NC)	19700	(NC)	19900	(NC)	38900	(64)	13600	(NC)	998	(NC)
	Salivary Gland	6740	(17)	19600	(3)	18800	(1)	17300	(NC)	8660	(4)	965	(9)	BQL	(NC)
Fatty	Brown Fat	3250	(9)	15800	(30)	13800	(7)	13600	(13)	8710	(NC)	1210	(27)	BQL	(NC)
	White Fat	4820	(21)	13500	(19)	12700	(21)	13300	(13)	4080	(3)	245	(173)	BQL	(NC)
Gonads/Accessory Reproductive Organs	Epididymis	1470	(22)	6470	(27)	5550	(13)	8150	(5)	6370	(40)	3050	(NC)	1170	(NC)
	Prostate Gland	2510	(49)	8210	(8)	7970	(8)	11700	(4)	5080	(14)	1070	(NC)	BQL	(NC)
	Seminal Vesicles	1090	(27)	5730	(53)	5990	(32)	3340	(44)	1860	(28)	1120	(NC)	BQL	(NC)
	Testis	1120	(35)	4330	(5)	5080	(3)	6690	(6)	4650	(8)	682	(NC)	BQL	(NC)
Muscular	Myocardium	7190	(NC)	16300	(3)	14300	(3)	13000	(1)	6550	(3)	779	(8)	BQL	(NC)
	Skeletal Muscle	2250	(29)	8420	(12)	8730	(8)	8920	(7)	4330	(2)	BQL	(NC)	BQL	(NC)
Skeletal	Bone	690	(88)	2000	(NC)	3610	(41)	2540	(81)	953	(94)	BQL	(NC)	BQL	(NC)
	Bone Marrow	4620	(6)	13000	(NC)	10900	(8)	9600	(12)	4750	(13)	231	(173)	BQL	(NC)
Ocular	Eyeball	BQL	(NC)	735	(NC)	1460	(NC)	1510	(NC)	776	(22)	BQL	(NC)	BQL	(NC)
	Eye-Lens	BQL	(NC)	BQL	(NC)	BQL	(NC)	BQL	(NC)	220	(173)	BQL	(NC)	BQL	(NC)

SCH 619734 PHARMACOKINETICS PAGE 27 STUDY NO. DM27343

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Tissue Group	Tissue Name	Radiocarbon Concentration [SCH 619734 ng equiv/g (CV, %)][a]													
		1-hr		2-hr		4-hr		8-hr		24-hr		48-hr		168-hr	
Miscellaneous	Lung	8440	(4)	25300	(1)	22400	(16)	16300	(4)	11300	(4)	1060	(13)	BQL	(NC)
	Pancreas	11200	(18)	20800	(9)	20600	(22)	18100	(3)	10300	(19)	623	(91)	BQL	(NC)
	Spleen	9410	(NC)	17600	(NC)	17500	(10)	15000	(NC)	7260	(NC)	1190	(NC)	BQL	(NC)
	Skin	2160	(9)	8090	(8)	8140	(12)	6470	(11)	3240	(13)	222	(173)	BQL	(NC)
Gastro-Esophageal and Intestinal Tract Walls	Esophagus	7140	(NC)	12300	(18)	10200	(NC)	9480	(NC)	3800	(13)	310	(173)	231	(173)
	Stomach	15700	(94)	10200	(30)	9650	(6)	9480	(35)	2760	(40)	804	(NC)	BQL	(NC)
	Small Intestine	45200	(90)	26800	(40)	31900	(61)	20200	(25)	13700	(22)	1130	(40)	BQL	(NC)
	Large Intestine	3000	(61)	9170	(7)	8960	(15)	13500	(23)	7720	(30)	2460	(44)	BQL	(NC)

a: Mean (CV, %) values based on digital sampling or digital re-sampling (up to 3 samples) from tissue sections collected from a single rat at different levels.
BQL: Below quantifiable limits (646 ng equiv/g). Value assigned to zero (0) for summary statistics.
NC: Not calculable when the number of replicate samples that were measured was <3 or when mean value was BQL.

Table 4 Mean (CV, %) Tissue Radiocarbon Concentrations After a Single Oral 25 mg [14C]-SCH 619734/kg Suspension Dose to Female Albino Rats (Group 2)

Tissue Group	Tissue Name	Radiocarbon Concentration [SCH 619734 ng equiv/g (CV, %)][a]													
		1-hr		2-hr		4-hr		8-hr		24-hr		48-hr		168-hr	
Vascular	Blood	1930	(10)	2010	(10)	2960	(36)	3730	(1)	3110	(5)	1680	(9)	BQL	(NC)
Lymphatic	Lymph Node	7500	(3)	6490	(16)	8920	(16)	16100	(26)	12600	(15)	3750	(NC)	BQL	(NC)
Metabolic/ Excretory	Bladder	5750	(NC)	2760	(NC)	6870	(NC)	10900	(27)	7760	(NC)	3310	(NC)	BQL	(NC)
	Kidney	13400	(14)	10100	(12)	16900	(13)	24200	(NC)	17100	(8)	7180	(19)	BQL	(NC)
	Liver	26800	(10)	17700	(7)	23300	(10)	39200	(9)	26000	(2)	12200	(2)	748	(7)
Central Nervous System	Brain	4620	(7)	3700	(7)	5560	(2)	13200	(2)	5830	(NC)	2660	(1)	BQL	(NC)
	Spinal Cord	3210	(NC)	3250	(16)	4680	(NC)	15100	(2)	8460	(NC)	3830	(2)	BQL	(NC)
Endocrine	Adrenal Gland	21900	(NC)	18100	(NC)	30600	(NC)	50700	(12)	28200	(NC)	11900	(NC)	337	(NC)
	Pituitary Gland	9860	(NC)	9460	(NC)	16000	(NC)	21300	(NC)	15300	(NC)	7810	(NC)	BQL	(NC)
	Thymus	6340	(4)	5910	(16)	9440	(4)	17800	(4)	12900	(2)	5350	(4)	BQL	(NC)
	Thyroid Gland	10500	(NC)	6360	(NC)	10700	(NC)	19000	(NC)	13300	(NC)	6120	(NC)	BQL	(NC)
Secretory	Harderian Gland	8210	(NC)	10600	(NC)	31900	(19)	88900	(3)	91800	(NC)	27600	(NC)	627	(89)
	Salivary Gland	13000	(NC)	10900	(16)	16300	(14)	33700	(6)	21800	(NC)	9530	(6)	BQL	(NC)
Fatty	Brown Fat	7610	(13)	6360	(16)	17800	(NC)	28900	(8)	14300	(3)	6830	(5)	BQL	(NC)
	White Fat	7620	(38)	8040	(36)	14600	(26)	23800	(31)	13800	(24)	7260	(29)	BQL	(NC)
Gonads/ Accessory Reproductive Organs	Ovary	12200	(NC)	6890	(NC)	12100	(22)	19300	(NC)	18100	(NC)	8050	(NC)	BQL	(NC)
	Uterus	5420	(35)	3910[b]	(NC)	10000	(20)	13100	(14)	10900	(26)	5260	(NC)	BQL	(NC)
Muscular	Myocardium	14200	(4)	9740	(17)	13600	(5)	26800	(8)	18900	(6)	7770	(4)	BQL	(NC)
	Skeletal Muscle	4190	(16)	4190	(4)	7710	(9)	17300	(9)	11700	(5)	6240	(17)	BQL	(NC)
Skeletal	Bone	939	(16)	1660	(45)	1180	(38)	3920	(61)	1260	(31)	1060	(NC)	BQL	(NC)
	Bone Marrow	8680	(1)	4910	(12)	10500	(14)	16700	(33)	9520	(19)	5620	(NC)	BQL	(NC)
Ocular	Eyeball	1220	(NC)	BQL	(NC)	1730	(48)	3010	(17)	1160	(NC)	446	(NC)	BQL	(NC)
	Eye - Lens	BQL	(NC)	BQL	(NC)	BQL	(NC)	BQL	(NC)	678	(NC)	BQL	(NC)	BQL	(NC)

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Tissue Group	Tissue Name	Radiocarbon Concentration [SCH 619734 ng equiv/g (CV, %)][a]													
		1-hr		2-hr		4-hr		8-hr		24-hr		48-hr		168-hr	
Miscellaneous	Lung	24500	(15)	15300	(28)	33800	(23)	45900	(5)	20500	(24)	11000	(6)	BQL	(NC)
	Pancreas	15500	(15)	13700	(7)	18700	(12)	35000	(8)	23600	(7)	9720	(18)	BQL	(NC)
	Spleen	16200	(6)	9770	(NC)	18200	(9)	27600	(NC)	18500	(NC)	8120	(2)	BQL	(NC)
	Skin	3960	(9)	3480	(14)	7100	(21)	13300	(14)	7200	(12)	3580	(4)	BQL	(NC)
Gastro-Esophageal and Intestinal Tract Walls	Esophagus	4150	(NC)	6030	(57)	7480	(NC)	14500	(NC)	8790	(NC)	2660	(NC)	BQL	(NC)
	Stomach	10100	(22)	9280	(34)	12400	(20)	13700	(7)	8940	(4)	4430	(13)	BQL	(NC)
	Small Intestine	7420	(34)	9860	(13)	15300	(35)	20000	(34)	15000	(3)	5150	(26)	BQL	(NC)
	Large Intestine	5720	(24)	4640	(6)	6890	(35)	17800	(5)	30000	(65)	8000	(10)	315	(173)

a: Mean (CV, %) values based on digital sampling or digital re-sampling (up to 3 samples) from tissue sections collected from a single rat at different levels.
BQL: Below quantifiable limits (646 ng equiv/g). Value assigned to zero (0) for summary statistics.
NC: Not calculable when the number of replicate samples that were measured was <3 or when mean value was BQL.

Table 5 Mean (CV, %) Tissue Radiocarbon Concentrations After a Single Oral 25 mg [14C]-SCH 619734/kg Suspension Dose to Male Pigmented Rats (Group 3)

Tissue Group	Tissue Name	Radiocarbon Concentration [SCH 619734 ng equiv/g (CV, %)][a]													
		1-hr		2-hr		4-hr		8-hr		24-hr		48-hr		168-hr	
Vascular	Blood	834	(15)	1320	(7)	3100	(10)	3430	(9)	787	(4)	BQL	(NC)	BQL	(NC)
Lymphatic	Lymph Node	1430	(33)	3160	(36)	9300	(24)	13200	(12)	2100	(4)	308	(172)	BQL	(NC)
Metabolic/ Excretory	Bladder	2140	(15)	8560	(NC)	11600	(11)	13800	(NC)	2630	(51)	2220	(117)	261	173
	Kidney	4090	(9)	5750	(NC)	18000	(1)	18500	(16)	3470	(11)	1100	(NC)	BQL	(NC)
	Liver	9960	(7)	12300	(2)	32200	(12)	31600	(1)	8920	(3)	3180	(4)	799	11
Central Nervous System	Brain	988	(3)	1470	(5)	5530	(6)	6550	(7)	BQL	(NC)	BQL	(NC)	BQL	(NC)
	Spinal Cord	775	(NC)	1640	(30)	5810	(NC)	7670	(NC)	892	(22)	BQL	(NC)	BQL	(NC)
Endocrine	Adrenal Gland	6200	(NC)	8740	(NC)	35000	(NC)	28500	(NC)	4680	(NC)	1400	(12)	223	173
	Pituitary Gland	2650	(19)	4150	(NC)	11300	(NC)	18600	(NC)	3270	(NC)	411	(NC)	BQL	(NC)
	Thymus	1390	(4)	2710	(13)	9740	(2)	14200	(5)	2230	(7)	BQL	(NC)	BQL	(NC)
	Thyroid Gland	3890	(NC)	5360	(NC)	15000	(NC)	19600	(NC)	3120	(NC)	1020	(NC)	BQL	(NC)
Secretory	Harderian Gland	2510	(NC)	5860	(14)	33000	(NC)	54100	(24)	20500	(NC)	795	(NC)	BQL	(NC)
	Salivary Gland	3710	(3)	5320	(4)	18700	(3)	21700	(NC)	3670	(10)	990	(NC)	BQL	(NC)
Fatty	Brown Fat	2640	(8)	4570	(12)	17700	(16)	21500	(20)	2580	(2)	525	(87)	BQL	(NC)
	White Fat	2330	(14)	3780	(1)	17200	(11)	19600	(4)	1510	(8)	BQL	(NC)	BQL	(NC)
Gonads/Accessory Reproductive Organs	Epididymis	BQL	(NC)	1420	(12)	6950	(9)	11500	(NC)	2380	(41)	2350	(53)	307	(173)
	Prostate Gland	1430	(16)	2770	(16)	9690	(43)	16200	(19)	2530	(22)	BQL	(NC)	218	(173)
	Seminal Vesicles	740	(91)	1310	(18)	7360	(3)	9730	(8)	1390	(5)	266	(173)	BQL	(NC)
	Testis	BQL	(NC)	1240	(2)	6290	(3)	10300	(NC)	2630	(2)	810	(4)	BQL	(NC)
Muscular	Myocardium	3310	(6)	4820	(6)	13800	(8)	18200	(7)	2640	(4)	887	(14)	BQL	(NC)
	Skeletal Muscle	1100	(12)	2530	(7)	9280	(9)	14200	(16)	1730	(7)	BQL	(NC)	BQL	(NC)
Skeletal	Bone	BQL	(NC)	899	(32)	2300	(24)	4200	(13)	291	(174)	BQL	(NC)	BQL	(NC)
	Bone Marrow	2000	(25)	2930	(39)	11600	(8)	12000	(3)	2000	(10)	BQL	(NC)	BQL	(NC)

Tissue Group	Tissue Name	Radiocarbon Concentration [SCH 619734 ng equiv/g (CV, %)][a]													
		1-hr		2-hr		4-hr		8-hr		24-hr		48-hr		168-hr	
Ocular	Eyeball	BQL	(NC)	1130	(12)	3620	(NC)	4730	(NC)	1610	(NC)	BQL	(NC)	BQL	(NC)
	Eye - Lens	BQL	(NC)	284	(173)	BQL	(NC)	BQL	(NC)	BQL	(NC)	BQL	(NC)	BQL	(NC)
Miscellaneous	Lung	5110	(11)	8520	(15)	26700	(3)	33700	(5)	4260	(7)	1040	(9)	BQL	(NC)
	Pancreas	7250	(51)	6160	(NC)	20900	(8)	25100	(8)	3400	(22)	1290	(NC)	BQL	(NC)
	Spleen	7440	(NC)	6840	(NC)	17900	(NC)	20700	(3)	2870	(NC)	943	(NC)	BQL	(NC)
	Skin	1240	(15)	2410	(24)	5980	(21)	11000	(14)	1320	(26)	703	(87)	457	(173)
Gastro-Esophageal and Intestinal Tract Walls	Esophagus	1410	(33)	4860	(NC)	14600	(27)	11300	(NC)	1570	(26)	BQL	(NC)	BQL	(NC)
	Stomach	7270	(45)	14900	(39)	12100	(NC)	12100	(27)	2680	(41)	246	(174)	BQL	(NC)
	Small Intestine	4460	(53)	10400	(39)	25400	(20)	22000	(6)	4760	(14)	844	(15)	BQL	(NC)
	Large Intestine	1710	(14)	1980	(20)	6570	(30)	23100	(18)	9700	(63)	1410	(25)	BQL	(NC)

a: Mean (CV, %) values based on digital sampling or digital re-sampling (up to 3 samples) from tissue sections collected from a single rat at different levels.

BQL: Below quantifiable limits (646 ng equiv/g). Value assigned to zero (0) for summary statistics.

NC: Not calculable when the number of replicate samples that were measured was <3 or when mean value was BQL.

Table 6 Mean (CV, %) Tissue Radiocarbon Concentrations After a Single Oral 25 mg [14C]-SCH 619734/kg Suspension Dose to Female Pigmented Rats (Group 4)

Tissue Group	Tissue Name	Radiocarbon Concentration [SCH 619734 ng equiv/g (CV, %)][a]													
		1-hr		2-hr		4-hr		8-hr		24-hr		48-hr		168-hr	
Vascular	Blood	1800	(19)	3010	(5)	3340	(6)	5520	(24)	3370	(16)	1620	(27)	BQL	(NC)
Lymphatic	Lymph Node	5440	(45)	9560	(17)	9000	(18)	14800	(NC)	12400	(52)	4020	(32)	591	(87)
Metabolic/ Excretory	Bladder	2940	(NC)	7130	(NC)	11500	(NC)	10800	(NC)	15400	(NC)	11400	(NC)	481	(NC)
	Kidney	8790	(NC)	15700	(18)	16100	(7)	20500	(1)	15300	(7)	6950	(1)	1380	(13)
	Liver	21400	(4)	25200	(4)	23600	(11)	30800	(4)	23700	(4)	11100	(8)	2250	(3)
Central Nervous System	Brain	3250	(6)	5950	(13)	8000	(6)	12000	(0)	8190	(8)	3020	(3)	221	(173)
	Spinal Cord	3160	(27)	6550	(NC)	7100	(NC)	13900	(NC)	11300	(5)	3880	(1)	754	(NC)
Endocrine	Adrenal Gland	16700	(NC)	21700	(NC)	25100	(NC)	34100	(NC)	23800	(11)	7570	(NC)	1860	(NC)
	Pituitary Gland	9010	(12)	12300	(28)	18400	(NC)	25500	(NC)	19300	(NC)	8520	(16)	1900	(NC)
	Thymus	4550	(5)	8880	(3)	11500	(3)	16700	(4)	13300	(5)	5900	(4)	1050	(9)
	Thyroid Gland	9380	(NC)	14800	(2)	20000	(NC)	24100	(NC)	14000	(NC)	6330	(13)	1500	(NC)
Secretory	Harderian Gland	8480	(NC)	20300	(NC)	39200	(NC)	49400	(NC)	47300	(NC)	26000	(NC)	6390	(NC)
	Salivary Gland	10100	(5)	17600	(4)	21100	(5)	28500	(12)	21200	(6)	9460	(4)	1700	(8)
Fatty	Brown Fat	9650	(22)	16800	(7)	18100	(1)	26100	(5)	18700	(2)	7740	(12)	1460	(9)
	White Fat	4470	(32)	11100	(11)	16400	(8)	18600	(30)	18200	(12)	7400	(20)	1330	(8)
Gonads/Accessory Reproductive Organs	Ovary	7310	(NC)	17400	(NC)	12400	(NC)	17700	(NC)	13400	(NC)	5420	(NC)	931	(NC)
	Uterus	2290	(NC)	7670	(NC)	8760	(NC)	10300	(23)	8960	(NC)	6080	(NC)	502	(87)
Muscular	Myocardium	9410	(15)	14600	(1)	14800	(4)	21600	(5)	17500	(4)	7790	(5)	1430	(3)
	Skeletal Muscle	3840	(16)	7230	(23)	8970	(8)	13300	(9)	10800	(3)	5310	(8)	882	(16)
Skeletal	Bone	1010	(NC)	1750	(16)	2680	(60)	5370	(39)	3450	(39)	702	(91)	BQL	(NC)
	Bone Marrow	7150	(NC)	10500	(7)	11500	(2)	15000	(11)	12900	(11)	4010	(32)	635	(92)
Ocular	Eyeball	4210	(57)	2510	(NC)	4010	(NC)	4410	(NC)	4880	(NC)	3000	(NC)	850	(NC)
	Eye - Lens	663	(173)	BQL	(NC)	BQL	(NC)	BQL	(NC)	BQL	(NC)	1070	(NC)	BQL	(NC)
Miscellaneous	Lung	18600	(20)	23400	(6)	22600	(10)	34400	(7)	24200	(11)	13000	(9)	2200	(9)
	Pancreas	14000	(NC)	19500	(11)	23600	(9)	31000	(3)	21900	(20)	10900	(12)	1840	(12)
	Spleen	13100	(NC)	17700	(NC)	16400	(NC)	23000	(NC)	17200	(NC)	6960	(NC)	1670	(27)
	Skin	3340	(10)	5650	(20)	8140	(6)	11200	(18)	10100	(28)	3370	(30)	592	(88)
Gastro-Esophageal and Intestinal Tract Walls	Esophagus	7880	(43)	17100	(15)	6610	(NC)	12200	(NC)	11700	(34)	4470	(NC)	BQL	(NC)
	Stomach	9780	(36)	9090	(26)	9740	(8)	11000	(9)	7050	(2)	3730	(19)	882	(29)
	Small Intestine	9460	(15)	26400	(3)	17200	(20)	23600	(12)	16000	(8)	6510	(48)	1210	(17)
	Large Intestine	4860	(39)	7440	(54)	7520	(44)	14600	(27)	15100	(15)	6720	(NC)	1280	(24)

a: Mean (CV, %) values based on digital sampling or digital re-sampling (up to 3 samples) from tissue sections collected from a single rat at different levels.

BQL: Below quantifiable limits (646 ng equiv/g). Value assigned to zero (0) for summary statistics.

NC: Not calculable when the number of replicate samples that were measured was <3 or when mean value was BQL.

Tissue-to blood concentration ratios in male and female albino and pigmented are shown in the following tables (from page 35-38 of the report).

Table 7 Tissue-to-Blood Concentration Ratios for Male Albino Rats After a Single Oral 25 mg [14C]-SCH 619734/kg Suspension Dose (Group 1)

Tissue Group	Tissue Name	Tissue-to-Blood Concentration Ratios						
		1-hr	2-hr	4-hr	8-hr	24-hr	48-hr	168-hr
Vascular	Blood	1.00	1.00	1.00	1.00	1.00	NC	NC
Lymphatic	Lymph Node	2.56	2.32	2.95	2.55	2.74	NC	NC
Metabolic/ Excretory	Bladder	2.96	3.47	3.01	4.12	2.45	NC	NC
	Kidney	6.52	5.41	5.01	4.46	5.44	NC	NC
	Liver	14.8	9.21	8.94	7.65	8.43	NC	NC
Central Nervous System	Brain	1.12	1.23	1.25	1.06	1.23	NC	NC
	Spinal Cord	1.20	1.08	1.14	1.30	1.16	NC	NC
Endocrine	Adrenal Gland	8.65	8.28	6.16	6.32	8.43	NC	NC
	Pituitary Gland	3.03	3.80	3.44	5.29	5.57	NC	NC
	Thymus	1.54	2.44	2.74	2.91	3.48	NC	NC
	Thyroid Gland	1.70	3.69	3.95	3.87	3.31	NC	NC
Secretory	Harderian Gland	2.34	4.97	5.64	6.16	27.8	NC	NC
	Salivary Gland	4.35	5.36	5.39	5.36	6.19	NC	NC
Fatty	Brown Fat	2.10	4.32	3.95	4.21	6.22	NC	NC
	White Fat	3.11	3.69	3.64	4.12	2.91	NC	NC
Gonads/Accessory Reproductive Organs	Epididymis	0.948	1.77	1.59	2.52	4.55	NC	NC
	Prostate Gland	1.62	2.24	2.28	3.62	3.63	NC	NC
	Seminal Vesicles	0.703	1.57	1.72	1.03	1.33	NC	NC
	Testis	0.723	1.18	1.46	2.07	3.32	NC	NC
Muscular	Myocardium	4.64	4.45	4.10	4.02	4.68	NC	NC
	Skeletal Muscle	1.45	2.30	2.50	2.76	3.09	NC	NC
Skeletal	Bone	0.445	0.546	1.03	0.786	0.681	NC	NC
	Bone Marrow	2.98	3.55	3.12	2.97	3.39	NC	NC
Ocular	Eyeball	NC	0.201	0.418	0.467	0.554	NC	NC
	Eye - Lens	NC	NC	NC	NC	0.157	NC	NC
Miscellaneous	Lung	5.45	6.91	6.42	5.05	8.07	NC	NC
	Pancreas	7.23	5.68	5.90	5.60	7.36	NC	NC
	Spleen	6.07	4.81	5.01	4.64	5.19	NC	NC
	Skin	1.39	2.21	2.33	2.00	2.31	NC	NC
Gastro-Esophageal and Intestinal Tract Walls	Esophagus	4.61	3.36	2.92	2.93	2.71	NC	NC
	Stomach	10.1	2.79	2.77	2.93	1.97	NC	NC
	Small Intestine	29.2	7.32	9.14	6.25	9.79	NC	NC
	Large Intestine	1.94	2.51	2.57	4.18	5.51	NC	NC

NC: Not calculable because blood and/or tissue concentrations cannot be measured.

Table 8 Tissue-to-Blood Concentration Ratios for Female Albino Rats After a Single Oral 25 mg [14C]-SCH 619734/kg Suspension Dose (Group 2)

Tissue Group	Tissue Name	Tissue-to-Blood Concentration Ratios						
		1-hr	2-hr	4-hr	8-hr	24-hr	48-hr	168-hr
Vascular	Blood	1.00	1.00	1.00	1.00	1.00	1.00	NC
Lymphatic	Lymph Node	3.89	3.23	3.01	4.32	4.05	2.23	NC
Metabolic/ Excretory	Bladder	2.98	1.37	2.32	2.92	2.50	1.97	NC
	Kidney	6.94	5.02	5.71	6.49	5.50	4.27	NC
	Liver	13.9	8.81	7.87	10.5	8.36	7.26	NC
Central Nervous System	Brain	2.39	1.84	1.88	3.54	1.87	1.58	NC
	Spinal Cord	1.66	1.62	1.58	4.05	2.72	2.28	NC
Endocrine	Adrenal Gland	11.3	9.00	10.3	13.6	9.07	7.08	NC
	Pituitary Gland	5.11	4.71	5.41	5.71	4.92	4.65	NC
	Thymus	3.28	2.94	3.19	4.77	4.15	3.18	NC
	Thyroid Gland	5.44	3.16	3.61	5.09	4.28	3.64	NC
Secretory	Harderian Gland	4.25	5.27	10.8	23.8	29.5	16.4	NC
	Salivary Gland	6.74	5.42	5.51	9.03	7.01	5.67	NC
Fatty	Brown Fat	3.94	3.16	6.01	7.75	4.60	4.07	NC
	White Fat	3.95	4.00	4.93	6.38	4.44	4.32	NC
Gonads/Accessory Reproductive Organs	Ovary	6.32	3.43	4.09	5.17	5.82	4.79	NC
	Uterus	2.81	1.95	3.38	3.51	3.50	3.13	NC
Muscular	Myocardium	7.36	4.85	4.59	7.18	6.08	4.63	NC
	Skeletal Muscle	2.17	2.08	2.60	4.64	3.76	3.71	NC
Skeletal	Bone	0.487	0.826	0.399	1.05	0.405	0.631	NC
	Bone Marrow	4.50	2.44	3.55	4.48	3.06	3.35	NC
Ocular	Eyeball	0.632	NC	0.584	0.807	0.373	0.265	NC
	Eye - Lens	NC	NC	NC	NC	0.218	NC	NC
Miscellaneous	Lung	12.7	7.61	11.4	12.3	6.59	6.55	NC
	Pancreas	8.03	6.82	6.32	9.38	7.59	5.79	NC
	Spleen	8.39	4.86	6.15	7.40	5.95	4.83	NC
	Skin	2.05	1.73	2.40	3.57	2.32	2.13	NC
Gastro-Esophageal and Intestinal Tract Walls	Esophagus	2.15	3.00	2.53	3.89	2.83	1.58	NC
	Stomach	5.23	4.62	4.19	3.67	2.87	2.64	NC
	Small Intestine	3.84	4.91	5.17	5.36	4.82	3.07	NC
	Large Intestine	2.96	2.31	2.33	4.77	9.65	4.76	NC

NC: Not calculable because blood and/or tissue concentrations cannot be measured.

Table 9 Tissue-to-Blood Concentration Ratios for Male Pigmented Rats After a Single Oral 25 mg [14C]-SCH 619734/kg Suspension Dose (Group 3)

Tissue Group	Tissue Name	Tissue-to-Blood Concentration Ratios						
		1-hr	2-hr	4-hr	8-hr	24-hr	48-hr	168-hr
Vascular	Blood	1.00	1.00	1.00	1.00	1.00	NC	NC
Lymphatic	Lymph Node	1.71	2.39	3.00	3.85	2.67	NC	NC
Metabolic/ Excretory	Bladder	2.57	6.48	3.74	4.02	3.34	NC	NC
	Kidney	4.90	4.36	5.81	5.39	4.41	NC	NC
	Liver	11.9	9.32	10.4	9.21	11.3	NC	NC
Central Nervous System	Brain	1.18	1.11	1.78	1.91	NC	NC	NC
	Spinal Cord	0.929	1.24	1.87	2.24	1.13	NC	NC
Endocrine	Adrenal Gland	7.43	6.62	11.3	8.31	5.95	NC	NC
	Pituitary Gland	3.18	3.14	3.65	5.42	4.16	NC	NC
	Thymus	1.67	2.05	3.14	4.14	2.83	NC	NC
	Thyroid Gland	4.66	4.06	4.84	5.71	3.96	NC	NC
Secretory	Harderian Gland	3.01	4.44	10.6	15.8	26.0	NC	NC
	Salivary Gland	4.45	4.03	6.03	6.33	4.66	NC	NC
Fatty	Brown Fat	3.17	3.46	5.71	6.27	3.28	NC	NC
	White Fat	2.79	2.86	5.55	5.71	1.92	NC	NC
Gonads/Accessory Reproductive Organs	Epididymis	NC	1.08	2.24	3.35	3.02	NC	NC
	Prostate Gland	1.71	2.10	3.13	4.72	3.21	NC	NC
	Seminal Vesicles	0.887	0.992	2.37	2.84	1.77	NC	NC
	Testis	NC	0.939	2.03	3.00	3.34	NC	NC
Muscular	Myocardium	3.97	3.65	4.45	5.31	3.35	NC	NC
	Skeletal Muscle	1.32	1.92	2.99	4.14	2.20	NC	NC
Skeletal	Bone	NC	0.681	0.742	1.22	0.370	NC	NC
	Bone Marrow	2.40	2.22	3.74	3.50	2.54	NC	NC
Ocular	Eyeball	NC	0.856	1.17	1.38	2.05	NC	NC
	Eye - Lens	NC	0.215	NC	NC	NC	NC	NC
Miscellaneous	Lung	6.13	6.45	8.61	9.83	5.41	NC	NC
	Pancreas	8.69	4.67	6.74	7.32	4.32	NC	NC
	Spleen	8.92	5.18	5.77	6.03	3.65	NC	NC
	Skin	1.49	1.83	1.93	3.21	1.68	NC	NC
Gastro-Esophageal and Intestinal Tract Walls	Esophagus	1.69	3.68	4.71	3.29	1.99	NC	NC
	Stomach	8.72	11.3	3.90	3.53	3.41	NC	NC
	Small Intestine	5.35	7.88	8.19	6.41	6.05	NC	NC
	Large Intestine	2.05	1.50	2.12	6.73	12.3	NC	NC

NC: Not calculable because blood and/or tissue concentrations cannot be measured.

Table 10 Tissue-to-Blood Concentration Ratios for Female Pigmented Rats After a Single Oral 25 mg [14C]-SCH 619734/kg Suspension Dose (Group 4)

Tissue Group	Tissue Name	Tissue-to-Blood Concentration Ratios						
		1-hr	2-hr	4-hr	8-hr	24-hr	48-hr	168-hr
Vascular	Blood	1.00	1.00	1.00	1.00	1.00	1.00	NC
Lymphatic	Lymph Node	3.02	3.18	2.69	2.68	3.68	2.48	NC
Metabolic/ Excretory	Bladder	1.63	2.37	3.44	1.96	4.57	7.04	NC
	Kidney	4.88	5.22	4.82	3.71	4.54	4.29	NC
	Liver	11.9	8.37	7.07	5.58	7.03	6.85	NC
Central Nervous System	Brain	1.81	1.98	2.40	2.17	2.43	1.86	NC
	Spinal Cord	1.76	2.18	2.13	2.52	3.35	2.40	NC
Endocrine	Adrenal Gland	9.28	7.21	7.51	6.18	7.06	4.67	NC
	Pituitary Gland	5.01	4.09	5.51	4.62	5.73	5.26	NC
	Thymus	2.53	2.95	3.44	3.03	3.95	3.64	NC
	Thyroid Gland	5.21	4.92	5.99	4.37	4.15	3.91	NC
Secretory	Harderian Gland	4.71	6.74	11.7	8.95	14.0	16.0	NC
	Salivary Gland	5.61	5.85	6.32	5.16	6.29	5.84	NC
Fatty	Brown Fat	5.36	5.58	5.42	4.73	5.55	4.78	NC
	White Fat	2.48	3.69	4.91	3.37	5.40	4.57	NC
Gonads/Accessory Reproductive Organs	Ovary	4.06	5.78	3.71	3.21	3.98	3.35	NC
	Uterus	1.27	2.55	2.62	1.87	2.66	3.75	NC
Muscular	Myocardium	5.23	4.85	4.43	3.91	5.19	4.81	NC
	Skeletal Muscle	2.13	2.40	2.69	2.41	3.20	3.28	NC
Skeletal	Bone	0.561	0.581	0.802	0.973	1.02	0.433	NC
	Bone Marrow	3.97	3.49	3.44	2.72	3.83	2.48	NC
Ocular	Eyeball	2.34	0.834	1.20	0.799	1.45	1.85	NC
	Eye - Lens	0.368	NC	NC	NC	NC	0.660	NC
Miscellaneous	Lung	10.3	7.77	6.77	6.23	7.18	8.02	NC
	Pancreas	7.78	6.48	7.07	5.62	6.50	6.73	NC
	Spleen	7.28	5.88	4.91	4.17	5.10	4.30	NC
	Skin	1.86	1.88	2.44	2.03	3.00	2.08	NC
Gastro-Esophageal and Intestinal Tract Walls	Esophagus	4.38	5.68	1.98	2.21	3.47	2.76	NC
	Stomach	5.43	3.02	2.92	1.99	2.09	2.30	NC
	Small Intestine	5.26	8.77	5.15	4.28	4.75	4.02	NC
	Large Intestine	2.70	2.47	2.25	2.64	4.48	4.15	NC

NC: Not calculable because blood and/or tissue concentrations cannot be measured.

Overall, following a single oral dose of 15 mg/kg of ^{14}C-SCH 619734, radioactivity was absorbed rapidly into circulating blood and was widely distributed to the tissues. There was no apparent strain or gender difference in the qualitative distribution pattern of radioactivity in tissues. Excretion of radioactivity in the urine over the 168 hour post-dose was greater in males (~24%) than that in females (~2.4%). Most ^{14}C-SCH 619734-derived radioactivity was recovered in the feces (~80% of the dose).

Formulation Excipient Effects on Plasma Pharmacokinetics and Brain Uptake of SCH 619734 in Rats (Study No. DM27349)

Methods: The objective of this study was to compare SCH 619734 brain uptake and plasma pharmacokinetics (PK) in male rats administered an IV dose of 5 mg/kg of SCH 619734 in either a Solutol HS 15- or a hydroxypropyl-beta-cyclodextrin (HPβCD)-based formulation. An additional objective was to compare SCH 619734 uptake in rats receiving the 5 mg/kg of SCH 619734 by either the IV or the oral route of administration. The following table (from page 8 of the report) shows the study design.

	Dose and Dose Formulation						Plasma/ Brain Samples (hr)	
Group No.	Formulation[a]	Route[b]	Vehicle[c]	Dose[d] (mg/kg)	Volume (mL/kg)	Conc. (mg/mL)		Gender/n
1	SCH 619734 in Sterile Solution	IV	20% HPβCD	5	2	2.5	0.083, 0.5, 1, 2, 6 and 24	Male/18
2		IV	22% Solutol		0.5	10		Male/18
3	SCH 619734 di-HCl Salt in Suspension	PO	0.4% HPMC		5	1	0.5, 1, 2, 6 and 24	Male/15

a: Di-HCl Salt, di-hydrochloride salt

b: IV (intravenous); PO (oral)

c: 20% HPβCD: 20% (w/v)hydroxypropyl-beta-cyclodextrin in water, pH 4.0, 22% Solutol: 22% (v/v) Solutol HS 15; polyethylene glycol 660 12-hydroxystearate in phosphate buffer, pH 7.0, 0.4% HPMC: 0.4% (w/v) hydroxypropyl methylcellulose in water, pH 3.0

d: Dose expressed as free base. Dose to Group 3 was 5.85 mg/kg when expressed as di-HCl monohydrate salt (1.17 salt correction factor)

Results: There were no appreciable differences in SCH 619734 brain uptake or plasma PK following the IV dose in either the HPβCD- or the Solutol-based solution formulation. No significant differences in SCH 619734 brain uptake were observed following an IV or oral dose. Brain and plasma concentrations and PK parameters of SCH 619734 are shown in the following table (from 9 of the report).

Brain and Plasma SCH 619734 Concentrations

Mean brain and plasma concentrations (ng/g or mL) and concentration ratios are presented in Table 1, Table 2 and Table 3 and plasma concentration-times profiles shown in Figure 1 and Figure 2.

Dose Route/ Vehicle (Study No.)	IV/HPβCD (DM27349)			IV/Solutol (DM27349)			PO/HPMC (DM27349)			PO/HPMC (NKC352)		
Time Point (hr)	B	P	B:P[e]	B	P	B:P	B	P	B:P	B	P	B:P
0.083	3350	872	3.13	3310	1070	2.54	NM	NM	NC			
0.5	2870	866	3.28	4250	952	4.53	137	150	0.937			
1	2310	690	3.34	2950	717	4.17	361	248	1.47	NM	NM	NC
2	1720	509	3.46	2420	561	4.33	875	419	2.13			
6	833	259	3.22	806	213	3.94	943	320	2.96			
24	50.5	17.6	2.69	56.2	25.9	2.34	133	39.1	3.25	34.7	8.00	4.03

a: Ratio of brain (B)-to-plasma (P) is considered unitless by assuming a density of 1.0

NM = Not measured

NC = Not calculable

Selected Brain and Plasma SCH 619734 Pharmacokinetic Parameters (presented in Table 4)

Dose Route/Vehicle (Study No.)	IV/HPβCD (DM27349)		IV/Solutol (DM27349)		PO/HPMC (DM27349)	
Parameter	B	P	B	P	B	P
C^0 (ng/mL)[f]	3450	873	3310	1100	NA	NA
Cmax[g] (ng/mL)	NA	NA	NA	NA	943	419
Tmax[g] (hr)	NA	NA	NA	NA	6	2
t1/2[c] (hr)	4.36	4.56	4.23	5.22	NC	NC
AUC(0-24 hr)[d] (ng·hr/mL)	17900	5450	20500	5270	14100	5180
B:P	3.29		3.89		2.72	

a: Initial concentration extrapolated to time zero (0)

b: Observed values for maximum concentration (Cmax) and time to reach Cmax (Tmax)

c: Terminal half-life

d: Area under the plasma concentration-time curve from time zero (0) to 24 hr post-dose

NA = Not applicable

SCH 720881 Binding to Human, Rat, and Monkey Plasma Proteins (Study No. KB-0046-DV-EB)

Methods: The percent binding of metabolite SCH 720881 to human, rat, and monkey plasma proteins was determined using an equilibrium dialysis approach. SCH 720881 was tested at a concentration of 2 µM, and binding to plasma proteins following 6 h of dialysis at 37ºC was evaluated.

Results: SCH 720881 plasma protein binding ranged from 99.0 to 99.2% in all species. The following table copied from the study report summarizes the protein binding for the test compound and warfarin (control).

Compound ID	Species	Mean % Protein Bound	Mean Unbound Fraction (f_u)	Mean % Remaining in Matrix
SCH 720881	Human	**99.1** ± 0.4	0.00901	60.3
SCH 720881	SD Rat	**99.0** ± 0.1	0.0101	82.5
SCH 720881	Cynomolgus Monkey	**99.2** ± 0.1	0.00847	68.9
Warfarin	Human	**98.6** ± 0.5	0.0144	129.8
Warfarin	SD Rat	**98.8** ± 0.02	0.0116	100.4
Warfarin	Cynomolgus Monkey	**99.0** ± 0.3	0.00978	97.1

SCH 619734 and SCH 720881 Binding to Rat Brain Proteins (Study No. KB-0048-DV-EB)

Methods: The percent binding of SCH 619734 and metabolite SCH 720881 to rat brain homogenate proteins was determined using equilibrium dialysis. Both compounds were tested at concentrations of 2 and 10 µM, and binding to rat brain homogenate following 6 h of dialysis at 37ºC was evaluated

Results: SCH 619734 binding to rat brain proteins was 99.9%. The percent binding of SCH 720881 to rat brain proteins was 99.6% and 99.5% at 2 and 10 µM, respectively. The following table copied from the study report summarizes the protein binding for both test compounds and warfarin (control).

Compound ID	Concentration (µM)	Species / Matrix	Mean % Protein Bound	Mean % Free	Mean Unbound Fraction (f_u)	Mean % Remaining in Matrix
SCH 720881	2	SD Rat Brain Homogenate	**99.6** ± 0.02	0.43	0.00433	100.2
SCH 720881	10	SD Rat Brain Homogenate	**99.5** ± 0.04	0.49	0.00494	103.2
SCH 619734	2	SD Rat Brain Homogenate	**99.9** ± 0.01	0.10	0.000973	96.4
SCH 619734	10	SD Rat Brain Homogenate	**99.9** ± 0.01	0.12	0.00124	99.6
Warfarin	2	SD Rat Brain Homogenate	**29.3** ± 6.3	70.6	0.707	108.9
Warfarin	10	SD Rat Brain Homogenate	**23.7** ± 4.8	76.1	0.763	107.4

Brain Exposure of SCH 720881 in Male Sprague-Dawley Rats Following Oral Dose Administration of Rolapitant (Study No. KB-0043-DA-RI)

Methods: The purpose of this study was to evaluate whether metabolite SCH 720881 can penetrate the blood-brain barrier. A single oral gavage dose of rolapitant was administered to fasted male Sprague-Dawley rats at dose levels of 10 and 25 mg/kg (n=6/group). The vehicle was 0.4% (w/v) hydroxypropyl methylcellulose in water (pH=4). Atenolol (control article) was administered at a dose of 5 mg/kg by intravenous injection 15 min prior to scheduled euthanasia. Terminal blood samples were collected from 3 animals/group/time point at 24 and 48 h post-dose. Plasma and brain samples

were analyzed for SCH 720881 and atenolol by LC-MS/MS. Concentrations of atenolol (which has very poor blood-brain barrier penetration) were used to calculate the fraction of plasma in brain samples. Concentrations of SCH 720881 were corrected by subtracting the contribution from residual plasma volume in the brain samples.

Results: At 10 mg/kg, concentrations of SCH 720881 in the brain (corrected for the contribution of residual plasma in brain samples) were 102 and 30.9 ng/kg at 24 and 48 h post-dosing, respectively. The brain:plasma concentrations ratios were 0.68 and 0.43 at 24 and 48 h, respectively. At 25 mg/kg, concentrations of SCH 720881 in the brain (corrected for the contribution of residual plasma in brain samples) were 298 and 48.1 ng/kg at 24 and 48 h post-dosing, respectively, and the brain:plasma ratios were 0.70 and 0.79, respectively at these time points. Thus, metabolite SCH 720881 does penetrate the blood-brain barrier, although concentrations were higher in plasma relative to brain. The following table copied from the study report presents the brain:plasma concentration ratios for SCH 720881.

Table 5 SCH 720881 Concentrations in Plasma and Brain Samples and Brain-to-Plasma Concentration Ratios Following a Single Oral Gavage Dose of Rolapitant to Fasted Male Sprague-Dawley Rats at Target Dose Levels of 10 mg/kg and 25 mg/kg

Group No.	Hour Nominal	Animal No.	Plasma Concentration (ng/mL)	Original Brain Concentration (ng/g)	Plasma Contribution to Brain (mL/g)	Corrected Brain Concentration (ng/g)	Corrected Brain:Plasma Concentration Ratio
1 (10 mg/kg)	24	1	197	123	0.0393	115	0.585
		2	191	128	0.0369	121	0.633
		3	82.6	72.2	0.0467	68.3	0.827
		Mean	**157**	**108**	**0.0410**	**102**	**0.682**
		SD	**64.4**	**30.9**	**0.00508**	**28.9**	**0.128**
	48	4	9.85	BQL<(10.0)	BQL<(10.0)	BQL<(10.0)	NA
		5	20.2	10.6	0.0421	9.75	0.483
		6	135	59.4	0.0547	52.0	0.385
		Mean	**55.0**	**35.0**	**0.0484**	**30.9**	**0.434**
		SD	**69.5**	**NA**	**NA**	**NA**	**NA**
2 (25 mg/kg)	24	7	491	332	0.0793	293	0.597
		8	311	259	0.0405	246	0.792
		9	504	371	0.0345	354	0.702
		Mean	**435**	**321**	**0.0514**	**298**	**0.697**
		SD	**108**	**56.9**	**0.0243**	**53.8**	**0.0978**
	48	10	117	92.6	0.0651	85.0	0.726
		11	25.4	21.6	0.0684	19.9	0.782
		12	45.8	41.8	0.0528	39.4	0.860
		Mean	**62.7**	**52.0**	**0.0621**	**48.1**	**0.789**
		SD	**48.1**	**36.6**	**0.00822**	**33.4**	**0.0671**

BQL Below quantification limit

Metabolism

Reviews of Study Nos. DM27251, DM27282, and DM27384 are incorporated below from the pharmacology review of IND [redacted] (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D. DGIEP).

Identification of Human Cytochrome P450 Enzyme Capable of Metabolizing SCH 619734 (Study No. DM27251)

Methods: In this study, human liver microsomes were incubated with ^{14}C-SCH 619734 (specific activity = 112.3 µCi/mg) for 2 h at 37^{0}C in the presence of NADPH-generating system in the presence and absence of inhibitors. The following CYP450s and three human flavin monooxygenases (FMOs, FMO1, FMO3 and FMO5) were examined: CYP1A1, CYP1A2, CYP2A6, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4A11, CYP4F2, CYP4F3A, CYP4F3B, and CYP4F12.

Results: In human liver microsomes, SCH 619734 was converted to the oxidative metabolite SCH 720881. This was mediated by CYP3A4 and CYP3A5. No metabolite was detected when incubated with FMO1, FMO3 and FMO5 enzymes. The results of this study suggested that the formation of the oxidative metabolite (SCH 720881) from SCH 619734 in human liver microsomes was primarily mediated by CYP3A4.

Determination of Metabolite Profiles of SCH 619734 Following a Single and Multiple Oral Dose of 25 mg/kg to Male CD-1 Mice (Study No. DM27282)

Methods: This study was conducted in male CD-1 mice after administration of a single and multiple oral doses of 25 mg/kg of SCH 619734. Plasma samples were collected at 4 hr post-dose on Day 1 (Group 1) and at 4 hr post-dose on Day 5 (Group 2) for metabolic profiling using LC-MS.

Results: On Day 1 at 4-hr, SCH 720881 (1.1%) and M21 (5.8%) were detected at concentrations greater than 1% of SCH 619734. On Day 5 at 4-hr, SCH 720881 and M21 were 2.98% and 19.4%, respectively, of the parent drug, SCH 619734. In addition, several other metabolites were detected in both plasma samples. These metabolites included M14, M22, and M23. Overall, M21 and SCH 720881 were the two most significant circulating metabolites in CD-1 mice.

Pharmacokinetics, Excretion and Metabolism of ^{14}C-SCH 619734 Following a Single Oral Administration of ^{14}C-SCH 619734 Suspension to Male and Female Rats (DM27384)

Methods: In this study, metabolism of SCH 619734 was examined following a single oral administration of 25 mg/kg ^{14}C-SCH 619734 to male and female rats. Plasma samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 hr time points from male rats, and at 0, 1, 2, 4, 6, 8, 10, 12, 24, 30, 48 hr time points from female rats (n = 3/sex). Urine was collected at 0-8, 8-24 hr and thereafter in 24-hr block intervals up to 168 hr, while feces were collected at 24-hr intervals up to 168 hr.

Results: The unchanged drug was the predominant drug-related component in the plasma. The major human metabolite M19 or SCH 720881, a hydroxy-SCH 619734, as well as hydroxy-O-desalkyl metabolites M4a and M6, and dihydroxy-O-desalkyl metabolite M4 were major circulating metabolites in male rats. In female rats, no circulating metabolite exceeded 6% of the parent drug concentration. Minor metabolites in the plasma included several isomeric hydroxy-SCH 619734 and several isomeric M+14 (m/z 515) metabolites in both sexes. In male rats, urine (0-48 hr) represented 23.8% of the administered radioactivity and contained three major metabolites. M6 accounted for 8.0% of the dose while M4 and hydroxy-O-desalkyl-SCH 619734 (M4a) accounted for 8.6% of the dose. Minor metabolites included dihydroxy-O-desalkyl-SCH 619734 (M1), and *O*-desalkyl-SCH 619734 (M7) and its glucuronide (M5). Most of these metabolites were found in minor amounts in the female rat urine (0-96 hr) which represented 1.84% of the administered radioactivity. No parent compound was detected in the urine from either sex. Feces represented 62.4% and 72.8% of the administered radioactivity in males and females, respectively. Major fecal metabolites included two hydroxy-metabolites (M21, M24), an M+14 (m/z 515) metabolite (M14a), and an M+30 metabolite (M12a) in the female, which were less prominent in the male. M6 was a prominent fecal metabolite in male rats, which was not detected in female rat feces. The following diagram (from page 22 of the report) shows the proposed metabolic pathway of SCH 619734 in rats.

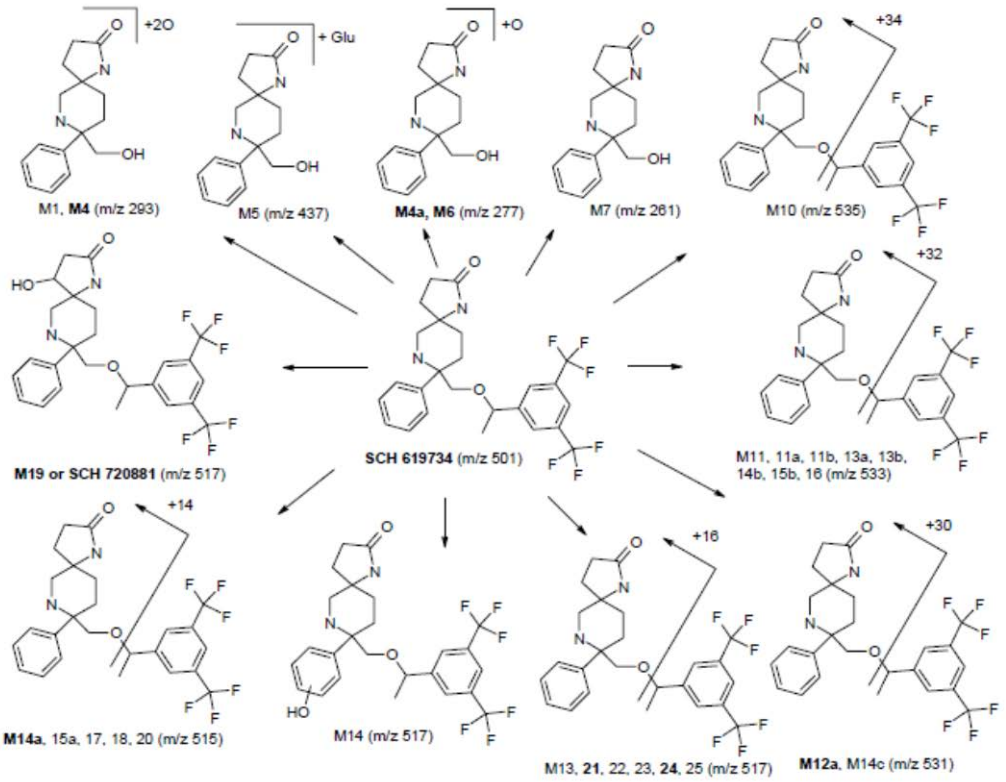


Figure 1 Proposed Biotransformation Pathway of SCH 619734 in Rats Following a Single Oral Dose (25 mg/kg)
Bold labels represent major drug related components.

Overall, SCH 619734 was the predominant component in the rat plasma from both sexes. The major human circulating metabolite M19 (SCH 720881) was also the major circulating metabolite in male rats but was a minor metabolite in the female rat plasma. In both sexes, oxidation and M+14 metabolite formation were two major biotransformation pathways. O-dealkylation appeared to be a significant metabolic pathway in male rats but was a minor pathway in the females.

Excretion

Reviews of Study Nos. DM27382 and PR-10-5008-N are incorporated below from the pharmacology review of IND [redacted] (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

Transfer of ^{14}C-SCH 619734-Derived Radioactivity into Milk following a Single Oral Administration to 12-Day Postpartum Rats (Study No. DM27382)

Methods: The objective of this study was to determine the extent of transfer of drug-derived radioactivity into milk after a single oral (gavage) administration of 25 mg of ^{14}C-SCH 619734 (112.3 µCi/mg) to 12-day postpartum (pp) female Sprague Dawley rats (n = 21). Maternal blood, plasma and milk (n = 3 dam rats/time point) and pooled blood and plasma from pups (n = 10 pups/sample) were collected from the vehicle (0.4 % w/v aqueous HPMC) control (n = 1) and treated animals at 1, 2, 4, 8, 12, 24, and 48 hr post-dose.

Results: Peak concentrations of radioactivity were observed at 8 hr post-dose in the blood and plasma. Transfer of radioactivity into milk was detected at 1 hr post-dose. Milk radioactivity concentrations were higher than those observed in the blood and plasma. Pups were exposed to less drug-derived radioactivity compared to dams and the plasma $AUC_{0\text{-}48hr}$ value was 7.69% that of dams. The sponsor commented that based upon average daily consumption of milk (2 mL/day), and the maximum milk radioactivity concentration determined, pup exposure was expected to be 0.322% of the orally administered dose. SCH 619734 was excreted through the milk in lactating rats.

Pharmacokinetics of Rolapitant in 5/6 Nephrectomized Female Rats Following a Single Intravenous Infusion or Single Oral Gavage Dose (PR-10-5008-N)

Methods: The objective of this study was to determine the pharmacokinetics of rolapitant following a single IV infusion (15 minutes, 5 mg/kg) or a single oral (10 mg/kg) gavage dose to female 5/6 nephrectomized (a model of renal insufficiency) or sham-operated SD rats. The following table (from page 6 of the report) shows the study design. The vehicle was 0.4% aqueous HPMC (pH 4.0).

Group No.	Dose Route	Dose Level (mg/kg)	Dose Volume (mL/kg)	Infusion rate (mL/kg/hr)	Dose Concentration (mg/mL)	No. of Animals Females
1/sham-operated	Intravenous [a]	5	2.5	10	2	12
2/5/6 nephrectomized	Intravenous [a]	5	2.5	10	2	12
3/sham-operated	Oral	10	5	N/A	2	12
4/5/6 nephrectomized	Oral	10	5	N/A	2	12

N/A: not applicable.
[a] 15 minutes infusion.

Renal insufficiency of the 5/6 nephrectomized animals was confirmed by measuring serum urea nitrogen, serum creatinine and urine creatinine levels before treatment. Blood was collected at specified time points.

Results: An increase of both serum urea nitrogen and serum creatinine and a decrease of urine creatinine for the 5/6 nephrectomized animals as compared to sham-operated rats were considered suggestive of renal insufficiency. The Cmax was observed at 15 min post-infusion. The Cmax and AUC_{0-24h} of rolapitant were similar for both the groups. The Cmax of the metabolite, SCH 720881, was observed at 24 hours post-dose. The Cmax and AUC_{0-24h} of the metabolite were higher in 5/6 nephrectomized rats than the sham operated animals.

Following the oral gavage dose, the Cmax was observed at 3 hours and 6 hours for Groups 3 and 4, respectively. The Cmax and AUC_{0-24h} of rolapitant were similar for both sham-operated animals and 5/6 nephrectomized rats. The Cmax of the metabolite, SCH 720881, was observed at 24 hours post-dose. The Cmax and AUC_{0-24h} of the metabolite were higher in 5/6 nephrectomized rats than the sham operated animals. The absolute bioavailability of the oral formulation from both sham-operated and 5/6 nephrectomized animals was 75-81% for rolapitant and 103-111% for SCH 720881.

In conclusion, systemic exposure (Cmax and AUC_{0-24h}) for rolapitant were similar for both sham-operated and 5/6 nephrectomized rats while the Cmax and AUC_{0-24h} of the metabolite, SCH 720881, was higher in 5/6 nephrectomized rats than sham-operated animals. The results indicated that the exposure to the metabolite may be higher in renal sufficiency.

Pharmacokinetic Drug Interactions

Reviews of Study Nos. DM27366, 12TESAP1, 12TESAP2R1, DM27353, XT113090, DM27427, and DM27495 are incorporated from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

Evaluation of SCH 619734 as an Inhibitor of the MDR1 Transporter (p-Glycoprotein) Using the Caco-2 Bi-Directional Permeability Assay (DM27366)

Methods: The potency of SCH619734 for Pgp inhibition was assayed by the evaluation of the effect of SCH 619734 on the efflux of digoxin, a known Pgp substrate. In addition, the effect of the reference Pgp inhibitors, GF120918 and Cyclosporin A (CSA), on the digoxin efflux was also assayed as positive controls. The dosing solutions containing digoxin (5 µM) were added to the apical side (A-to-B) or basolateral side (B-to-A) and incubated at 37°C for 2 hours.

Results: SCH619734 inhibited digoxin efflux transport in Caco-2 cells with an estimated IC50 of approximately 7.36 µM. The inhibitory potency of SCH619734 was less than that for CSA (estimated 0.78 µM) and considerably less than that for GF120918 (approximately 87 % inhibition at 0.2 µM).

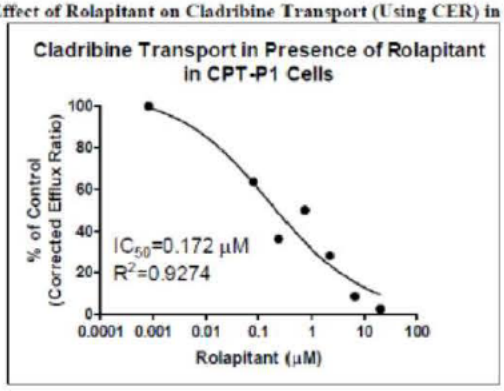
Evaluation of Inhibitory Potential of Rolapitant on Breast Cancer Resistance Protein (BCRP) Transporter Using CPT-P1 Cell Monolayers (Study No. 12TESAP1)

Methods: In this study, BCRP inhibition potential of rolapitant was evaluated *in vitro* using CPT-P1 cell monolayers with cladribine as a BCRP probe substrate. CPT-P1 cell line was derived from Caco-2 cells, with lower expression of P-gp. The objective was to have less P gp involvement with the test article and more accurate assessment on BCRP interaction. The bidirectional transport of cladribine was measured in the

absence and presence of rolapitant (20 µM) or positive control BCRP inhibitor (Ko143, 10 µM) in CPT-P1 cells.

Results: Rolapitant was shown to be a BCRP inhibitor with IC50 value of 0.172 µM. The following figure (from page 12 of the report) shows the effect of rolapitant in CPT-P1 cells.

Figure 1. Effect of Rolapitant on Cladribine Transport (Using CER) in CPT-P1 Cells



Study I: Evaluation of Substrate Potential of Rolapitant and SCH720881 for OATP1B1 and OATP1B3 Uptake Transporters, Study II: Evaluation of Inhibitory Potential of Rolapitant and SCH720881 on Uptake of [^{3}H]Taurocholic Acid (TCA) by the ATP-dependent Bile Salt Export Pump (BSEP) Transporter, Study III: Evaluation of Inhibitory Potential of SCH720881 on Breast Cancer Resistance Protein (BCRP) Transporter Using CPT-P1 Cell Monolayers (Study No. 12TESAP2R1)

Methods: The objectives of these studies were as follows:

- To assess if rolapitant and/or its metabolite (SCH720881) is a substrate of the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3)
- To determine if rolapitant (SCH619734) and/or SCH720881 is an inhibitor of the ATP-dependent bile salt export pump (BSEP) transporter
- To evaluate if SCH720881 was an inhibitor of breast cancer resistance protein (BCRP) using CPT-P1 cell monolayers

In this study, human embryonic kidney epithelial cells (HEK293) transfected with individual uptake transporters (OATP1B1 and OATP1B3) were used to assess the substrate potential of rolapitant (0.5, 2, 10 µM) and SCH720881 (0.5, 2, 7 µM) toward the corresponding transporter.

The inhibitory potential of rolapitant for BSEP was assessed using BSEP vesicles. The assay was based on measuring BSEP-mediated [^{3}H]TCA uptake into inside-out BSEP-expressing membrane vesicles. BSEP vesicles and [^{3}H]TCA were incubated for 30 min

in the absence and presence of the test compounds or a positive control inhibitor (10 µM CsA). After incubation, the vesicle-associated [^{3}H]-TCA and free [^{3}H]-TCA were separated by rapid filtration and the radioactivity of vesicle associated [^{3}H]-TCA was measured by scintillation counting after washing.

The BRCP assay was conducted as discussed above.

Results: Rolapitant or SCH720881 was found to be a substrate for OATP1B1 or OATP1B3. Both rolapitant and SCH720881 did not show significant inhibition potential on [^{3}H]TCA uptake by BSEP transporter at the concentrations tested. SCH720881 was not considered a BCRP inhibitor at the concentration tested.

***In Vitro* Evaluation of SCH 619734 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes (Study No. DM27353)**

Methods: The objective of this study was to examine the effect of SCH 619734 on the activity of CYP450 enzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4/5) in primary cultures of human hepatocytes. In this study, three preparations of cultured human hepatocytes from three separate human livers were treated once daily for three consecutive days with dimethyl sulfoxide (vehicle, 0.1% v/v), SCH 619734 (0.1, 1, 10, 30 and 100 µM) or known human CYP450 enzyme inducers, namely omeprazole (100 µM) or rifampin (10 µM).

Results: SCH 619734 caused a concentration-dependent increase in CYP1A2 and CYP3A4/5 activity up to 10 µM concentration. There was small or no increase in CYP2C8, CYP2C9 and CYP2C19 activity following treatment with SCH 619734; however, there was a tendency towards a concentration-dependent increase in CYP2C8 and CYP2C19 enzyme activity (2.1-fold and 2.42-fold, respectively) at up to 10 µM SCH 619734. At 30 µM, SCH 619734 caused a decrease in the activity of all the enzymes tested, except CYP2C19. This generalized decrease in CYP enzyme activity was attributed to the toxicity observed in hepatocytes treated with high concentrations (30 and 100 µM) of SCH 619734.

***In Vitro* Evaluation of Rolapitant as an Inducer of Cytochrome P4502B6 Expression in Cultured Human Hepatocytes (Study No. XT113090)**

Methods: The objective of this study was to investigate the effects of rolapitant on the expression of CYP2B6 enzyme using human hepatocytes. Cultured human hepatocytes from three separate livers were treated once daily for three consecutive days with dimethyl sulfoxide (DMSO, 0.1% v/v, vehicle control), rolapitant (0.1, 1, 10 or 20 µM) or one known human CYP inducer (phenobarbital, 750 µM). After treatment, the cells were incubated with the appropriate marker substrates for the analysis of bupropion hydroxylation (marker for CYP2B6) by LC/MS/MS.

Results: Rolapitant caused little or no effect on CYP2B6 activity (on average, < 2.0-fold increase and < 20% as effective as the positive control, phenobarbital).

In Vitro Evaluation of SCH 619734 as an Inhibitor of Human Cytochrome P450 Enzymes (Study No. DM27427)

Methods: This study was conducted to evaluate the ability of SCH 619734 to inhibit the major CYP enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5) in human liver microsomes in order to determine the potential of SCH 619734 to inhibit the metabolism of concomitantly administered drugs. Human liver microsomes from a pool of sixteen individuals were incubated with marker substrates, at concentrations approximately equal to their apparent *K*m, in the presence or absence of SCH 619734. The target concentrations of SCH 619734 ranged from 0.1 to 100 µM. Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls.

Results: SCH 619734 caused direct inhibition of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 with IC50 values of 22, 13, 23, 9.6, 8.7, 7.1 and 49 and 41 µM, respectively. There was evidence of activation of CYP1A2 and CYP2E1 as the activities for these enzymes in the presence of SCH 619734 (0.3-30 µM for CYP1A2 and 10-30 µM for CYP2E1) were higher than the control. At 100 µM, there was a decrease in CYP1A2 and CYP2E1 activities. In addition, SCH 619734 was shown to be a competitive inhibitor of CYP2D6 with a Ki value of 3.4 µM. Based on these results, it appears that there is a potential for drug-drug interaction between SCH 619734 and drugs that are substrates of these CYP450s.

An Exploratory _In Vitro_ Evaluation of SCH 619734 as an Inhibitor of human CYP2D6 (Study No. DM27495)

Methods: In this study, the ability of SCH 619734 to inhibit the CYP2D6 enzyme was examined with a pool of 16 individual human liver microsomal samples at the following concentrations: 0.1, 0.3, 1, 3, 10, 30, and 100 µM.

Results: SCH 619734 caused direct inhibition of CYP2D6 at three different microsomal protein concentrations (0.1, 0.4 and 0.8 mg/mL) with IC50 values of 12, 35 and 73 µM.

Determination of Human CYP450 Inhibition by SCH 720881 (Study No. KB-0046-DV-BA)

Methods: This study was conducted to evaluate the ability of metabolite SCH 720881 to inhibit CYP enzymes (CYP1A2, CYP2A8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). Pooled human liver microsomes were incubated with marker substrates at concentrations approximately equation to their Km in the presence or absence of SCH 720881 at 1 and 10 µM. Positive control inhibitors were tested at concentrations of 10 and 50 µM. For determination of the IC_{50}, the concentrations of SCH 720881 used in the assay were 0, 0.1, 0.25, 0.5, 1, 2, 5, 10, 25, and 50 µM.

Results: Inhibition of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 by SCH 720881 was less than 50% at 1 and 10 µM (inhibition ranged from -23.9% to 44.9%). Therefore, IC_{50} values for these CYP enzymes were assumed to be >10 µM. For CYP2B6, 10 µM SCH 720881 produced 57.1% inhibition. The IC_{50} was determined to be 8.65 µM. Results from the study are summarized in the following tables copied from the study report.

Compound ID	CYP Isozyme	CYP Substrate	Mean % Inhibition at 1 µM	Mean % Inhibition at 10 µM
SCH 720881	1A2	Phenacetin	4.1	-9.3
	2B6	Buproprion	0.5	57.1
	2C8	Amodiaquine	-23.9	-7.4
	2C9	Diclofenac	-10.1	21.1
	2C19	Mephenytoin	6.9	44.8
	2D6	Dextromethorphan	-8.1	31.4
	3A4	Midazolam	0.1	-3.2
	3A4	Testosterone	-15.1	17.5
Control Inhibitors:			Mean % Inhibition at 10 µM:	Mean % Inhibition at 50 µM:
Fluvoxamine	1A2	Phenacetin	100.6	102.7
Ticlopidine	2B6	Buproprion	101.2	103.4
Quercetin	2C8	Amodiaquine	48.0	98.5
Sulfaphenazole	2C9	Diclofenac	92.5	101.8
Omeprazole	2C19	Mephenytoin	53.6	94.0
Quinidine	2D6	Dextromethorphan	90.0	98.7
Ketoconazole	3A4	Midazolam	106.4	108.1
Ketoconazole	3A4	Testosterone	103.6	104.4

Compound ID	CYP Isozyme	CYP Substrate	IC_{50} (µM)
SCH 720881	2B6	Bupropion	8.65
Ticlopidine (control)	2B6	Bupropion	0.108

Determination of Human CYP450 Induction by SCH 720881 (Study No. KB-0046-DV-DA)

Methods: The purpose of this study was to examine the potential for metabolite SCH 720881 to induce the activity of CYP450 enzymes (CYP1A2, CYP2B6, CYP2C9, CYP3A4). In this study, three individual lots of human hepatocytes were incubated with 0.1, 1, and 10 µM SCH 720881, or known inducers (50 µM omeprazole, 1 mM phenobarbital, and 25 µM rifampacin) over a total assay incubation time of 48 h. CYP450 enzyme activity was measured using CYP450 substrates (phenacetin, bupropion, diclofenac, and testosterone for CYP1A2, CYP2B6, CYP2C9, and CYP3A4, respectively).

Results: Relative to vehicle controls, SCH 720881 enzyme induction ranged from 0.6- to 1.8-fold for CYP1A2, 0.3- to 1.2-fold for CYP2B6, 0.3 to 1.3-fold for CYP2C9, and 0.2- to 1.4-fold for CYP2B6. The highest fold induction was 1.8 at 0.1 µM SCH 720881, although induction in this lot of hepatocytes was 1.1- and 0.8-fold at higher concentrations. Positive control enzyme induction relative to vehicle controls ranged from 5.4- to 16-fold for CYP1A2, 5.6- 16.3-fold for CYP2B6, 1.6- to 2.8-fold for CYP2C9, and 7.5- to 12.3-fold for CYP3A4. The study results indicate that SCH 720881 does not induce the four CYP enzymes evaluated at concentrations up to 10 µM.

5.2 Toxicokinetics

Rolapitant: A Toxicokinetic Evaluation During Pregnancy in Rats (Study No. 2013-010)

Methods: The purpose of this study was to determine the toxicokinetics of rolapitant (SCH 619734) and metabolite SCH 720881 in pregnant rats. In this study, pregnant CD® [Crl:CD®(SD)] rats were administered 5, 15, and 25 mg/kg/day SCH 619734 (or vehicle, 0.4% Methocel E15 Premium LV in deionized water, pH 4) once daily by oral gavage from gestational days (GD) 6 to 17. Maternal blood samples were collected for analysis of plasma concentrations of the test compound and its metabolite up to 24 h post-dosing on GD 6 and 17. Blood samples from fetuses were collected and pooled per litter at 4, 6, 8, and 24 h post-dosing on GD 17.

Results: In this TK study, there were statistically significant decreases in body weight gain and decreases in food consumption (compared to controls) over GD 6-9 at 15 and 25 mg/kg/day SCH 619734. These treatment-related effects were transient, and no significant differences in body weight occurred over the periods of GD 6-17 or 0-17. Food consumption was significantly decreased (-17% compared to controls) at 25 mg/kg/day over the period of GD 6-17. Maternal systemic exposure to SCH 619734 and SCH 720881 increased with increasing dose. Maternal exposure to the parent compound was much higher than exposure to the metabolite. Maternal exposure to SCH 619734 was higher on GD 17 than GD 6 at the 5 mg/kg/day dose level, whereas increased exposure to SCH 720881 occurred on GD 17 relative to GD 6 at all dose levels. In the fetuses, systemic exposure to the parent compound was also much higher than exposure to the metabolite. Fetal systemic exposure to SCH 619734 was lower than maternal exposure at 5 mg/kg/day, but similar at 15 and 25 mg/kg/day. Fetal systemic exposure to SCH 720881 was lower than maternal exposure at all dose levels. The following tables copied from the study report summarize the TK parameters.

Toxicokinetic Parameters for Rolapitant and SCH 720881 in Pregnant Rats after Daily Oral Gavage Doses of Rolapitant on Gestation Days 6 through 17

Analyte	Gestation Day	Dose (mg/kg/day)	AUC_{0-24} (hr•ng/mL)	AUC_{0-24}/Dose ((hr•ng/mL)/mg/kg)	C_{max} (ng/mL)	C_{max}/Dose ((ng/mL)/mg/kg)	T_{max} (hr)
Rolapitant	6	5	17600	3520	942	188	8.00
		15	43800	2920	2240	149	8.00
		25	60300	2410	3510	141	4.00
	17	5	35700	7130	2040	408	4.00
		15	59400	3960	3250	216	6.00
		25	60700	2430	4450	178	6.00
SCH 720881	6	5	133	26.6	11.4	2.28	24.0
		15	432	28.8	37.9	2.52	24.0
		25	821	32.8	71.4	2.86	24.0
	17	5	1220	243	59.4	11.9	24.0
		15	2680	179	118	7.88	8.00
		25	2730	109	151	6.03	6.00

Toxicokinetic Parameters for Rolapitant and SCH 720881 in Pregnant Rats after Daily Oral Gavage Doses of Rolapitant on Gestation Days 6 through 17

			Accumulation ratio (GD 17/GD 6)		Metabolite to Parent ratio	
Analyte	Gestation Day	Dose (mg/kg/day)	AUC_{0-24}	C_{max}	AUC_{0-24}	C_{max}
Rolapitant	6	5	NA	NA	NA	NA
		15	NA	NA	NA	NA
		25	NA	NA	NA	NA
	17	5	2.03	2.17	NA	NA
		15	1.35	1.45	NA	NA
		25	1.01	1.27	NA	NA
SCH 720881	6	5	NA	NA	0.00756	0.0121
		15	NA	NA	0.00986	0.0169
		25	NA	NA	0.0136	0.0203
	17	5	9.13	5.21	0.0341	0.0291
		15	6.21	3.12	0.0452	0.0364
		25	3.32	2.11	0.0449	0.0339

NA – Not Applicable

Toxicokinetic Parameters for Rolapitant and SCH 720881 in Gestation Day 17 Litters from Pregnant Rats given Daily Oral Gavage Doses of Rolapitant on Gestation Days 6 through 17						
Analyte	Dose (mg/kg/day)	AUC_{0-24} (hr•ng/mL)	AUC_{0-24}/Dose ((hr•ng/mL)/mg/kg)	C_{max} (ng/mL)	C_{max}/Dose ((ng/mL)/mg/kg)	T_{max} (hr)
Rolapitant	5	15300	3060	804	161	8.00
	15	42300	2820	3030	202	8.00
	25	45100	1800	4350	174	6.00
SCH 720881	5	316	63.3	16.7	3.35	24.0
	15	628	41.9	32.4	2.16	8.00
	25	706	28.2	46.6	1.87	6.00

Toxicokinetic Parameters for Rolapitant and SCH 720881 in Gestation Day 17 Litters from Pregnant Rats given Daily Oral Gavage Doses of Rolapitant on Gestation Days 6 through 17					
		Metabolite to parent ratio		Maternal to fetal ratio	
Analyte	Dose (mg/kg/day)	AUC_{0-24}	C_{max}	AUC_{0-24}	C_{max}
Rolapitant	5	NA	NA	2.33	2.53
	15	NA	NA	1.40	1.07
	25	NA	NA	1.35	1.02
SCH 720881	5	0.0207	0.0208	3.86	3.55
	15	0.0148	0.0107	4.27	3.65
	25	0.0157	0.0107	3.87	3.22
NA – Not Applicable					

Additional TK data are reviewed with the associated general toxicity study under Section 6 (General Toxicology).

6 General Toxicology

6.1 Single-Dose Toxicity

Single-dose toxicity studies with SCH 619734 (hydrochloride salt) were conducted in rats and monkeys. Full study reports were provided with the NDA and are briefly summarized here.

In Study No. 03101, Crl:CD®[SD]IGS BR VAF/Plus® rats were administered a single oral dose of SCH 619734 (or vehicle, 0.4% [w/v] methylcellulose). In males, the test compound was administered at doses of 100, 500, 1000, and 2000 mg/kg. In females, dose levels of 50, 250, 500, and 1000 mg/kg SCH 619734 were used. SCH 619734 produced mortality in females at ≥500 mg/kg. A single male rat treated with 2000 mg/kg was sacrificed in moribund condition six days after dosing. Clinical signs of toxicity such as hunched posture, hypoactivity, and tremors occurred at ≥250 mg/kg in females and ≥500 mg/kg in males, with additional clinical signs at higher doses. In another single

dose study (Study No. 03102), SCH 619734 (or vehicle, 0.4% [w/v] methylcellulose) was administered intraperitoneally to male rats at 125, 250, 500, and 1000 mg/kg and female rats at 125, 250, and 500 mg/kg. SCH 619734 produced mortality at 1000 mg/kg in males and 500 mg/kg in females. Clinical signs occurred at ≥250 mg/kg (e.g., hypoactivity, abnormal stool, slight dehydration). Additional more severe clinical signs were observed at higher doses (e.g., tremors at ≥500 mg/kg; convulsions at 1000 mg/kg).

In an acute, rising-dose toxicity study in cynomolgus monkeys (Study No. 03126), one animal/sex was administered single oral doses of 25, 50, 75, 100, 150, and 200 mg/kg SCH 619734 with at least a 24 h between each dose level. The female was sacrificed in moribund condition one day after dosing at 200 mg/kg. Clinical signs preceding death included convulsions, emesis, hypothermia, moribund condition, and prostration. At ≥50 mg/kg, clinical signs such as abnormal stool [none, scant, and/or soft], hyperactivity, and excessive vocalization occurred.

Due to incidences of convulsions in monkeys administered 60 and 100 mg/kg SCH 619734 in a one-month, repeat-dose oral toxicity study (Study No. 05015) and findings of convulsions in Study No. 03126, two single-dose studies were conducted to further investigate this finding. In Study No. 08134, female monkeys (n=8) were administered a single oral (gavage) dose of 100 mg/kg SCH 619734. The animals were observed and plasma samples were collected out to 48 h post-dosing. At 16 h after treatment, emesis occurred in 5/8 monkeys and hypoactivity with hunched posture was observed in one animal. No convulsions occurred. The mean C_{max} values for SCH 619734 and metabolite 720881 were 6,480 ng/mL and 875 ng/mL, respectively. In Study No. 06581, four female monkeys were pre-treated with diazepam prior to receiving a single dose of 100 mg/kg SCH 619734 by oral gavage. No convulsions or other adverse effects related to SCH 619734 occurred. C_{max} concentrations ranged from 5,550 – 8,980 ng/mL.

6.2 Repeat-Dose Toxicity

Mouse

Reviews of Study Nos. 05220 and 03665 are incorporated below from the pharmacology review of IND 72,754 dated March 10, 2006 (Ke Zhang, Ph.D., DGP).

3-day oral dose range-finding study of SCH 619734 in mice (05220)

Testing Laboratory: [redacted] (b) (4)

Study Start and Completion Dates: November 11, 2005 and draft report in January 6, 2006

GLP and QAU Compliance Statement: Sponsor included a statement of compliance with GLP regulations and a quality assurance statement.

Animals: Crl:CD-1 (ICR) vaf/pLUS mice, ~6 week old,
Males: 24-30 g, females: 19.6-23.7 g.
Drug lot No.: SZ-03-PHG-TX-001

Methods: The sponsor conducted a tolerability study at higher doses in mice. In this study, SCH 619734 was tested by oral gavage at 300 mg/kg/day for 3 days and at single doses of 450, 900, and 1800 mg/kg in mice (5/sex/group). All animals received physical examination and body weight was determined on day 0 and at termination.

Results:

Clinical Signs of toxicity: The results indicated that the following clinical signs of toxicity were observed in all treatment groups: convulsions, tremor, excessive chewing of cage, hypoactivity, impaired equilibrium, partial closure of eyes, prostration and twitching, cold to touch, gasping, yellow/red material on various body surfaces. The incidences and severity of these signs were dose related. These clinical signs of toxicity were observed in 4, 8, 8, and 10 animals in the dose groups of 300, 450, 900, and 1800 mg/kg (10 animals in each group), respectively.

Mortality: Deaths occurred in the dose groups of 450 (2 males and 3 females), 900 (4 males and 4 females), and 1800 mg/kg (5 males and 3 females). One female in the 300 mg/kg group and 2 females in 1800 mg/kg were sacrificed in extremis on the first day of dosing. All surviving mice in the 450 and 900 mg/kg groups were sacrificed on the second day.

Body weight: There was no control group in this study. No treatment related changes on the body weight were found over 3 days of treatment in the 300 mg/kg/day group. Body weights in the other groups were not determined due to mortality.

In summary, SCH 619734 was lethal at doses of 450 mg/kg or higher. SCH 619734 induced clinical signs of toxicity including convulsions, tremor, and yellow/red material on various body surfaces at dose of 300 mg/kg/day.

3-month oral dose range-finding study of SCH 619734 in mice
(03665)

Testing Laboratory: Safety Evaluation Center
Schering-Plough research Institute
Lafayette, NJ

Study Start and Completion Dates: March 2, 2005 and January 4, 2006

GLP and QAU Compliance Statement: Sponsor included a statement of compliance with GLP regulations and a quality assurance statement.

Animals: Crl:CD-1 (ICR) vaf/pLUS mice, ~6 week old,
Males: 24.9-32.2 g, females: 19.6-25.4 g.
Drug lot No.: SZ-03-PHG-TX-001

Methods: To assess the repeated oral dose toxicity of SCH 619734 in mice and to assist with dose selection for the 2-year carcinogenicity study in mice, SCH 619734 was given by oral gavage to mice (10/sex/group) at 0, 25, 75, and 150 mg/kg/day for 3 months. In the toxicokinetic study, 30 animals per sex per group were included. Mortality and clinical signs of toxicity were observed daily. Body weights and food consumption were recorded weekly. Hematology and clinical chemistry were performed at termination. Ophthalmologic examination was conducted in weeks 4 and 11. Gross pathological examination was conducted at termination and organ weights were determined. Following tissues or organs were examined microscopically:

Tissues Collected[a]	
Adrenal Glands	Parathyroid Gland(s)[e]
Aorta – Thoracic	Peripheral Nerve – Sciatic
Bone – (Femur and Sternum)	Pituitary Gland
Bone Marrow Section – Sternum	Prostate Gland
Bone Marrow for Cytology – Sternum[b]	Salivary Glands – Mandibular
Brain	Seminal Vesicles
Epididymides	Skeletal Muscle – Biceps Femoris
Esophagus	Skin
Eyes[c]	Small Intestine – (Duodenum, Jejunum, Ileum)
Gallbladder	Spinal Cord – Thoracolumbar
Harderian Glands[c]	Spleen
Head[d]	Stomach
Heart	Testes[f]
Kidneys	Thymus
Large Intestine – (Cecum and Colon)	Thyroid Gland
Liver	Tongue[d]
Lungs	Trachea
Lymph Nodes – Mandibular and Mesenteric	Urinary Bladder
Mammary Gland[e]	Uterus (plus Cervix)
Ovaries	Vagina
Pancreas	Animal Identification[d]

a: Collected in 10% neutral buffered formalin unless otherwise indicated
b: Bone marrow smears were prepared for all toxicity portion mice but were not evaluated because it was not warranted by changes in the peripheral blood.
c: Collected in 3% glutaraldehyde
d: Collected but not processed
e: Examined histopathologically when present in routine section
f: Collected in modified Davidson's fixative

Histopathological examination was conducted in all animals in the control and high dose animals, the animals that died or were sacrificed, all gross findings, and the liver from all animals in all groups. Plasma level of the test drug (SCH 619734) was determined at 1, 2, 4, 8, and 24 hours after dosing on days 0 and 57.

The sponsor also conducted P450 gene expression analysis for CYP1A1, 1A2, 2B1, 2B2, 3B1, and 4A1 from the left lateral lobe of the liver in the control and high dose animals.

Results:

1. Clinical Signs of Toxicity: One mid dose male was sacrificed on day 63 due to clinical signs of toxicity including abdominal distention, labored breathing, and loose stool. One toxicokinetic high dose male was sacrificed on day 24 due to clinical signs of toxicity

including abdominal distention, abnormal stool, dehydration, and hypoactivity. Since similar clinical signs of toxicity (abdominal distention and abnormal stool) were observed in both mid and high dose groups (one animal in each group), these clinical signs of toxicity are considered treatment related.

2. Mortality: There were no clear treatment related deaths. In the main toxicity study, one control female was found dead due to gavage error. One toxicokinetic low dose male was sacrificed due to gavage error. One toxicokinetic high dose female was found dead due to head injury following a cage accident.

3. Body Weight: The mean initial and final body weights of the control animals were 29 g and 36.6 g for males and 22 g and 29.4 g for females. There were no treatment related changes.

4. Food Consumption: The average food consumption in the control group was 4.6-5.4 g/animal/day for males and 4.4-4.6 g/animal/day for females. There were no treatment related changes.

5. Hematology: There were no clear treatment related changes.

6. Clinical Chemistry: There were no treatment related changes.

7. P540 gene expression: The results indicated that the animals in the high dose group had induction of CYP 2B1/2B2 and 3A1. The results were summarized in a table on page 33 in Volume C5.5. This table is attached below.

CYP Gene Expression Fold-Change Over Control Group Mean Values

Dose (mg/kg)	Sex		Fold-Change in CYP mRNA				
			CYP 1A1	CYP 1A2	CYP 2B1/2B2	CYP 3A1	CYP 4A1
150	Male	Mean:	1.11	0.22	6.99*	6.66*	0.19
		Range:	0.15 – 6.2	0.05 – 1.4	4.0 – 15.5	3.1 – 27.7	0.07 – 0.35
	Female	Mean:	5.11	1.98	4.35*	8.89*	1.58
		Range:	1.4 – 15.1	0.06 – 9.1	1.8 – 10.1	2.4 – 22.5	0.12 – 5.8

* = Test article-related finding

8. Ophthalmology: There were no treatment related changes.

9. Organ Weight: The absolute and relative weight (to body weight) of the liver was slightly higher in the mid and high dose groups than those in the control. The absolute and relative weights of the uterus was slightly lower in the mid and high dose group than those in the control. The results were summarized in a table on page 34 and this table is attached below.

Principal Organ Weight Changes: Percent Difference from Concurrent Control Mean

Dose Group (mg/kg):	0 (Control)		25 (SCH 619734)		75 (SCH 619734)		150 (SCH 619734)	
Sex:	M	F	M	F	M	F	M	F
Organ	Mean Weight		Percent Difference from Concurrent Control Mean (%)					
Liver								
-Absolute weight	1.24 g	1.02 g	+9	+2	+13*	+11*	+22*	+17*
-Relative weight[a]	3.88%	4.03%	+7	+2	+9*	+11*	+21*	+19*
Uterus								
-Absolute weight	NA	0.25 g	NA	-4	NA	-10	NA	-20*
-Relative weight[a]	NA	1.00%	NA	-3	NA	-11	NA	-19*

a: Relative to body weight
* = Test article-related finding
NA = Not applicable

10. Gross Pathology: There were no treatment related changes.

11. Histopathology: Treatment with test drug produced liver hypertrophy. The incidence and severity were summarized in a table on page 36 in Volume C5.5. and this table is attached below.

Principal Histopathologic Findings

Dose Group (mg/kg):	0 (Control)		25 (SCH 619734)		75 (SCH 619734)		150 (SCH 619734)	
Sex:	M	F	M	F	M	F	M	F
Organ/Finding/Severity	Incidence[a]							
Liver								
-hypertrophy, centrilobular								
minimal	4/10	0/10	8/10*	0/10	2/10*	7/10*	5/10*	5/10*
mild	0/10	0/10	0/10	0/10	8/10*	0/10	5/10*	0/10

a: Incidence = Number affected/Number examined.
* = Test article-related finding

12. Plasma level of test drug: The plasma levels of the test drug were summarized in a table on page 30 in Volume C5.5. and this table is attached below.

SCH 619734 Toxicokinetic Parameters on Day 0 and Day 57 Following Oral (Gavage) Administration of 25, 75 or 150 mg/kg SCH 619734 to Female and Male Mice

Day	Dose[a] (mg/kg)	Sex	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)	Accumulation Ratio[b]	M:F Ratio[c]
0	25	Female	3250	4	37300	NA	NA
		Male	3770	4	49100	NA	1.31
	75	Female	8630	1	92300	NA	NA
		Male	10100	1	121000	NA	1.31
	150	Female	12700	2	140000	NA	NA
		Male	13800	2	169000	NA	1.21
57	25	Female	3210	4	33500	0.897	NA
		Male	3540	1	30100	0.614	0.899
	75	Female	7060	1	69500	0.753	NA
		Male	6190	1	60700	0.503	0.873
	150	Female	8830	2	113000	0.813	NA
		Male	13500	1	128000	0.759	1.13

a: Doses are expressed as the hydrochloride monohydrate salt. When expressed as the free base, daily doses equal 22.5, 67.5 and 135 mg/kg for the 25, 75 and 150 mg/kg doses, respectively.

b: Accumulation Ratio: $AUC(0\text{-}24\ hr)_{Day\ 57} \div AUC(0\text{-}24\ hr)_{Day\ 0}$

c: M:F Ratio (Male:Female Ratio) = $AUC(0\text{-}24\ hr)_{Male} \div AUC(0\text{-}24\ hr)_{Female}$

NA = Not applicable

The results indicated that the plasma level of the test drug was increased with dose and there were no apparent drug accumulation over time. The exposure ratio of mouse to human cannot be calculated since a valid, accurate human AUC was not provided.

In summary, SCH 619734 was given by oral gavage to mice at 0, 25, 75, and 150 mg/kg/day for 3 months. Treatment related clinical signs of toxicity including abdominal distention and abnormal stool were observed in both mid and high dose groups (one animal in each group). Treatment with SCH 619734 increased the liver weight and produced hepatocellular hypertrophy. Since the treatment related clinical signs of toxicity were observed in both mid and high dose groups (one animal in each group), the low dose of 25 mg/kg/day is considered as No Observable Adverse Effect Level (NOAEL).

Rat

The following review of Study No. 07395 is incorporated from the pharmacology review of IND 72,754 dated December 5, 2012 (Tamal Chakraborti, Ph.D., DGIEP).

Study title: 2-Week Intravenous (Infusion) Toxicity and Toxicokinetic Study of Rolapitant in Rats	
Study no.:	07395
Report No.	07395
Study report location:	Section 4.2.3.2.1
Conducting laboratory and location:	Safety Evaluation Center, Schering-Plough Research Institute (SPRI), Lafayette, NJ
Date of study initiation:	February 8, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Rolapitant (2 mg/mL solution in 4.4% (v/v) Solutol, HS15, 1.1% (v/v) Miglyol and 0.66% (v/v) soybean oil in 20 mM phosphatebuffered saline (pH 7.5), Batch No. K-H08771, 100.1%

Key Study Findings:

- In a 2-week IV infusion study in rats, animals were treated with rolapitant at 4.5, 18 and 36 mg/kg/day.
- Treatment at 36 mg/kg/day was terminated after Day 0 as required 20 mL/kg dose volume could not be reliably administered at this dose level over a 15-minute infusion period.
- The NOAEL was considered as 18 mg/kg/day. The target organ could not be identified in the absence of any significant treatment-related histopathology findings in any organ/tissue.

Methods:	
Doses:	4.5, 18 and 36 mg/kg/day
Frequency of dosing:	Daily
Route of administration:	Intravenous (IV) (15-minute infusion)
Dose volume:	2.5-20 mL/kg
Formulation/Vehicle:	0.9% Sodium Chloride for Injection, U.S.P.
Species/Strain:	SD Rats
Placebo Control:	4.4% (v/v) Solutol HS15, 1.1% (v/v) Miglyol and 0.66% (v/v) soybean oil in 20 mM phosphate buffered-saline (pH 7.5)
Number/Sex/Group:	Shown in the study design below
Age:	8 weeks old
Weight:	Males: 240.1 to 296.4 g (toxicity portion) Females: 178.6 to 234.5 g (toxicity portion)
Satellite groups:	Yes
Study design:	Shown in the table below.
Deviation from study protocol:	Protocol deviations (1 and 2) associated with difficulties administering a 20 mL/kg dose volume, resulted in early termination of Group T3 (Protocol Amendment No. 3). The remaining listed protocol deviations did not adversely affect either the quality or integrity of the study or the interpretation of the results.

*: The study design is shown in the table below (from page 12 of the study report).

2-Week Intravenous (Infusion) Toxicity and Toxicokinetic Study of SCH 619734 in Rats (SN 07395): **Study Design**							
		No. of Rats/Sex					
Group	Test/Control Article	Toxicity Portion	Satellite Portion[a]	Total Daily Dose (mg/kg) (Free Base)[b]	Dose Volume (mL/kg)	Dose Conc. (mg/mL) (Salt)[c]	Duration of Dosing for Toxicity Portion (Days)
C1	Vehicle Control (0.9% sodium chloride)	5	3	0	2.5	0	15 or 16
C2	Placebo Control (4.4% Solutol HS15, 1.1% Miglyol and 0.66% soybean oil in 20 mM phosphate buffer, pH 7.5)	5	3	0	2.5	0	15 or 16
C3	Placebo Control (4.4% Solutol HS15, 1.1% Miglyol and 0.66% soybean oil in 20 mM phosphate buffer, pH 7.5)	5	3	0	10[d]	0	15 or 16
T1	Low-Dose (SCH 619734)	10	12	4.5	2.5	2	15 or 16
T2	Mid-Dose (SCH 619734)	10	12	18	10	2	15 or 16
T3	High-Dose (SCH 619734)	10	0[d]	36	20	2	1[d]

a: These animals were designated for toxicokinetic analysis only.
b: Doses are expressed as the free base. When expressed as the hydrochloride monohydrate salt, these doses are equivalent to 5, 20 and 40 mg/kg for Groups T1, T2 and T3, respectively.
c: Concentrations are expressed as the hydrochloride monohydrate salt. When expressed as the free base, this concentration is equivalent to 1.8 mg/mL for Groups T1, T2 and T3.
d: Toxicity portion rats in Group T3 were dosed on Day 0 only and euthanized on Day 1 because the 20 mL/kg dose volume could not be reliably administered over the 15-minute intravenous infusion period. Consequently, satellite portion rats designated for Group T3 were not dosed and were returned to the stock supply of animals and the dose volume for Group C3 was lowered to 10 mL/kg effective Day 1.

Observations and Times:

Mortality: Animals were observed for mortality once daily.

Clinical Signs: Clinical signs were observed twice daily during the dosing period.

Body Weights: Body weights were recorded on a weekly basis.

Food Consumption: Food consumption was recorded on a weekly basis.

Ophthalmoscopy: Ophthalmoscopic examinations were conducted once at pretest and then on Week 2

Hematology: Blood samples were collected from the high-dose rats for clinical pathology evaluation prior to sacrifice. Blood samples were collected from all other control and rolapitant dose groups during Week 2 or Week 3.

Clinical Chemistry: Serum chemistry was conducted on Day 1 and Week 2.

Urinalysis: Urinalysis was conducted on Week 2.

Gross Pathology: Gross pathology was conducted at necropsy.

Organ Weights: The following (from 460 of the report) organs were weighed.

Organs Weights and Calculated Organ-to-Body Weight Ratios	Adrenal glands Brain Epididymides Heart Kidneys Liver Lungs Ovaries	Pituitary gland Prostate gland (ventral) Spleen Testes Thymus Thyroid gland/parathyroid glands[a] Uterus (plus cervix)
a: Thyroid gland/parathyroid glands will be weighed post-fixation.		

Histopathology: The following (from page 459 of the report) listed organs/tissues were collected from animals in the control and high dose groups.

Tissues Collected[a]	Adrenal glands Aorta – thoracic Bone – (femur and sternum) Bone marrow section – sternum Bone marrow for cytology – sternum[b] Brain Epididymides Esophagus Eyes[c] Gross findings[d] Harderian glands Head[e] Heart Kidneys Large intestine – (cecum and colon) Larynx/Pharynx Liver Lungs Lymph nodes – mandibular and mesenteric Mammary gland[f] Ovaries Pancreas	Parathyroid gland(s)[f] Peripheral nerve – sciatic Pituitary gland Prostate gland Salivary glands – mandibular Seminal vesicles Skeletal muscle – Biceps femoris Skin Small intestine – (duodenum, jejunum, ileum) Spinal cord – thoracolumbar Spleen Stomach Testes[g] Thymus Thyroid gland Tongue[e] Trachea Urinary bladder Uterus (plus cervix) Vagina Animal identification[h] Injection site

Toxicokinetics: Blood samples were collected from TK animals on Days 0 and 13 (rolapitant-treated: three rats/sex/group at 20 min, 8 hr and 24 hr postdose, and three rats/sex/group at 1 hr and 4 hr postdose; control animals: 20 min post-infusion).

Dosing Formulation Analysis: Details of the dosing formulation analyses were not provided.

Results:

Mortality: The high-dose group was terminated early (Day 1) as required 20 mL/kg dose volume could not be reliably administered at this dose level over a 15-minute infusion period. Mortality in the high-dose group was not considered to be test-article related. A single mid-dose female rat (No. 2509) was found dead on Day 10 immediately after a scheduled blood collection procedure. Necropsy findings were limited to hemorrhage in the subcutaneous layer of the axilla. This necropsy finding was confirmed to be acute hemorrhage. The cause of death was attributed to the blood collection procedure.

Clinical Signs: There were no significant treatment-related clinical signs.

Body Weights: The mean initial (Week -1) and final (Week 3) body weights of the control (vehicle) males were 209.6 and 351.4 g, respectively. The mean initial (Week -1) and final (Week 3) body weights of the control (vehicle) females were 175.2 and 238.2 g, respectively. No significant treatment-related changes in body weights were noted.

Food Consumption: The mean initial (Week 1) and final (Week 3) food consumption of the control (vehicle) males were 30.3 and 27.8 g/animal/day, respectively. The mean initial (Week 1) and final (Week 3) food consumption of the control (vehicle) females were 22.4 and 20.7 g/animal/day, respectively. There were no significant treatment-related changes.

Ophthalmoscopy: There were no significant treatment-related changes.

Clinical pathology: All clinical pathology findings were limited to the 36 mg/kg/day (terminated on Day 1). The relation to the treatment was uncertain due to lack of Day 1 data from any other test or control group, as well as the lack of a control group that received the same dose volume as the high-dose group (20 mL/kg) prior to blood sample collection. The following changes were observed: lower red blood cell count, hemoglobin and leukocytes in both sexes on Day 1 compared to placebo group on Day 9, minimally lower hematocrit, and mild elevations of the reticulocyte count and mean corpuscular volume in males, lower cholesterol and triglyceride concentrations in both sexes on Day 1 compared to the placebo control group on Day 9, and mildly higher glucose concentrations.

Urinalysis: There were no significant treatment-related changes.

Gross Pathology: There were no significant treatment-related gross pathology findings.

Organ Weights: There were no significant treatment-related organ weight findings.

Histopathology: There were no significant treatment-related histopathological findings.

Toxicokinetics:

Rolapitant

There was a sex-related difference in systemic exposure to rolapitant following 4.5 or 18 mg/kg doses. Systemic exposure to rolapitant was greater in females than that in males. Female-to-male (F:M) AUC ratios ranged between 1.36 and 2.38. Systemic exposure to rolapitant increased with increasing rolapitant dose. For females, systemic exposure to rolapitant increased following repeated administration of 4.5 mg/kg but decreased following repeated administration of 18 mg/kg. Accumulation ratios were 1.52 and 0.700 at the 4.5 and 18 mg/kg doses, respectively. For males, systemic exposure to rolapitant did not change following repeated administration of 4.5 and 18 mg/kg doses. Accumulation ratios were 0.930 and 0.829 at the 4.5 and 18 mg/kg doses, respectively.

SCH 720881 (Metabolite)

In males, peak SCH 720881 plasma concentrations were observed at 8 hr and 1 hr after treatment on Day 0, and at 4 hr and 0.33 hr after treatment on Day 13, at 4.5 and 18 mg/kg, respectively. In females, peak SCH 720881 plasma concentrations were observed at 24 hr postdose on Day 0, and at 0.33 hr postdose on Day 13, at 4.5 and 18 mg/kg dose groups. There was a sex-related difference in systemic exposure to SCH 720881 following IV infusion of 4.5 or 18 mg/kg of rolapitant. Systemic exposure to SCH 720881 was greater in males than that in females. Female-to-male AUC ratios (F:M) ranged between 0.0828 and 0.515. On both study days, systemic exposure to SCH 720881 increased with increasing rolapitant dose. For females, exposure to SCH 720881 increased with increasing dose at 4.5 or 18 mg/kg of rolapitant. The accumulation ratio at 18 mg/kg dose was 2.29. For males, systemic exposure to SCH 720881 did not change at 4.5 or 18 mg/kg of rolapitant. In males, accumulation ratios were 0.959 and 0.921 at 4.5 and 18 mg/kg doses, respectively.

For females, metabolite:parent (M:P) $AUC_{0\text{-}24\ hr}$ ratios, which were lower than males, increased after repeated administration. In females, the M:P ratios at 18 mg/kg dose were 0.0115 and 0.0377 on Days 0 and 13, respectively. For males, M:P ratios were similar after repeated administration. In males, the M:P $AUC_{0\text{-}8\ hr}$ ratios at the 4.5 mg/kg dose were 0.162 and 0.196 on Days 0 and 13, respectively, and the M:P $AUC_{0\text{-}24\ hr}$ ratios at 18 mg/kg dose were 0.233 and 0.260 on Days 0 and 13, respectively.

The following tables (from pages 513 and 514 of the report) show the TK parameters for rolapitant and SCH 720881.

Table 1 SCH 619734 Toxicokinetic Parameters on Day 0 and Day 13 Following Intravenous (Infusion) Administration of 4.5 or 18 mg/kg SCH 619734 to Female and Male Rats

Day	Sex	SCH 619734 Dose (mg/kg)[a]	$C_{End\ of\ Infusion}$ (ng/mL)[b]	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-8 hr) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	R[c]	F:M[d]
0	Female	4.5	2230	24	20800	8130	20800	NA[e]	1.36[f]
		18	12800	24	76100	34500	76100	NA	1.68
	Male	4.5	2060	8	5970	5970	NR[g]	NA	NA
		18	13800	24	45400	29600	45400	NA	NA
13	Female	4.5	2860	24	31700	13200	31700	1.52	2.38[f]
		18	13400	24	53300	32700	53300	0.700	1.42
	Male	4.5	2200	8	5550	5550	NR	0.930[h]	NA
		18	12600	24	37600	26000	37600	0.829	NA

a: Doses are expressed as free base. When expressed as the hydrochloride monohydrate salt, these doses are equivalent to 5 and 20 mg/kg for the low- and mid-dose groups, respectively.
b: $C_{End\ of\ Infusion}$ values are extrapolated values at 0.25 hr. They are based on the observed plasma concentrations at 0.33 and 1 hr after the start of the infusion.
c: R = $AUC(0\text{-}24\ hr)_{Day\ 13}$ ÷ $AUC(0\text{-}24\ hr)_{Day\ 0}$ unless otherwise noted
d: F:M = $AUC(0\text{-}24\ hr)_{Female}$ ÷ $AUC(0\text{-}24\ hr)_{Male}$ unless otherwise noted
e: NA = Not applicable
f: F:M = $AUC(0\text{-}8\ hr)_{Female}$ ÷ $AUC(0\text{-}8\ hr)_{Male}$
g: NR = Not reported. AUC(0-24 hr) not reported when %AUC extrapolated > 25%.
h: R = $AUC(0\text{-}8\ hr)_{Day\ 13}$ ÷ $AUC(0\text{-}8\ hr)_{Day\ 0}$

Table 2 SCH 720881 Toxicokinetic Parameters on Day 0 and Day 13 Following Intravenous (Infusion) Administration of 4.5 or 18 mg/kg SCH 619734 to Female and Male Rats

Day	Sex	SCH 619734 Dose (mg/kg)[a]	Cmax (ng/mL)	Tmax (hr)	AUC(0-8 hr) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	R[b]	F:M[c]	M:P[d]
0	Female	4.5	17.8	24.00	NR[e]	NR	NA[f]	NA	NA
		18	62.6	24.00	135	877	NA	0.0828	0.0115
	Male	4.5	163	8.00	966	2590	NA	NA	0.162[g]
		18	539	1.00	3840	10600	NA	NA	0.233
13	Female	4.5	65.4	0.33	426	1280	NA	0.515	0.0404
		18	180	0.33	873	2010	2.29	0.206	0.0377
	Male	4.5	145	4.00	1090	2490	0.959	NA	0.196[g]
		18	912	0.33	4870	9760	0.921	NA	0.260

a: Doses are expressed as free base. When expressed as the hydrochloride monohydrate salt, these doses are equivalent to 5 and 20 mg/kg for the low- and mid-dose groups, respectively.
b: R = $AUC(0\text{-}24\ hr)_{Day\ 13}$ ÷ $AUC(0\text{-}24\ hr)_{Day\ 0}$
c: F:M = $AUC(0\text{-}24\ hr)_{Female}$ ÷ $AUC(0\text{-}24\ hr)_{Male}$
d: M:P = $AUC(0\text{-}24\ hr)_{SCH\ 720881}$ ÷ $AUC(0\text{-}24\ hr)_{SCH\ 619734}$ unless otherwise noted
e: NR = Not reported. AUC not reported when N equals less than four consecutive quantifiable time points.
f: NA = Not applicable
g: M:P = $AUC(0\text{-}8\ hr)_{SCH\ 720881}$ ÷ $AUC(0\text{-}8\ hr)_{SCH\ 619734}$

Overall, systemic exposure to rolapitant was higher in females than males and systemic exposure to metabolite, SCH 720881 was higher in males than females. Systemic exposure to rolapitant and SCH 720881 increased with increasing rolapitant dose. For females, systemic exposure to rolapitant increased following repeated administration at 4.5 mg/kg but decreased following repeated administration at 18 mg/kg. For males, systemic exposure to rolapitant did not change following repeated administration at both 4.5 and 18 mg/kg. Systemic exposure to SCH 720881 increased following repeated administration of 4.5 and 18 mg/kg of rolapitant in females and did not change following repeated rolapitant administration in males. Systemic exposure to SCH 720881 was less than the exposure to rolapitant at the 4.5 and 18 mg/kg doses in both sexes. Metabolite to parent (M:P) $AUC_{0\text{-}24\ hr}$ ratios did not change in males but increased in females after repeated administration.

Summary: In a 2-week IV infusion study in rats, animals were treated with rolapitant at 4.5, 18 and 36 mg/kg/day. Treatment at 36 mg/kg/day was terminated after Day 0 as

required 20 mL/kg dose volume could not be reliably administered at this dose level over a 15-minute infusion period. The NOAEL was considered as 18 mg/kg/day. The target organ could not be identified in the absence of any significant treatment-related histopathology findings in any organ/tissue.

Study title: Three-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 619734 in Rats

Study no.:	03409
Study report location:	EDR Section 4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute Lafayette, NJ 07848
Date of study initiation:	February 27, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734 hydrochloride monohydrate, micronized, SZ-03-PHG-TX-001, 99.5%

Key Study Findings

SCH 619734 was tested at 0, 5, 25, and 100 mg/kg/day in males and 0, 1, 5, and 25 mg/kg/day in females under dietary restriction conditions. In males, 100 mg/kg/day SCH 619734 produced treatment-related clinical findings (excessive salivation and peri-oral substance) and a decrease in body weight and body weight gain (compared to controls). In high dose males (100 mg/kg/day) and females (25 mg/kg/day), there were minimal increases in total protein, albumin, and globulin values (up to +13%) and decreased A/G ratios (up to -9%), compared to controls. At the high dose, absolute and relative liver weights were increased (up to 31% and 12% in males and females, respectively), but there were no corresponding histopathological changes. Minimal vacuolation of the epithelium of the epididymides occurred in 9/10 and 10/10 males in the 25 and 100 mg/kg/day dose groups, respectively. The NOAEL was considered to be 5 mg/kg/day.

Methods

Doses:	Males: 5, 25, and 100 mg/kg/day Females: 1, 5, and 25 mg/kg/day
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose, pH 4
Species/Strain:	Rat, Crl:CD®[SD]IGS BR VAF/Plus®
Number/Sex/Group:	Main study: 10/sex/group TK: 30/sex/group (low-, mid-, and high dose only)
Age:	6 weeks old
Weight:	Main study: Males: 171.8-205.1 g; Females: 126.0-155.0 g TK: Males: 162.2-215.5 g; Females: 121.1-166.2 g
Satellite groups:	Yes (TK animals)
Unique study design:	Prior to Day -7, animals were fed ad libitum. Beginning on Day -7, males and females were offered 21 g and 17 g of food daily, respectively.
Deviation from study protocol:	Protocol deviations did not affect the quality or integrity of the study.

Observations and Results

Mortality

Viability checks were conducted at least once daily.

There was no mortality.

Clinical Signs

Main study animals were observed for changes in appearance and behavior at or prior to dosing, 2-4 h post-dose, and at least once on the day of sacrifice.

Treatment-related clinical findings observed in males at 100 mg/kg/day included excessive salivation and peri-oral substance (primarily brown and attributed to food adhering to the snout as a result of salivation).

Body Weights

Body weights of main study animals were measured weekly.

In high dose males, body weight and body weight gain were decreased by 12% and 20%, respectively, compared to controls on Day 90. While body weight gain was decreased by 13% in mid-dose females, body weights were not affected in the low- and

high dose groups and thus this did not appear to be treatment related. The following table copied from the study report summarizes the body weight data.

Summary of Body Weight Data - % Difference								
	Control		Low-Dose SCH 619734		Mid-Dose SCH 619734		High-Dose SCH 619734	
	Male	Female	Male	Female	Male	Female	Male	Female
Interval	Mean Body Weight (g)		% Difference in Mean Absolute Body Weight Values (Relative to Controls)					
Day 90	454.4	272.2	-2.4	+0.7	-4.6	-5.9	-11.9	+0.2
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Interval	Mean Body Weight Gain (g)		% Difference In Mean Body Weight Gains (Relative to Controls)					
Day 0 – Day 90	263.7	131.1	-4.9	0	-7.8	-12.5	-20.4	+0.5
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
(N) = Number of surviving rats at Day 90								

Feed Consumption

Food consumption was measured weekly (main study animals).

There were no treatment-related changes in food consumption. The mean daily food consumption values were frequently equal to the maximum amount of food provided.

Ophthalmoscopy

Ophthalmological examinations were conducted once pretest and once during Weeks 4 and 12 (main study animals).

No treatment-related findings were identified.

ECG

Not conducted.

Hematology

Blood samples were collected during Weeks 4/5 and 13 from main study animals for analysis of standard hematological parameters and coagulation parameters (prothrombin time and activated partial thromboplastin time).

There were no clear treatment-related effects on hematological or coagulation parameters.

Clinical Chemistry

Samples were analyzed for standard serum clinical chemistry parameters.

In high dose animals, there were minimal increases in total protein, albumin, and globulin values (up to +13%) and decreased A/G ratios (up to -9%), compared to controls. The following table copied from the study report summarizes changes in total protein, albumin, globulin, and A/G ratios.

SCH 619734-Related Differences in Mean Total Serum Protein Values[a]					
		Group			
		Control		High-Dose SCH 619734	
Finding (Units)	Week	Male	Female	Male	Female
Total Protein (g/dL)	4/5	6.59	6.71	--	7.40
	13	6.99	7.58	7.68	7.90
Albumin (g/dL)	4/5	3.47	3.58	--	3.86
	13	3.79	4.31	4.06	--
Globulin (g/dL)	4/5	3.12	3.13	3.37	3.54
	13	3.20	3.27	3.62	3.60
A/G	4/5	1.11	1.14	1.02	1.09
	13	1.19	1.32	1.12	1.20
a: Only values from control and affected groups shown.					

Urinalysis

Urinalysis was conducted for samples collected from main study animals during Weeks 4/5 and 13.

No treatment-related findings were identified.

Gross Pathology

Necropsies were conducted on all main study animals during Week 14.

Enlarged livers were observed in 1 mid- dose male (focal) and 1 high dose male.

Organ Weights

The following organs were weighed at necropsy and organ-to-body weight ratios (i.e., relative weights) were calculated: adrenal glands, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate gland (ventral), spleen, testes, thymus, thyroid gland/parathyroid glands, and uterus (plus cervix).

In high dose males and females, absolute and relative liver weights were increased compared to controls, as summarized in the following table copied from the study report.

Principal Organ Weight Changes: Percent Difference from Concurrent Control Mean								
Group:	Control		Low-Dose SCH 619734		Mid-Dose SCH 619734		High-Dose SCH 619734	
Sex:	M	F	M	F	M	F	M	F
Organ	Mean Weight		Percent Difference from Concurrent Control Mean (%)					
Liver								
-Absolute weight	11.52 g	6.78 g	-6	+1	+2	-2	+15*	+12
-Relative weight[a]	2.59%	2.62%	-3	-1	+7	+3	+31*	+11
a: Relative to body weight								
* = Test article-related finding								

Absolute prostate gland weights were decreased by 18%, 20%, and 31% (compared to controls) and relative weights were decreased by 16%, 16%, and 21% (compared to controls) at 5, 25, and 100 mg/kg/day, respectively. The mean prostate gland weight of controls was reported to have been higher than that of concurrent controls from other studies of similar duration at the testing facility. Mean relative epididymis weights were increased by 11%, 11%, and 15% (compared to controls) at 5, 25, and 100 mg/kg/day, respectively. Relative testes weights were increased by 17% in high dose animals. Relative kidney weights in males were increased by 12% and 18% in males administered 25 and 100 mg/kg/day, respectively.

In females, absolute pituitary gland weights were decreased by 12% and 24% at 5 and 25 mg/kg/day, respectively. Relative pituitary gland weights were decreased by 21% at 25 mg/kg/day.

Histopathology

The tissues collected and preserved from main study animals at scheduled necropsy are listed in the Applicant's table below.

Tissues Collected[a]	
Adrenal Glands	Peripheral Nerve – Sciatic
Aorta – Thoracic	Pituitary Gland
Bone – (Femur and Sternum)	Prostate Gland
Bone Marrow Section – Sternum	Salivary Glands – Mandibular
Bone Marrow for Cytology – Sternum[b]	Seminal Vesicles
Brain	Skeletal Muscle – Biceps Femoris
Epididymides	Skin
Esophagus	Small Intestine – (Duodenum, Jejunum, Ileum)
Eyes[c]	Spinal Cord – Thoracolumbar
Harderian Glands[c]	Spleen
Head[d]	Stomach
Heart	Testes[f]
Kidneys	Thymus
Large Intestine – (Cecum and Colon)	Thyroid Gland
Liver	Tongue[d]
Lungs	Trachea
Lymph Nodes – Mandibular and Mesenteric	Urinary Bladder
Mammary Gland[e]	Uterus (plus Cervix)
Ovaries	Vagina
Pancreas	Animal Identification[d]
Parathyroid Gland(s)[e]	

a: Collected in 10% neutral buffered formalin unless otherwise indicated
b: Bone marrow smears were prepared for all toxicity portion rats but were not evaluated because it was not warranted by changes in the peripheral blood.
c: Collected in 3% glutaraldehyde
d: Collected but not processed
e: Examined histopathologically when present in routine section
f: Collected in modified Davidson's fixative

Histopathological evaluation was performed on all organs/tissues from control and high dose group animals and gross findings. Liver and thyroid gland (identified as potential target organs by the pathologist) were evaluated for animals in all other dose groups. For males, epididymides (also identified as a potential target organ) from all other dose groups were also evaluated.

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

In males, SCH 619734 produced minimal vacuolation of the epithelial cells of the epididymides at 25 and 100 mg/kg/day as shown in the Applicant's table below. The finding was segmental and affected the head (caput) of the epididymis. While this was reported to be a common degenerative change in aged rats (Pathology of the Fischer Rat: Reference and Atlas. Boorman GA et al. 1990), this finding occurred only at the mid- and high doses and therefore is treatment-related. The pathology report indicates that the significance of this finding in younger rats is unknown.

Principal Histopathologic Findings								
Group:	Control		Low-Dose SCH 619734		Mid-Dose SCH 619734		High-Dose SCH 619734	
Sex:	M	F	M	F	M	F	M	F
Organ/Finding/Severity	Incidence[a]							
Epididymides								
-Vacuolation, epithelial, segmental minimal	0/10	NA	0/10	NA	9/10*	NA	10/10*	NA
a: Incidence = Number affected/Number examined. * = Test article-related finding NA = Not applicable								

Other findings in high dose animals (but not controls) included minimal colloid depletion in the thyroid gland (2/10 high dose males) and minimal myofiber regeneration in the esophagus (2/10 high dose males).

Special Evaluation

None

Toxicokinetics

Blood samples were collected from satellite animals on Days 0, 14, and 62 at 1-24 h after dosing. On Day 0, samples were collected from 15 animals/sex/group. Samples were collected from the remaining animals on Days 14 and 62 (15 animals/sex/group). Plasma samples were analyzed for SCH 619734 concentration using a validated LC-MS/MS assay.

Exposure to SCH 619734 (measured as C_{max} and $AUC_{0\text{-}24\ h}$) increased with increasing dose. In females, accumulation ratios (relative to Day 0) ranged from 1.55 to 2.98 for Days 14 and 62 at 1 and 5 mg/kg/day indicating accumulation of SCH 619734 at the low- and mid-dose levels. At comparable dose levels, exposures in females were greater than those in males. The Applicant's table below summarizes the SCH 619734 TK parameters.

SCH 619734 Toxicokinetic Parameters					
Day	Dose (mg/kg)	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)	Accumulation Ratio
Female					
0	1	155	4	2470	NA
	5	638	8	10700	NA
	25	2510	8	42100	NA
14	1	315	4	4320	1.75
	5	1110	2	16600	1.55
	25	3100	2	41200	0.980
62	1	454	4	7370	2.98
	5	1290	4	21900	2.04
	25	2710	4	33500	0.795
Male					
0	5	331	2	4050	NA
	25	1600	2	16400	NA
	100	4320	4	59500	NA
14	5	476	2	3570	0.883
	25	1460	4	14700	0.894
	100	4490	4	49200	0.827
62	5	535	1	4550	1.12
	25	1730	4	18100	1.10
	100	4420	4	45300	0.762
n = 3 rats/sex/dose group/time point NA = Not applicable					

Dosing Solution Analysis

Samples of dosing solutions at all dose levels were collected during Weeks 1, 4, and 11 for concentration analysis. During Week 1, samples were collected from the 1 and 100 mg/kg/day dose level for homogeneity analysis. The percent of nominal concentration was acceptable (range of 96.5-104%).

The review of Study No. 03664 is incorporated below from the pharmacology review of IND 72,754 dated March 10, 2006 (Ke Zhang, Ph.D., DGP).

3-month oral dose range-finding study of SCH 619734 in rats (03664)

Testing Laboratory: Safety Evaluation Center
Schering-Plough research Institute
Lafayette, NJ

Study Start and Completion Dates: February 15, 2005 and January 17, 2006

GLP and QAU Compliance Statement: Sponsor included a statement of compliance with GLP regulations and a quality assurance statement.

Animals: Crl:CD (SD) vaf/Plus rats, ~6 week old,
Males: 187.3-258 g, females: 144.9-195.1 g.
Drug lot No.: SZ-03-PHG-TX-001

Methods: To assess the repeated oral dose toxicity of SCH 619734 and to assist with dose selection for the 2-year carcinogenicity study in rats, SCH 619734 was given by oral gavage to rats (10/sex/group) at 0, 50, 75, and 125 mg/kg/day for 3 months. The animals were under "ad libitum feeding regimen". In the toxicokinetic study, 15 animals per sex per group were included. Mortality and clinical signs of toxicity were observed daily. Body weights and food consumption were recorded weekly. Hematology, clinical chemistry, and urinalysis were performed at termination. Ophthalmologic examination was conducted before dosing, during weeks 5 and 12. Gross pathological examination was conducted at termination and organ weights were determined. Histopathological examination was performed on animals in the control and high dose groups, the sacrificed animals prior to the termination, all gross findings, adrenal glands, kidneys, liver, and thyroid glands, and the liver from males in all other dose groups. Following tissues or organs were examined microscopically:

Tissues Collected[a]	
Adrenal Glands	Peripheral Nerve – Sciatic
Aorta – Thoracic	Pituitary Gland
Bone – (Femur and Sternum)	Prostate Gland
Bone Marrow Section – Sternum	Salivary Glands – Mandibular
Bone Marrow for Cytology – Sternum[b]	Seminal Vesicles
Brain	Skeletal Muscle – Biceps Femoris
Epididymides	Skin
Esophagus	Small Intestine – (Duodenum, Jejunum, Ileum)
Eyes[c,d]	Spinal Cord – Thoracolumbar
Harderian Glands[c]	Spleen
Head[e]	Stomach
Heart	Testes[c]
Kidneys	Thymus
Large Intestine – (Cecum and Colon)	Thyroid Gland
Liver	Tongue[g]
Lungs	Trachea
Lymph Nodes – Mandibular and Mesenteric	Urinary Bladder
Mammary Gland[f]	Uterus (plus Cervix)
Ovaries	Vagina
Pancreas	Animal Identification[e]
Parathyroid Gland(s)[f]	

a: Collected in 10% neutral buffered formalin unless otherwise indicated
b: Bone marrow smears were prepared for all toxicity portion rats but were not evaluated because it was not warranted by changes in the peripheral blood.
c: Collected in 3% glutaraldehyde
d: Eyes for animal No. 108M in the control group were inadvertently collected in 10% neutral buffered formalin (see **Protocol Deviation No. 5**).
e: Collected but not processed
f: Examined histopathologically when present in routine section
g: Collected in modified Davidson's fixative

Plasma level of the test drug was determined at 1, 2, 4, 8, and 24 hours after dosing on days 0 and 61.

The sponsor also conducted P450 gene expression analysis for CYP1A1, 1A2, 2B1, 2B2, 3B1, and 4A1 from the left lateral lobe of the liver in the control and high dose animals.

Results:

1. Clinical Signs of Toxicity: Excessive salivation and peri-oral substance (brown, orange, red, tan, yellow or white) were noted in all dose groups (none in the control).

2. Mortality: Two mid dose males were sacrificed due to clinical signs of toxicity. One of these males had

physical trauma in the left hindlimb causing immobility. The another male was sacrificed on day 86. This male was diagnosed with leukemic lymphoma. Since it occurred only in one mid dose animal, it is not considered treatment related.

3. Body Weight: The mean initial and final body weights of the control animals were 220.5 g and 529.5 g for males and 169.2 g and 289.5 g for females. The terminal body weight gain was decreased by ~13% in the high dose females as compared to the control. The terminal body weight was approximately 6% lower in the high dose females than that in the control. The terminal body weight was not affected in males.

4. Food Consumption: The average food consumption in the control group was 23.4-25.8 g/animal/day for males and 17.2-19.1 g/animal/day for females. There were no clear treatment related changes.

5. Hematology: Slight decreases in the mean red blood cell counts, hemoglobin, and hematocrit were noted in the high dose females and the results were presented in a table on page 39 in Volume C5.1. This table is attached below.

SCH 619734-Related Differences in Mean Erythrocyte Values

Finding (Units)	Week	Dose Group (mg/kg) 0 (Control)	50 (SCH 619734)	75 (SCH 619734)	125 (SCH 619734)
Female Values					
Red Blood Cells (M/µL)	3	7.9	7.8	7.6	7.4*
	12	9.1	8.8	8.7	8.5*
Hemoglobin (g/dL)	3	15.6	15.4	15.0	14.4*
	12	16.5	15.5	15.2	14.2*
Hematocrit (%)	3	46.6	46.6	45.2	43.2*
	12	49.6	48.0	47.0	44.4*

* = Test article-related finding

6. Clinical Chemistry: Increase in mean serum globulin and total protein and decrease in triglyceride were noted mainly in the high dose group. The results were presented in a table on page 40 in Volume C5.1. This table is attached below.

SCH 619734-Related Differences in Mean Serum Chemistry Values					
Finding (Units)	Week	Dose Group (mg/kg) 0 (Control)	50 (SCH 619734)	75 (SCH 619734)	125 (SCH 619734)
Male Values					
Total Protein (g/dL)	12	7.1	7.4	7.3	7.7*
Globulin (g/dL)	12	3.3	3.6	3.5	3.7*
Triglycerides (mg/dL)	12	119	120	103	55*
Female Values					
Total Protein (g/dL)	3	7.0	7.3	7.4	7.6*
	12	7.9	8.1	8.4*	8.6*
Globulin (g/dL)	3	2.9	3.3	3.4	3.6*
	12	3.4	3.8	4.0*	4.1*
Triglycerides (mg/dL)	3	83	29*	35*	50*
	12	79	46*	39*	39*
* = Test article-related finding					

7. Urinalysis: There were no treatment related changes.

8. P540 gene expression: The results indicated that the animals in the high dose group had induction of CYP 2B1/2B2 and 3A1. The results were summarized in a table on page 42 in Volume C5.1. This table is attached below.

CYP Gene Expression Fold-Change Over Control Group Mean Values							
Dose (mg/kg)	Sex		Fold-Change in CYP mRNA CYP 1A1	CYP 1A2	CYP 2B1/2B2	CYP 3A1	CYP 4A1
125	Male	Mean:	3.93	0.70	12.93*	11.81*	0.50
		Range:	2.3 – 12.3	0.51 – 0.95	6.9 – 34.8	6.6 – 17.6	0.38 – 0.64
	Female	Mean:	1.57	0.61	6.61*	43.79*	1.02
		Range:	0.43 – 3.3	0.45 – 0.91	4.2 – 16.8	33.4 – 50.4	0.44 – 1.2
* = Test article-related finding							

9. Ophthalmology: There were no treatment related changes.

10. Organ Weight: The absolute and relative weights (to body weight) of the liver, kidney, adrenal, thyroid, and uterus were higher in the treatment groups than those in the control. The results were summarized in a table on page 43 and this table is attached below.

Principal Organ Weight Changes: Percent Difference from Concurrent Control Mean								
Dose Group (mg/kg):	0 (Control)		50 (SCH 619734)		75 (SCH 619734)		125 (SCH 619734)	
Sex:	M	F	M	F	M	F	M	F
Organ	Mean Weight		Percent Difference from Concurrent Control Mean (%)					
Adrenal Glands								
-Absolute weight	0.062 g	0.070 g	+12	-6	+14	-1	+22*	-1
-Relative weight[a]	0.012%	0.024%	+4	-7	+12	-2	+21*	+2
Kidneys								
-Absolute weight	3.19 g	1.91 g	+21*	+10	+15*	+12	+24*	+9
-Relative weight	0.63%	0.66%	+13*	+9	+14*	+11	+26*	+14
Liver								
-Absolute weight	11.77 g	8.60 g	+31*	+21*	+32*	+44*	+48*	+57*
-Relative weight	2.32%	2.95%	+22*	+21*	+30*	+42*	+51*	+65*
Thyroid Gland								
-Absolute weight	0.030 g	0.025 g	+13	+15	+11	+11	+14*	+1
-Relative weight	0.006%	0.008%	+5	+18	+4	+11	+17*	+7
Uterus								
-Absolute weight	NA	0.61 g	NA	-6	NA	-16*	NA	-37*
-Relative weight	NA	0.21%	NA	-6	NA	-17*	NA	-34*

* = Test article-related finding; NA = Not applicable

a: Relative to body weight

11. Gross Pathology: There were no treatment related changes.

12. Histopathology: Treatment with test drug produced liver hypertrophy (all treatment groups), hyperplasia of tubular cells in the kidneys (mid and high dose males), hyperplasia of follicular cell of the thyroid, and hyperplasia of zona fasciculate in the adrenal glands in the high dose males. The results were summarized in a table on page 45 in Volume C5.1. and this table is attached below.

Test Article-Related Histopathologic Findings								
Dose Group (mg/kg):	0 (Control)		50 (SCH 619734)		75 (SCH 619734)		125 (SCH 619734)	
Sex:	M	F	M	F	M	F	M	F
Organ/Finding/Severity	Incidence[a]							
Adrenal Glands								
-Hyperplasia, zona fasciculata								
minimal	0/10	0/10	0/10	0/1	0/10	NA	1/10	0/10
Kidneys								
-Hyperplasia, tubular cell, outer stripe, multifocal								
minimal	0/10	0/10	0/10	0/1	3/10	NA	6/10	0/10
Liver								
-Hypertrophy, centrilobular								
minimal	0/10	0/10	3/10	5/10	4/10	9/10	10/10	4/10
mild	0/10	0/10	0/10	0/10	0/10	1/10	0/10	6/10
-Multinucleated hepatocytes								
minimal	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10
mild	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10
Thyroid Gland								
-Hyperplasia, follicular cell								
minimal	0/9	0/10	0/10	NA	0/10	NA	5/10	0/10

NA = Not applicable
a: Incidence = Number affected/Number examined.

12. Plasma level of test drug: The plasma levels of the test drug were summarized in a table on page 37 in Volume C5.1. and this table is attached below.

Day	Dose[a] (mg/kg)	Sex	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)	R[b]	F:M[c]
0	50	Female	5810	8	103000	NA[d]	1.58
		Male	4190	8	65300	NA	
	75	Female	6980	2	116000	NA	1.50
		Male	5710	2	77500	NA	
	125	Female	7310	2	107000	NA	1.07
		Male	5760	4	100000	NA	
61	50	Female	5010	2	62900	0.609	1.40
		Male	3110	4	44800	0.685	
	75	Female	5200	4	65200	0.561	1.63
		Male	3140	2	40000	0.517	
	125	Female	5910	4	84400	0.787	1.31
		Male	4290	8	64300	0.643	

a: SCH 619734 expressed as the hydrochloride monohydrate salt. When expressed as the free base, daily doses equal 45, 67.5 and 112.5 mg/kg for the 50, 75 and 125 mg/kg doses, respectively

b: Accumulation Ratio; calculated as $AUC(0\text{-}24\ hr)_{Day\ 61} \div AUC(0\text{-}24\ hr)_{Day\ 0}$

c: Female:Male; calculated as $AUC(0\text{-}24\ hr)_{Female} \div AUC(0\text{-}24\ hr)_{Male}$

d: NA = Not applicable

The results indicated that the plasma level of the test drug was higher in females thin in males. The exposure ratio of rat to human cannot be calculated since a valid, accurate human AUC was not provided.

In summary, SCH 619734 was given by oral gavage to rats at 0, 50, 75, and 125 mg/kg/day for 3 months. Treatment with SCH 619734 induced excessive salivation and peri-oral substance (brown, orange, red, tan, yellow or white) and liver hypertrophy in all treatment groups, hyperplasia of tubular cells in the kidneys (mid and high dose males), hyperplasia of follicular cell of the thyroid, and hyperplasia of zona fasciculate in the adrenal glands in the high dose males. Treatment with SCH 619734 decreased the terminal body weight gain by ~13% in the high dose females as compared to the control (not in males). Since the treatment related clinical signs of toxicity including excessive salivation were observed in all treatment groups, the NOAEL cannot be clearly identified.

Study title: A 26-Week Oral Gavage Toxicity and Toxicokinetic Study of SCH 619734 in the Rat

Study no.:	03115
Study report location:	EDR Section 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 21, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734 hydrochloride monohydrate, parenteral grade, micronized, SZ-04-619734-TX-005, 100.2%

Key Study Findings

Treatment with SCH 619734 produced salivation primarily at ≥50 mg/kg/day. In females, body weight and body weight gain were decreased at all dose levels (up to -13% and -21%, respectively, compared to controls), but effects were similar at all dose levels with no apparent dose-relationship. The following clinical chemistry changes occurred in both sexes at all dose levels: deceased conjugated bilirubin, triglycerides, albumin, and albumin/globulin (A/G) ratio and increased globulin levels (compared to controls). In females, cholesterol was increased (compared to controls). There was a dose-dependent increase in absolute and relative liver weights in both sexes, which correlated with histopathological findings in this organ. In the livers of males, there was an increased incidence of minimal to slight hepatocellular hypertrophy and vacuolation (not dose-related) at all doses, with additional changes at 100 mg/kg/day (minimal to slight eosinophilic cell foci, minimal single cell necrosis, and minimal multinucleated hepatocytes). In females, an increased incidence of minimal to slight hepatocellular hypertrophy occurred at all doses, with minimal single cell necrosis and multinucleated hepatocytes at 50 mg/kg/day. At 100 mg/kg/day, there was slight to moderate hepatocellular hypertrophy, minimal to slight single cell necrosis, and minimal to moderate multinucleated hepatocytes. In the thyroid, the incidence of follicular cell hypertrophy was increased at all doses in both sexes and relative thyroid weights were increased at the high dose. In the epididymis, minimal vacuolation of the tubular epithelium occurred in 15/15 low-, mid-, and high dose males, compared to 0/15 controls. A NOAEL was not established in this study. However, the findings in the liver and thyroid appear to be related to the activation of drug metabolizing enzymes. Changes in clinical chemistry parameters may be related to effects on the liver.

Methods

Doses:	25, 50, and 100 mg/kg/day
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Rat, *Rattus norvegicus* (Crl:CD[SD])
Number/Sex/Group:	Main toxicity study animals: 15/sex/group TK animals: 9/sex/group Health screen animals: 12/sex
Age:	6 weeks old
Weight:	Males: 177-216 g; Females: 139-172g
Satellite groups:	Yes (TK animals)
Unique study design:	Health screen animals were used for viral/serology evaluation, and subject to internal and external gross examination only. Animals in this cohort were not dosed with the test compound or vehicle.
Deviation from study protocol:	Protocol deviations did not affect the quality or integrity of the study.

Observations and Results

Mortality

Mortality was observed twice daily.

There was no test compound-related mortality. Although a single low-dose TK female was found dead on Day 125, this was considered incidental since no mortalities occurred at the mid- and high dose levels.

Clinical Signs

Clinical signs were observed twice daily. A complete detailed examination of main study animals was performed weekly.

Salivation occurred primarily at ≥50 mg/kg/day SCH 619734. Salivation occurred in only a single male animal at 25 mg/kg/day. An increased incidence of red staining of the fur also occurred (primarily at the mid- and high dose levels).

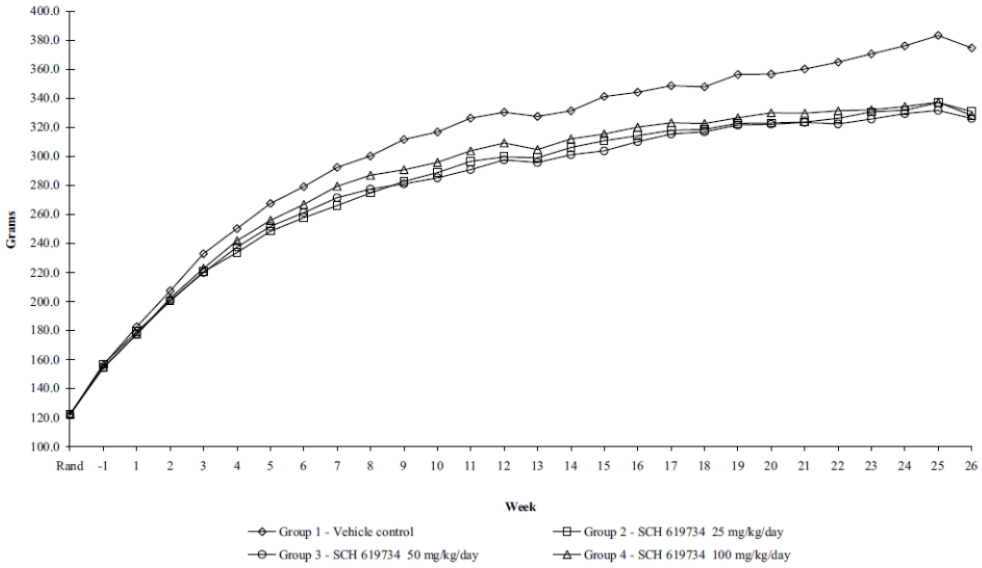
Body Weights

Body weights were measured weekly and at terminal sacrifice (main study animals).

In males, there were no treatment-related changes in body weight or body weight gain. In females, lower body weights and body weight gain occurred at all dose levels. Body weight gain over the course of the study was reduced by 20.4%, 21.4%, and 20.6%

(compared to controls) in low-, mid-, and high dose females. At the end of the dosing period, low-, mid-, and high dose female body weights were 11.7%, 13%, and 12.4% lower than controls. Based on the apparent lack of dose-dependency and minimal change in body weight at the end of the study compared to controls, changes in body weight gain and body weight were considered treatment-related but not adverse. The Applicant's figure below illustrates group mean body weight values for main study females.

Figure 2 Group Mean Body Weight Values - Main Study - Females



Feed Consumption

Food consumption was measured weekly (main study animals).

There were no treatment-related effects on food consumption.

Ophthalmoscopy

Ophthalmological examinations were conducted pre-study (all animals), and during Week 27 (main study animals).

No treatment-related findings were identified.

ECG

Not conducted

Hematology

Blood samples were collected from all main study animals during Weeks 13 and 27 for analysis of standard hematological parameters. Coagulation parameters were determined for samples collected at necropsy.

There were no treatment-related changes.

Clinical Chemistry

Blood samples were analyzed for standard clinical chemistry parameters.

In both sexes, total and conjugated bilirubin, triglycerides, and albumin/globulin (A/G) ratio were decreased at all dose levels. Decreases in A/G ratio corresponded to decreased albumin and increased globulin levels. Cholesterol was increased in a dose-dependent manner in females. The findings were considered test-compound related and may be associated with changes in the liver. The changes were characterized as minimal and reported to be within historical range values for rats of this age and species. The Applicant's table below summarizes the treatment-related changes in these parameters.

SCH 619734-Related Differences in Mean Serum Chemistry Values

		Dose Group			
		0 mg/kg	SCH 619734		
Finding (Units)	Week	(Control)	25 mg/kg	50 mg/kg	100 mg/kg
Male Values					
Total Bilirubin (mg/dL)	13	0.141	0.117	0.115	0.090
	26	0.115	0.081	0.078	0.071
Conjugated Bilirubin (mg/dL)	13	0.044	0.041	0.035	0.034
	26	0.049	0.031	0.033	0.033
Triglycerides (mg/dL)	13	114.6	71.7	52.7	26.1
	26	113.1	84.7	55.6	37.3
Albumin/Globulin Ratio (calculated)	13	1.554	1.392	1.321	1.288
	26	1.579	1.383	1.345	1.252
Female Values					
Total Bilirubin (mg/dL)	13	0.161	0.081	0.1	0.088
	26	0.130	0.089	0.093	0.1
Conjugated Bilirubin (mg/dL)	13	0.045	0.033	0.034	0.036
	26	0.045	0.034	0.04	0.044
Cholesterol (mg/dL)	13	97.5	107.1	133.3	147.7
	26	81.3	112.1	140.5	168.7
Triglycerides (mg/dL)	13	137.2	66.3	71.3	51.6
	26	81.8	44.0	45.8	33.3
Albumin/Globulin Ratio (calculated)	13	1.799	1.509	1.37	1.299
	26	2.368	1.881	1.639	1.551

Urinalysis

Urinalysis was conducted during Weeks 13 and 27 (main study animals).

There were no treatment-related changes.

Gross Pathology

At terminal sacrifice, necropsies consisting of external examination, identification of all clinically recorded findings, and detailed internal examination were conducted on main study animals.

Enlarged livers were observed in 1 low- and mid-dose male each, which correlated with increased liver weights.

Organ Weights

The following organs were weighed at the scheduled necropsy of main study animals: adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate, spleen, testes, thymus, thyroid gland/parathyroid gland, and uterus (plus cervix). Paired organs were weighed together, and organ-to-body weight ratios (i.e., relative weights) were calculated.

Absolute and relative liver weights increased in a dose-dependent manner in both males and females as shown in the Applicant's table below. The increased liver weights correlated with hepatocellular hypertrophy, and were considered consistent with P450 induction.

Text Table 1 Principal Organ Weight Changes (Terminal Sacrifice): Percent Difference from Vehicle Control Mean

SCH 619734 (mg/kg/day)	0 (control)		25		50		100	
Sex:	M	F	M	F	M	F	M	F
Liver								
-Absolute weight	15.3848	8.0306	15	5	25[a]	26[a]	33[a]	59[a]
-Relative weight[b]	2.40921	2.25805	9	20	23[a]	47[a]	39[a]	82[a]

a: Test article-related finding
b: Relative to body weight

Relative thyroid weights were increased by 20% and 17% (compared to controls) in high dose males and females, respectively. This may also be related to treatment-related enzyme induction.

In high dose males, absolute and relative kidney weights were increased by 13% and 18%, respectively. In females, absolute pituitary weights were decreased by 41%, 44%, and 48% at 25, 50, and 100 mg/kg/day, respectively, compared to controls. Relative pituitary weights were decreased by up to 40% in treated females compared to controls. Absolute uterus weights were decreased by 18%, 21%, and 43% at 25, 50, and 100 mg/kg/day, compared to controls. Relative uterus weights were decreased by 8%, 10%, and 35% in low-, mid-, and high dose females, compared to controls. The significance of these changes is unknown given the lack of histopathological findings.

Histopathology

The Applicant's table below identifies the tissues collected at necropsy.

Tissues Collected	
Abnormalities (gross findings) Animal Identification[f] Aorta (thoracic) Adrenal glands Bone and marrow (sternum)[a,b] Brain (forebrain, midbrain, cerebellum and medulla oblongata) Epididymides[c] Esophagus Eyes with optic nerves[c,d] Harderian glands Heart (including section of aorta) Kidneys Large intestine (cecum, colon) Larynx/pharynx Liver (sample of 2 lobes) Lungs (sample of 2 lobes)[e] Lymph nodes (mandibular, unilateral; mesenteric) Mammary gland (inguinal)[d] Parathyroid gland(s)[d] Peripheral nerve-sciatic	Ovaries Pancreas Pituitary Prostate Rectum[f] Salivary glands (mandibular, unilateral) Seminal vesicles Skeletal muscle Skin (inguinal) Small intestine (duodenum, jejunum, ileum) Spinal cord (thoracolumbar) Spleen Stomach Testes[c] Thymus Thyroid glands Tongue[f] Trachea Urinary bladder Uterus (horns and cervix) Vagina
a: Bone decalcified prior to sectioning. b: Bone marrow smears (3) were prepared and stained for all main study animals euthanized at the scheduled necropsies but were not evaluated. c: Fixed in Davidson's fixative. d: Examined histopathologically only if present in routine sections of eyes (optic nerves), thyroid lobes (and parathyroid glands), or skin (mammary gland). e: Infused with neutral buffered 10% formalin. f: Retained but not processed.	

Histopathological evaluation was performed on all tissues identified in the table above from control and high dose main study animals. In addition, liver, epididymides, thyroid, and macroscopic abnormalities were examined in low- and mid- dose main study animals.

Adequate Battery: Yes

Peer Review: A peer review was performed by the Applicant

Histological Findings

Dose-related histopathological changes occurred in the liver, thyroid, and epididymis.

Findings in the liver included eosinophilic cell foci, hepatocellular hyper trophy, single cell necrosis, multinucleated hepatocytes, and hepatocellular vacuolation. Hepatocellular hypertrophy occurred in both sexes, and correlated with increased liver weights. Findings in the liver are summarized in the Applicant's table below.

Text Table 2 Incidence and Severity of SCH 619734-related changes in the Liver								
Tissue/Finding Sex	Male				Female			
Dose (mg/kg/day):	0	25	50	100	0	25	50	100
No. in Group	15	15	15	15	15	15	15	15
Eosinophilic cell focus								
Minimal	0	0	0	3	0	0	0	0
Slight	0	0	0	1	0	0	0	0
Total	0	0	0	4	0	0	0	0
Hepatocellular hypertrophy								
Minimal	0	4	12	7	0	1	6	0
Slight	0	0	0	8	0	1	6	1
Moderate	0	0	0	0	0	0	0	14
Total	0	4	12	15	0	2	12	15
Single cell necrosis								
Minimal	0	0	0	2	0	0	2	2
Slight	0	0	0	0	0	0	0	1
Total	0	0	0	2	0	0	2	3
Multinucleated hepatocytes								
Minimal	0	0	0	8	0	0	1	3
Slight	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	0	0	0	1
Total	0	0	0	8	0	0	1	5
Hepatocellular vacuolation								
Minimal	2	4	3	4	1	1	0	1
Slight	0	3	2	2	0	0	0	0
Total	2	7	5	6	1	1	0	1

In the thyroid, minimal to slight follicular cell hypertrophy occurred in 4/15, 5/15, 8/15, and 12/15 control, low-, mid-, and high dose males, respectively. In females, the incidence was 0/15, 2/15, 9/15, and 11/15 in controls, low-, mid-, and high-dose animals, respectively. This finding was considered to occur as a secondary effect to hepatic enzyme induction and correlated with increased thyroid weights.

In the epididymis, minimal vacuolation of the tubular epithelium occurred in 15/15 low-, mid-, and high dose males, compared to 0/15 controls. The vacuoles were found to be generally round, clear, and located between the nuclei and basement membranes. Their location was segmental, and they were typically present in the segment adjacent to the epididymal head. In the absence of a recovery group, it is unknown whether these changes are reversible.

Other findings which occurred at a greater incidence in treated animals included histiocytosis in the lung (4/15 high dose males compared to 1/15 controls and 1/1 mid-dose males each). In females, histiocytosis in the lung occurred in 2/15 high dose females.

Special Evaluation

None.

Toxicokinetics

Blood samples from TK animals were collected on Day 1 and during Week 21 at time points ranging from 1 to 24 h post-dose. Plasma samples were shipped to the Applicant for analysis of SCH 619734 and metabolite SCH 720881.

Exposure to SCH 619734 increased in a less than dose-proportional manner in males from 25 to 100 mg/kg/day and females from 25 to 50 mg/kg/day. Exposures in females were similar at 50 and 100 mg/kg/day. At the 25 and 50 mg/kg/day dose levels, exposures in females were higher than males (the ratio of female:male AUC values ranged from 1.41 to 1.79). At the low dose level only, exposures on Day 142 were higher than Day 1. The ratio of AUC values on Day 142 to Day 1 at 50 and 100 mg/kg/day ranged from 0.737 to 1.08, and the lack of accumulation was considered to be consistent with enzyme induction.

Exposure to metabolite 720881 increased in a less than dose-proportional manner in males. In females, systemic exposures also increased in a less than dose-dependent manner on Day 1. On Day 142, female AUC values at 50 and 100 mg/kg/day were similar. Exposures in males were higher than females with female:male exposure ratios ranging from 0.0791 to 0.476. At 50 and 100 mg/kg/day, exposure to SCH 720881 decreased with repeated exposure in males and increased in females. Ratios of metabolite to parent compound ranged from 0.323 to 0.389 on Day 1 and 0.187 to 0.247 on Day 142.

Toxicokinetic parameters for SCH 619734 and 720881 are shown in the Applicant's tables below.

SCH 619734 Toxicokinetic Parameters on Day 1 and Day 142 Following Oral (Gavage) Administration of 25, 50 or 100 mg/kg SCH 619734 to Male and Female Rats

SCH 619734 Dose (mg/kg)[a]	Dose	Sex	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)	R[b]	F:M[c]
25	1	Female	3150	4	49600	NA[d]	1.77
		Male	2560	4	28000	NA	NA
	142	Female	5280	4	65200	1.32	1.41
		Male	3580	2	46200	1.65	NA
50	1	Female	5640	8	92100	NA	1.79
		Male	3470	8	51400	NA	NA
	142	Female	5780	4	80200	0.871	1.44
		Male	4930	4	55700	1.08	NA
100	1	Female	6030	4	97700	NA	1.23
		Male	6390	4	79500	NA	NA
	142	Female	5900	2	72000	0.737	0.903
		Male	5530	4	79700	1.00	NA

a: Expressed as the hydrochloride salt. When expressed as the free base, daily doses were 22.5, 45.0 and 90.0 mg/kg for the 25, 50 and 100 mg/kg dose groups, respectively.

b: $R = AUC(0\text{-}24\ hr)_{Day\ 142} \div AUC(0\text{-}24\ hr)_{Day\ 1}$

c: $F{:}M = AUC(0\text{-}24\ hr)_{Female} \div AUC(0\text{-}24\ hr)_{Male}$

d: NA = Not Applicable

SCH 720881 Toxicokinetic Parameters on Day 1 and Day 142 Following Oral (Gavage) Administration of 25, 50 or 100 mg/kg SCH 619734 to Male and Female Rats

SCH 619734 Dose (mg/kg)[a]	Dose	Sex	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)	R[b]	F:M[c]	M:P[d]
25	1	Female	63.7	24	1200	NA[e]	0.109	0.0242
		Male	726	8	10900	NA	NA	0.389
	142	Female	209	4	3430	2.87	0.297	0.0526
		Male	617	8	11500	1.06	NA	0.249
50	1	Female	129	24	1880	NA	0.112	0.0204
		Male	1200	8	16800	NA	NA	0.327
	142	Female	334	8	5020	2.66	0.476	0.0626
		Male	719	2	10500	0.625	NA	0.189
100	1	Female	103	24	2030	NA	0.0791	0.0208
		Male	1510	8	25700	NA	NA	0.323
	142	Female	312	4	4760	2.34	0.319	0.0661
		Male	1030	4	14900	0.581	NA	0.187

a: Expressed as the hydrochloride salt. When expressed as the free base, daily doses were 22.5, 45.0 and 90.0 mg/kg for the 25, 50 and 100 mg/kg dose groups, respectively.

b: $R = AUC(0\text{-}24\ hr)_{Day\ 142} \div AUC(0\text{-}24\ hr)_{Day\ 1}$

c: $F{:}M = AUC(0\text{-}24\ hr)_{Female} \div AUC(0\text{-}24\ hr)_{Male}$

d: $M{:}P = AUC(0\text{-}24\ hr)_{SCH\ 720881} \div AUC(0\text{-}24\ hr)_{SCH\ 619734}$

e: NA = Not Applicable

Dosing Solution Analysis

Dosing solution samples were collected on the day of preparation from Weeks 1, 6, 13, and 26 for concentration analysis. Samples collected from Week 1 were also analyzed for homogeneity, and on one occasion, a sample was collected from each group for density measurement. All samples were within the acceptance criteria.

The percent of nominal concentration was within the acceptance criteria of ±15% (range of 95.3-107%).

Rhesus Monkey

Assessment of Tolerability and Collection of Samples for Pharmacokinetic Analysis of Rolapitant in Male Rhesus Monkeys Following 3 Days of Repeat Intravenous Dosing (2013-003, Non-GLP)

Methods: This exploratory study was conducted to evaluate the pharmacokinetics and tolerability of rolapitant in rhesus monkeys. The study was also used for evaluation of proposed doses for an IV self-administration study in monkeys. The test article was administered via a 4 minute IV infusion once a day for three consecutive days to three male, non-naïve rhesus monkeys at a dose level of 7.5 mg/kg (dose volume = 0.75 mL/kg, dose concentration = 10 mg/mL). The vehicle used for the test article was 4.4% Solutol, 1.1% Miglyol, 0.66% Soybean Oil, pH 7.5 in sterile water for injection. Animals were observed for morbidity, mortality, injury, and food and water availability twice daily. Body weights were recorded pre-study and on Day 4. Clinical pathology evaluations

(blood and urine) were conducted pretest, prior to dosing on Day 1, and 6 h post-dose on Day 3. Blood samples for PK analysis were collected at designated time points on Days 1, 2, and 3.

Results: No treatment-related effects were identified, and it was concluded that 1.5 mg/kg administered as 5 IV injections over 2 h (total dose = 7.5 mg/kg) should be a safe and well tolerated dose in a monkey self-administration study. The mean rolapitant Cmax (5453 ng/mL) was achieved within approximately 2 min of dosing, and the mean terminal elimination half-life was 21 h. The mean Cmax for metabolite SCH 720881 was 162 ng/mL (median Tmax = 24 h). Exposure to the metabolite was estimated to be 8% of that achieved for the parent compound. Mean Cmax and AUC_{last} values are summarized in the following table.

Day	Rolapitant		SCH 720881	
	Cmax (ng/mL)	AUC_{last} (ng.hr/mL)	Cmax (ng/mL)	AUC_{last} (ng.hr/mL)
1	5453	33789	162	2673
3	2620	44589	367	8023

Cynomolgus Monkey

Review of Study No. 2013-004 is incorporated directly below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

Exploratory Infusion Toxicity Study of One Rolapitant Formulation with Two Different Infusion Times in Cynomolgus Monkeys (Study No. 2013-004)

Methods: This study (Non-GLP) was conducted to examine the tolerability and pharmacokinetics of SCH 619734 by IV infusion at two different infusion rates (15 and 30 min) at 10 mg/kg (5 mL/kg). The test article was administered by IV infusion once daily for five consecutive days at 10 mg/kg/day (5 mL/kg). Doses were administered for 15 or 30 minutes as shown in the table below. The study design is shown below (from page 7 of the report).

Group Assignments			
Group Number	Dose Level (mg/kg/day)	Duration (minute)	Animal Numbers Male
1	10	15	1001 to 1003
2	10	30	2001 to 2003

Animals were observed for morbidity, mortality and clinical signs on a daily basis. Body weights were recorded daily. Clinical pathology evaluations were conducted on all animals pretest (Day -1) and 24 hours post-dose on Day 5. Blood samples were collected from all animals for determination of the plasma concentrations of SCH 619734 and its metabolite SCH720881 at 0.5, 1, 3, 6, 8, and 24 hours post-dose on Day 1, and at pre-dose, and 1, 3, 6, and 24 hours post-dose on Day 5. Urine samples were collected for at least 16 hours.

Results: There was no mortality. There were no significant treatment-related effects on body weight. At 24 hours post-dose on Day 5, there were mild reductions in erythrocyte mass (erythrocytes, hemoglobin, and hematocrit) in both treatment groups (up to 18%) relative to pretest values. There were concurrent mild increases in absolute reticulocytes (up to 2.8-fold). The magnitude of changes in erythrocyte mass and reticulocytes were similar in both treatment groups. There were occasional mild increases in total leukocytes (up to 1.5-fold) and neutrophils (up to 3.0-fold), relative to individual pretest values in both treatment groups. Clinical chemistry changes included occasional mild increases in globulins (up to 1.3-fold) relative to pretest values. There were no treatment-related changes in urinalysis parameters in either treatment group.

Mean AUC and Cmax values were similar between monkeys that received a 10 mg/kg rolapitant dose from a 15 minute or 30 minute IV infusion. Systemic exposure to rolapitant appeared to increase following repeated administration.

For the Group 1 at 10 mg/kg (15 min infusion), mean AUC_{Tlast} and Cmax values were 43600 ng.hr/mL and 7510 ng/mL, respectively, on Day 1 and 58000 ng.hr/mL and 4720 ng/mL, respectively, on Day 5. Mean systemic exposure to rolapitant appeared to increase following repeated administration. The mean accumulation ratio was 1.34.

For the Group 2 at 10 mg/kg (30 min infusion), mean AUC_{Tlast} and Cmax values were 48000 ng.hr/mL and 6240 ng/mL, respectively, on Day 1 and 59100 ng.hr/mL and 4510 ng/mL, respectively, on Day 5. Mean systemic exposure to rolapitant appeared to increase following repeated administration. The mean accumulation ratio was 1.23.

The following table (from page 310 of the report) shows the TK data of SCH 619734 following a 15 or 30 min IV infusion at 10 mg/kg in male Cynomolgus monkeys.

Table 1 Mean (CV) Rolapitant Toxicokinetic Parameters Following a 15 or 30 minute Intravenous Infusion of 10 mg/kg Rolapitant to Male Monkeys

Group[a]	Day	Cmax (ng/mL)	Cmax/Dose (kg*ng/mL/mg)	Tmax (hr)	Tlast (hr)	AUCTlast (ng*hr/mL)	AUCTlast /Dose (hr*kg*ng/mL/mg)	R Value[b]	$T_{1/2}$ (hr)	Vz (mL/kg)	Cl (mL/hr/kg)	Vss (mL/kg)
1[c]	1	7510 (31)	751 (31)	0.25 (0)	24.25 (0)	43600 (20)	4360 (20)	NA[e]	11.0 (35)	2850 (23)	190 (26)	2540 (27)
	5	4720 (13)	472 (13)	1.25 (0)	24.25 (0)	58000 (21)	5800 (21)	1.34 (17)	10.6 (31)	2080 (5)	146 (35)	1860 (7)
2[d]	1	6240 (21)	624 (21)	0.50 (0)	24.50 (0)	48000 (7)	4800 (7)	NA	13.7 (12)	2990 (10)	151 (8)	2740 (11)
	5	4510 (6)	451 (6)	1.50 (0)	24.50 (0)	59100 (3)	5910 (3)	1.23 (6)	12.6 (15)	2270 (6)	127 (10)	2110 (8)

a: N=3/ group
b: R = AUC_{Tlast} Day 5 ÷ AUC_{Tlast} Day 1
c: 15 minute intravenous infusion administration
d: 30 minute intravenous infusion administration
e: NA = Not Applicable

Overall, the tolerability of SCH 619734 when administered by IV infusion at two different infusion rates (15 and 30 min) at 10 mg/kg (5 mL/kg) was comparable. Both infusion rates/durations were well tolerated and no mortality or compound related clinical observations were noted. The Cmax and AUC values were also comparable between 15 and 30 minute infusions.

Review of Study No. 07393 is incorporated below from the pharmacology review of IND 72,754 dated December 5, 2012 (Tamal Chakraborti, Ph.D., DGIEP).

Study title: 14-Day Intravenous Infusion Study in Cynomolgus Monkeys

Study no.:	07393
Study report location:	EDR Section 4.2.3.2.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 8, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Rolapitant IV Solution (2 mg/mL), Batch No. K-H08771, 100.1%

Key Study Findings:

- In a 2-week IV infusion study in Cynomolgus monkeys, animals were treated with rolapitant at 5, 10, and 20 mg/kg/day.
- Mortality was observed at all doses in males and at 10 and 20 mg/kg/day in females.
- The NOAEL was considered as 5 mg/kg/day for females; however, the NOAEL could not be established in males.
- The CNS may be the target organ based on the clinical signs (hypoactivity, hunched posture, ataxia, etc.) of animals sacrificed preterminally.

Methods:

Doses:	5,10 and 20 mg/kg/day
Frequency of dosing:	Daily
Route of administration:	IV infusion (15-minute)
Dose volume:	2.5-10 mL/kg
Formulation/Vehicle:	[4.4% (v/v) Solutol®HS15, 1.1% (v/v) Miglyol®, 0.66% (v/v) soybean oil in 20 mM phosphate-buffered saline, pH 7.5]
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	4/sex/group
Age:	31-47 months
Weight:	Males: 2.5 to 3.5 kg; Females: 2.3 to 3.3 kg
Satellite groups:	None
Unique study design:	The study design is shown below (from page 15 of the report)
Deviation from study protocol:	The listed deviations from the protocol did not adversely affect either the quality or integrity of the study or the interpretation of the results.

14-Day Intermittent Intravenous Infusion Toxicity and Toxicokinetic Study with SCH 619734 in Cynomolgus Monkeys (SPRI 07393): **Study Design**					
Group	Test/Control Article	No. of Monkeys/Sex[a]	Dose[a] (mg/kg)	Dose Volume (mL/kg)	Dose Concentration[b] (mg/mL)
1	Control (0.9% Sodium Chloride for Injection)[c]	4	0	10	0
2	Placebo (4.4% (v/v) Solutol® HS15, 1.1% (v/v) Miglyol®, 0.66% (v/v) soybean oil in 20 mM phosphate-buffered saline, pH 7.5)[d]	4	0	10	0
3	Low-Dose (SCH 619734)	4	5	2.5	2
4	Mid-Dose (SCH 619734)	4	10	5	2
5	High-Dose (SCH 619734)	4	20	10	2

a: Doses are expressed as the hydrochloride monohydrate salt. When expressed as the free base, these doses were equivalent to 4.5, 9.1, and 18.2 mg/kg for Groups 3, 4, and 5, respectively.

b: Concentration is expressed as the hydrochloride monohydrate salt. When expressed as the free base, this dose concentration was equivalent to 1.8 mg/mL for Groups 3, 4, and 5.

c: Group 1 received control article (0.9% Sodium Chloride for Injection) only.

d: Group 2 received SCH 619734 IV Placebo [4.4% (v/v) Solutol® HS15, 1.1% (v/v) Miglyol®, 0.66% (v/v) soybean oil in 20 mM phosphate-buffered saline, pH 7.5] only.

Observations and Results:

Mortality: Mortality was observed twice daily. Fourteen monkeys were pre-terminally sacrificed as presented in the following table (from page 34 of the report). On Day 4, all high dose males and females were sacrificed. One low dose male was sacrificed on Day 4 and the remaining three low dose males were sacrificed on Day 10. One mid dose male and one mid dose female were sacrificed on Day 5.

Unscheduled Sacrifices				
Animal No.	Sex	Dose (mg/kg)	Study Day of Sacrifice	No. of Doses Received
I05741	M	20	4	3
I05742	M	20	4	3
I05743	M	20	4	3
I05744	M	20	4	3
I05761	F	20	4	3
I05762	F	20	4	3
I05763	F	20	4	3
I05764	F	20	4	3
I05736	M	5	4	4
I05737	M	10	5	5
I05759	F	10	5	5
I05733	M	5	10	9
I05735	M	5	10	9
I05734	M	5	10	10

On Day 3, 3 of 4 males and 4 of 4 females at 20 mg/kg had clinical signs of hunched posture and/or lying down behavior (prostration) and one female (Animal No. I05762)

had abdominal pain. Several of these animals (2 of 4 males and 3 of 4 females) also showed coughing/gagging or retching behavior and vomitus (foamy or containing food) during or shortly after dose administration. Due to excessive toxicity, dosing of all high-dose animals was terminated after Day 3, and they were sacrificed on Day 4 for humane reasons. On Day 4 after dosing, one male at 5 mg/kg had hunched posture with hypoactivity and/or abdominal pain and was sacrificed for humane reasons. On Day 5, one male and one female at 10 mg/kg were observed with hunched posture and lying down behavior (prostration) and were sacrificed for humane reasons. On Day 10, two males (Animal No. I05733 and I05735) at 5 mg/kg had hypoactivity and hunched posture. Animal No. I05733 was also ataxic. Based on these signs, all three surviving males at 5 mg/kg dose group were sacrificed on Day 10. No apparent cause for the clinical condition of any of the pre-terminally sacrificed monkeys could be determined based on the pathology data. All remaining animals survived to scheduled sacrifice on Day 15.

Clinical Signs: Clinical signs were observed twice daily. Treatment-related clinical signs were seen at 10 mg/kg dose group and included hunched posture (3 of 3 males), coughing/gagging (1 of 3 females), foamy vomitus (1 of 3 females), and excessive salivation (1 of 3 females). As mentioned above, two males (Animal No. I05733 and I05735) at 5 mg/kg sacrificed on Day 10 had hypoactivity and hunched posture. Animal No. I05733 was also ataxic. Based on these signs, all three surviving males at 5 mg/kg/day dose group were sacrificed on Day 10. In addition, episodes of foamy vomitus were seen at 20 mg/kg (sacrificed preterminally) and in 10 mg/kg dose group females and vomitus containing food in the 20 mg/kg dose group monkeys were considered test article-related due to association with coughing/gagging and retching. These test article-related clinical signs were generally observed either at unscheduled observations or at 45 minute post-dose, and hunched posture and prostration often persisted through the 1 to 3-hour postdose.

Body Weights: Body weights were recorded on a weekly basis. The mean initial (Day 1) and final (Day 15) body weights of control (vehicle) males were 2.6 and 2.7 kg, respectively. The mean initial (Day 1) and final (Day 15) body weights of control (vehicle) females were 2.6 and 2.6 kg, respectively. There were no significant treatment-related effects.

Food Consumption: Food consumption was measured qualitatively and data were not provided.

Ophthalmoscopy: Ophthalmoscopy was conducted once during the predose and once during Week 2. There were no significant treatment-related effects.

Electrocardiography (ECG): Electrocardiography was conducted twice during the predose phase and once during Week 2 (1 to 3 hours postdose). There were no significant treatment-related effects.

Hematology: Hematology was conducted twice during the predose phase, on Day 7, and before scheduled sacrifice. Animals sacrificed preterminally had clinical pathology findings including mildly higher white blood cell and absolute neutrophil counts; minimally to mildly lower red cell mass. Two males at 5 mg/kg/day (Animal Nos. I05733 and I05735) sacrificed on Day 10 had a more pronounced decrease in red cell mass (hematocrit = 24.4 and 24.1%, respectively). In addition, animal No. I05733 also had a notable decrease in reticulocyte (2900/uL) and platelet (105,000/uL) counts and higher mean platelet volume (23.7 fL). There were no significant treatment-related effects on hematology of scheduled sacrifice animals.

Clinical Chemistry: Serum chemistry analysis was conducted twice during the predose phase, on Day 7, and before scheduled sacrifice. Animals sacrificed preterminally had minimally to mildly lower total protein, albumin, calcium and inorganic phosphorus. Two males at 5 mg/kg dose group sacrificed on Day 10 (Animal Nos. I05733 and I05735) had a more pronounced decrease in albumin (2.9 and 3.0 g/dL, respectively) with higher cholesterol and triglycerides. There were no significant treatment-related effects on serum chemistry of animals that survived until schedule sacrifice.

Urinalysis: Urinalysis was conducted twice during the predose phase, on Day 7, and before scheduled sacrifice. There were no significant treatment-related effects.

Gross Pathology: Gross pathology was conducted at necropsy. There were no rolapitant-related necropsy findings.

Organ Weights: The following (from page 16 of the protocol) listed organs were weighed.

adrenal (2)
brain
epididymis (2)
heart
kidney (2)
liver with gallbladder (drained)
lung
ovary (2)
pituitary gland
prostate
spleen
testis (2)
thymus
thyroid (2 lobes) with parathyroid
uterus with cervix

There were no significant treatment-related effects on organ weights.

Histopathology: The following (from page 17 of the protocol) list shows the organs/tissues from all animals from control, placebo and high dose groups for histopathology.

adrenal (2)	mammary gland
animal identification[a]	optic nerve (2)[b]
aorta (thoracic)	oropharynx
brain	ovary (2)
cecum	pancreas
cervix	pituitary gland
colon	prostate gland
duodenum	rib with bone marrow[a]
epididymis (2)	salivary gland [mandibular (2)]
esophagus	sciatic nerve
eye (2)[b]	seminal vesicle
femur with bone marrow (articular surface of the distal end)	skeletal muscle (biceps femoris)
gallbladder	skin/subcutis
heart	spinal cord (cervical, thoracic, and lumbar)
ileum	spleen
infusion site	sternum with bone marrow
jejunum	stomach
kidney (2)	testis (2)[b]
lacrimal gland	thymus
larynx	thyroid (2 lobes) with parathyroid
lesions	tongue[a]
liver	trachea
lung with large bronchi	urinary bladder
lymph node (mandibular)	uterus
lymph node (mesenteric)	vagina

a collected but not processed
b Preserved in modified Davidson's fixative.

Histological Findings: There were no significant treatment-related histopathological findings.

Toxicokinetics: Blood samples were collected on Days 1, 7, and 13 at approximately 0.25, 1, 4, 8, and 24 hours posttreatment. There was no apparent sex-related difference in exposure to parent drug or the metabolite. Generally, systemic exposure to rolapitant and SCH 720881 increased with increasing dose. Following repeated administration, systemic exposure to rolapitant increased at 5 mg/kg/day and did not change at 10 mg/kg/day, and systemic exposure to SCH 720881 increased at 5 and 10 mg/kg/day. Systemic exposure to SCH 720881 was lower than systemic exposure to rolapitant. Metabolite-to-parent $AUC_{0\text{-}24\ hr}$ ratios remained constant with increasing dose and increased following repeated administration. The following table (from page 587 of the report) shows the TK parameters.

Results

Mean (CV) SCH 619734 Toxicokinetic Parameters on Day 1, Day 7 and Day 13 Following Intravenous Infusion Administration of 5, 10 or 20 mg/kg SCH 619734 to Cynomolgus Monkeys (Males and Females Combined)

Dose (mg/kg)[a,b]	Day	$C_{end\ of\ infusion}$ (ng/mL)	tf (hr)[c]	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	R[d]
5	1	3360 (17)	24 (8-24)	12900 (26)	14400 (14)	NA[e]
	7[f]	3830 (28)	24 (24-24)	21700 (39)	21700 (39)	1.67 (28)[g,h]
	13[i]	2900 (7)	24 (24-24)	26900 (19)	26900 (19)	1.92 (20)[j,k]
10	1	9280 (16)	24 (24-24)	37200 (18)	37200 (18)	NA
	7[l]	8080 (17)	24 (24-24)	39700 (40)	39700 (40)	1.20 (57)[g]
	13[l]	6740 (13)	24 (24-24)	34800 (33)	34800 (33)	1.01 (31)[j]
20	1[m]	22600 (14)	24 (24-24)	98900 (16)	98900 (16)	NA

a: SCH 619734 doses are expressed as the hydrochloride monohydrate salt. When expressed as the free base, these doses are equivalent to 4.5, 9.1 and 18.2 mg/kg for the 5, 10 and 20 mg/kg dose groups, respectively.

b: N = 8/dose group unless otherwise noted.

c: Median (min-max)

d: $R = AUC(0\text{-}24\ hr)_{Multiple\ Dose} \div AUC(0\text{-}24\ hr)_{Single\ Dose}$

e: NA = Not applicable

f: N = 7

g: $R = AUC(0\text{-}24\ hr)_{Day\ 7} \div AUC(0\text{-}24\ hr)_{Day\ 1}$

h: N = 5

i: N = 4

j: $R = AUC(0\text{-}24\ hr)_{Day\ 13} \div AUC(0\text{-}24\ hr)_{Day\ 1}$

k: N = 3

l: N = 6

m: Monkeys in the 20 mg/kg dose group were sacrificed on Day 4 due to high incidence of mortality.

Mean (CV) SCH 720881 Toxicokinetic Parameters on Day 1, Day 7 and Day 13 Following Intravenous Infusion Administration of 5, 10 or 20 mg/kg SCH 619734 to Cynomolgus Monkeys (Males and Females Combined)

Dose (mg/kg)[a,b]	Day	Cmax (ng/mL)	Tmax (hr)[c]	AUC(0-24 hr) (ng·hr/mL)	R[d]	M:P[e]
5	1	57.6 (21)	6 (4-8)	999 (19)	NA[f]	0.072 (9)[g]
	7[h]	130 (42)	4 (4-8)	2370 (42)	2.35 (34)[i]	0.109 (5)
	13[j]	202 (4)	8 (8-8)	3500 (10)	3.90 (21)[k]	0.131 (11)
10	1	149 (29)	8 (4-8)	2840 (26)	NA	0.076 (10)
	7[g]	232 (34)	4 (4-4)	4050 (45)	1.65 (62)[i]	0.101 (7)
	13[g]	232 (35)	8 (4-8)	4310 (38)	1.66 (39)[k]	0.122 (9)
20	1[l]	323 (17)	8 (8-8)	6210 (17)	NA	0.063 (8)

a: SCH 619734 doses are expressed as the hydrochloride monohydrate salt. When expressed as the free base, these doses are equivalent to 4.5, 9.1 and 18.2 mg/kg for the 5, 10 and 20 mg/kg dose groups, respectively.

b: N = 8/dose group unless otherwise noted.

c: Median (min-max)

d: $R = AUC(0\text{-}24\ hr)_{Multiple\ Dose} \div AUC(0\text{-}24\ hr)_{Single\ Dose}$

e: $M:P = AUC(0\text{-}24\ hr)_{SCH\ 720881} \div AUC(0\text{-}24\ hr)_{SCH\ 619734}$

f: NA = Not applicable

g: N = 6

h: N = 7

i: $R = AUC(0\text{-}24\ hr)_{Day\ 7} \div AUC(0\text{-}24\ hr)_{Day\ 1}$

j: N = 4

k: $R = AUC(0\text{-}24\ hr)_{Day\ 13} \div AUC(0\text{-}24\ hr)_{Day\ 1}$

l: Monkeys in the 20 mg/kg dose group were sacrificed on Day 4 due to high incidence of mortality.

Dosing Formulation Analysis: Details of dosing formulation analysis were not provided.

Summary: In a 2-week IV infusion study in Cynomolgus monkeys, animals were treated at 5, 10, and 20 mg/kg/day. Mortality was observed at all doses in males and at 10 and 20 mg/kg/day in females. The NOAEL was considered as 5 mg/kg/day for females; however, the NOAEL could not be established in males. The CNS may be the target organ based on the clinical signs (hypoactivity, hunched posture, ataxia, etc.) of the animals sacrificed preterminally.

Review of Study No. 2013-009 is incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP). It is noted that Dr. Chakraborti reviewed a draft version of the report, which was subsequently finalized. The final study report and QA statement (signed October 2, 2013) were submitted under this NDA. Review of the final report indicates no significant differences from the draft report which would impact the overall study conclusions. For reference, differences identified in the final report (compared to the draft report) include the incorporation of additional vehicle and test article information (Appendix A) and a complete copy of Appendix H (Bioanalytical Analysis Report) including LC-MS/MS Ion Chromatograms. Finally, in Dr. Chakraborti's review below, the section entitled "Basis of Dose Selection" also summarizes Study No. 2013-011.

Study title: 2-Week Intravenous Toxicity Study of Rolapitant in Cynomolgus Monkeys with a 14-Day Recovery Period (Draft Report)

Study no.:	2013-009
Study report location:	EDR Section 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 17, 2003
GLP compliance:	The GLP statement was not signed
QA statement:	The QA statement was not signed
Drug, lot #, and % purity:	Rolapitant, 6068642 (API), 98%

Key Study Findings:

- In a 2-week IV infusion study in Cynomolgus monkeys, animals were treated with rolapitant at 0 (saline), 0 (vehicle), 3, 10 and 20/15 mg/kg/day.
- There was no mortality.
- Due to treatment-related adverse clinical signs at 20 mg/kg/day, dose was reduced to 15 mg/kg/day on Day 4.
- There were no significant treatment-related histopathology findings.
- The NOAEL was considered as 10 mg/kg/day.

Methods

Doses:	0 (saline), 0 (vehicle), 3, 10 20/15* mg/kg
Frequency of dosing:	Once daily
Route of administration:	Intravenous infusion for 30-45 min
Dose volume:	The dose volumes were 10, 10, 1.5, 5, and 10 mL/kg at 0 (saline), 0 (vehicle), 3, 10, and 20 mg/kg, respectively.
Formulation/Vehicle:	Sterile saline: 0.9% sodium chloride Vehicle control: 4.4% polyoxyl, 15 hydroxystearate, Kolliphor HS-15, 1.1% medium chain triglycerides and 0.66% refined soybean oil
Species/Strain:	Cynomolgus Monkeys
Number/Sex/Group:	
Age:	2-3 years
Weight:	Male: 2.12-2.84 kg; Female: 2.29-3.04 kg
Satellite groups:	None
Study design:	Study design is shown below (from page 16 of the report)
Deviation from study protocol:	Protocol deviations did not affect the quality or integrity of the study

*: Due to treatment-related adverse clinical signs, on Day 4, the infusion duration was extended to 45 minutes and the dose level and dose volume were decreased to 15 mg/kg and 7.5 mL/kg, respectively.

Group Assignments					
Group Number	Dose Level (mg/kg)	Dose Volume (mL/kg)	Duration (minutes)	Number of Animals	
				Male	Female
1	0[c]	10	30	4	4
2	0[d]	10	30	6[a]	6[a]
3	3	1.5	30	4	4
4	10	5	30	4	4
5	20/15[b]	10/7.5[b]	30/45[b]	6[a]	6[a]

[a]Two animals/group were maintained for a 2-week recovery period.
[b]Beginning on Day 4, the duration was extended and the dose level and volume were decreased due to adverse toxicity.
[c]Saline Control
[d]Vehicle Control

Basis of Dose selection: The dose levels were selected based on the results of a 14-day repeat-dose study in Cynomolgus monkeys [redacted] (b) (4) Study Number 2013-011) and the results of a 14-day repeated dose study in Cynomolgus monkeys (SN 07393, reviewed above). In the [redacted] (b) (4) study (2013-011), rolapitant was administered by IV infusion once daily at 2.5, 5 and 10 mg/kg/day, at respective dose volumes of 1.25, 2.5, and 5 mL/kg for 30 minutes or at 20 mg/kg (10 mL/kg) for 45 minutes. There were no significant treatment-related effects on body weight. At 20 mg/kg/day (45 minute infusion), convulsions, lateral recumbency, and ataxia were observed immediately post-dose on Day 6; however, all clinical findings had resolved by 10 minutes post-dose. Based on these results, a high dose of 20 mg/kg/day was selected to elicit moderate toxicity (more than those observed in [redacted] (b) (4) Study Number 2013-011 due to the decrease of infusion time from 45 minutes to 30 minutes, but less than those observed in Schering Plough Study SN 07393 due to the increase of infusion time from 15 minutes to 30 minutes). The low dose of 3.0 mg/kg/day was expected to have no adverse effects and the mid dose of 10 mg/kg/day was selected to establish dose-response relationships within 14 consecutive days of dosing.

Observations:

Mortality: Mortality was checked daily.

Clinical Signs: Clinical signs were observed on a daily basis.

Body Weights: Body weights were recorded weekly.

Food Consumption: Food consumption was not recorded (qualitative).

Ophthalmoscopy: Ophthalmoscopic examinations were conducted at pretest and prior to the terminal and recovery necropsies.

Electrocardiography (ECG): Electrocardiographic examinations were conducted at pretest, and at 30 minutes post-dose on Day 1, on Day 14 (Groups 1-4), on Day 16 (Group 5), and prior to the recovery necropsy.

Hematology: Hematology was conducted at pretest and prior to the terminal and recovery necropsies.

Clinical Chemistry: Clinical chemistry was conducted at pretest and prior to the terminal and recovery necropsies.

Urinalysis: Urinalysis was conducted at pretest and prior to the terminal and recovery necropsies.

Gross Pathology: Gross pathology was conducted at necropsy.

Organ Weights: The following tables show the list of organs/tissues that were weighed from all animals.

The following list constitutes the full complement of organs and tissues:

- Adrenal (2)*
- Aorta
- Bone with marrow [femur]
- Bone with marrow [rib]
- Bone with marrow [sternum]
- Bone marrow smear [2 collected][a]
- Brain [cerebrum, midbrain, cerebellum, medulla/pons]*
- Epididymis (2)
- Eye including optic nerve (2)
- Gallbladder
- GALT [gut associated lymphoid tissue]
- Gastrointestinal tract:
  - esophagus
  - stomach [cardia, fundus, and pylorus]
  - duodenum
  - jejunum
  - ileum
  - cecum
  - colon
  - rectum
- Gonads:
  - ovary (2)* with oviduct (2)
  - testis (2)*
- Gross lesions
- Heart*
- Infusion site, last
- Joint, tibiofemoral
- Kidney (2)*
- Larynx
- Liver [3 sections collected; 2 examined]*
- Lung with bronchi [collected whole; 2 sections examined]*
- Lymph nodes: mandibular [2 collected; 1 examined] and mesenteric
- Mammary gland [process females only]
- Pancreas
- Pituitary*
- Prostate* and seminal vesicle (2)
- Salivary gland, mandibular [2 collected; 1 examined][b]
- Salivary gland, parotid [2 collected; 1 examined]
- Salivary gland, sublingual [2 collected; 1 examined]
- Sciatic nerve
- Skeletal muscle, rectus femoris
- Skin
- Spinal cord [cervical, thoracic, and lumbar]
- Spleen*
- Thymus*
- Thyroid/parathyroid (2)*
- Tongue
- Trachea
- Ureter (2)
- Urinary bladder
- Uterus/Cervix*
- Vagina

[a]Bone marrow smears were collected at necropsy and read.
[b]Only the right mandibular salivary gland was weighed.

(2) Paired organ
*Weighed organ

Histopathology: Histopathology was conducted from all animals from the tissues listed in the above table.

Toxicokinetics: Blood samples were collected from all animals as follows for determination of the plasma concentrations of the test article on Day 1 (all animals at 1, 3, 6, 8, and 24 hours post-dose), Day 14 (all animals in Groups 1-4 at approximately 1, 3, 6, 8, and 24 hours post-dose) and Day 17 (all Group 5 animals at approximately 1, 3, 6, 8, and 24 hours post-dose).

Dosing Solution Analysis: Details of the dosing solution analysis were not provided.

Results:

Mortality: There was no mortality.

Clinical Signs: Treatment-related clinical signs at the high dose included clonic/tonic convulsions, ataxia, decreased activity, lateral recumbency, dilated pupils, partially and/or completely closed eyelids, and shallow breathing. These observations were noted during the study Day 2 (one male) and Day 3 (three males and one female) at 20 mg/kg/day and generally recovered during the 45 minute post-dose. As stated above, due to these adverse clinical observations, on Day 4, the infusion duration for these animals was extended to 45 minutes and the dose level and dose volume were decreased to 15 mg/kg/day and 7.5 mL/kg, respectively. However, treatment-related dilated pupils were still observed at this dose level until Day 8. At 3 and 10 mg/kg/day, dilated pupils were noted in some animals through Day 12. These observations were generally resolved prior to the 4 hour post-dose observation for both groups. However, there were no ophthalmoscopic or microscopic correlates and pupil dilation was not considered adverse due to its mild, transient and completely recoverable nature.

Body Weights: The mean initial (Week 1) body weights of saline and vehicle control males were 2.62 and 2.60 kg, respectively. The mean final (Week 2) body weights of saline and vehicle control males were 2.57 and 2.57 kg, respectively. The mean initial (Week 1) body weights of saline and vehicle control females were 2.74 and 2.64 kg, respectively. The mean final (Week 2) body weights of saline and vehicle control males were 2.72 and 2.64 kg, respectively. There was no significant treatment-related effect on body weight.

Food Consumption: Quantitative food consumption was not recorded (qualitative).

Ophthalmoscopy: There was no significant treatment-related effect.

ECG: There was no significant treatment-related effect.

Hematology: Reductions in red cell mass (erythrocytes, hemoglobin and hematocrit) were of comparable magnitude in most treatment groups, but were more pronounced in males (16% reduction) and females (14% reduction) at 20/15 mg/kg/day and were considered treatment-related. At the end of the recovery, red cell mass was similar to the pretest values among animals in the vehicle control and 20/15 mg/kg/day group. At the terminal collection, males at 20/15 mg/kg/day had a mild increase in total leukocytes (1.1-fold), which was primarily attributable to a mild increase in lymphocytes (1.3-fold), monocytes (1.7-fold), eosinophils (4.0-fold), basophils (1.4-fold) and other cells (1.8-fold), relative to pretest values. These were considered treatment-related. Increases in lymphocytes, monocytes and eosinophils persisted at the end of the recovery period. At the terminal collection, mild prolongations in APTT were observed in both sexes (1.1 to 1.2-fold, and approximately 3-5 seconds) in the vehicle control and 20/15 mg/kg/day group, relative to pretest values. At the end of the recovery interval, individual APTT

values were similar to pretest values in both sexes receiving the vehicle control and 20/15 mg/kg/day of rolapitant.

Clinical Chemistry: At 20/15 mg/kg/day, there were mild reductions in sodium (up to 5%), chloride (up to 5%) and phosphorus (up to 9%), relative to pretest values. These were not considered treatment-related due to low magnitude. In addition, at 20/15 mg/kg/day in both sexes, there were mild increases in globulins (1.2-fold) and mild reductions in albumin (up to 13%), which resulted in a mildly reduced albumin/globulin ratio (up to 25%), relative to pretest values. These changes persisted at the end of the recovery period and were considered treatment-related.

Urinalysis: There was no significant treatment-related effect.

Gross Pathology: There were no significant treatment-related changes.

Organ Weights: There were no treatment-related organ weights changes in terminal or recovery groups.

Histopathology: There were no significant treatment-related microscopic findings in terminal or recovery animals.

Toxicokinetics: Mean systemic exposure ($AUC_{0\text{-}24h}$) to rolapitant and SCH720881 generally increased in an approximately dose proportional manner from 3 to 20 mg/kg on Day 1, from 3 to 10 mg/kg/day on Day 14, and at 15 mg/kg on Day 17. Following repeated administration, mean systemic exposure to rolapitant did not appear to change at the 3 mg/kg/day, but appeared to decrease at the 10 mg/kg. Mean systemic exposure to SCH720881 on Day 14 was greater than mean systemic exposure on Day 1, and systemic exposure to SCH720881 was lower than systemic exposure to rolapitant. Metabolite to parent exposure ratio did not appear to change with increasing dose, and appeared to increase following repeated administration. There were no apparent gender differences in TK parameters. The mean TK parameters for rolapitant and SCH720881 are shown in the following tables (from page 630 and 631 of the report).

Table 1 Mean Rolapitant and CV Toxicokinetic Parameters on Days 1, 14 and 17 Following an Intravenous Infusion of 3, 10, 15 and 20 mg/kg Rolapitant to Cynomolgus Monkeys (Males and Females Combined)

Rolapitant Dose (mg/kg/day)[a]	Day		Cmax (ng/mL)	Cmax/Dose (kg*ng/mL/mg)	Tmax (hr)[b]	AUC(0-24 hr) (hr*ng/mL)	AUC(0-24 hr)/Dose (kg*hr*ng/mL/mg)	R[c]
3	1	Mean	1070	357	1 (1-1)	12100	4030	NA[d]
		CV%	20	20		19	19	NA
	14	Mean	1200	399	1 (1-1)	13400	4460	1.11
		CV%	15	15		22	22	11
10	1	Mean	4240	424	1 (1-1)	46600	4660	NA
		CV%	18	18		12	12	NA
	14	Mean	3380	338	1 (1-3)	31800	3180	0.691
		CV%	11	11		16	16	20
15[e]	17	Mean	6780	452	1 (1-3)	62200	4150	NA
		CV%	12	12		13	13	NA
20[e]	1	Mean	9900	495	1 (1-3)	101000	5040	NA
		CV%	21	21		11	11	NA

a: N=8/dose group, unless otherwise noted.
b: Median (minimum-maximum)
c: $R = AUC(0\text{-}24hr)_{Day\ 14} / AUC(0\text{-}24hr)_{Day\ 1}$
d: NA = Not applicable
e: N=12

Table 2 Mean SCH 720881 and CV Toxicokinetic Parameters on Days 1, 14 and 17 Following an Intravenous Infusion of 3, 10, 15 and 20 mg/kg Rolapitant to Cynomolgus Monkeys (Males and Females Combined)

Rolapitant Dose [a] (mg/kg/day)	Day		Cmax (ng/mL)	Cmax/Dose (kg*ng/mL/mg)	Tmax (hr)[b]	AUC(0-24 hr) (hr*ng/mL)	AUC (0-24 hr)/Dose (kg*hr*ng/mL/mg)	R[c]	M:P[d]
3	1	Mean	46.6	15.5	24 (6-24)	888	296	NA[e]	0.0751
		CV%	18	18		18	18	NA	21
	14	Mean	84.1	28.0	6 (0-8)	1810	603	2.09	0.136
		CV%	17	17		22	22	27	9
10	1	Mean	156	15.6	24 (8-24)	2990	299	NA	0.0641
		CV%	18	18		23	23	NA	19
	14	Mean	192	19.2	3 (3-8)	3810	381	1.35	0.120
		CV%	9	9		14	14	34	8
15[f]	17	Mean	423	28.2	3 (1-8)	7780	518	NA	0.125
		CV%	16	16		17	17	NA	9
20[f]	1	Mean	320	16.0	8 (6-24)	6510	325	NA	0.0648
		CV%	13	13		13	13	NA	11

a: N=8/dose group, unless otherwise noted.
b: Median (minimum-maximum).
c: $R = AUC(0\text{-}24hr)_{Day\ 14} / AUC(0\text{-}24hr)_{Day1}$
d: $M:P = AUC(0\text{-}24hr)_{SCH\ 720881} / AUC(0\text{-}24hr)_{Rolapitant}$
e: NA = Not applicable
f: N=12

Dosing Solution Analysis: Details of the dosing solution analysis were not provided.

Summary: In a 14-day IV infusion study in Cynomolgus monkeys, animals were treated with rolapitant at 0 (saline), 0 (vehicle), 3, 10 and 20/15 mg/kg/day. There was no mortality. Due to treatment-related adverse clinical signs at 20 mg/kg/day, the 20 mg/kg/day dose was reduced to 15 mg/kg/day on Day 4. There were no significant treatment-related histopathology findings. The NOAEL was considered as 10 mg/kg/day.

Study title: One-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 619734 in Cynomolgus Monkeys

Study no.:	05015
Study report location:	EDR Section 4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute Lafayette, NJ 07848
Date of study initiation:	March 31, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734 hydrochloride monohydrate, micronized, SZ-03-PHG-TX-001, 100.1%

Key Study Findings

At 60 and 100 mg/kg/day, SCH 619734 produced severe toxicity (e.g., hypoactivity, ataxia, prostration, and convulsions) which necessitated premature sacrifice of animals in these dose groups. At the mid- and high dose, there were increases in white blood cell and neutrophil counts, decreases in lymphocyte counts, and increased or decreased glucose levels. On Day 20, serum triglyceride levels were increased by 130% and 122% in low dose males and females, respectively, compared to controls.

Treatment-related histopathological changes in mid- and/or high dose monkeys occurred in the pancreas (minimal to mild vacuolar degeneration of acinar cells), stomach (minimal to mild vacuolar degeneration of the glandular epithelium), heart (minimal multifocal arteriolar degeneration) and kidney (renal tubular dilatation). Findings in the heart and kidney were considered potentially related to convulsions or due to associated stress, dehydration, and/or debilitation. The NOAEL was 30 mg/kg/day.

Methods

Doses:	30, 60, and 100 mg/kg/day
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Cynomolgus monkey (*Macaca fascicularis*)
Number/Sex/Group:	4/sex/group
Age:	Juvenile to young adult
Weight:	Male: 2.5-3.8 kg; Female: 2.5-3.5 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	Protocol deviations did not affect the quality or integrity of the study.

Observations and Results

Mortality

Animals were observed at least once daily for viability.

High dose females and males were sacrificed prior to dosing on Days 1 and 2, respectively, due to severe toxicity. Mid-dose group animals were sacrificed after dosing on Day 2 due to severe toxicity.

Clinical Signs

Clinical observations were made at least twice daily during the dosing period and at least once on the day of sacrifice. General veterinary examinations were conducted pretest and during Week 3 (control and low dose animals only).

Treatment-related clinical signs were observed at ≥60 mg/kg/day. Prior to sacrifice for humane reasons, mid- and high dose animals exhibited clinical signs of severe toxicity (e.g., hunched appearance, hypoactivity, ataxia, prostration, loose or soft stool, convulsions, and emesis). No treatment-related clinical or veterinary examination findings were observed at 30 mg/kg/day.

Body Weights

Body weights were measured weekly.

There were no treatment-related effects on body weight at 30 mg/kg/day. Body weights at ≥60 mg/kg/day were not evaluated due to unscheduled sacrifice of these animals.

Feed Consumption

Food consumption was estimated daily by pairs of animals.

Transient decreases in food consumption observed on a small subset of the treatment days at 30 mg/kg/day normalized by the end of the study. Prior to sacrifice, treatment-related decreases in food consumption occurred in mid- and high dose animals.

Ophthalmoscopy

Ophthalmological examinations were conducted pretest and during Week 3 (control and low dose animals only).

There were no treatment-related ophthalmological findings.

ECG

Physical examinations (including measurement of heart rate [HR] and blood pressure [BP] and ECGs were conducted twice pretest and once during Week 4 (control and low dose animals only). PR, QRS, and QT interval durations were determined, and QTc interval duration was calculated according to the method of Fridericia.

In low-dose females, decreases in HR (-10% compared to predose) and BP (up to -17% compared to predose) occurred but were considered within normal variation in cynomolgus monkeys. No treatment-related changes in ECG parameters were identified.

Hematology

Blood samples were collected twice pretest and once during Week 3/4 for evaluation of standard hematological and coagulation parameters. When possible, samples were also collected from all animals sacrificed prior to scheduled termination.

In a subset of mid- and high dose animals, treatment-related changes in samples collected prior to sacrifice included increased white blood cell (WBC) and neutrophil counts and decreased lymphocyte counts. These changes occurred in animals that exhibited seizure activity. The Applicant's table below summarizes changes in mean neutrophil and lymphocyte counts.

SCH 619734-Related Differences in Mean Neutrophil and Lymphocyte Values					
Finding (Units)	Week[a]	Dose Group (mg/kg)			
		0 (Control)	30 (SCH 619734)	60 (SCH 619734)	100 (SCH 619734)
Male Values					
Neutrophils (K/µL)	1 or 3	1.42	1.57	14.27*[,b]	4.03*
Lymphocytes (K/µL)	1 or 3	6.01	6.75	2.47*	3.72*
Female Values					
Neutrophils (K/µL)	1 or 3	2.70	2.48	17.41*[,c]	10.75*[,d]
Lymphocytes (K/µL)	1 or 3	4.65	6.85	2.87*	3.07*

* = Test article-related finding

a: Week 1 applies to the 60 and 100 mg/kg dose groups and Week 3 applies to the 0 and 30 mg/kg dose groups.

b: Mean count includes a mild increase in neutrophils of 25.7 K/µL for monkey No. 2001M, which resulted in an increased WBC count.

c: Mean count includes a moderate increase in neutrophils of 38.7 K/µL for monkey No. 952F, which resulted in an increased WBC count.

d: Mean count includes a mild increase in neutrophils of 22.1 K/µL for monkey No. 3503F, which resulted in an increased WBC count.

Clinical Chemistry

Samples were analyzed for standard clinical chemistry parameters.

At 30 mg/kg/day, serum triglyceride levels were increased by 130% and 122% in males and females, respectively, compared to controls on Day 20. An increased glucose level (231 mg/dL) was measured in a high dose male that exhibited seizure activity, as compared to the Week 3 control group mean (95.5 mg/dL). In addition, one mid- and high dose female each had decreased serum glucose values in samples collected prior to sacrifice which may be due to decreased food consumption.

Urinalysis

Urinalysis was conducted for samples collected twice pretest and during Week 3/4.

No treatment-related changes occurred.

Gross Pathology

High dose females were sacrificed and necropsied on Day 1. High-dose males were sacrificed after 2 doses and necropsied on Day 2. The mid-dose group was sacrificed after 3 doses and necropsied on Day 2. Controls and the low-dose groups were sacrificed and necropsied during Week 5.

Skin trauma related to seizures was observed macroscopically in two monkeys.

Organ Weights

At the scheduled terminal necropsy, weights of the following organs were determined and organ-to-body weight ratios (i.e., relative weights) were calculated for control and low dose animals only: adrenal glands, brain, epididymides, heart, kidneys, liver, lungs,

ovaries, pituitary gland, prostate gland, spleen, testes, thymus, thyroid gland/parathyroid glands, and uterus (plus cervix). Organ weights of mid- and high dose animals were not evaluated.

In low dose males, there were increased mean absolute and/or relative heart (up to +17%), liver (up to +16%), and pituitary gland (up to +17%) weights, and decreased mean absolute and/or relative lung (up to -25%), testes (up to -36%), and thymus (up to -40%) weights, as compared to controls. In low dose females, there were increased mean absolute and/or relative thymus (up to +23%), thyroid gland (up to +66%), and uterus (up to +29%) weights, as compared to controls. Changes in organ weights were attributed to biologic variation associated with age, body weight, and/or sexual maturity of males or the stage of menstrual cycle of females.

Histopathology

The Applicant's table below identifies the tissues collected and preserved at necropsy.

Tissues Collected[a]	
Adrenal Glands	Parathyroid Gland(s)
Aorta – Thoracic	Peripheral Nerve – Sciatic
Bone – (Femur, Rib[b] and Sternum)	Pituitary Gland
Bone Marrow Section – (Rib[b] and Sternum)	Prostate Gland
Bone Marrow for Cytology – Rib[c]	Salivary Glands – Mandibular
Brain	Seminal Vesicles
Epididymides	Skeletal Muscle – Biceps Femoris
Esophagus	Skin
Eyes[d]	Small Intestine – (Duodenum, Jejunum, Ileum)
Gallbladder	Spinal Cord – Thoracolumbar
Gross Findings[e]	Spleen
Heart	Stomach
Kidneys	Testes
Lacrimal Glands	Thymus
Large Intestine – (Cecum and Colon)	Thyroid Gland
Larynx/Pharynx	Tongue[b]
Liver	Trachea
Lungs	Urinary Bladder
Lymph Nodes – Mandibular and Mesenteric	Uterus (plus Cervix)
Mammary Gland	Vagina
Ovaries	Animal Identification[b]
Pancreas	
a: Collected in 10% neutral buffered formalin unless otherwise indicated	
b: Collected but not processed	
c: Bone marrow smears were prepared for all monkeys but were not evaluated because it was not warranted by changes in the peripheral blood.	
d: Collected in 3% glutaraldehyde	
e: As deemed necessary by the pathologist	

Organs/tissues collected from all monkeys and all gross findings were examined histopathologically.

Adequate Battery: Yes

Peer Review: Yes

Histological Findings:
As summarized in the Applicant's table below, treatment-related histopathological changes in mid- and high dose monkeys sacrificed prematurely were observed in the pancreas (minimal to mild vacuolar degeneration of acinar cells) and stomach (minimal to mild vacuolar degeneration of the glandular epithelium). Skin trauma observed macroscopically was associated with minimal, focal hemorrhage. In addition, minimal multifocal arteriolar degeneration in the heart and renal tubular dilatation were observed in a single male treated with 60 mg/kg/day. These findings were considered potentially related to convulsions or due to associated stress, dehydration, and/or debilitation.

Principal Histopathologic Findings								
Dose Group (mg/kg):	0 (Control)		30 (SCH 619734)		60[a] (SCH 619734)		100[a] (SCH 619734)	
Sex:	M	F	M	F	M	F	M	F
Organ/Finding/Severity	Incidence[b]							
Pancreas								
- degeneration, vacuolar, acinar cell								
minimal	0/4	1/4	0/4	0/4	3/4*	1/4*	1/4*	1/4*
mild	0/4	0/4	0/4	0/4	0/4	1/4*	2/4*	1/4*
Stomach								
- degeneration, vacuolar, glandular								
minimal	1/4	0/4	0/4	0/4	1/4*	3/4*	1/4*	4/4*
mild	0/4	0/4	0/4	0/4	3/4*	1/4*	3/4*	0/4
Heart								
- degeneration, arteriolar, multifocal								
minimal	0/4	0/4	0/4	0/4	1/4*	0/4	0/4	0/4
Kidneys								
- dilatation, tubular								
minimal	0/4	0/4	0/4	0/4	1/4*	0/4	0/4	0/4
Skin								
- hemorrhage(s), focal								
minimal	0/4	0/4	0/4	0/4	0/4	1/4*	0/4	1/4*

a: Monkeys in the mid- and high-dose group were sacrificed during the first three days on study due to severe toxicity.
b: Incidence = Number affected/Number examined.
* = Test article-related finding

In two low dose males, minimal or mild atrophy of the thymus (which correlated with decreased thymus weights) was considered consistent with physiologic involution and attributed to biologic variation. This finding did not appear to be dose related (0/4 and 1/4 males had thymic atrophy at 60 and 100 mg/kg/day, respectively). In addition, this finding was observed in two female control animals.

Special Evaluation

None

Toxicokinetics

Blood samples were collected from 1 to 24 h post-dosing on Days 0 and 27. Samples were also collected from all animals (except for high dose females) sacrificed prior to scheduled termination, when possible. Plasma samples were analyzed for SCH 619734 and metabolite SCH 720881 concentrations.

Systemic exposures to SCH 619734 and SCH 720881 increased with increasing dose. At 30 mg/kg/day, there was no evidence of SCH 619734 accumulation after 27 days. The ratio of AUC values for SCH 720881 on Day 27:Day 1 was 1.36. Gender differences were not observed, and thus TK parameters were calculated for males and females combined. Toxicokinetic parameters for SCH 619734 and SCH 720881 are shown in the Applicant's tables below.

Mean (CV) SCH 619734 Toxicokinetic Parameters on Day 0 and Day 27 Following Oral (Gavage) Administration of 30, 60 or 100 mg/kg SCH 619734 to Cynomolgus Monkeys (Males and Females Combined)

Dose (mg/kg)[a,b,c]	Day	Cmax (ng/mL)	Tmax (hr)[d]	AUC(0-24 hr) (ng·hr/mL)	R[e]	Metabolite:Parent[f]
30	0	4760 (15)[g]	4 (4-8)[g]	69700 (15)[g]	NA[h]	0.110 (6)[i]
	27	3660 (33)	6 (4-8)	64200 (31)	0.877 (28)[g]	0.171 (12)
60[j]	0	5360 (24)	4 (2-24)	102000 (26)	NA	0.110 (18)[k]
100[l]	0	6360 (12)	24 (4-24)	130000 (13)	NA	0.114 (13)[i]

a: SCH 619734

b: Doses are expressed as the hydrochloride salt. When expressed as the free base, daily doses were 27.0, 54.0 and 90.0 mg/kg for the 30, 60 and 100 mg/kg dose groups, respectively.

c: N = 8/dose group unless otherwise noted

d: Median (Range)

e: $R = AUC(0\text{-}24\ hr)_{Day\ 27} \div AUC(0\text{-}24\ hr)_{Day\ 0}$

f: $Metabolite{:}Parent = AUC(0\text{-}24\ hr)_{Metabolite} \div AUC(0\text{-}24\ hr)_{Parent}$

g: N = 7

h: NA = Not Applicable

i: N = 5

j: Due to severe toxicity, both sexes in this dose group were sacrificed for humane reasons after three doses.

k: N = 6

l: Due to severe toxicity, females in this dose group were sacrificed for humane reasons after one dose and males after two doses.

Mean (CV) SCH 720881 Toxicokinetic Parameters on Day 0 and Day 27 Following Oral (Gavage) Administration of 30, 60 or 100 mg/kg SCH 619734 to Cynomolgus Monkeys (Males and Females Combined)

Dose (mg/kg)[a,b,c]	Day	Cmax (ng/mL)	Tmax (hr)[d]	AUC(0-24 hr) (ng·hr/mL)	R[e]
30	0	403 (9)[f]	16 (8-24)[f]	7940 (10)[g]	NA[h]
	27	520 (27)	8 (4-24)	10800 (28)	1.36 (26)[g]
60[i]	0	682 (34)	24 (24-24)	10500 (27)[f]	NA
100[j]	0	975 (19)[f]	24 (24-24)[f]	14700 (14)[g]	NA

a: SCH 619734
b: Doses are expressed as the hydrochloride salt. When expressed as the free base, daily doses were 27.0, 54.0 and 90.0 mg/kg for the 30, 60 and 100 mg/kg dose groups, respectively.
c: N = 8/dose group unless otherwise noted
d: Median (Range)
e: $R = AUC(0\text{-}24\ hr)_{Day\ 27} \div AUC(0\text{-}24\ hr)_{Day\ 0}$
f: N = 6
g: N = 5
h: NA = Not Applicable
i: Due to severe toxicity, both sexes in this dose group were sacrificed for humane reasons after three doses.
j: Due to severe toxicity, females in this dose group were sacrificed for humane reasons after one dose and males after two doses.

Dosing Solution Analysis

Dosing solution samples were collected during Weeks 1/2 and 3/4 for concentration analysis. Samples were collected during Week 1/2 for evaluation of homogeneity. The analytical assay results were acceptable. The percent of nominal concentrations ranged from 96.8 to 99.5%.

Study title: Three-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 619734 in Cynomolgus Monkeys

Study no.:	03098
Study report location:	EDR Section 4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute Lafayette, NJ 07848
Date of study initiation:	January 30, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734 hydrochloride monohydrate, micronized, SZ-03-PHG-TX-001, 99.5%

Key Study Findings

In this three-month study, SCH 619734 produced no adverse treatment-related findings at any of the dose levels. The NOAEL was 15 mg/kg/day. In the absence of treatment-related findings, the target organ could not be identified.

Methods

Doses:	1, 5, and 15 mg/kg/day
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Cynomolgus monkey (*Macaca fascicularis*)
Number/Sex/Group:	4/sex/group
Age:	Juvenile to young adult
Weight:	Male: 2.8-4.4 kg; Female: 2.2-3.0 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	Protocol deviations did not affect the quality or integrity of the study.

Observations and Results

Mortality

Animals were observed at least once daily for viability.

There was no mortality.

Clinical Signs

Clinical observations were made at least twice daily during the dosing period, and at least once on the day of sacrifice. General veterinary examinations were conducted pretest and during Weeks 5 and 12. An additional examination of the lymph nodes was conducted during Week 6.

Based on findings observed prestudy and across the groups, there were no treatment-related clinical signs.

Body Weights

Body weights were measured weekly.

There were no treatment-related effects on body weight.

Feed Consumption

Food consumption was estimated daily by pairs of animals. Food consumption was collected individually for animals when individually housed for at least 24 h.

There were no treatment-related effects on food consumption.

Ophthalmoscopy

Ophthalmological examinations were conducted pretest and during Weeks 5 and 12.

There were no treatment-related findings.

ECG

Measurement of heart rate [HR] and blood pressure [BP] and ECGs were conducted twice pretest and once during Weeks 5 and 11. PR, QRS, and QT interval durations were determined, and QTc interval duration was calculated according to the method of Fridericia.

There were no test-compound related changes in BP, HR, or ECG parameters in females based on findings observed across groups, comparison to pretest values, and/or a lack of dose-response relationship. In males treated with 5 mg/kg/day, HR, and systolic and mean arterial pressures were decreased relative to controls and/or pretest values. However, this was not observed in high dose males and thus did not appear treatment-related. There were no apparent test compound-related changes in ECG parameters in males.

Hematology

Blood samples were collected twice pretest and during Weeks 4 and 12 for evaluation of standard hematological and coagulation parameters.

There were no apparent treatment-related changes.

Clinical Chemistry

Samples were analyzed for standard clinical chemistry parameters.

There were no apparent treatment-related changes.

Urinalysis

Urinalysis was conducted for samples collected twice pretest and during Weeks 4 and 12.

There were no apparent treatment-related changes in urinalysis parameters.

Gross Pathology

All monkeys were necropsied at terminal sacrifice.

There were no treatment-related findings. Incidental findings included altered contents in the large intestines of one low-dose female and two mid-dose females. This finding was not observed at the high dose.

Organ Weights

At the scheduled terminal necropsy, weights of the following organs were determined and organ-to-body weight ratios (i.e., relative weights) were calculated: adrenal glands, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate gland, spleen, testes, thymus, thyroid gland/parathyroid glands, and uterus (plus cervix).

In males, weights of reproductive tissues (testes, epididymides and prostate) varied among groups in a manner which was not dose-related. This was attributed to peripubescent variation in juvenile monkeys. Absolute and relative thymus weights were decreased in mid- and high dose males by up to 46% and 61% at these dose levels, respectively, compared to controls. This was considered incidental based on a lack of histological correlates, a high level of variation commonly observed in this tissue in peripubescent monkeys, and given that the thymus weights are within the normal range of historical control weights at the testing facility. Absolute and relative spleen weights were decreased at all doses (up to -14%, -18%, and -19%, respectively, in low-, mid-, and high dose groups, compared to controls). There were no histological correlates for the increased spleen weights.

In females, absolute and relative liver weights were increased at 15 mg/kg/day by up to 19%, compared to controls. Relative liver weights were increased by 13% and 16% at 1 and 5 mg/kg/day, respectively. In addition, increased mean absolute and relative thyroid weights occurred at 15 mg/kg/day (up to +89%, compared to controls). This was due to an individual high dose female with a thyroid gland 3-4-fold greater than the other 3 high dose animals. Absolute and relative ovary and uterus weights were increased by up to 23% and 31% in these organs, respectively, in SCH 619734 treated animals compared to controls. Changes in uterus and ovary weights were considered unrelated to treatment based upon the absence of a dose-relationship, variability in peripubescent animals, and given that weights were within the range of historical controls. There were no histological correlates for any of the organ weight changes.

Histopathology

The Applicant's table below identifies the tissues collected and preserved at necropsy.

Tissues Collected[a]	
Adrenal Glands	Peripheral Nerve – Sciatic
Aorta – Thoracic	Pituitary Gland
Bone - (Femur, Rib[b] and Sternum)	Prostate Gland
Bone Marrow Section – (Rib[b] and Sternum)	Salivary Glands – Mandibular
Bone Marrow for Cytology - Rib[c]	Seminal Vesicles
Brain	Skeletal Muscle - Biceps Femoris
Epididymides	Skin
Esophagus	Small Intestine – (Duodenum, Jejunum, Ileum)
Eyes[d]	Spinal Cord – Thoracolumbar
Gallbladder	Spleen
Heart	Stomach
Kidneys	Testes
Lacrimal Glands	Thymus
Large Intestine – (Cecum and Colon)	Thyroid Gland
Liver	Tongue[b]
Lungs	Trachea
Lymph Nodes - Mandibular and Mesenteric	Urinary Bladder
Mammary Gland	Uterus (plus Cervix)
Ovaries	Vagina
Pancreas	Animal Identification[b]
Parathyroid Gland(s)	

a: Collected in 10% neutral buffered formalin unless otherwise indicated
b: Collected but not processed
c: Bone marrow smears were prepared for all monkeys but were not evaluated because it was not warranted by changes in the peripheral blood.
d: Collected in 3% glutaraldehyde

Histopathological evaluation was performed on organs/tissues collected from all control and high dose animals, as well as gross findings.

Adequate Battery: Yes

Peer Review: Yes

Histological Findings:

Minimal to mild neutrophil infiltration of the mucosa occurred in the large intestine of one low- and two mid-dose females which were observed to have abnormal contents of the large intestine. This correlated with increased bacterial rods in the intestinal lumen and abnormal stools which occurred predose and during the dosing period. Based on clinical findings of abnormal stools prior to treatment and lack of findings in high dose females, these findings were considered unrelated to treatment with the test compound.

Mild lung fibrosis and minimal peribronchial eosinophil infiltration occurred in a single mid- and high-dose male, respectively. These findings were considered incidental findings that are common in monkeys and may be associated with previous infection by common lung mites. Mild lung fibrosis also occurred in a single female control.

Severe atrophy of the thymus occurred in a single low-dose female, but did not appear to be treatment-related based on a lack of findings in mid- and high dose animals.

Special Evaluation

None

Toxicokinetics

Blood samples were collected from 1 to 24 h post-dosing on Days 0 and 62. Plasma samples were analyzed for SCH 619734 concentrations.

Systemic exposures to SCH 619734 increased in a greater than dose-proportional manner. Exposures to SCH 619734 in the mid- and high dose groups were greater on Day 62 (accumulation ratios for Day 62:Day 1 AUC values ranged from 1.33-1.55). No gender differences occurred. Mean toxicokinetic parameters are presented in the Applicant's table below.

Table 1 Mean (CV) Toxicokinetic Parameters for SCH 619734 on Days 0 and 62 Following Oral (Gavage) Administration of 1, 5 or 15 mg/kg SCH 619734 to Cynomolgus Monkeys

		Cmax (ng/mL)			Tmax (hr)			AUC(0-24 hr)[a] (ng·hr/mL)			Accumulation Ratio		
Day	Dose (mg/kg)	Male	Female	M+F	Male	Female	M+F	Male	Female	M+F	Male	Female	M+F
0	1	190 (47)	172 (41)	181 (42)	3.50 (86)	2.28 (53)	2.89 (77)	2840[b] (NC)	1940[c] (NC)	2240[d] (59)	NA	NA	NA
	5	928 (6)	1070 (13)	999 (12)	3.00 (38)	2.50 (40)	2.75 (38)	10400 (18)	11600 (7)	11000 (13)	NA	NA	NA
	15	2800 (32)	3030 (8)	2910 (21)	5.00 (40)	3.50 (29)	4.25 (39)	39600 (30)	41300 (6)	40500 (19)	NA	NA	NA
62	1	140 (29)	161 (24)	150 (25)	1.75 (29)	2.00 (71)	1.88 (53)	2460[b] (NC)	1310[c] (NC)	1690[d] (53)	0.865[b] (NC)	0.798[c] (NC)	0.820[d] (24)
	5	1210 (17)	1220 (30)	1220 (23)	2.50 (40)	3.50 (29)	3.00 (36)	16800 (32)	17300 (32)	17000 (30)	1.61 (23)	1.50 (32)	1.55 (26)
	15	3510 (18)	3590 (12)	3550 (14)	4.00 (0)	5.00 (40)	4.50 (31)	49200 (15)	54800 (14)	52000 (15)	1.28 (18)	1.33 (14)	1.31 (15)

N = 4 monkeys/sex/dose group unless otherwise specified; M+F = male and female data combined;

NA = not applicable; NC = not calculated (n < 3)

a: Animals with >25% AUC (0-24 hr) extrapolated were excluded from mean AUC (0-24 hr) calculations.

b: N = 1; mean AUC(tf) values = 1280 and 1100 ng·hr/mL on Day 0 and 62, respectively (n = 4).

c: N = 2; mean AUC(tf) values = 1310 and 1100 ng·hr/mL on Day 0 and 62, respectively (n = 4).

d: N = 3; mean AUC (tf) values = 1290 and 1100 ng·hr/mL on Day 0 and 62, respectively (n = 8).

Dosing Solution Analysis

Dosing solution samples were collected during Weeks 1, 4, and 11 for concentration analysis. Dosing solution samples from the low and high dose groups were collected during Week 1 for evaluation of homogeneity. The analytical assay results were acceptable. The percent of nominal concentration ranged from 98.0 to 101%.

Study title: A 39-Week Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 619734 in the Cynomolgus Monkey

Study no.:	03663
Study report location:	EDR Section 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 29, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734 hydrochloride monohydrate, parental grade, micronized, SZ-04-619734-TX-005, 100.2%

Key Study Findings

Up to 30 mg/kg/day SCH 619734 did not produce any mortality or clinical signs. Although body weight gain from Week -1 to 39 was decreased by 59% (compared to controls) in high dose males, body weight gain was increased by up to 40% at the low- and mid-dose level indicating a lack of dose response. Furthermore, there was a high level of variability in body weights across groups, and mean body weights of high dose males during Week 39 were only slightly lower than controls (<10% difference). In males and females, there were dose-related increases in liver weights (compared to controls). While histopathological examination indicated minimal focal necrosis in the liver of 3/4 high dose males, this finding (which did not occur in females) was characterized as focal and minimal, was reported to represent a common finding in laboratory monkeys, and there were no correlating changes in clinical chemistry parameters in males. Minimal atrophy of the thymus occurred in 2/4 high dose males and females each, which correlated with decreased thymus weights in males only. Findings of mild and moderate atrophy of the thymus occurred in 2 low-dose males indicating a lack of dose-response, since atrophy at the high dose was characterized as minimal (i.e., less severe). While histopathological examination of the thymus from mid dose males was not conducted, small thymus was not noted in this group during necropsy. Based on the findings of this study, the NOAEL was considered to be 30 mg/kg/day.

Methods

Doses:	2.5, 15, and 30 mg/kg/day
Frequency of dosing:	Daily
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Monkey, *Macaca fascicularis* (Cynomolgus)
Number/Sex/Group:	4/sex/group
Age:	Young adult (~2-5 years old)
Weight:	Male: 2.7-4.7 kg; Female: 2.2-2.7 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	Protocol deviations did not affect the quality or integrity of the study.

Observations and Results

Mortality

Animals were observed at least once daily for viability.

There was no mortality.

Clinical Signs

Clinical observations were made at least twice daily. Detailed examinations were conducted once prestudy, and weekly during the dosing period. Veterinary examinations were conducted pretest and during Weeks 5, 24, and 39.

No treatment-related clinical signs were observed.

Body Weights

Body weights were measured weekly.

There did not appear to be any adverse treatment-related changes in body weight parameters. In high dose males, body weight gain was decreased compared to controls (-59%). However, body weight gain was increased by up to 40% (compared to controls) at the low- and mid-dose levels. Differences in body weights were considered to be related to individual animal variability. In females, body weight gain was higher in all treatment groups, compared to controls, but this did not occur in a dose-related manner.

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	2.5	15	30	0	2.5	15	30
BW (g) Week -1	3.83	3.43	3.25	3.83	2.50	2.48	2.53	2.55
BW (g) Week 39	4.50	4.38	4.15	4.10	2.75	3.20	2.88	2.85
BW (% control) Week 39	100%	97%	92%	91%	100%	116%	105%	104%
BW gain (g) Week -1 to 39	0.68	0.95	0.90	0.28	0.25	0.73	0.35	0.30

BW gain (% control) Week -1 to 39	100%	140%	132%	41%	100%	292%	140%	120%

Feed Consumption

Food consumption was visually evaluated daily and signs of reduced appetite or inappetence were recorded.

Reduced appetite was observed on a subset of days in all groups, including controls. While the incidences of reduced appetite occurred more frequently in SCH 619734-treated males, there was no apparent dose relationship.

Ophthalmoscopy

Ophthalmological examinations were conducted pretest and during Week 38.

There were no treatment-related changes.

ECG

ECG recordings were performed twice pretest and during Weeks 5, 24, and 38. Tracings were evaluated for rhythm, waveform morphologic (for P, QRS, and T wave), and apparent functional changes. Standard intervals and wave duration (PR, QRS, and QT) were calculated for lead II. QTc interval duration was calculated according to the method of Fridericia and RR was reported. Heart rate [HR], blood pressure [BP], and body temperature were also measured.

There were no treatment-related changes in ECG parameters, HR, BP or body temperature. HR, ECG waveform morphology, and intervals were considered within normal limits. Right ventricular conduction occurred in 1 control and high dose male each both pretest and during the study. Given the occurrence prior to treatment and in the control group, this was not considered treatment-related. In one mid-dose male, a single premature ventricular depolarization occurred during Week 38. This was not considered treatment-related based on the isolated incidence in a single animal and a lack of findings at the high dose.

Hematology

Blood samples were collected twice pretest and during Weeks 12, 24, and 38 for evaluation of standard hematological parameters. Prothrombin time and activated partial thromboplastin time were also determined.

There were no treatment-related changes.

Clinical Chemistry

Samples were analyzed for standard clinical chemistry parameters.

In high dose females, bilirubin levels were decreased relative to controls and prestudy values. At Week 39, total bilirubin and indirect bilirubin were decreased by 34% and 22%, respectively (compared to controls). Direct bilirubin was 0.04 mg/dL in controls compared to values lower than the measurement range (0.01-0.02 mg/dL) in high dose females. Triglyceride levels in high dose females were increased by 104% and 146% (compared to controls) during weeks 24 and 39. The week 39 triglyceride values in low- and mid-dose females were also increased (+46% and +38%, respectively, compared to controls). However, the increases in low- and mid-dose animals did not occur in a dose-related manner, and the values were similar to those measured in controls at other timepoints (including prestudy). Overall, differences in clinical chemistry parameters were not considered to be treatment-related.

Urinalysis

Urinalysis was conducted for samples collected twice pretest and during Weeks 12, 24, and 38.

There were no treatment-related changes.

Gross Pathology

At terminal sacrifice, necropsies (consisting of an external examination, including identification of all clinically recorded findings, and a detailed internal examination) were conducted on all animals.

All macroscopic findings were considered incidental and unrelated to treatment.

Organ Weights

At the scheduled terminal necropsy, weights of the following organs were determined and: adrenal glands, brain, epididymides, heart, kidneys, liver, lungs, ovaries, pituitary gland, prostate gland, spleen, testes, thymus, thyroid gland/parathyroid glands, and uterus (plus cervix). Organ-to-body weight ratios (i.e., relative weights) were calculated.

In males, absolute thymus weights were decreased (compared to controls) by 28%, 33%, and 38%, respectively, at 2.5, 15, and 30 mg/kg/day. Relative thymus weights were decreased by 23%, 30%, and 31%, respectively, at the low-, mid-, and high doses, respectively. At 15 mg/kg/day, absolute and relative liver weights were increased by 14% and 24%, respectively. At 30 mg/kg/day, absolute and relative liver weights were increased by 29% and 36%. Absolute and relative epididymis weights were decreased by 23% and 20% (compared to controls), respectively, at 30 mg/kg/day.

In females, there were dose-related increases in liver weights. Absolute liver weights were increased (compared to controls) by 14%, 16%, and 26%, respectively, at 2.5, 15, and 30 mg/kg/day. Relative liver weights were increased by 13% and 28% (compared to controls) at 15 and 30 mg/kg/day, respectively. At 30 mg/kg/day, absolute and relative thyroid weights were decreased (compared to controls) by 31%.

It was noted that there was a high level of variability of weights among animals, and any changes in weights were considered related to biological variation associated with age, body weight, and/or sexual maturity rather than treatment with the test compound.

Histopathology

The Applicant's table below identifies the tissues collected and preserved at necropsy.

Tissues Collected	
Abnormalities (gross findings) Animal Identification[a] Aorta (thoracic) Adrenal glands Bone (femur, rib[a] and sternum)[b] Bone marrow section (rib[a] and sternum)[b] Bone marrow for cytology (femur)[a,c] Brain (forebrain, midbrain, cerebellum, and medulla oblongata) Epididymides[d] Esophagus Eyes with optic nerves[d,e] Gall bladder Heart (including section of aorta) Kidneys Lacrimal glands Large intestine (cecum, colon) Larynx/pharynx Liver (sample of 2 lobes) Lungs[f] (sample of 2 lobes) Lymph nodes (mandibular, unilateral; and mesenteric) Mammary gland (thoracic)[e] Ovaries	Pancreas Parathyroid gland(s)[e] Peripheral nerve-sciatic nerve Pituitary Prostate Rectum[a] Salivary glands (mandibular, unilateral) Seminal vesicles Skeletal muscle (biceps femoris) Skin (ventral thoracic) Small intestine (duodenum, jejunum, ileum) Spinal cord (thoracolumbar) Spleen Stomach Testes[d] Thymus Thyroid glands Tongue[a] Trachea Urinary bladder Uterus (body and cervix) Vagina
a: Retained but not processed. b: Bone decalcified prior to sectioning. c: Bone marrow smears (3) were prepared and stained for all animals euthanized at the scheduled necropsies but were not evaluated. d: Fixed in Davidson's fixative. e: Examined histopathologically only if present in routine sections of eyes (optic nerves), thyroid lobes (and parathyroid glands), or skin (mammary gland). f: Infused with neutral buffered 10% formalin.	

All organs/tissues collected were processed for histopathological examination. The slides were shipped to the Applicant for histopathological examination. All organs/tissues from control and high dose animals and all gross findings were evaluated by the Applicant's pathologist.

Adequate Battery: Yes

Peer Review: A peer review was performed by the Applicant.

Histological Findings:

In the liver, minimal focal necrosis occurred in 3/4 high dose males, compared to 0/4 controls. It is unknown whether this finding occurred in the livers of low- and mid-dose males, as livers from those treatment groups were not evaluated microscopically. However, this finding did not occur in females, was characterized as focal and minimal,

and was reported to represent a common finding in laboratory monkeys. Furthermore, there were no correlating clinical chemistry findings in males indicative of liver injury.

Histopathological findings of mild focal epicardial fibrosis, minimal atrophy, and moderate adipose tissue accumulation in the heart of a single mid-dose male correlated with a pale area observed macroscopically. Based on the absence of this finding at the high dose, it appeared to be unrelated to treatment.

Minimal atrophy of the thymus occurred in 2/4 high dose males and females each, compared to zero controls. Findings of mild and moderate atrophy of the thymus occurred in 2 low-dose males indicating a lack of dose-response since atrophy at the high dose was characterized as minimal (i.e., less severe). While histopathological examination of the thymus from mid dose males was not conducted, small thymus was not noted in this group during necropsy. In regards to organ weights, decreased thymus weights occurred in males only.

Special Evaluation

None

Toxicokinetics

Blood samples were collected from 1 to 24 h post-dosing on Day 1 and during Week 30. Plasma samples were analyzed for SCH 619734 concentrations.

Systemic exposures to SCH619734 increased in a less than dose-proportional manner. At 2.5 mg/kg/day, exposures were increased after repeated administration (ratio of AUC values on Day 204:Day 1 equal to 1.43). The ratio of AUC values on Day 204:Day 1 decreased with increasing dose, indicating no accumulation after repeat dosing with 30 mg/kg/day. There were no gender differences, and thus the TK parameters shown in the Applicant's table below are for males and females combined.

Mean (CV) SCH 619734 Toxicokinetic Parameters on Day 1 and Day 204 Following Oral (Gavage) Administration of 2.5, 15 or 30 mg/kg SCH 619734 to Cynomolgus Monkeys (Males and Females Combined)

Dose (mg/kg)[a,b]	Day	Cmax (ng/mL)	Tmax (hr)[c]	AUC(0-24 hr) (ng·hr/mL)	R[d]
2.5	1	453 (11)	2 (2-4)	5840 (24)	NA[e]
	204	603 (31)	2 (1-4)	8220 (36)	1.43 (37)
15	1	2830 (23)	4 (1-8)	44100 (22)	NA
	204	3230 (20)	2 (2-8)	47100 (26)	1.11 (33)
30	1	4400 (20)	4 (2-8)	73700 (14)	NA
	204	4330 (30)	4 (4-8)	70100 (29)	0.957 (28)

a: Doses are expressed as the hydrochloride salt. When expressed as the free base, daily doses were 2.25, 13.5 and 27 mg/kg for the 2.5, 15 and 30 mg/kg dose groups, respectively.
b: N = 8/dose group
c: Median (Minimum-Maximum)
d: $R = AUC(0\text{-}24\ hr)_{Day\ 204} \div AUC(0\text{-}24\ hr)_{Day\ 1}$
e: NA = Not applicable

Dosing Solution Analysis

Dosing solution samples were collected during Week 1 for concentration and homogeneity analysis and measurement of density. Samples were collected during Weeks 13, 26, and 38 for concentration analysis. All samples were within the acceptance criteria of ±15% of their nominal concentrations (range 97.3-111%).

7 Genetic Toxicology

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

The review of Study No. 03113 is incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

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

Study title: Ames Test with SCH 619734

Study no.:	SN03113
Study report location:	EDR 4.2.3.3.1
Conducting laboratory and location:	Safety Evaluation Center Schering-Plough Research Institute Lafayette, NJ
Date of study initiation:	August 3, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734 (HCl monohydrate salt), SZ-03-PHG-TX-001, 99.6%

Key Study Findings: The sponsor conducted six trials. Trial 1 and 2 were not valid for (b) (4)

(b) (4) Trial 5 and 6 were conducted with TA1535 only and were valid.

Methods: Plate Incorporation Method

Strains:	*Salmonella typhimurium* tester strains TA1535, TA97a, TA98, TA100 and TA102, and *Escherichia coli* tester strain WP2*uvr*A
Concentrations in definitive study:	Shown in the table below (from page 11 of the report)
Basis of concentration selection:	Cytotoxicity
Negative control:	DMSO
Positive control:	Shown in the table below (from page 13 of the report)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	40-56 hours

The following table shows the concentrations tested.

Dose Ranges Evaluated in Valid Trials for Each Bacterial Strain				
Bacterial Strain	SCH 619734 (µg/plate)			
	Initial Trial		Confirmatory Trial	
	S9-	S9+	S9-	S9+
TA1535	156.2 - 5000	156.2 - 5000	156.2 - 5000	156.2 - 5000
TA97a	7.8 - 250	15.6 -1000	31.2 - 500	31.2 - 2000
TA98	7.8 - 250	15.6 -1000	31.2 - 500	62.5 - 2000
TA100	7.8 - 250	15.6 -1000	31.2 - 500	31.2 - 500
TA102	7.8 - 250	15.6 -1000	15.6 - 250	15.6 - 500
WP2*uvr*A	156.2-5000	156.2 -5000	312.5 - 5000	312.5 - 5000
S9- = Nonactivation phase ; S9+ = Activation phase				

The following table shows the positive controls.

Positive Controls:

Bacterial Strains	Nonactivation Phase (µg/plate)	Activation Phase (µg/plate)
Salmonella typhimurium		
TA1535 and TA100	Sodium azide (5)	2-Aminoanthracene (2.5)
TA97a	9-Aminoacridine (75)	2-Aminoanthracene (2.5)
TA98	2-Nitrofluorene (5)	2-Aminoanthracene (2.5)
TA102	Cumene hydroperoxide (200)	2-Aminoanthracene (5)
Escherichia coli		
WP2*uvr*A	1-Methyl-3-nitro-1-nitrosoguanidine (MNNG) (4)	2-Aminoanthracene (20)

Study Validity: The sponsor conducted six trials. Overall, Trial 1 and 2 were not valid (b) (4)

Trial 5 and 6 were conducted with TA1535 only and were valid.

Results: Negative. As mentioned before, the sponsor conducted a total of six trials (Trial 1 through 6). Brief overview of each trial is provided below.

Trial 1: For TA1535, Trial 1 was considered invalid due to (b) (4)

Trial 2: Trial 2 was a repeat of Trial 1. (b) (4)
Trial 2 was considered invalid due to (b) (4)

Trial 3: (b) (4)

Therefore, trial 3 was considered invalid. (b) (4)

This trial was repeated in Trial 5.

Trial 4: (b) (4)

Therefore, trial 4 was considered invalid. (b) (4)

This was repeated in Trial 6.

Trial 5: (b) (4) Trial 5 was conducted with TA1535. SCH 619734 did not induce an increase in revertant colony counts for TA1535 in the presence or absence of S9.

Trial 6: (b) (4) Trial 6 was conducted with TA1535. SCH 619734 did not induce an increase in revertant colony counts for TA1535 in the presence or absence of S9

Overall, the sponsor conducted six trials. Trial 1 and 2 were not valid for (b) (4) Trial 3 and 4 were conducted (b) (4) were also invalid because of (b) (4) Trial 5 and 6 were conducted with TA1535 only and were considered valid.

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Table 7 Mutagenicity Assay – Trial 5: Nonactivation and Activation Phase

Summary of Results: Mean (n=3) Revertants Per Plate (Cytotoxicity)		
	Bacterial Strain TA1535	
Dose (µg/plate)	Nonactivation	Activation
0 (Solvent Control: DMSO)	11 (0)	16 (0)
156.2 (SCH 619734)	14 (0)	15 (0)
312.5 (SCH 619734)	11 (0)	17 (0)
625 (SCH 619734)	19 (0)	15 (0)
1250 (SCH 619734)	13 (0)	13 (0)
2500 (SCH 619734)	16 (0)	19 (0)
5000 (SCH 619734)	9 (0)	17 (0)
5 (Sodium Azide)	565 (0)	---
2.5 (2-Aminoanthracene)	---	119 (0)
Cytotoxicity to Background Lawn: (0) = none --- = Not applicable		

Table 8 Mutagenicity Assay – Trial 6: Nonactivation and Activation

Summary of Results: Mean[a] Revertants Per Plate (Cytotoxicity)		
	Bacterial Strain TA1535	
Dose (µg/plate)	Nonactivation	Activation
0 (Solvent Control: DMSO)	11 (0)[b]	17 (0)[b]
156.2 (SCH 619734)	11 (0)	17 (0)
312.5 (SCH 619734)	18 (0)	19 (0)
625 (SCH 619734)	17 (0)	18 (0)
1250 (SCH 619734)	13 (0)	13 (0)
2500 (SCH 619734)	9 (0)	16 (0)
5000 (SCH 619734)	8 (0)	15 (0)
5 (Sodium Azide)	529 (0)	---
2.5 (2-Aminoanthracene)	---	142 (0)
Cytotoxicity to Background Lawn: (0) = none --- = Not applicable a: n = 2 unless otherwise noted b: n = 3		

7.2 *In Vitro* Assays in Mammalian Cells

The review of Study No. 03114 is incorporated below from the pharmacology review of IND [redacted] (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

Study title: Chromosome Aberration Assay of SCH 619734 in Human Peripheral Blood Lymphocytes (HPBL)

Report no.:	03114
Study no.:	6377-542
Study report location:	EDR 4.2.3.3.1
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	August 9, 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734, SZ-03-PHG-TX-001, 99.6%

Key Study Findings: Negative

Methods:

Cell line:	HPBL
Concentrations in definitive study:	-S9: 0.5, 1, 2, 4, 6, 10, 15, 22.5, 30, 40, and 50 µg/mL (Trial 2); +S9: 6, 10, 15, 22.5, 30, 40, 50, 60, 70, and 80 µg/mL (Trial 2)
Basis of concentration selection:	Cytotoxicity (mitotic index/MI)
Negative control:	RPMI
Positive control:	-S9: Mitomycin C (MMC): 0.75, 1 and 1.5 µg/mL (~ 4-hour treatment) (Trial 1) and 0.2, 0.3 and 0.4 µg/mL (~ 19-hour treatment) (Trial 2) +S9: Cyclophosphamide (CP): 20, 25 and 40 µg/mL (Trial 1 and Trial 2)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	-S9: 4-hr treatment, 22-hr harvest (Trial1) +S9: 19-hr treatment, 22-hr harvest (Trial 2)

Study Validity: The study was considered valid as it met the criteria for a valid assay.

Results: SCH 619734 did not induce chromosome aberrations in cultured human peripheral blood lymphocytes in the presence or absence of an exogenous metabolic activation system under the conditions of this study. The following tables (from page 28-** of the study report) show the results.

Table 3: Chromosome Aberrations in Human Lymphocytes - Without Metabolic Activation (Trial 1)
~ 4-Hour Treatment, ~22-Hour Harvest
Assay No.: 26413-0-449 Date: 08/19/04 Lab No.: CY082004 Test Article: SCH 619734

				# Cells Scored for Aberrations	% Mitotic Index Reduction[a]	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judgement (+/-)[b]	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations: gaps	simple breaks	chte	chre	mab	Totals[c] -g	Totals[c] +g	Judgement (+/-)[d]
Controls																	
Negative:	RPMI 1640		A	100		100	0	0		1					0	1	
			B	100		100	0	0		2					0	2	
			Total	200		200				3					0	3	
			Average	%	--		0.0	0.0		1.5					0.0	1.5	
Vehicle:	DMSO	10 µL/mL	A	100		100	1	0		2					0	2	
			B	100		100	0	0		4					0	4	
			Total	200		200				6					0	6	
			Average	%	0		0.5	0.0		3.0					0.0	3.0	
Positive:	MMC	1 µg/mL	A	50		100	0	0		6	26	14			35	36	
			B	50		100	0	0		5	20	8		1	26	30	
			Total	100		200				11	46	22		1	61	66	
			Average	%	67		0.0	0.0	-	11.0	46.0	22.0		1.0	61.0	66.0	+
Test Article		2.93 µg/mL	A	100		100	0	0		1					0	1	
			B	100		100	0	0		2					0	2	
			Total	200		200				3					0	3	
			Average	%	2		0.0	0.0	-	1.5					0.0	1.5	-
		5.86 µg/mL	A	100		100	1	0		4					0	4	
			B	100		100	0	0		3	1				1	4	
			Total	200		200				7	1				1	8	
			Average	%	13		0.5	0.0	-	3.5	0.5				0.5	4.0	-
		11.7 µg/mL	A	100		100	0	0		2					0	2	
			B	100		100	0	0		2					0	2	
			Total	200		200				4					0	4	
			Average	%	34		0.0	0.0	-	2.0					0.0	2.0	-
		23.4 µg/mL	A	100		100	0	0		2					0	2	
			B	100		100	0	0		2					0	2	
			Total	200		200				4					00	4	
			Average	%	49		0.0	0.0	-	2.0					0.0	2.0	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication
a: % Mitotic index reduction as compared to the vehicle control.
b: Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.
c: -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.
d: Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640 = culture medium DMSO = dimethylsulfoxide MMC = Mitomycin C

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Table 7: Chromosome Aberrations in Human Lymphocytes - With Metabolic Activation (Trial 1)
~ 4-Hour Treatment, ~ 22-Hour Harvest
Assay No.: 26413-0-449 Date: 08/19/04 Lab No.: CY082004 Test Article: SCH 619734

				# Cells Scored for Aberrations	% Mitotic Index Reduction[a]	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judgement (+/-)[b]	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations: gaps	simple breaks	chte	chre	mab	Totals[c] -g	Totals[c] +g	Judgement (+/-)[d]
Controls																	
Negative:	RPMI 1640		A	100		100	0	0		4					0	4	
			B	100		100	0	0		1	2		1		3	4	
			Total	200		200				5	2		1		3	8	
			Average	%	--		0.0	0.0		2.5	1.0		0.5		1.5	4.0	
Vehicle:	DMSO	10 µL/mL	A	100		100	0	0		1					0	1	
			B	100		100	0	0		2	1				1	3	
			Total	200		200				3	1				1	4	
			Average	%	0		0.0	0.0		1.5	0.5				0.5	2.0	
Positive:	CP	25 µg/mL	A	50		100	0	0		8	16	1		1	18	22	
			B	50		100	0	0		3	19	3			21	23	
			Total	100		200				11	35	4		1	39	45	
			Average	%	69		0.0	0.0	-	11.0	35.0	4.0		1.0	39.0	45.0	+
Test Article		5.86 µg/mL	A	100		100	0	0		5	3				3	8	
			B	100		100	0	0		4					0	4	
			Total	200		200				9	3				3	12	
			Average	%	13		0.0	0.0	-	4.5	1.5				1.5	6.0	-
		11.7 µg/mL	A	100		100	0	0		1					0	1	
			B	100		100	1	0		1					0	1	
			Total	200		200				2					0	2	
			Average	%	16		0.5	0.0	-	1.0					0.0	1.0	-
		23.4 µg/mL	A	100		100	0	0		2					0	2	
			B	100		100	0	0		3					0	3	
			Total	200		200				5					0	5	
			Average	%	48		0.0	0.0	-	2.5					0.0	2.5	-
		46.9 µg/mL	A	100		100	0	0		5					0	5	
			B	100		100	0	0		5	1				1	5	
			Total	200		200				10	1				1	10	
			Average	%	53		0.0	0.0	-	5.0	0.5				0.5	5.0	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication
a: % Mitotic index reduction as compared to the vehicle control.
b: Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.
c: -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.
d: Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640 = culture medium DMSO = dimethylsulfoxide CP = Cyclophosphamide

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Table 5: Chromosome Aberrations in Human Lymphocytes - Without Metabolic Activation (Trial 2)
~ 19-Hour Treatment, ~ 22-Hour Harvest
Assay No.: 26413-0-449 Date: 09/15/04 Lab No.: CY091204 Test Article: SCH 619734

				# Cells Scored for Aberrations	% Mitotic Index Reduction[a]	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judgement (+/-)[b]	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations: gaps	simple breaks	chte	chre	mab	Totals[c] -g	Totals[c] +g	Judgement (+/-)[d]
Controls																	
Negative:	RPMI 1640		A	100		100	0	0							0	0	
			B	100		100	0	0		2					0	2	
			Total	200		200				2					0	2	
			Average	%	--		0.0	0.0		1.0					0.0	1.0	
Vehicle:	DMSO	10 µL/mL	A	100		100	0	0		1	1				1	2	
			B	100		100	0	0		3					0	3	
			Total	200		200				4	1				1	5	
			Average	%	0		0.0	0.0		2.0	0.5				0.5	2.5	
Positive:	MMC	0.3 µg/mL	A	50		100	0	0		11	18	6			22	27	
			B	51		100	0	0		6	8	8			15	18	
			Total	101		200				17	26	14			37	45	
			Average	%	38		0.0	0.0	-	16.8	25.7	13.9			36.6	44.6	+
Test Article		10 µg/mL	A	100		100	0	0		1	1				1	2	
			B	100		100	0	0				1			0	1	
			Total	200		200				1	1	1			1	3	
			Average	%	0		0.0	0.0	-	0.5	0.5	0.5			0.5	1.5	-
		22.5 µg/mL	A	100		100	0	0		1					0	1	
			B	100		100	0	0							0	0	
			Total	200		200				1					0	1	
			Average	%	5		0.0	0.0	-	0.5					0.0	0.5	-
		30 µg/mL	A	100		100	0	0		1					0	1	
			B	100		100	0	0		1	1				1	2	
			Total	200		200				2	1				1	3	
			Average	%	26		0.0	0.0	-	1.0	0.5				0.5	1.5	-
		40 µg/mL	B	200		100	0	0		4					0	4	
			Average	%	51[e]		0.0	0.0	-	2.0					0.0	2.0	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication
a: % Mitotic index reduction as compared to the vehicle control.
b: Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.
c: -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.
d: Significantly greater in –g than the vehicle control, $p \leq 0.01$.
e: % Mitotic Index reduction for B culture only RPMI 1640 = culture medium DMSO = dimethylsulfoxide MMC = Mitomycin C

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Table 9: Chromosome Aberrations in Human Lymphocytes - With Metabolic Activation (Trial 2)
~ 4-Hour Treatment, ~ 22-Hour Harvest
Assay No.: 26413-0-449 Date: 09/15/04 Lab No.: CY091204 Test Article: SCH 619734

				# Cells Scored for Aberrations	% Mitotic Index Reduction[a]	# Cells Scored for pp and er	# of pp Cells	# of er Cells	Judgement (+/-)[b]	Numbers and Percentages of Cells Showing Structural Chromosome Aberrations: gaps	simple breaks	chte	chre	mab	Totals[c] -g	Totals[c] +g	Judgement (+/-)[d]
Controls																	
Negative:	RPMI 1640		A	100		100	0	0		3	1				1	4	
			B	100		100	0	0		1					0	1	
			Total	200		200				4	1				1	5	
			Average	%	--		0.0	0.0		2.0	0.5				0.5	2.5	
Vehicle:	DMSO	10 µL/mL	A	100		100	0	0							0	0	
			B	100		100	0	0							0	0	
			Total	200		200									0	0	
			Average	%	0		0.0	0.0							0.0	0.0	
Positive:	CP	25 µg/mL	A	75		100	0	0		6	20	2			21	23	
			B	50		100	0	0		5	15				15	17	
			Total	125		200				11	35	2			36	40	
			Average	%	40		0.0	0.0	-	8.8	28.0	1.6			28.8	32.0	+
Test Article		40 µg/mL	A	100		100	0	0		4	1				1	5	
			B	100		100	0	0		1					0	1	
			Total	200		200				5	1				1	6	
			Average	%	5		0.0	0.0	-	2.5	0.5				0.5	3.0	-
		50 µg/mL	A	100		100	0	0		1					0	1	
			B	100		100	0	0		1	1				1	2	
			Total	200		200				2	1				1	3	
			Average	%	3		0.0	0.0	-	1.0	0.5				0.5	1.5	-
		60 µg/mL	A	100		100	0	0		3					0	3	
			B	100		100	0	0		3					0	3	
			Total	200		200				6					0	6	
			Average	%	30		0.0	0.0	-	3.0					0.0	3.0	-
		70 µg/mL	A	200		200	0	0		2	1				1	3	
			B	200		100	0	0		3					0	3	
			Total	400		300				5	1				1	6	
			Average	%	43		0.0	0.0	-	1.3	0.3				0.3	1.5	-

chte: chromatid exchange chre: chromosome exchange mab: multiple aberrations, greater than 4 aberrations pp: polyploidy er: endoreduplication
a: % Mitotic index reduction as compared to the vehicle control. b: Significantly greater in % polyploidy and % endoreduplication than the vehicle control, $p \leq 0.01$.
c: -g = # or % of cells with chromosome aberrations; +g = # or % of cells with chromosome aberrations + # or % of cells with gaps.
d: Significantly greater in -g than the vehicle control, $p \leq 0.01$. RPMI 1640 = culture medium DMSO = dimethylsulfoxide CP = Cyclophosphamide

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

The review of Study No. 03261 is incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

Study title: Mouse Bone Marrow Erythrocyte Micronucleus Study of SCH 619734 by Intraperitoneal (IP) Route

Report no:	03261
Study no.:	6377-552
Study report location:	EDR 4.2.3.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 21, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734, SZ-03-PHG-TX-001, 99.6%

Key Study Findings: Negative

Methods:

Doses in definitive study:	31.25, 62.5, and 125 mg/kg/day in male and female mice
Frequency of dosing:	Once a day for two consecutive days
Route of administration:	IP
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose, pH 4.0
Species/Strain:	CD-1
Number/Sex/Group:	Six/sex/dose
Satellite groups:	None
Basis of dose selection:	Dose range study*
Vehicle control:	0.4% (w/v) aqueous methylcellulose, pH 4.0
Positive control:	Cyclophosphamide, 50 mg/kg, IP

*: Dose range study: In the dose range-finding assay in mice, animals (five-six mice/sex/dose) were treated with SCH 619734 at 125, 250, 500, 1000, or 2000 mg/kg/day by IP injection once a day for two consecutive days (10 mL/kg). For the evaluation of bone marrow cytotoxicity, three mice per sex were sacrificed at 24 hours after the second dose for the vehicle control group and the 125 mg/kg/day dose group. No higher treatment groups were analyzed for PCE/NCE ratios in the dose range-finding assay due to mortality. Mortality was observed in five males and four females at 250 mg/kg/day on Day 2 and in all males and females at 500, 1000, and 2000 mg/kg/day on Day 2. Clinical signs (hypoactivity, convulsions, ataxia, tremors, squinted eyes, red oral discharge and irregular respiration) were observed at all doses in both sexes. Bone marrow cytotoxicity was observed in the females at 125 mg/kg/day. In male mice, the mean PCE/NCE ratio at 125 mg/kg/day was 0.55, which was 67% of the mean PCE/NCE ratio (0.82) of the vehicle control. In female mice, the mean PCE/NCE ratio at 125 mg/kg/day was 0.41, which was 45% of the mean PCE/NCE ratio (0.91) of

the vehicle control. The doses of the confirmatory assay were selected based on the above results of the dose ranging study.

Study Validity: The assay met the criteria for a valid study.

Results: SCH 619734 did not induce micronuclei in bone marrow polychromatic erythrocytes in male or female mice under the conditions of this study. The summary results are shown in the table below (from page 37 of the report).

Table 7: Results of the Micronucleus Assay – Summary

Assay No.: 26413-0-455OECD

Test Article: SCH 619734

Initiation of Dosing: March 14, 2005

Test/Control Article	Dose (mg/kg/day)	Harvest Time (hr)	Mean % Micronucleated PCE per 2000 PCE ± S.E.		Mean Estimated % Micronucleated NCE per 2000 PCE ± S.E.		PCE/NCE Ratio Mean ± S.E.	
			Males	Females	Males	Females	Males	Females
Controls								
Vehicle	10 mL/kg	24	0.10 ± 0.03	0.11 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.97 ± 0.06	0.71 ± 0.10
0.4% MC		48	0.12 ± 0.02	0.07 ± 0.01	0.03 ± 0.01	0.01 ± 0.01	0.87 ± 0.07	0.90 ± 0.04
Positive	50	24	2.15 ± 0.29[a]	2.61 ± 0.12[a]	0.18 ± 0.03[a]	0.17 ± 0.04[a]	0.49 ± 0.05[b]	0.38 ± 0.05[b]
(CP)	40	48	1.86 ± 0.19[a]	1.39 ± 0.18[a]	0.11 ± 0.04	0.18 ± 0.07	0.30 ± 0.08[b]	0.59 ± 0.09
SCH 619734	31.25	24	0.12 ± 0.03	0.10 ± 0.02	0.03 ± 0.02	0.00 ± 0.00	0.66 ± 0.13	0.97 ± 0.03
		48	0.10 ± 0.02	0.07 ± 0.01	0.02 ± 0.01	0.00 ± 0.00	0.88 ± 0.03	0.90 ± 0.07
	62.5	24	0.12 ± 0.02	0.11 ± 0.02	0.02 ± 0.01	0.00 ± 0.00	0.74 ± 0.06	0.77 ± 0.07
		48	0.12 ± 0.01	0.08 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.82 ± 0.06	0.91 ± 0.11
	125	24	0.11 ± 0.01	0.11 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.81 ± 0.08	0.60 ± 0.13
		48	0.11 ± 0.02	0.07 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.40 ± 0.10[b]	0.51 ± 0.08[b]

a: Significantly greater than the corresponding vehicle control, $p \leq 0.01$.
b: A decrease of ≥40% in the PCE/NCE ratio relative to the vehicle control.
0.4% MC: 0.4% (w/v) aqueous methylcellulose, pH 4.0
CP: Cyclophosphamide
PCE: Polychromatic Erythrocyte
NCE: Normochromatic Erythrocyte

7.4 Other Genetic Toxicity Studies

Reviews of Study Nos. 03139, 08101, 08102, and 08190 are incorporated below from the pharmacology review of IND [redacted] (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

Exploratory Bacterial Mutagenicity Study of SCH 619734 (Study No. 03139)

Methods: The objective of this study was to assess the mutagenicity of SCH 619734 (HCl salt, amorphous, Batch No. 4) in the Ames test. *Salmonella typhimurium* strains

TA1535, TA97a, TA98, TA100 and TA102 and *Escherichia coli* strain WP2*uvr*A were tested at 0, 156.25, 312.5, 625, 1250, 2500 and 5000 µg/plate of SCH 619734 (free base) in Trial 1, in the presence and absence of metabolic activation (S9). Due to excessive cytotoxicity, Trial 2 was conducted at lower doses of 0, 6.25, 12.5, 25, 50, 100 and 200 µg/plate in the absence of S9, and TA97a was also tested in the presence of S9. All strains were tested with their respective positive controls. The solvent control was dimethylsulfoxide (DMSO).

Results:

Trial 1 (-S9): Because of cytotoxicity, this trial did not provide two non-cytotoxic doses for evaluation. Trial 1 (nonactivation phase) was repeated in Trial 2 using lower doses.

Trial 1 (+S9): Because of cytotoxicity to the revertant colonies in TA97a, this trial did not provide two non-cytotoxic doses for evaluation. Trial 1 activation phase of TA97a was repeated in Trial 2 using lower doses.

Trial 2 (-S9): Trial 2 was conducted in the *Salmonella typhimurium* strains because two non-cytotoxic doses were not available in Trial 1 due to cytotoxicity to the revertant colonies. In Trial 2, TA1535, TA97a, TA98, TA100 and TA102 strains were tested at 6.25, 12.5, 25, 50, 100 and 200 µg/plate. SCH 619734 did not induce an increase in revertant colony counts at any dose in any strain tested. The positive control induced at least a 5.7-fold increase over the respective concurrent solvent controls. The results are shown below (from page 5 of the report).

Table 4 Summary of Results: Mean (n=3) Revertants per Plate (Cytotoxicity) SCH 619734 - Nonactivation Phase - Trial 2

Dose (µg/plate)	Bacterial Strain				
	TA1535	TA97a	TA98	TA100	TA102
0	11(0)	108(0)	14(0)	107(0)	267(0)
6.25	12(0)	112(0)	11(0)	88(0)	285(0)
12.5	13(0)	97(0)	15(0)	106(0)	269(0)
25	10(0)	99(0)	14(0)	94(0)	286(0)
50	11(0)	107(0)	16(0)	109(0)	230(0)
100	8(0)	56*(0)	13(0)	102(0)	203(0)
200	5*(0)	0*(0)	18(0)	98(0)	109*(0)
Positive Control	832(0)	945(0)	564(0)	1091(0)	1532(0)
Cytotoxicity to Background Lawn : (0) = none *Indicates cytotoxicity to revertant colonies (≥30% decrease in revertant counts)					

Trial 2 (+S9): Trial 2 was conducted for TA97a because two non-cytotoxic doses were not available in Trial 1 due to cytotoxicity to the revertant colonies. In Trial 2, TA97a was tested at 6.25, 12.5, 25, 50, 100 and 200 µg/plate. SCH 619734 did not induce an increase in revertant colony counts at any dose. The positive control induced a 9.7-fold

increase over the concurrent solvent control. The results are shown below (from page 5 of the report).

Table 5 Summary of Results: Mean (n=3) Revertants per Plate (Cytotoxicity) SCH 619734 - Activation Phase - Trial 2

Dose (µg/plate)	Bacterial Strain TA97a
0	124(0)
6.25	148(0)
12.5	154(0)
25	132(0)
50	139(0)
100	142(0)
200	64*(0)
Positive Control	1202(0)
Cytotoxicity to Background Lawn : (0) = none *Indicates cytotoxicity to revertant colonies (≥30% decrease in revertant counts)	

Overall, SCH 61934 was not mutagenic under the conditions of the assay.

Study title: Bacterial Mutagenicity Study of SCH 720881 (SN 08101)

Study no.:	SN 08101
Study report location:	EDR 4.2.3.7.5
Conducting laboratory and location:	Safety Evaluation Center Schering-Plough Research Institute Summit, NJ
Date of study initiation:	June 9, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 720881, 86558-067-13, 98.65%

Key Study Findings: Negative

Methods: The objective of this study was to evaluate the mutagenicity of SCH 720881, a metabolite of SCH 61934, in the Ames test (plate incorporation method)

Strains:	*Salmonella typhimurium* tester strains TA1535, TA97a, TA98, TA100 and TA102 and *Escherichia coli* tester strain WP2*uvr*A.
Concentrations in definitive study:	Please see the table below
Basis of concentration selection:	Cytotoxicity
Negative control:	DMSO
Positive control:	Please see the table below
Formulation/Vehicle:	DMSO
Incubation & sampling time:	44.5 hours

The following table (from page 10 of the report) shows the study design.

Bacterial Mutagenicity Study of SCH 720881 (SN 08101): **Study Design**

Bacterial Strain[a]	SCH 720881 (µg/plate)	
	Trial 1 Nonactivation[b]	Trial 1 Activation[c]
TA1535, TA97a, TA98, TA100, TA102 and WP2*uvr*A	0,[d] 78, 156, 313, 625, 1250, 2500, 5000	0,[d] 78, 156, 313, 625, 1250, 2500, 5000

a: Bacteria (0.1 mL) from an overnight culture were exposed to test or control articles (0.1 mL) in triplicate test tubes with 2 mL top agar (Histidine Top Agar-*Salmonella typhimurium* / Tryptophan Top Agar-*Escherichia coli*, 45-46°C), plated onto minimal glucose agar medium (25 mL) and incubated for approximately 44.5 hours at 36.8°C prior to colony counting.

b: 0.5 mL of a 0.1M sodium phosphate buffer (pH 7.4) was added to each culture tube prior to plating.

c: 0.5 mL S9 mix was added to each culture tube prior to plating.

d: Solvent control plates were dosed with 100 µL/plate DMSO.

Bacterial Mutagenicity Study of SCH 720881 (SN 08101): **Study Design - Positive Controls**

Bacterial Strain[a]	Nonactivation[b]		Activation[c]	
	Positive Control	Dose (µg/plate)	Positive Control	Dose (µg/plate)
TA1535	Sodium Azide	5	2-Aminoanthracene	2.5
TA97a	9-Aminoacridine	75	2-Aminoanthracene	2.5
TA98	2-Nitrofluorene	5	2-Aminoanthracene	2.5
TA100	Sodium Azide	5	2-Aminoanthracene	2.5
TA102	Cumene hydroperoxide	100	2-Aminoanthracene	5
WP2*uvr*A	MNNG[d]	4	2-Aminoanthracene	20

a: Dosing procedures and incubation conditions for the positive controls were the same as those for the test article.

b: 0.5 mL of a 0.1M sodium phosphate buffer (pH 7.4) was added to each culture tube prior to plating

c: 0.5 mL S9 mix was added to each culture tube prior to plating

d: MNNG = 1-Methyl-3-nitro-1-nitrosoguanidine

Study Validity: The study met the criteria for a valid study.

Results: SCH 720881 did not induce an increase in revertant colony counts at any dose in any strain tested in the presence or absence of S9. The following tables (from pages 17 and 18 of the report) show the results of the study.

Summary Table Report

GeneTox 2.2
Page 1 of 1

Study Number: 08101
Bacterial Mutagenicity Study of SCH 720881
Trial: Mutagenicity Trial 1
Phase: Nonactivation

Strain: TA 1535

Dose Group	Treatment	Dose Level	Dose Units	Mean Cytotoxicity	Mean Revertants Per Plate	Mean Fold Increase	n	Plate Codes
01	dimethylsulfoxide (Solvent Control)	0.0	µg/plate	0	13	1	3	
02	SCH 720881 (Test Article)	78.0	µg/plate	0	10	0.77	3	
03	SCH 720881 (Test Article)	156.0	µg/plate	0	9	0.69	3	
04	SCH 720881 (Test Article)	313.0	µg/plate	0	4	0.31	3	
05	SCH 720881 (Test Article)	625.0	µg/plate	0	1	0.08	3	
06	SCH 720881 (Test Article)	1,250.0	µg/plate	0	0	0	3	
07	SCH 720881 (Test Article)	2,500.0	µg/plate	1	0	0	3	pt
08	SCH 720881 (Test Article)	5,000.0	µg/plate	1	0	0	3	pt
09	Sodium Azide (50 ug/mL) (Positive Control)	5.0	µg/plate	0	905 *	69.62	3	

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* Meets or exceeds minimum fold increase; Negative Control Dose Group: 01

Plate Code: ct-contamination,hpt-heavy precipitation,mc-microcolonies,pt-precipitation,sp-severe polarity
Cytotoxicity to the Background Lawn: 0-none,1-slight,2-moderate,3-complete

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Summary Table Report

GeneTox 2.2

Study Number: 08101
Bacterial Mutagenicity Study of SCH 720881
Trial: Mutagenicity Trial 1
Phase: Nonactivation

Strain: TA 97a

Dose Group	Treatment	Dose Level	Dose Units	Mean Cytotoxicity	Mean Revertants Per Plate	Mean Fold Increase	n	Plate Codes
01	dimethylsulfoxide (Solvent Control)	0.0	µg/plate	0	105	1	3	
02	SCH 720881 (Test Article)	78.0	µg/plate	0	100	0.95	3	
03	SCH 720881 (Test Article)	156.0	µg/plate	0	102	0.97	3	
04	SCH 720881 (Test Article)	313.0	µg/plate	0	90	0.86	3	
05	SCH 720881 (Test Article)	625.0	µg/plate	0	33	0.31	3	
06	SCH 720881 (Test Article)	1,250.0	µg/plate	0	1	0.01	3	
07	SCH 720881 (Test Article)	2,500.0	µg/plate	0	0	0	3	
08	SCH 720881 (Test Article)	5,000.0	µg/plate	0	0	0	3	
09	9-Aminoacridine (750µg/ml) (Positive Control)	75.0	µg/plate	0	885 *	8.43	3	

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* Meets or exceeds minimum fold increase; Negative Control Dose Group: 01

Plate Code: ct-contamination,hpt-heavy precipitation,mc-microcolonies,pt-precipitation,sp-severe polarity
Cytotoxicity to the Background Lawn: 0-none,1-slight,2-moderate,3-complete

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Study title: Chromosome Aberration Assay of SCH 720881 IN Human Peripheral Blood Lymphocytes

Study no.:	08102
Study report location:	EDR 4.2.3.7.5
Conducting laboratory and location:	Safety Evaluation Center Schering-Plough Research Institute Summit, NJ
Date of study initiation:	June 9, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 720881, 86558-067-13, 98.65%

Key Study Findings: Negative

Methods:

Cell line:	Human peripheral blood lymphocytes (HPBL)
Concentrations in definitive study:	Please see the table below
Basis of concentration selection:	Cytotoxicity
Negative control:	DMSO

Positive control: Please see the table below
Formulation/Vehicle: DMSO
Incubation & sampling time: -S9: 4 hr, 19 hr
+S9: 4 hr

The following table (from page 10 and 11 of the report) shows the study design.

Chromosome Aberration Study of SCH 720881 in Human Peripheral Blood Lymphocytes (SN 08102): **Study Design**		
4-Hour Exposure, Trial 1[a]		
Test/Control Article	Doses[b]	
	Nonactivation (S9-)[c]	Activation (S9+)[d]
Negative Control (Complete Medium)	100 µL/culture	100 µL/culture
Vehicle Control (DMSO)	100 µL/culture	100 µL/culture
Test Article (SCH 720881)	15, 30, 60, 80, 100, 150, 200 µg/mL	
Positive Control (Mitomycin C)	0.75, 1.0 µg/mL	NA
Positive Control (Cyclophosphamide)	NA	20, 25 µg/mL
19-Hour Exposure, Trial 1[a]		
Test/Control Article	Doses[b]	
	Nonactivation (S9-)[c]	
Negative Control (Complete Medium)	100 µL/culture	
Vehicle Control (DMSO)	100 µL/culture	
Test Article (SCH 720881)	3.75, 7.5, 15, 30, 60, 80, 100, 150, 200 µg/mL	
Positive Control (Mitomycin C)	0.2, 0.3 µg/mL	

NA = Not applicable

a: A single 3-arm trial was conducted.

b: 0.1 mL of test article, vehicle control or positive control article was added to duplicate cultures (0.6 mL heparinized blood in 8.4 mL of Complete Medium containing 0.2 mL of phytohemagglutinin-M) that had been initiated 48 hours prior to dosing.

c: Complete Medium (0.75 mL) was added to each culture tube directly after the addition of test article, vehicle control or positive control.

d: CORE/S9 Mix (0.75 mL) was added to each culture tube directly after addition of test article, vehicle control or positive control.

Chromosome Aberration Study of SCH 720881 in Human Peripheral Blood Lymphocytes (SN 08102):
Summary of Assay Schedule

Trial 1 Schedule (Hours)					
Test Condition	Test Article Added	Exposure Completed	Wash Completed	Colcemid® Added	Harvest Started[a]
-S9	0	4 (± 0.5)	5 (± 0.5)[b]	20 (± 0.5)	22 (± 1)
+S9	0	4 (± 0.5)	5 (± 0.5)[b]	20 (± 0.5)	22 (± 1)
-S9	0	19 (± 0.5)	20 (± 0.5)[c]		22 (± 1)

a. Cultures were centrifuged and the supernatant discarded. The cells were swollen with 75 mM KCl, fixed in methanol:glacial acetic acid (3:1, v/v), dropped onto glass slides, and dried. The slides were stained with 5% Giemsa in water and dried. After drying, those slides which would be analyzed for aberrations were mounted permanently.

b. Cultures were washed twice with Phosphate Buffered Saline Solution (PBS), Complete Medium was added and the cultures were re-incubated.

c. Cultures were washed twice with PBS, Complete Medium and Colcemid® were added, and the cultures were re-incubated.

Study Validity: The study met the criteria for a valid study.

Results: SCH 720881 did not induce chromosome aberrations in HPBL in the presence or absence of S9 under the conditions of this study. The following tables (from page 20-**) show the results.

Summary of Results — GeneTox 2.2
Study Number: 08102
Chromosome Aberration Study of SCH 720881 in Human Peripheral Blood Lymphocytes
Trial: 1A
Phase/Treatment Time/Harvest Time: S9-/~4 Hour/~22 Hour

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						Numbers and Percentages of Cells with Chromosome Aberrations									
								Chromatid Type		Chromosome Type				Totals	
Treatment	Dose Level	M.I.	% Change M.I.	Endo.	Poly.	# Cells Scored	Gaps	chtb	chte	chrb	chre	ace	mabs	Without Gaps	With Gaps
Untreated Control		4.2		0	0	100	0	0	0	0	0	0	0	0	0
Untreated Control		5.8		0	0	100	0	0	0	0	0	1	0	1	1
	%	-		0.0	0.0	-	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.5	0.5
	Total	5.0	-9	0	0	200	0	0	0	0	0	1	0	1	1
Vehicle Control	10 ul/mL	6.4		0	1	100	0	0	0	0	0	0	0	0	0
Vehicle Control	10 ul/mL	4.5		0	1	100	0	0	0	0	0	0	0	0	0
	%	-		0.0	1.0	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Total	5.5	0	0	2	200	0	0	0	0	0	0	0	0	0
Positive Control	0.75 ug/mL	2.6		0	0	25	2	5	3	3	1	2	0	9	10
Positive Control	0.75 ug/mL	2.0		0	0	25	1	5	6	0	0	0	0	10	11
	%	-		0.0	0.0	-	6.0	20.0	18.0	6.0	2.0	4.0	0.0	38.0	42.0
	Total	2.3	-58	0	0	50	3	10	9	3	1	2	0	19a	21a
SCH 720881	15 ug/mL	6.9		0	4	100	1	0	0	0	0	0	0	0	1
SCH 720881	15 ug/mL	7.7		0	0	100	2	1	1	0	2	0	0	3	5
	%	-		0.0	2.0	-	1.5	0.5	0.5	0.0	1.0	0.0	0.0	1.5	3.0
	Total	7.3	33	0	4	200	3	1	1	0	2	0	0	3	6
SCH 720881	30 ug/mL	8.3		0	4	100	0	0	1	0	0	1	0	2	2

a: Significantly greater than vehicle control ($p <= 0.01$)
b: Cochran-Armitage Trend Test ($p <= 0.01$) for dose levels as entered
Endo.=Endoreduplication Poly.=Polyploidy chtb=chromatid break chte=chromatid exchange chrb=chromosome break chre=chromosome exchange ace=acentric fragment mabs=> 4 aberrations
Vehicle Control = Dimethylsulfoxide Untreated Control = RPMI 1640 Positive Control = Mitomycin C - 75 ug/mL M.I. = Mitotic Index

Summary of Results GeneTox 2.2

Study Number: 08102

Chromosome Aberration Study of SCH 720881 in Human Peripheral Blood Lymphocytes

Trial: 1A

Phase/Treatment Time/Harvest Time: S9+/~4 Hour/~22 Hour

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						Numbers and Percentages of Cells with Chromosome Aberrations									
								Chromatid Type		Chromosome Type				Totals	
Treatment	Dose Level	M.I.	% Change M.I.	Endo.	Poly.	# Cells Scored	Gaps	chtb	chte	chrb	chre	ace	mabs	Without Gaps	With Gaps
Untreated Control		6.7		0	0	100	0	0	0	0	0	0	0	0	0
Untreated Control		6.7		0	3	100	0	1	0	0	0	0	0	1	1
	%	-		0.0	1.5	-	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.5	0.5
	Total	6.7	8	0	3	200	0	1	0	0	0	0	0	1	1
Vehicle Control	10 ul/mL	5.7		0	2	100	0	0	0	0	0	1	0	1	1
Vehicle Control	10 ul/mL	6.7		0	0	100	0	3	0	0	0	0	0	3	3
	%	-		0.0	1.0	-	0.0	1.5	0.0	0.0	0.0	0.5	0.0	2.0	2.0
	Total	6.2	0	0	2	200	0	3	0	0	0	1	0	4	4
Positive Control	20 ug/mL	2.3		0	0	25	0	5	3	0	0	0	0	7	7
Positive Control	20 ug/mL	4.0		0	0	25	1	3	0	0	0	3	0	6	7
	%	-		0.0	0.0	-	2.0	16.0	6.0	0.0	0.0	6.0	0.0	26.0	28.0
	Total	3.2	-48	0	0	50	1	8	3	0	0	3	0	13a	14a
SCH 720881	30 ug/mL	3.8		0	0	100	0	0	0	0	1	2	0	3	3
SCH 720881	30 ug/mL	4.4		0	0	100	0	0	0	0	0	0	0	0	0
	%	-		0.0	0.0	-	0.0	0.0	0.0	0.0	0.5	1.0	0.0	1.5	1.5
	Total	4.1	-34	0	0	200	0	0	0	0	1	2	0	3	3
SCH 720881	60 ug/mL	4.2		0	0	100	2	1	0	0	0	0	0	1	3

a: Significantly greater than vehicle control ($p <= 0.01$)

b: Cochran-Armitage Trend Test ($p <= 0.01$) for dose levels as entered

Endo.=Endoreduplication Poly.=Polyploidy chtb=chromatid break chte=chromatid exchange chrb=chromosome break chre=chromosome exchange ace=acentric fragment mabs=> 4 aberrations

Vehicle Control = Dimethylsulfoxide Untreated Control = RPMI 1640 Positive Control = Cyclophosphamide - 2.0 mg/mL M.I. = Mitotic Index

Summary of Results GeneTox 2.2

Study Number: 08102

Chromosome Aberration Study of SCH 720881 in Human Peripheral Blood Lymphocytes

Trial: 1A

Phase/Treatment Time/Harvest Time: S9-/~19 Hour/~22 Hour

SCHERING-PLOUGH RESEARCH INSTITUTE

						Numbers and Percentages of Cells with Chromosome Aberrations									
								Chromatid Type		Chromosome Type				Totals	
Treatment	Dose Level	M.I.	% Change M.I.	Endo.	Poly.	# Cells Scored	Gaps	chtb	chte	chrb	chre	ace	mabs	Without Gaps	With Gaps
Untreated Control		3.7		0	0	100	1	0	0	0	1	0	0	1	2
Untreated Control		4.0		0	0	100	0	0	0	0	0	1	1	1	1
	%	-		0.0	0.0	-	0.5	0.0	0.0	0.0	0.5	0.5	0.5	1.0	1.5
	Total	3.9	11	0	0	200	1	0	0	0	1	1	1	2	3
Vehicle Control	10 ul/mL	3.4		0	0	100	0	0	0	0	0	0	0	0	0
Vehicle Control	10 ul/mL	3.6		0	0	100	0	1	0	0	0	0	0	1	1
	%	-		0.0	0.0	-	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.5	0.5
	Total	3.5	0	0	0	200	0	1	0	0	0	0	0	1	1
Positive Control	0.2 ug/mL	2.3		0	0	25	1	2	4	0	0	1	0	7	8
Positive Control	0.2 ug/mL	2.0		0	1	25	5	1	2	1	0	0	0	4	9
	%	-		0.0	2.0	-	12.0	6.0	12.0	2.0	0.0	2.0	0.0	22.0	34.0
	Total	2.2	-37	0	1	50	6	3	6	1	0	1	0	11a	17a
SCH 720881	7.5 ug/mL	3.2		0	0	100	0	2	0	0	0	1	0	3	3
SCH 720881	7.5 ug/mL	4.0		0	0	100	0	0	0	0	0	0	0	0	0
	%	-		0.0	0.0	-	0.0	1.0	0.0	0.0	0.0	0.5	0.0	1.5	1.5
	Total	3.6	3	0	0	200	0	2	0	0	0	1	0	3	3
SCH 720881	15 ug/mL	4.1		0	0	100	0	0	0	0	0	0	0	0	0

a: Significantly greater than vehicle control ($p <= 0.01$)

b: Cochran-Armitage Trend Test ($p <= 0.01$) for dose levels as entered

Endo.=Endoreduplication Poly.=Polyploidy chtb=chromatid break chte=chromatid exchange chrb=chromosome break chre=chromosome exchange ace=acentric fragment mabs=> 4 aberrations

Vehicle Control = Dimethylsulfoxide Untreated Control = RPMI 1640 Positive Control = Mitomycin C - 20 ug/mL M.I. = Mitotic Index

Mitotic Index Assay of SCH 720881 in Human Peripheral Blood Lymphocytes (Study No. 08190)

Methods: This study was conducted as per the standard protocol for chromosome aberration assay except that cells were scored only for mitotic index, not chromosomal aberrations. Cells were exposed for approximately 4 hours in the presence of S9 followed by 19-hour recovery period in the absence of test article. Incubation time was 17 hours. Duplicate cultures were used for each test article dose or vehicle control. Dimethylsulfoxide (DMSO) was the vehicle control. Approximately one thousand (1000) cells were analyzed for mitotic index (% cells in mitosis) from the treated and vehicle control.

Results: SCH 720881 was cytotoxic at > 62.5 µg/mL in the absence of S9 and at > 125 µg/mL in the presence of S9. Complete reductions of mitotic indices were observed at > 125 µg/mL in the absence of S9 and at > 250 µg/mL in the presence of S9 in compared to the vehicle control. Overall, SCH 720881 was cytotoxic at > 62.5 µg/mL in the absence of S9 and at > 125 µg/mL in the presence of S9.

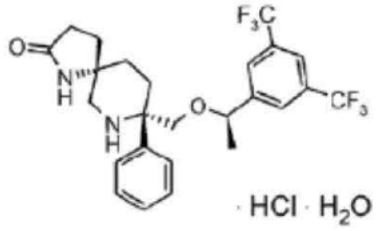
8 Carcinogenicity

Reviews of Study Nos. 03662 and 03361 are incorporated below from the pharmacology review of IND 72,754 dated May 9, 2012 (Tamal Chakraborti, Ph.D., DGIEP). Also incorporated below is Attachment-4 (ECAC Meeting Minutes dated May 2, 2012) to Dr. Chakraborti's review.

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET
Review of Mouse Carcinogenicity Study Results

P/T REVIEWER: Tamal K. Chakraborti, Ph.D.
DATE: May 1, 2012

IND: 72,754
DRUG CODE#: SCH 619734
CAS#: 552292-08-7
DIVISION: Division of Gastroenterology and Inborn Errors Products (DGIEP)
DRUG NAME: Rolapitant
CHEMICAL STRUCTURE:



SPONSOR: Tesaro, Inc.
LABORATORY: (b) (4)
CARCINOGENICITY STUDY REPORT DATE: March 16, 2010
THERAPEUTIC CATEGORY: Antiemetic for the treatment of chemotherapy induced nausea and vomiting (CINV)
PHARMACOLOGICAL CLASSIFICATION: Neurokinin-1 (NK-1) receptor antagonist
MUTAGENIC/GENOTOXIC: Rolapitant was negative in the Ames test, chromosome aberration assay in human blood lymphocytes and the *in vivo* mouse bone marrow micronucleus test.

MOUSE CARCINOGENICITY STUDY:

STUDY DURATION (weeks): 104
STUDY STARTING DATE: March 17, 2006
STUDY ENDING DATE: March 16, 2010
MOUSE STRAIN: Mouse (Crl:CD1[SD] [ICR] VAF/Plus®)
ROUTE: Oral (Gavage)
DOSING COMMENTS: Doses were selected based on the ECAC recommendations (ECAC meeting minutes dated March 22, 2006, Attachment-1).

NUMBER OF MICE:
- Control-1 (C1): 50/sex
- Control-2 (C2): 50/sex
- Low Dose (LD): 50/sex
- Middle Dose (MD): 50/sex
- High Dose (HD): 50/sex

MOUSE DOSE LEVELS:
- Low Dose: 25 mg/kg/day
- Middle Dose: 75 mg/kg/day
- High Dose: 150 mg/kg/day

BASIS FOR DOSES SELECTED: Maximum tolerated dose (MTD)

PRIOR FDA DOSE CONCURRENCE: Yes (ECAC meeting minutes dated March 22, 2006, Attachment-1).

MOUSE CARCINOGENICITY: Negative

MOUSE TUMOR FINDINGS: There were no significant SCH 619734-related tumor findings.

MOUSE STUDY COMMENTS: The dose selection was based on the MTD as per the ECAC recommendations. The study conduct was acceptable and valid.

CARCINOGENICITY:

Study title: 104-Week Carcinogenicity Study in CD-1 Mice

Key study findings:

- Male and female CD-1 mice were administered SCH 619734 at daily oral (gavage) doses of 0, 0, 25, 75, or 150 mg/kg/day for 104 weeks.
- There was no statistically significant effect on mortality in either sex.
- Body weight was decreased at the high dose in males when compared to control.
- Treatment-related non-neoplastic findings were observed in the stomach (hyperplasia and lymphoid cell aggregates) at the high dose in both sexes.
- There were no statistically significant drug-related neoplastic findings in male or female mice (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

Study number: (b) (4) -370058 (SN-03362)

Volume #, and page #: EDR submission dated May 26, 2011

Conducting laboratory and location: (b) (4)

Date of study initiation: March 17, 2006

Date of study completion: March 16, 2010

GLP compliance: A statement of compliance was included.

QA report: yes (X) no ( )

Drug, lot #, and % purity: SCH 619734, SZ-05-619734-TX-009 (March 31, 2006 through October 11, 2007 [Weeks 0 through 79, respectively]) and SZ-03-PHG-TX-001 (October 1 2 , 2007 through April 2, 2008 [Weeks 80 through 104, respectively]), 100.1-100.2%%

CAC concurrence: Yes (ExecCAC meeting minutes dated March 22, 2006, Attachment-1)

Study Type: 2-year bioassay

Species/strain: Mouse (Crl:CD1[SD] [ICR] VAF/Plus®)

Number/sex/group; age at start of study; body weight: 50/sex/group; 7 weeks old; Males: 25.6-35.7 g, Females: 20.0-28.2 g

Animal housing: Upon receipt, all animals were housed 2 or 3 per cage for approximately 3 days. Thereafter, all animals were housed individually in suspended, stainless steel cages in a separate room from animals of other studies.
Formulation/vehicle: 0.4% (w/v) aqueous methylcellulose, adjusted to pH 4.0

Drug stability/homogeneity: SCH 619734 in 0.4% (w/v) aqueous methylcellulose (adjusted to pH 4.0), at a concentration range of 0.1 to 200 mg/mL, was homogeneous, stable frozen and was found to be stable for at least 15 days when stored at controlled room temperature or refrigerated. Analytical assay results indicated that the average dosing concentrations used in this study were within current Standard Operating Procedure specifications (± 15%) for a dosing suspension.

Methods:

Doses: 25, 75 and 150 mg/kg/day

Basis of dose selection: MTD as per the ECAC recommendations

Restriction paradigm for dietary restriction studies: Not applicable

Route of administration: Oral gavage

Frequency of drug administration: Daily

Dual controls employed: Yes

Interim sacrifices: None

Study Design: The study design is shown in the table below (from page 26 of the study report).

A 104-Week Oral (Gavage) Carcinogenicity Study in Mice with SCH 619734 (SPRI 03862): **Study Design**						
Toxicology Groups						
Group	Test/Control Article	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Animals	
					Males	Females
1	Control (Methylcellulose)	0	5	0	50	50
2	Control (Methylcellulose)	0	5	0	50	50
3	Low-Dose (SCH 619734)	25	5	5	50	50
4	Mid-Dose (SCH 619734)	75	5	15	50	50
5	High-Dose (SCH 619734)	150	5	30	50	50
Toxicokinetic Groups [a]						
Group	Test/Control Article	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Animals	
					Males	Females
1A	Control (Methylcellulose)	0	5	0	20	20
3A	Low-Dose (SCH 619734)	25	5	5	20	20
4A	Mid-Dose (SCH 619734)	75	5	15	20	20
5A	High-Dose (SCH 619734)	150	5	30	20	20
a: Animals in these groups were designated for plasma concentration analysis only; animals were dosed daily for 27 or 167 days.						

Satellite group for toxicokinetics: Yes (shown in the above table).

Deviations from original study protocol: Protocol deviations did not adversely affect either the quality or integrity of the study or the interpretation of the results.

Statistical methods:

Survival Data:

Sponsor's analysis: Survival data were analyzed using the same statistical methodologies as discussed before.

FDA analysis: Survival data were analyzed by using similar methodologies as discussed before.

Tumor Data:

Sponsor's analysis: Tumor data from the mouse study were also analyzed using the same statistical methodologies as discussed before.

FDA Analysis: Tumor data were analyzed using similar methodologies as discussed before.

Observations and times:

Mortality: Twice daily

Clinical Signs: Weekly

Body weights: Weekly during Weeks 0 through 23, every 2 weeks during Weeks 24 through 35, and every 4 weeks thereafter.

Food consumption: Weekly during acclimation through 24 weeks of dosing, every 2 weeks during Weeks 24 through 35, and every 4 weeks thereafter.

Ophthalmoscopy: At pretest (Week -1) and during Weeks 51 and 103

Hematology: At necropsy.

Gross pathology: At necropsy

Histopathology: All tissues from all main study animals were examined. The following Table (from page 31 of the report) shows the list of tissues for histopathology.

Tissues Collected[a]	
Adrenal Glands (2)	Lymph Nodes (Mandibular and Mesenteric)
Aorta (Thoracic)	Mammary Gland[f]
Bone with Marrow - (Femur and Sternum)	Ovaries (2)
Bone Marrow Smear (Sternum)[b]	Pancreas
Brain (Cerebrum [2 levels] and Cerebellum with Pons/Medulla)	Peripheral Nerve (Sciatic)
Epididymides (2)[c]	Pituitary Gland
Eyes with Optic Nerves[d]	Prostate Gland
Gallbladder	Salivary Glands (Mandibular [2])
Gastrointestinal Tract	Seminal Vesicles (2)
Esophagus	Skeletal Muscle (Rectus femoris)
Stomach	Skin (Inguinal)
Duodenum	Spinal Cord (Thoracic and Lumbar)
Jejunum	Spleen
Ileum	Testes (2)[c]
Cecum	Thymus (If Present)
Colon	Thyroid Gland (Both Lobes with Parathyroids [2])[g]
Harderian Glands (2)	Tongue[e]
Head[e]	Trachea
Heart	Urinary Bladder
Kidneys (2)	Uterus with Cervix
Larynx/Pharynx	Vagina
Liver (Sections of 2 Lobes)	All Gross Findings (Including Masses)
Lungs (Including Bronchi, Fixed by Inflation with Fixative)	

a: Collected in 10% neutral buffered formalin unless otherwise indicated
b: Obtained at the scheduled necropsy and from animals euthanized *in extremis*, but not placed in formalin; not examined.
c: Placed in Bouin's solution
d: Placed in Davidson's solution
e: Collected but not processed
f: Examined histopathologically when present in routine section
g: Examined microscopically when in the plane of section and in all cases when a gross lesion was present

Toxicokinetics: Blood samples were collected from 3 toxicokinetic rats/sex/group (Groups 1A and 3A-5A) at each time point for plasma analysis for SCH 619734 and its metabolite, SCH 720881 (Week 23 only). Blood samples were obtained at 1, 2, and 4 hours postdose on Day 26 and Day 166 (Weeks 3 and 23, respectively).

Results:

Mortality: Survival data analysis showed 24%, 34%, 32%, 34%, and 40% survival of male mice and 46%, 40%, 52%, 36%, and 52% survival of female mice in control 1,

control 2, low, medium, and high dose groups, respectively. There was no statistically significant dose response relationship for the mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups compared to the combined control. The pairwise comparisons also did not show statistically significant differences in mortalities between the two controls in either sex.

The percent survival at Week 104 is shown in the following Table.

Treatment	Male	% Survival	Female	% Survival
Control 1	12/50	24%	23/50	46%
Control 2	17/50	34%	20/50	40%
25 mg/kg/day	16/50	32%	26/50	52%
50 mg/kg/day	17/50	34%	18/50	36%
100 mg/kg/day	20/50	40%	26/50	52%

The Kaplan-Myer survival curves for male and female animals are shown in Figure 2A and Figure 2B (from page 28 of FDA statistical review dated December 8, 2011), respectively.

Figure 2A: Kaplan-Meier Survival Functions for Male Mice

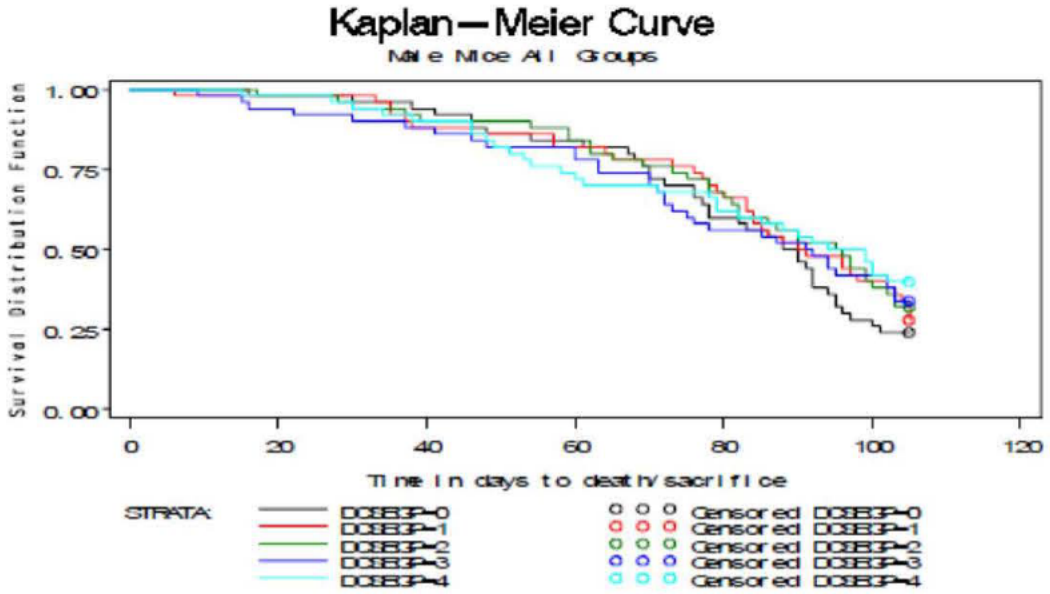
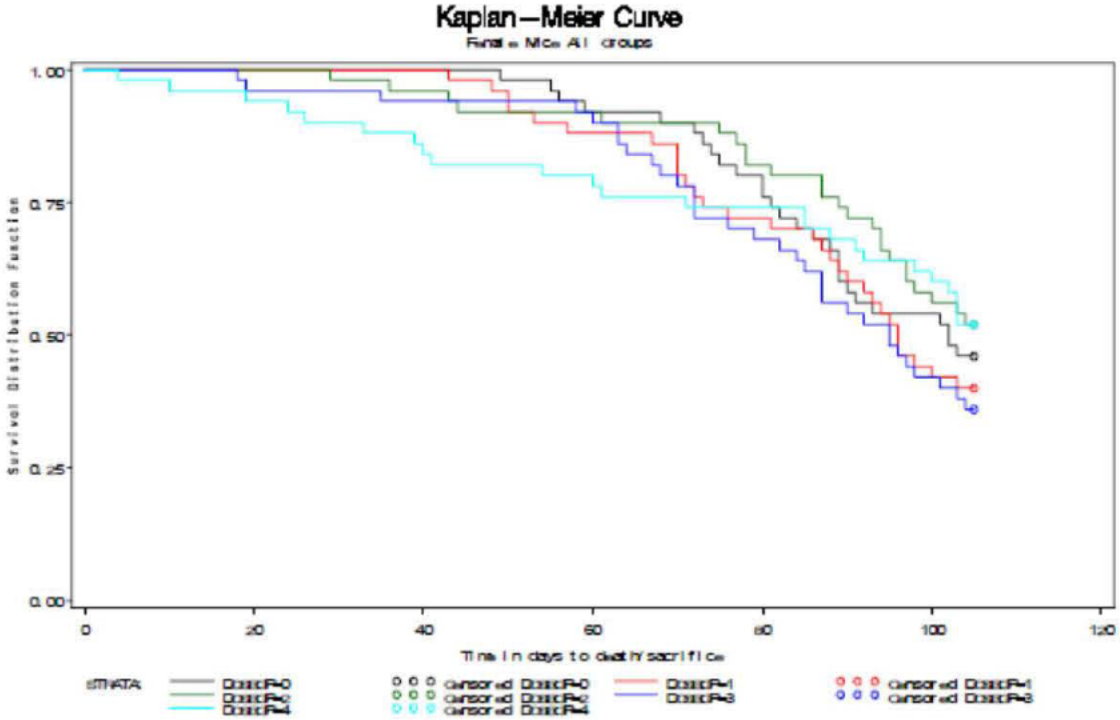


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



Clinical signs: There were no SCH 619734-related clinical observations.

Body weights: The mean initial (Week 0) and final (Week 104) body weights of control 1 (Group 1) males were 30.5 and 39.1 g, respectively. The mean initial and final body weights of control 1 (Group 1) females were 23.2 and 30.7 g, respectively. Treatment-related lower mean body weights were observed for 150 mg/kg/day group males. The following table shows the absolute bodyweights (g) and bodyweight gains (g) for males and females.

Male	1*	2*	3*	4*	5*
Wk 0	30.1	30.1	30.1	30.1	30.1
Wk 26	40.7	40.5	38.7	38.4	37.4
% of Control, Wk 26	100.00	99.51	95.09	94.35	91.89
ΔWk24-Wk0	10.6	10.4	8.6	8.3	7.3
BW Gain, % of Initial BW	35.22	34.55	28.57	27.57	24.25
BW Gain, % Of Control	100	98.11	81.13	78.30	68.87

Male	1	2	3	4	5
Wk 0	30.1	30.1	30.1	30.1	30.1

Wk 56	42.6	41.6	40.1	40.5	38.8
% of Control, Wk 56	100.00	97.65	94.13	95.07	91.08
ΔWk24-Wk0	12.5	11.5	10	10.4	8.7
BW Gain, % of Initial BW	41.53	38.21	33.22	34.55	28.90
BW Gain, % Of Control	100	92.00	80.00	83.20	69.60

Male	1	2	3	4	5
Wk 0	30.1	30.1	30.1	30.1	30.1
Wk 80	41.3	40.8	38.7	38.8	37.3
% of Control, Wk 80	100.00	98.79	93.70	93.95	90.31
ΔWk24-Wk0	11.2	10.7	8.6	8.7	7.2
BW Gain, % of Initial BW	37.21	35.55	28.57	28.90	23.92
BW Gain, % Of Control	100	95.54	76.79	77.68	64.29

Male	1	2	3	4	5
Wk 0	30.1	30.1	30.1	30.1	30.1
Wk 104	39.1	39.5	37.6	37.7	36.7
% of Control, Wk 104	100.00	101.02	96.16	96.42	93.86
ΔWk24-Wk0	9	9.4	7.5	7.6	6.6
BW Gain, % of Initial BW	29.90	31.23	24.92	25.25	21.93
BW Gain, % Of Control	100	104.44	83.33	84.44	73.33

Female	**1***	**2***	**3***	**4***	**5***
Wk 0	23.4	23.1	23.1	23.1	23.2
Wk 26	30.8	30.4	29.8	29.1	29.4
% of Control, Wk 24	100.00	98.70	96.75	94.48	95.45
ΔWk24-Wk0	7.4	7.3	6.7	6	6.2
BW Gain, % of Initial BW	31.62	31.60	29.00	25.97	26.72
BW Gain, % Of Control	100	99.93	91.72	82.13	84.51

Female	1	2	3	4	5
Wk 0	23.4	23.1	23.1	23.1	23.2
Wk 56	32.2	33.1	31.6	32.1	31.3
% of Control, Wk 56	100.00	102.80	98.14	99.69	97.20
ΔWk24-Wk0	8.8	10	8.5	9	8.1
BW Gain, % of Initial BW	37.61	43.29	36.80	38.96	34.91
BW Gain, % Of Control	100	115.11	97.85	103.60	92.84

Female	1	2	3	4	5
Wk 0	23.4	23.1	23.1	23.1	23.2
Wk 80	33.1	33.9	33.1	32.2	32.1
% of Control, Wk 80	100.00	102.42	100.00	97.28	96.98
ΔWk24-Wk0	9.7	10.8	10	9.1	8.9
BW Gain, % of Initial BW	41.45	46.75	43.29	39.39	38.36
BW Gain, % Of Control	100	112.79	104.43	95.03	92.54

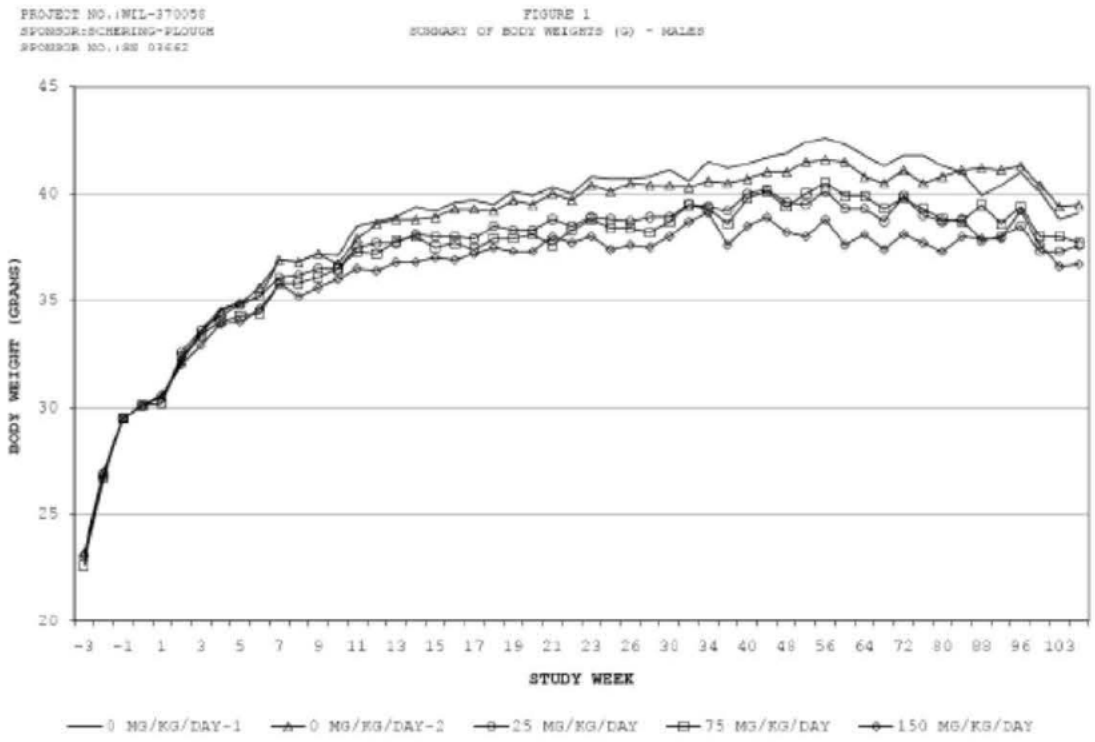
Female	1	2	3	4	5
Wk 0	23.4	23.1	23.1	23.1	23.2
Wk 104	30.7	31.7	33	30.7	30.6

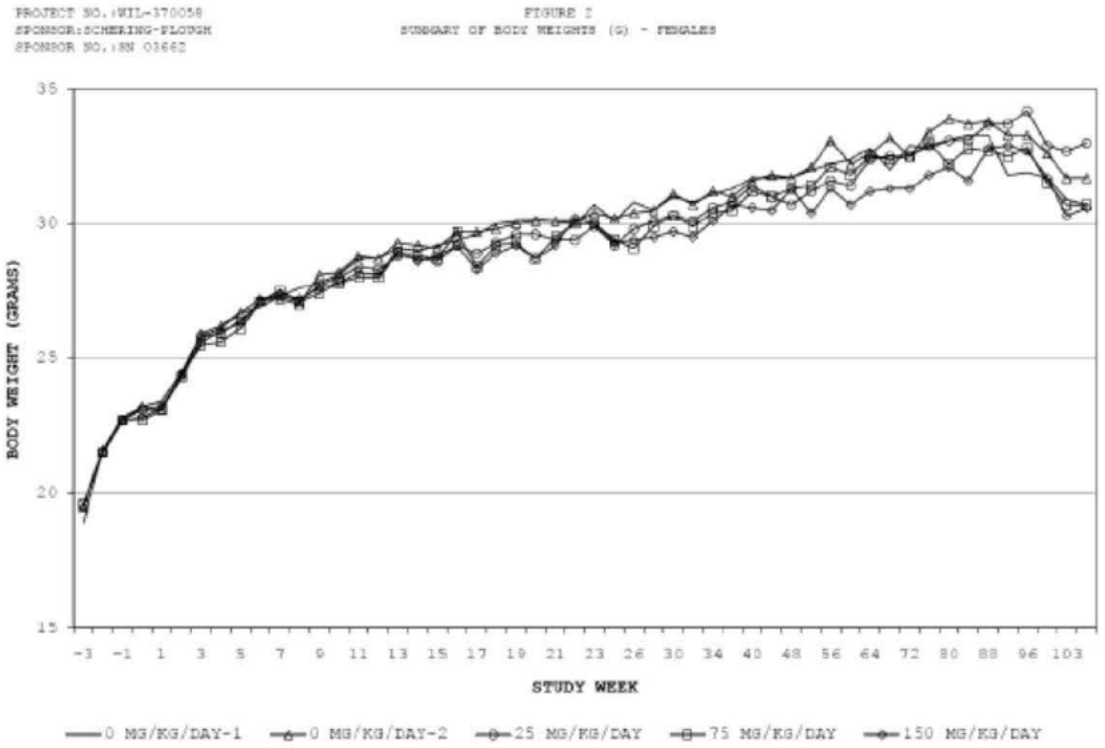
% of Control, Wk 104	100.00	103.26	107.49	100.00	99.67
ΔWk24-Wk0	7.3	8.6	9.9	7.6	7.4
BW Gain, % of Initial BW	31.20	37.23	42.86	32.90	31.90
BW Gain, % Of Control	100	119.34	137.38	105.46	102.24

*GROUP:

1. Control 1
2. Control 2
3. 25 mg/kg/day
4. 75 mg/kg/day
5. 150 mg/kg/day

The following figures (from page 3484 and 3885 of the study report) show the growth curves for males and females.





Food consumption: The mean initial (Week 0) and final (Week 104) food consumption for control (Group 1) males was 6.5 and 5.1 g/animal/day, respectively. The mean initial (Week 0) and final (Week 104) food consumption for control (Group 1) females was 5.6 and 4.6 g/animal/day, respectively. There was no significant effect of treatment on food consumption.

Ophthalmoscopy: There were no significant treatment-related effects.

Gross pathology: There were no significant treatment-related findings.

Histopathology:

Non-neoplastic: SCH 619734-related non-neoplastic findings were observed in the glandular stomach (increased incidence and severity of lymphoid aggregates and mucosal hyperplasia at the high dose in both sexes). The following table (from page 3704 of the study report) shows the non-neoplastic findings.

Principal Non-Neoplastic Findings – Stomach: All Animals										
	Males					Females				
Dose (mg/kg/day):	0	0	25	75	150	0	0	25	75	150
Organ/Finding/Severity	Incidence[a]									
Stomach	(49)[b]	(50)	(50)	(48)	(50)	(50)	(50)	(50)	(48)	(49)
-aggregate(s), lymphoid (total No. affected)	8	4	5	2	7	13	7	7	9	19*
minimal	8	2	3	2	7	12	7	7	8	12
mild		1	2						1	7
moderate		1								
severe						1				
- hyperplasia, glandular stomach (total No. affected)	12	9	12	14	22*	11	14	14	16	29*
minimal	6	5	6	10	14	8	10	13	8	12
mild	4	2	3	3	7	3	4	1	7	11
moderate	2	1	3	1	1				1	6
severe		1								

* = Test article-related

a: Incidence = Number affected

b: ( ) = Total number examined microscopically (survivors and decedents).

Principal Non-Neoplastic Findings - Stomach: Males										
	Survivors					Decedents				
Dose (mg/kg/day):	0	0	25	75	150	0	0	25	75	150
Organ/Finding/Severity	Incidence[a]									
Stomach	(12)[b]	(14)	(16)	(17)	(20)	(37)	(36)	(34)	(31)	(30)
- hyperplasia, glandular stomach (total No. affected)	8	3	11	8	15*	4	6	1	6	7*
minimal	2		5	4	10	4	5	1	6	4
mild	4	2	3	3	4					3
moderate	2		3	1	1		1			
severe		1								
* = Test article-related a: Incidence = Number affected. b: ( ) = Total number examined microscopically.										

Principal Non-Neoplastic Findings - Stomach: Females										
	Survivors					Decedents				
Dose (mg/kg/day):	0	0	25	75	150	0	0	25	75	150
Organ/Finding/Severity	Incidence[a]									
Stomach	(23)[b]	(20)	(26)	(18)	(25)	(27)	(30)	(24)	(30)	(23)
-aggregate(s), lymphoid (total No. affected)	9	3	6	3	15*	4	4	1	6	4
minimal	8	3	6	3	10	4	4	1	5	2
mild					5				1	2
severe	1									
- hyperplasia, glandular stomach (total No. affected)	7	11	12	9	21*	4	3	2	7	8
minimal	6	7	11	4	7	2	3	2	4	5
mild	1	4	1	4	9	2			3	2
moderate				1	5					1
* = Test article-related a: Incidence = Number affected. b: ( ) = Total number examined microscopically.										

Neoplastic: There were no statistically significant drug-related neoplastic findings in male or female mice (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

Toxicokinetics: Mean plasma concentrations of SCH 619734 and SCH 72088 (metabolite) are shown in the following Tables (from page 3668 and 3669 of the report).

Table 9 Mean Plasma Concentrations of SCH 619734 in Mouse Plasma Samples

Dose Group	Study Day	Gender	1 hr Post-Dose			2 hr Post-Dose			4 hr Post-Dose		
			Mean[a] (ng/mL)	SD	%CV	Mean[a] (ng/mL)	SD	%CV	Mean[a] (ng/mL)	SD	%CV
0 mg/kg	26	Male	0.00	NC[b]	NC	0.00[c]	NC	NC	0.00	NC	NC
		Female	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
		Overall	0.00	NC	NC	0.00[d]	NC	NC	0.00	NC	NC
	166	Male	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
		Female	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
		Overall	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
25 mg/kg	26	Male	4290	1200	28.0	3580	397	11.1	2230	562	25.2
		Female	2580[c]	35.4	1.4	2610	809	31.0	1760[c]	170	9.7
		Overall	3600[d]	1270	35.3	3100	778	25.1	2040[d]	482	23.6
	166	Male	2280	240	10.5	1830	566	30.9	1860[a]	177	9.5
		Female	1840	487	26.5	2180	282	12.9	1430	113	7.9
		Overall	2060	420	20.4	2010	443	22.0	1600[d]	261	16.3
75 mg/kg	26	Male	7690	743	9.7	7100	1560	22.0	5030	488	9.7
		Female	5400	2140	39.6	4980	852	17.1	4320	733	17.0
		Overall	6540	1900	29.1	6040	1620	26.8	4670	678	14.5
	166	Male	5030	2590	51.5	5370	1360	25.3	3570	634	17.8
		Female	4870	1100	22.6	4900	1010	20.6	3450	531	15.4
		Overall	4950	1780	36.0	5130	1100	21.4	3510	527	15.0
150 mg/kg	26	Male	10300	2640	25.6	8240	496	6.0	6950	1330	19.1
		Female	9560	308	3.2	7030	605	8.6	6170	1310	21.2
		Overall	9940	1730	17.4	7640	826	10.8	6560	1250	19.1
	166	Male	8480	1080	12.7	6290	1250	19.9	5600	932	16.6
		Female	9600	2510	26.1	5350	780	14.6	5850	2020	34.5
		Overall	9040	1840	20.4	5820	1060	18.2	5730	1410	24.6

a: n = 3 male or female mice and n = 6 for overall (males and females combined), except as noted.
b: Not calculated (NC) when mean is zero.
c: n = 2
d: n = 5

Table 10 Mean Plasma Concentrations of SCH 720981 in Mouse Plasma Samples

Dose Group	Study Day	Gender	1 hr Post-Dose			2 hr Post-Dose			4 hr Post-Dose		
			Mean[a] (ng/mL)	SD	%CV	Mean[a] (ng/mL)	SD	%CV	Mean[a] (ng/mL)	SD	%CV
0 mg/kg	166	Male	0.00	NC[b]	NC	0.00	NC	NC	0.00	NC	NC
		Female	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
		Overall	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
25 mg/kg	166	Male	88.1	15.8	17.9	91.5	43.8	47.9	135[c]	13.4	9.9
		Female	74.9	16.2	21.6	127	31.8	25.0	114	10.1	8.9
		Overall	81.5	16.0	19.6	109	39.4	36.1	122[d]	15.0	12.3
75 mg/kg	166	Male	239	112	46.9	384	119	31.0	313	27.7	8.8
		Female	252	49.2	19.5	295	32.2	10.9	294	9.64	3.3
		Overall	246	77.9	31.7	340	92.1	27.1	304	21.4	7.0
150 mg/kg	166	Male	498	23.5	4.7	493	55.8	11.3	546	123	22.5
		Female	530	69.1	13.0	403	56.5	14.0	533	168	31.5
		Overall	514	49.4	9.6	448	70.4	15.7	540	132	24.4

a: n = 3 male or female mice and n = 6 for overall (males and females combined), except as noted.
b: Not calculated (NC) when mean is zero.
c: n = 2
d: n = 5

Summary of individual study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model: The study was considered adequate. The doses were selected as per the ECAC recommendations and were based on the MTD.

Evaluation of tumor findings: There were no statistically significant drug-related neoplastic findings in male or female mice (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

Carcinogenicity Summary: In the 104-week oral (gavage) carcinogenicity study in CD-1 mice, animals (n = 50/sex/dose) were treated at 0, 0, 25, 75, and 150 mg/kg/day in 0.5% carboxymethylcellulose. The dose selection was based on the MTD as per the ECAC recommendations. There was no significant treatment-related effect on mortality in either sex. Treatment-related non-neoplastic findings were observed in the glandular stomach (increased incidence and severity of lymphoid aggregates and mucosal hyperplasia) at the high dose in both sexes. There were no statistically significant drug-related neoplastic findings in male or female mice (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

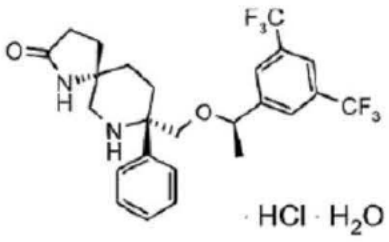
Carcinogenicity conclusions:

1. The study was considered adequate.
2. There were no statistically significant drug-related neoplastic findings in male or female mice (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET
Review of Rat Carcinogenicity Study Results

P/T REVIEWER: Tamal K. Chakraborti, Ph.D.
DATE: May 1, 2012

IND: 72,754
DRUG CODE#: SCH 619734
CAS#: 552292-08-7
DIVISION: Division of Gastroenterology and Inborn Errors Products (DGIEP)
DRUG NAME: Rolapitant
CHEMICAL STRUCTURE:



SPONSOR: Tesaro, Inc.
LABORATORY: (b) (4)
CARCINOGENICITY STUDY REPORT DATE: March 11, 2010
THERAPEUTIC CATEGORY: Antiemetic for the treatment of chemotherapy induced nausea and vomiting (CINV)
PHARMACOLOGICAL CLASSIFICATION: Neurokinin-1 (NK-1) receptor antagonist
MUTAGENIC/GENOTOXIC: Rolapitant was negative in the Ames test, chromosome aberration assay in human blood lymphocytes and the *in vivo* mouse bone marrow micronucleus test.

RAT CARCINOGENICITY STUDY:

STUDY DURATION (weeks): 104
STUDY STARTING DATE: February 27, 2007
STUDY ENDING DATE: March 11, 2010
RAT STRAIN: Rat (Crl:CD[SD] VAF/Plus®)
ROUTE: Oral (Gavage)
DOSING COMMENTS: Doses were selected based on the ECAC recommendations (ECAC meeting minutes dated March 22, 2006, Attachment-1).

NUMBER OF RATS:

- Control-1 (C1): 50/sex
- Control-2 (C2): 50/sex
- Low Dose (LD): 50/sex
- Middle Dose (MD): 50/sex
- High Dose-1 (HD1): 50/sex
- High Dose-2 (HD2)*: 50 males

RAT DOSE LEVELS:

- Low Dose: 5/25* mg/kg/day
- Middle Dose: 25/50* mg/kg/day
- High Dose-1: 75/100* mg/kg/day
- High Dose-2: 250 mg/kg/day

*: On study Days 0 through 10, rats in the 25, 50, and 100 mg/kg dose groups received 5, 25, and 75 mg/kg, respectively. An additional group of male rats was administered 250 mg/kg daily for 9 days.

BASIS FOR DOSES SELECTED: Maximum tolerated dose (MTD)

PRIOR FDA DOSE CONCURRENCE: Yes (ECAC meeting minutes dated March 22, 2006, Attachment-1).

RAT CARCINOGENICITY: Negative (Exec CAC meeting minutes dated May 2, 2012, Attachment-4)

RAT TUMOR FINDINGS: There was a higher incidence of benign pheochromocytomas in the adrenal glands of males at 50 and 100 mg/kg/day and a higher incidence of follicular cell adenomas in the thyroid glands of males and females at 100 mg/kg/day, as well as a higher incidence of follicular cell carcinomas in the thyroid glands of males at 100 mg/kg/day. However, tumor data analyses did not show a statistically significant dose response (trend test) relationship among the treated groups, or higher tumor rates in the treated groups compared to the combined control for any of the tumor types in either sex. Overall, there were no statistically significant drug-related neoplastic findings in male or female rats (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

RAT STUDY COMMENTS: The high dose selection was based on the MTD as per the ECAC recommendations. The study conduct was considered adequate. The tumor incidences in the adrenal and thyroid glands did not appear to be treatment-related in the absence of a significant trend. Overall, there were no statistically significant drug-related neoplastic findings in male or female rats (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

Study number: (b) (4) 370057 (SN-03361)

Volume #, and page #: EDR submission dated May 26, 2011

Conducting laboratory and location: (b) (4)

Date of study initiation: March 16, 2006

GLP compliance: A statement of compliance was included.

QA report: yes (X) no ( )

Drug, lot #, and % purity: SCH 619734, SZ-05-619734-TX-009 (Weeks 0 through 81) SZ-05-619734-TX-010 (Weeks 82 through 99) SZ-03-PHG-TX-001 (Weeks 100 through 104), 100.2%

CAC concurrence: Yes (ExecCAC meeting minutes dated March 22, 2006, Attachment-1)

Study Type: 2-year bioassay

Species/strain: Rats/Sprague Dawley (SD)

Number/sex/group; age at start of study; body weight: 50/sex/group; 6-7 weeks old; Males: 172-232 g, Females: 130-185 g

Animal housing: Upon receipt, all animals were housed 2 or 3 per cage for approximately 3 days. Thereafter, all animals were housed individually in suspended, stainless steel cages in a separate room from animals of other studies.

Formulation/vehicle: 0.4% (w/v) aqueous methylcellulose, adjusted to pH 4.0

Drug stability/homogeneity: SCH 619734 in 0.4% (w/v) aqueous methylcellulose (adjusted to pH 4.0), at a concentration range of 0.1 to 200 mg/mL, was homogeneous, stable frozen and was found to be stable for at least 15 days when stored at controlled room temperature or refrigerated. Analytical assay results indicated that the average dosing concentrations used in this study were within current Standard Operating Procedure (SOP) specifications (± 15%) for a dosing suspension.

Methods:

Doses: 25, 50 and 100 mg/kg/day

Basis of dose selection: MTD as per the ECAC recommendations

Restriction paradigm for dietary restriction studies: Not applicable

Deviations from original study protocol: Protocol deviations did not adversely affect either the quality or integrity of the study or the interpretation of the results.

Statistical methods:

Survival Data: The survival data were analyzed by the Kaplan-Meier product limit method (FDA review attached). The dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test.

Tumor Data:

Sponsor's analysis: Dose-related positive trends in tumor incidence rates were evaluated using the Peto Mortality-Prevalence method. To correct for mortality differences while analyzing incidental tumors, the study period was partitioned into the following strata: 1- 365 days, 366-546 days, 547-728 days, and terminal sacrifice. These intervals correspond to approximately Weeks 1-52, 53-78, 79-104 and terminal sacrifice, respectively. Data for male and female animals were analyzed separately. Within each gender, the two control groups were combined for all analyses involving tumor data. The significance level was set at 0.005 for common tumors and 0.025 for rare tumors. All analyses were carried out using SAS (version 9.1).

FDA analysis: The tumor data were analyzed for positive dose response relationships and pairwise comparisons of combined control with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

Observations and times:

Mortality: Twice daily

Clinical Signs: Weekly

Body weights: Weekly during Weeks 0 through 23, every 2 weeks during Weeks 24 through 35, and every 4 weeks thereafter.

Food consumption: Weekly during acclimation through 24 weeks of dosing, every 2 weeks during Weeks 24 through 35, and every 4 weeks thereafter.

Ophthalmoscopy: At pretest (Week -1) and during Weeks 51 and 103

Hematology: At necropsy.

Gross pathology: At necropsy

Histopathology: All tissues from all main study animals were examined. The following table (from page 36 of the report) shows the list of tissues for histopathology.

Tissues Collected[a]	
Adrenal Glands (2)	Lymph Nodes (Mandibular and Mesenteric)
Aorta (Thoracic)	Mammary Gland[f]
Bone with marrow - (Femur and Sternum)	Ovaries (2)
Bone Marrow Smear (Sternum)[b]	Pancreas
Brain (Cerebrum [2 levels] and Cerebellum with Pons/Medulla)	Peripheral Nerve (Sciatic)
Epididymides (2)[c]	Pituitary Gland
Eyes with Optic Nerves[d]	Prostate Gland
Gastrointestinal Tract	Salivary Glands (Mandibular [2])
Esophagus	Seminal Vesicles (2)
Stomach	Skeletal Muscle (Rectus femoris)
Duodenum	Skin (Inguinal)
Jejunum	Spinal Cord (Thoracic and Lumbar)
Ileum	Spleen
Cecum	Testes (2)[c]
Colon	Thymus (If Present)
Rectum	Thyroid Gland (Both Lobes with Parathyroids [2])[g]
Harderian Glands (2)	Tongue[e]
Head[e]	Trachea
Heart	Urinary Bladder
Kidneys (2)	Uterus with Cervix
Larynx/Pharynx	Vagina
Liver (Sections of 2 Lobes)	All Gross Findings (Including Masses)
Lungs (Including Bronchi, Fixed by Inflation with Fixative)	

a: Collected in 10% neutral buffered formalin unless otherwise indicated
b: Obtained at the scheduled necropsy and from animals euthanized *in extremis*, but not placed in formalin; not examined.
c: Placed in Bouin's solution
d: Placed in Davidson's solution; left eye and optic nerve of male No. 3593 (Group 5) removed surgically, retained, and processed with other protocol-specified tissues collected at the time of necropsy.
e: Collected but not processed
f: Examined histopathologically when present in routine section
g: Examined microscopically when in the plane of section and in all cases when a gross lesion was present

Toxicokinetics: Blood samples were collected from 3 toxicokinetic rats/sex/group (Groups 1A and 3A-5A) at each time point for plasma analysis for SCH 619734 and its metabolite, SCH 720881 (Week 23 only). Blood samples were obtained at 1, 4, and 6 hours postdose on Day 27 and Day 166.

Route of administration: Oral gavage

Frequency of drug administration: Once daily

Dual controls employed: Yes

Interim sacrifices: None

Study Design: The study design is shown in the table below (from page 31 of the study report).

A 104-Week Oral (Gavage) Carcinogenicity Study in Rats with SCH 619734 (SPRI 03661): **Study Design**

Toxicology Groups						
Group	Test/Control Article	No. of Rats/Sex	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Duration of Dosing (Days)
1	Control (Methylcellulose)	50	0	5	0	728-734
2	Control (Methylcellulose)	50	0	5	0	728-734
3	Low-Dose (SCH 619734)	50	5/25 [a]	5	1/5 [a]	728-734
4	Mid-Dose (SCH 619734)	50	25/50 [a]	5	5/10 [a]	728-734
5	High-Dose (SCH 619734)	50	75/100 [a]	5	15/20 [a]	728-734
6 [b]	High-Dose (SCH 619734)	50	250	5	50	9
Toxicokinetic Groups [c]						
Group	Test/Control Article	No. of Rats/Sex	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Duration of Dosing (Days)
1A	Control (Methylcellulose)	10	0	5	0	167
3A	Low-Dose (SCH 619734)	10	5/25 [a]	5	1/5 [a]	167
4A	Mid-Dose (SCH 619734)	10	25/50 [a]	5	5/10 [a]	167
5A	High-Dose (SCH 619734)	10	75/100 [a]	5	15/20 [a]	167
6A [b]	High-Dose (SCH 619734)	10 (males)	250	5	50	9

a: Dose levels were increased on March 27, 2006 (Day 11). All data and discussion are presented for dose levels of 25, 50, and 100 mg/kg for Groups 3, 4, and 5 and 3A, 4A, and 5A, respectively.

b: Dosing initiated on April 17, 2006 and was discontinued on April 25, 2006; surviving animals were euthanized and discarded.

c: Animals in these groups were designated for plasma concentration analysis only.

Satellite group for toxicokinetics: Yes (shown in the above table).

CARCINOGENICITY:

Study title: 104-Week Carcinogenicity Study in Sprague Dawley Rats

Key study findings:

- Male and female rats were administered SCH 619734 at daily oral (gavage) doses of 0, 0, 25, 50, or 100 mg/kg. On study Days 0 through 10, rats in the 25, 50, and 100 mg/kg dose groups received doses of 5, 25, and 75 mg/kg, respectively. An additional group of male rats was administered 250 mg/kg daily for 9 days.
- Mortality was observed at 250 mg/kg/day and the group was terminated on Day 9 due to mortality and adverse clinical signs.
- The survival data showed 28%, 38%, 38%, 52%, and 46% survival of male rats and 34%, 48%, 72%, 78%, 88% survival of female rats in control 1, control 2, low, medium, and high dose groups, respectively. There was no statistically significant positive dose response relationship for mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups compared to the combined control in either sex. There was no statistically significant difference in mortalities between the two controls in either sex.
- Clinical signs included wet and/or dry, clear and/or red material around the mouth at low dose.
- Body weight was decreased at Week 104 at 50 and 100 mg/kg/day in both sexes when compared to control.
- Macroscopic findings included masses in the thyroid gland in one 50 mg/kg/day male and in two 100 mg/kg/day males.
- Although no statistical significance was observed, a higher incidence of benign pheochromocytomas was observed in the adrenal glands of males at 50 and 100 mg/kg/day and a higher incidence of follicular cell adenomas was seen in the thyroid glands of 100 mg/kg/day in males and females, as well as a higher incidence of follicular cell carcinomas in the thyroid glands at 100 mg/kg/day in males. These tumor findings did not appear to be treatment-related in the absence of any statistical significance.
- Treatment-related non-neoplastic findings were observed in the adrenal glands of males at 100 mg/kg/day and in the liver of both sexes at all doses. Cystic cortical degeneration was seen in the adrenal glands of males at 100 mg/kg/day. Findings in the liver included multinucleated hepatocytes in both sexes at 50 and 100 mg/kg/day, foci of cellular alteration, eosinophilic cell in females at all doses, foci of cellular alteration, basophilic cell in males at all doses and centrilobular hypertrophy in both sexes at all doses. However, these non-neoplastic findings in the liver were not accompanied by higher incidences of liver tumors.
- Overall, there were no statistically significant drug-related neoplastic findings in male or female rats (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

Results:

Mortality: Seven male animals were found dead and two animals were euthanized *in extremis* from study Day 5 to study Day 8 in the 250 mg/kg/day group. All remaining animals in this group were euthanized and discarded on study Day 9 due to mortality and adverse clinical signs (hypoactivity, impaired equilibrium, intermittent tremors, dermal atonia, thin, and body cool to touch). The survival data showed 28%, 38%, 38%, 52%, and 46% survival of male rats and 34%, 48%, 72%, 78%, 88% survival of female rats in control 1, control 2, low, medium, and high dose groups, respectively. There was no statistically significant positive dose response relationship in mortality across treatment groups in either sex. The pairwise comparisons also did not show statistically significant increased mortality in any of the treated groups compared to the combined control in either sex. The pairwise comparisons did not show statistically significant difference in mortalities between the two controls in either sex.

The percent survival is shown in the following table.

Treatment	Male	% Survival	Female	% Survival
Control 1	14/50	28%	17/50	34%
Control 2	19/50	38%	24/50	48%
25 mg/kg/day	19/50	38%	36/50	72%
50 mg/kg/day	26/50	52%	39/50	78%
100 mg/kg/day	23/50	46%	44/50	88%

The Kaplan-Meier curves for survival rates are shown (from page 28 and 29 of the FDA statistical review dated December 8, 2011) in Figures 1A and 1B for male and female rats, respectively.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

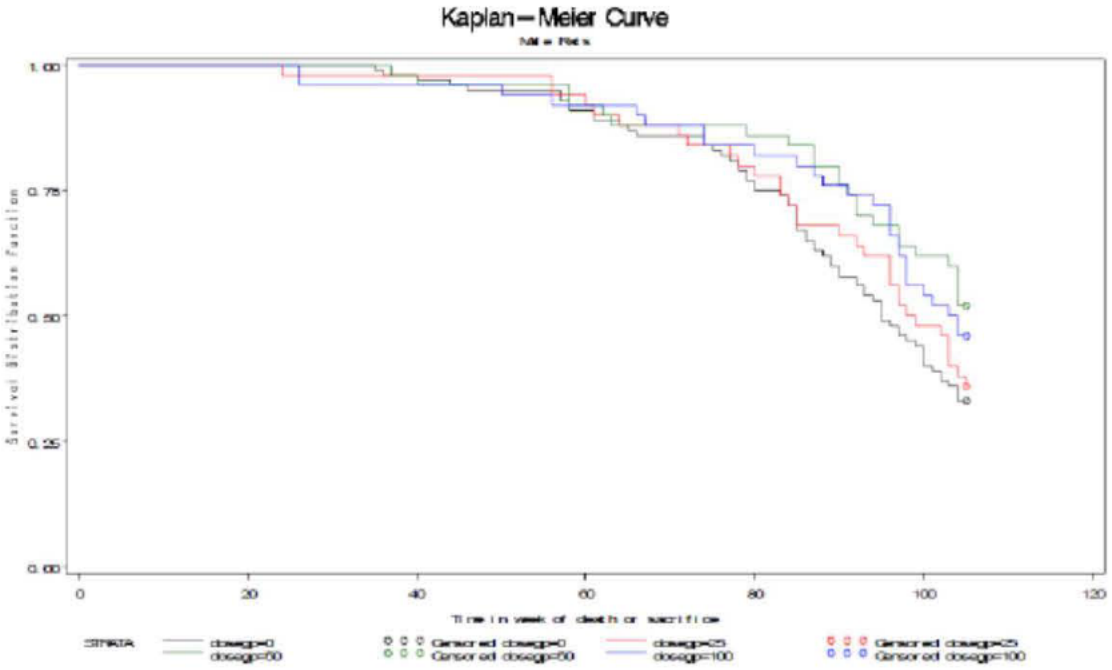
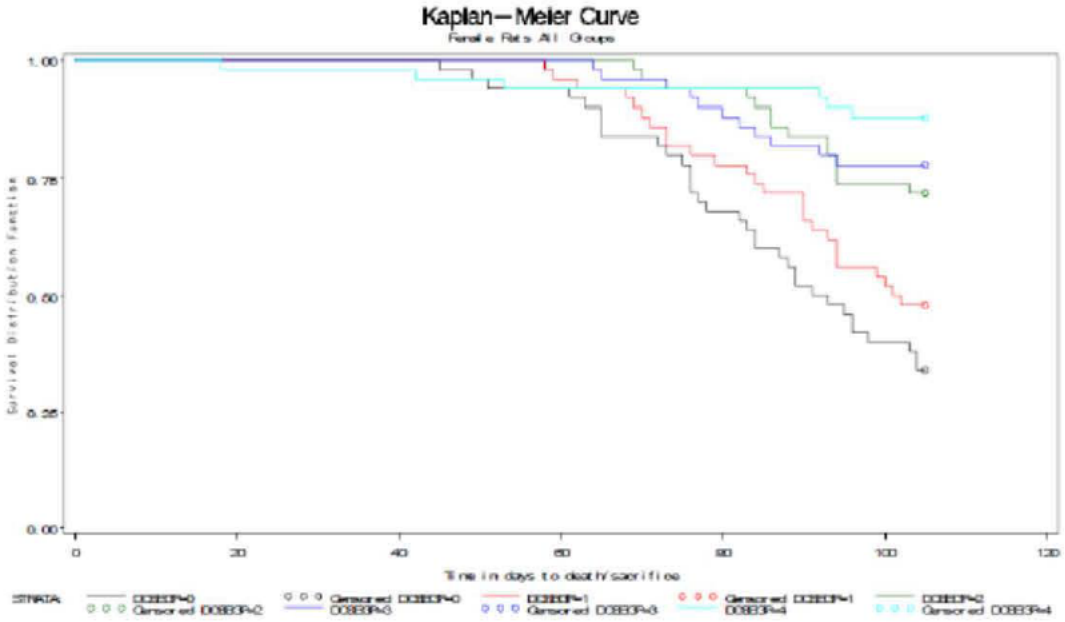


Figure 1B: Kaplan-Meier Survival Functions for Female Rats



Clinical signs: SCH 619734-related clinical observations of wet and/or dry, clear and/or red material around the mouth were noted in the 25 mg/kg/day group males and 50 and 100 mg/kg/day group males and females.

Body weights: The mean initial (Week 0) and final (Week 104) body weights of control 1 (Group 1) males were 203.0 and 690.0 g, respectively. The mean initial and final weights of control 1 (Group 1) females were 153.0 and 450.0 g, respectively. Lower mean body weights and cumulative body weight gains were noted at study Week 104 in the 50 and 100 mg/kg/day SCH 619734-dosed males and females. In males, final bodyweights were 99.5%, 92.5%, and 87.3% of control at 25, 50 and 100 mg/kg/day, respectively. In females, final body weights were 93.5%, 90.2% and 74.0% of control at 25, 50 and 100 mg/kg/day, respectively. The following table shows the absolute bodyweights (g) and bodyweight gains (g) for males and females.

Male	**1***	**2***	**3***	**4***
Wk 0	203	202	201	201
Wk 25	610	632	614	599
% of Control, Wk 25	100.00	103.61	100.66	98.20
ΔWk25-Wk0	407	430	413	398
BW Gain, % of Initial BW	200.49	212.87	205.47	198.01
BW Gain, % Of Control	100	106.17	102.48	98.76

Male	1	2	3	4
Wk 0	203	202	201	201
Wk 55	724	728	702	681
% of Control, Wk 55	100.00	100.55	96.96	94.06
ΔWk24-Wk0	521	526	501	480
BW Gain, % of Initial BW	256.65	260.40	249.25	238.81
BW Gain, % Of Control	100	101.46	97.12	93.05

Male	1	2	3	4
Wk 0	203	202	201	201
Wk 79	751	740	706	695
% of Control, Wk 79	100.00	98.54	94.01	92.54
ΔWk24-Wk0	548	538	505	494
BW Gain, % of Initial BW	269.95	266.34	251.24	245.77
BW Gain, % Of Control	100	98.66	93.07	91.04

Male	1	2	3	4
Wk 0	203	202	201	201
Wk 104	690	684	647	622
% of Control, Wk 104	100.00	99.13	93.77	90.14

ΔWk24-Wk0	487	482	446	421
BW Gain, % of Initial BW	239.90	238.61	221.89	209.45
BW Gain, % Of Control	100	99.46	92.49	87.31

Female	1	2	3	4
Wk 0	153	152	153	151
Wk 25	329	311	309	296
% of Control, Wk 25	100.00	94.53	93.92	89.97
ΔWk24-Wk0	176	159	156	145
BW Gain, % of Initial BW	115.03	104.61	101.96	96.03
BW Gain, % Of Control	100	90.94	88.64	83.48

Female	1	2	3	4
Wk 0	153	152	153	151
Wk 55	400	352	350	323
% of Control, Wk 55	100.00	88.00	87.50	80.75
ΔWk24-Wk0	247	200	197	172
BW Gain, % of Initial BW	161.44	131.58	128.76	113.91
BW Gain, % Of Control	100	81.50	79.76	70.56

Female	1	2	3	4
Wk 0	153	152	153	151
Wk 79	447	394	385	352
% of Control, Wk 79	100.00	88.14	86.13	78.75
ΔWk24-Wk0	294	242	232	201
BW Gain, % of Initial BW	192.16	159.21	151.63	133.11
BW Gain, % Of Control	100	82.85	78.91	69.27

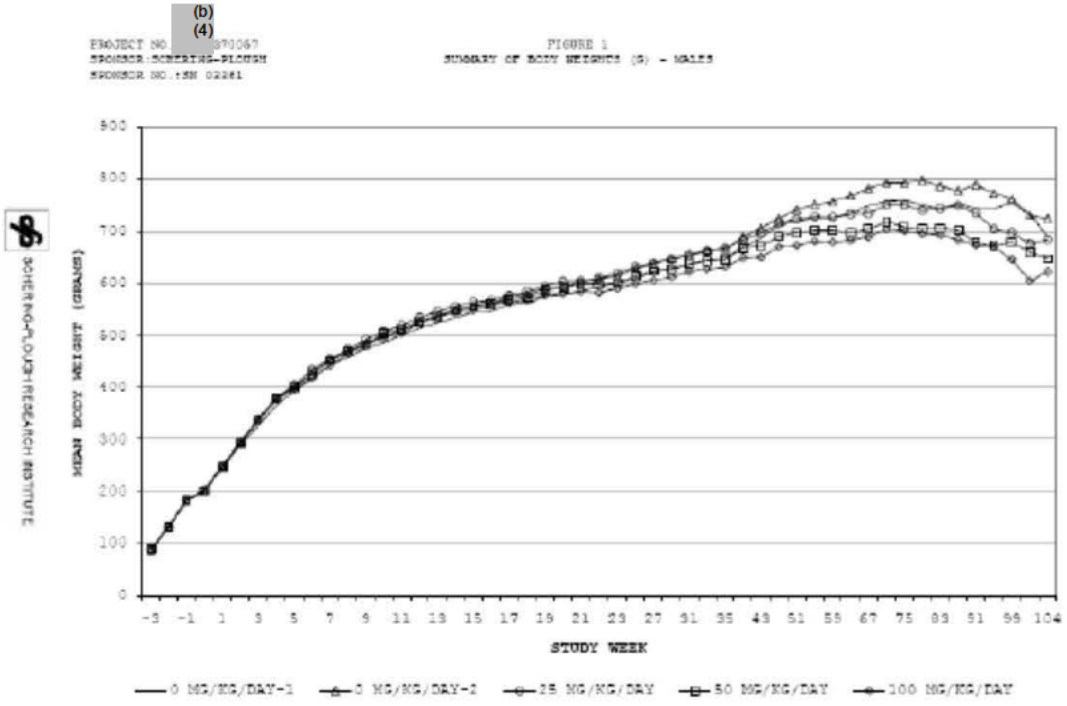
Female	1	2	3	4
Wk 0	153	152	153	151
Wk 104	450	428	421	368
% of Control, Wk 104	100.00	95.11	93.56	81.78
ΔWk24-Wk0	297	276	268	217
BW Gain, % of Initial BW	194.12	181.58	175.16	143.71
BW Gain, % Of Control	100	93.54	90.24	74.03

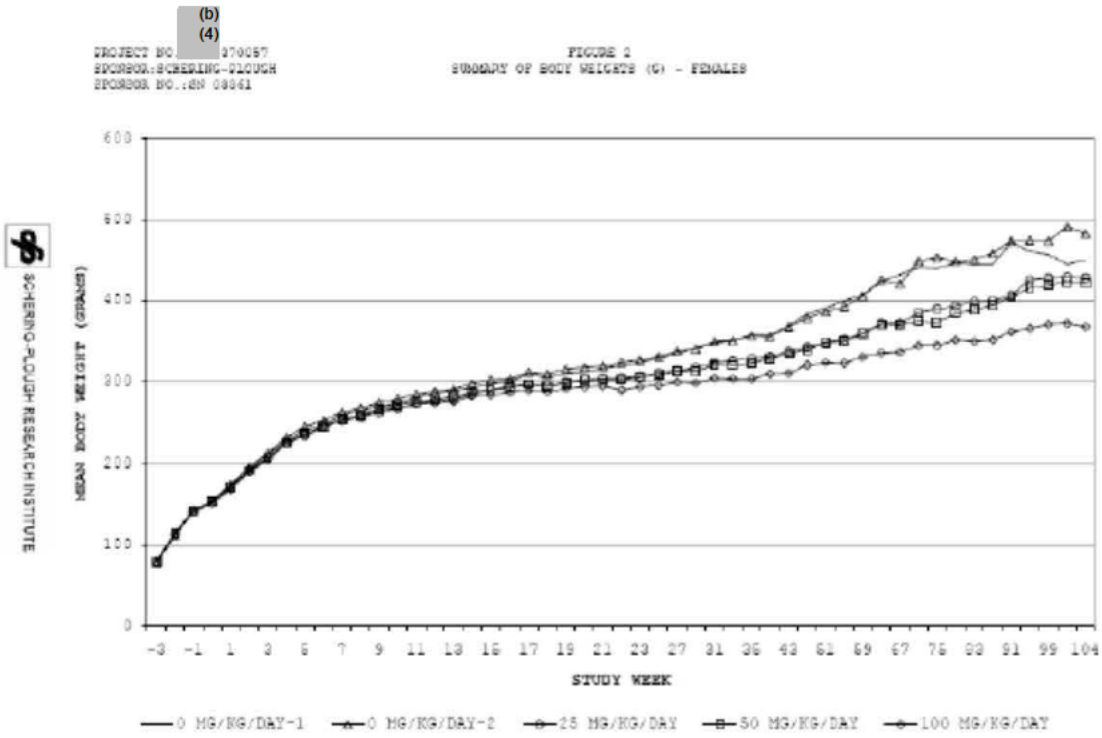
*GROUP:

1. Control 1
2. 25 mg/kg/day
3. 50 mg/kg/day
4. 100 mg/kg/day

The following figures (from page 3813 and 3814 of the study report) show the growth curves in males and females.

(b) (4)





Food consumption: The mean initial (Week 0) and final (Week 104) food consumption in control (Group 1) males was 22 and 25 g/animal/day, respectively. The mean initial (Week 0) and final (Week 104) food consumption in control (Group 1) females was 18 and 20 g/animal/day, respectively. There was no significant effect of treatment on food consumption.

Ophthalmoscopy: There were no significant treatment-related effects.

Gross pathology: Treatment-related masses were observed in the thyroid gland of one male at 50 mg/kg/day and two males at 100 mg/kg/day, which were correlated histologically to follicular cell carcinoma of the thyroid gland. However, these were not seen in females. The following table (from page 4100 of the report) shows the necropsy findings.

Principal Necropsy Findings										
	Males					Females				
Dose (mg/kg/day):	0	0	25	50	100	0	0	25	50	100
Organ/Finding	Incidence[a]									
Thyroid Gland	(50)[b]	(50)	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)
- mass	1	1	0	1*	2*	0	0	0	0	0
* = Test article-related a: Incidence = Number affected. b: ( ) = Number examined.										

Histopathology:

Non-neoplastic: SCH 619734-related non-neoplastic findings were observed in the adrenal glands of males and in the liver of both sexes. Males in the 100 mg/kg/day dose group had an increased incidence of cystic cortical degeneration in the adrenal glands, as compared to concurrent controls. In the liver, there were increased incidence and severity of multinucleated hepatocytes in males and females at 50 and 100 mg/kg/day. Centrilobular hypertrophy was noted in both sexes at all doses. In addition, in the liver, eosinophilic and basophilic foci of cellular alteration was present in females at all doses and in males at all doses. Non-neoplastic findings are shown in the following table (from page 4104 of the report).

Principal Non-Neoplastic Findings										
	Males					Females				
Dose (mg/kg/day):	0	0	25	50	100	0	0	25	50	100
Organ/Finding/Severity	Incidence[a]									
Adrenal Glands	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- degeneration, cystic, cortical										
minimal	6	6	9	8	12*	1	4	1	5	4
mild	4	12	12	10	14*	24	22	18	14	15
moderate	1	2	1	1	3*	16	21	22	24	23
severe	0	0	0	0	0	0	0	8	7	7
Liver	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- multinucleated hepatocytes										
minimal	1	1	0	14*	26*	1	1	4	17*	11*
mild	0	0	0	2*	11*	0	0	0	5*	27*
moderate	0	0	0	0	0	0	0	0	0	6*
- focus(i) of cellular alteration, eosinophilic cell										
minimal	4	3	6	7	5	1	1	10*	9*	10*
mild	2	1	3	5	1	1	0	2*	2*	1*
moderate	0	0	0	1	0	0	0	0	0	0
- focus(i) of cellular alteration, basophilic cell										
minimal	5	11	20*	19*	18*	10	7	15	10	12
mild	3	2	6*	5*	4*	4	10	6	2	4
moderate	1	0	1*	1*	2*	4	5	1	1	1
- hypertrophy, centrilobular										
minimal	0	0	2*	3*	7*	1	0	1	5*	19*
mild	0	0	0	0	1*	0	0	1*	0	1*

* = Test article-related

a: Incidence = Number affected.

b: ( ) = Number examined.

Neoplastic: Administration of SCH 619734 was associated with a higher but not statistically significant incidence of benign pheochromocytomas in the adrenal glands of males at 50 and 100 mg/kg/day (as shown in the following table). A higher incidence of follicular cell adenomas in the thyroid glands was seen in 100 mg/kg/day-dosed males and females, as well as follicular cell carcinomas in the thyroid glands of 100 mg/kg/day-dosed males. However, no statistical significance was observed in the trend test. Overall, there were no statistically significant drug-related neoplastic findings in male or female rats.

Principal Neoplastic Findings According to Tissue or Organ of Origin												
Sex	Males						Females					
Dose (mg/kg/day)	0	0	25	50	100	P (trend test)*	0	0	25	50	100	P (trend test)*
Adrenal Glands	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(50)	(50)	(50)	
Pheochromocytoma, [B]	6 (12%)	5 (10%)	8 (16%)	12 (24%)	14 (28%)	0.0103	1 (2%)	4 (8%)	1 (2%)	3 (6%)	0 (0%)	0.9578
Thyroid Gland	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(50)	(50)	(50)	
Follicular cell adenoma [B]	2 (4%)	3 (6%)	3 (6%)	3 (6%)	7 (14%)	0.0554	2 (4%)	1 (2%)	3 (6%)	2 (4%)	5 (10%)	0.1144
Follicular cell carcinoma [M]	0 (0%)	1 (2%)	0 (0%)	2 (4%)	2 (4%)	0.1177	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0.2471

[B]: Benign tumor; [M]: Malignant tumor
(): Number examined
P*: P value for Trend test (FDA statistical review dated December 8, 2011)

Toxicokinetics: Mean plasma concentrations of SCH 619734 and SCH 72088 (metabolite) are shown in the following Tables (from page 4102 and 4103 of the report).

Table 9 Mean Plasma Concentrations of SCH 619734 in Rat Plasma Samples

Dose Group	Study Day	Gender	1 hr Post-Dose			4 hr Post-Dose			6 hr Post-Dose		
			Mean[a] (ng/mL)	SD	%CV	Mean[a] (ng/mL)	SD	%CV	Mean[a] (ng/mL)	SD	%CV
0 mg/kg	27	Male	0.00	NC[b]	NC	0.00	NC	NC	0.00	NC	NC
		Female	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
		Overall	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
	166	Male	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
		Female	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
		Overall	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
25 mg/kg	27	Male	1160	414	35.7	1900	1100	57.9	1180	233	19.7
		Female	2370	462	19.5	2960	807	27.3	2820	304	10.8
		Overall	1770	773	43.7	2430	1040	42.8	2000	933	46.7
	166	Male	1290	389	30.2	2480	1210	48.8	2310	591	25.6
		Female	3480	1090	31.3	3610	305	8.4	3330	422	12.7
		Overall	2380	1410	60.2	3050	1010	33.1	2820	726	25.6
50 mg/kg	27	Male	1210	222	18.3	1920	405	21.1	2270	226	10.0
		Female	4030	1390	34.5	3390	865	25.5	3150	263	8.3
		Overall	2620	1780	67.9	2650	1010	38.1	2710	529	19.5
	166	Male	2200	928	42.2	2710	257	9.5	3530	470	13.3
		Female	4710	1650	35.0	4560	519	11.4	5330	825	15.5
		Overall	3460	1820	52.6	3630	1080	29.8	4430	1150	26.0
100 mg/kg	27	Male	1440	1040	72.2	2670	456	17.1	2730	489	17.9
		Female	4260	1310	30.8	3460	1350	39.0	4250	1670	39.3
		Overall	2850	1870	65.6	3060	998	32.6	3490	1380	39.5
	166	Male	2020	629	31.1	3430	1150	33.5	4290[c]	1040	24.2
		Female	4550	1160	25.5	6660	3170	47.6	5740	2870	50.0
		Overall	3290	1620	49.2	5040	2770	55.0	5020[d]	2090	41.6

a: n = 3 male or female rats and n = 6 for overall (males and females combined), except as noted.
b: Not calculated (NC) when mean is zero.
c: n = 2
d: n = 5

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Table 10 Mean Plasma Concentrations of SCH 720881 in Rat Plasma Samples

Dose Group	Study Day	Gender	1 hr Post-Dose			4 hr Post-Dose			6 hr Post-Dose		
			Mean[a] (ng/mL)	SD	%CV	Mean[a] (ng/mL)	SD	%CV	Mean[a] (ng/mL)	SD	%CV
0 mg/kg	166	Male	0.00	NC[b]	NC	0.00	NC	NC	0.00	NC	NC
		Female	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
		Overall	0.00	NC	NC	0.00	NC	NC	0.00	NC	NC
25 mg/kg	166	Male	243	26.5	10.9	390	199	51.0	557	5.86	1.1
		Female	117	15.9	13.6	145	24.8	17.1	132	23.7	18.0
		Overall	180	71.5	39.7	268	185	69.0	345	234	67.8
50 mg/kg	166	Male	264	14.1	5.3	604	184	30.5	642	253	39.4
		Female	150	39.4	26.3	210	26.8	12.8	230	21.2	9.2
		Overall	207	67.8	32.8	407	246	60.4	436	277	63.5
100 mg/kg	166	Male	296	65.9	22.3	608	176	28.9	837	179	21.4
		Female	157	55.9	35.6	384	143	37.2	363	74.2	20.4
		Overall	227	93.7	41.3	496	189	38.1	600	287	47.8

a: n = 3 male or female rats and n = 6 for overall (males and females combined), except as noted.
b: Not calculated (NC) when mean is zero.

Summary of individual study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model: The study was considered adequate. The doses were selected as per the ECAC recommendations and were based on the MTD.

Evaluation of tumor findings: Administration of SCH 619734 was associated with a higher but not statistically significant incidence of benign pheochromocytomas in the adrenal glands of males at 50 mg/kg/day and 100 mg/kg/day. A higher incidence of follicular cell adenomas in the thyroid glands was seen in 100 mg/kg/day-dosed males and females, as well as follicular cell carcinomas in the thyroid glands of 50 and 100 mg/kg/day males. However, tumor data analyses (trend test) did not show statistically significant dose response relationship among the treated groups, or higher tumor rates in the treated groups compared to the combined control in any of the tested tumor types in either sex. These tumor incidences did not appear to be treatment-related in the absence of statistically significant trend test. Overall, there were no statistically significant drug-related neoplastic findings in male or female rats (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

Carcinogenicity Summary: In a 104-week oral (gavage) carcinogenicity study in SD rats, animals (n = 50/sex/dose) were treated at 0, 0, 25, 50, and 100 mg/kg/day in 0.5% carboxymethylcellulose. The dose selection was based on the MTD as per the ECAC recommendations. There was no statistically significant treatment-related effect on mortality in either sex. Treatment-related non-neoplastic findings were observed in the adrenal glands (cystic cortical degeneration) of males at 100 mg/kg/day and in the liver of both sexes at all doses. Findings in the liver included multinucleated hepatocytes in both sexes at 50 and 100 mg/kg/day, foci of cellular alteration, eosinophilic cell in females at all doses, foci of cellular alteration, basophilic cell in males at all doses and centrilobular hypertrophy in both sexes at all doses. There were no statistically significant drug-related neoplastic findings in male or female rats.

Carcinogenicity conclusions:

1. The study was considered adequate.
2. There were no statistically significant drug-related neoplastic findings in male or female rats (Exec CAC meeting minutes dated May 2, 2012, Attachment-4).

Attachment-4

ECAC Meeting Minutes dated May 2, 2012

Executive CAC

Date of Meeting: May 1, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Lynnda Reid, Ph.D., DRUP, Alternate Member
Sushanta K. Chakder, Ph.D., DGIEP, Supervisor,
Tamal K. Chakraborti, Ph.D., DGIEP ,Presenting Reviewer,

Author of Draft: Tamal K. Chakraborti, Ph.D.

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

IND #: 72754
Drug Name: Rolapitant (SCH 619734)
Sponsor: Tesaro, Inc.

Background: Rolapitant (SCH 619734) is a neurokinin-1 (NK1) receptor antagonist, under development for the treatment of chemotherapy-induced nausea and vomiting (CINV). This submission contains the reports for the 2-year oral carcinogenicity studies in rats [SN 03361] and mice [SN 03662].

Mouse Carcinogenicity Study:

In a 104-week oral (gavage) carcinogenicity study in CD-1 mice, animals were treated at 0, 0, 25, 75, and 150 mg/kg/day in 0.5% carboxymethylcellulose. Dose selection was based on the maximum tolerated dose (MTD) as per the ECAC recommendations. There were no statistically significant drug-related neoplastic findings in male or female mice.

Rat Carcinogenicity Study:

In a 104-week oral (gavage) carcinogenicity study in SD rats, animals were treated at 0, 0, 25, 50, and 100 mg/kg/day in 0.5% carboxymethylcellulose.. Dose selection was based on the MTD as per the ECAC recommendations. There were no statistically significant drug-related neoplastic findings in male or female rats

Executive CAC Recommendations and Conclusions:

Mouse Study:

- The Committee agreed that the study was adequate.
- The Committee concurred that there were no drug-related neoplastic findings in male or female mice

Rat Study:

- The Committee agreed that the study was adequate.
- The Committee concurred that here were no drug-related neoplastic findings in male or female rats.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DGIEP
/SChakder, DGIEP
/TChakraborti, DGIEP
/RPM/JGrewal/DGIEP
/ASeifried, OND IO

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Reviews of Study Nos. 03117 and 05078 are incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP). Dr. Chakraborti's review of Study No. 03117 also summarizes two exploratory, non-GLP studies (Study Nos. 03108 and 04283). While not discussed in Dr. Chakraborti's review, it is noted that in Study No. 03117, there was a transient decrease in body weight gain during the first few days of dosing in maternal animals administered 10 mg/kg/day SCH 619734.

Study title: Fertility and Early Embryonic Development Study in Female Rats

Study no.:	03117
Study report location:	EDR 4.2.3.5.1
Conducting laboratory and location:	Safety Evaluation Center, Schering-Plough Research Institute (SPRI), Lafayette, NJ
Date of study initiation:	July 5, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734, SZ-03-PHG-TX-001, 99.8%

Key Study Findings:

- At 10 mg/kg/day, SCH 619734 caused increases in pre- and post-implantation losses.
- At 5 and 10 mg/kg/day, SCH 619734 decreased the number of corpora lutea.
- A decreased number of implantation sites were also observed at 5 and 10 mg/kg/day.

Methods:

Doses:	1, 5, 10 mg/kg/day
Frequency of dosing:	Daily. Females were dosed once daily for at least two weeks prior to and during the cohabitation period, and on gestation Days 0 through 7. Females were dosed for a total dosing period of 23 to 30 days.
Dose volume:	5 mL/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose, pH 4
Species/Strain:	SD rats
Number/Sex/Group:	25/dose
Satellite groups:	None
Study design:	Shown below
Deviation from study protocol:	The protocol deviations did not adversely affect either the quality or integrity of the study or the interpretation of the results.

The study design is shown below (from page 19 of the report)

Fertility and Early Embryonic Developmental Toxicity Study of SCH 619734 Administered Orally by Gavage in Female Rats (SN 03117): **Study Design**

Group	Test/Control Article	Total Daily Dose (mg/kg)[a]	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Females[b, c]
1	Control (Methylcellulose)	0	5	0	25
2	Low-Dose (SCH 619734)	1	5	0.2	25
3	Mid-Dose (SCH 619734)	5	5	1	25
4	High-Dose (SCH 619734)	10	5	2	25

a: Total daily dose is expressed as the hydrochloride monohydrate salt. When expressed as the free base, daily doses equal 0.9, 4.5 and 9 mg/kg for Groups 2, 3 and 4, respectively.

b: Female rats were dosed once daily for at least two weeks prior to and during the cohabitation period, and on gestation Days 0 through 7. Females were dosed for a total dosing period of 23 to 30 days.

c: Non-dosed males were used for cohabitation.

Observations and Results:

Mortality: Mortality was checked daily. There was no test article-related mortality.

Clinical Signs: Clinical signs were observed on a daily basis. There was no treatment related clinical signs.

Body Weight: Body weights were recorded twice weekly. The mean initial (Day 0) and final (Day 14) body weight of control animals were 231 and 248 g, respectively. There were no significant treatment-related effects.

Food Consumption: Food consumption was measured weekly. The mean initial (Day 0-7) and final (Day 7-14) food consumption in control females were 17 and 17 g/animal/day, respectively. There were no significant treatment-related effects.

Toxicokinetics: Not conducted

Dosing Solution Analysis: Not provided

Necropsy: Female rats were sacrificed on gestation Day 14. There were no significant treatment-related effects.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.): The numbers and distribution of corpora lutea, implantation sites, live fetuses, and early and late resorptions, mating index and fertility index were determined. There were no significant treatment-related effects on mating and fertility index. There were treatment-related increases in pre- and post-implantation losses at 10 mg/kg/day. The mean percent of pre-implantation loss per litter at 10 mg/kg/day was 21.1 versus 11.5 in the

control group. The mean percent of post-implantation loss per litter at 10 mg/kg/day was 20.3 versus 5.9 in the control group. There were also significant decreases in the number of corpora lutea at 5 and 10 mg/kg/day (mean of 14.9 and 14.5, respectively) compared to the control group (mean of 17.6). These decreases of mean number of corpora lutea at 5 and 10 mg/kg/day groups were below the historical control range (15.3 to 16.6). A decrease in the number of implantation sites was also observed at 5 and 10 mg/kg/day (mean of 13.1 and 11.3, respectively) compared to the control group (mean of 15.5).

It is to be mentioned here that the effects of SCH 619734 on female fertility and early embryo development in rats observed in this study were also previously reported in a pilot fertility and early embryonic development study (SN 03108) and in an investigative early embryonic developmental toxicity study (SN 04283). In the pilot study, female rats were treated with SCH 619734 at 25, 50 or 75 mg/kg/day for two weeks prior to and during the cohabitation period and through gestation Day 7. Female rats in the investigative study were treated with SCH 619734 at 1, 10 or 25 mg/kg/day on gestation Days 0 through 7. In these previous studies, SCH 619734 decreased number of corpora lutea and increased pre- and post-implantation losses at ≥ 25 mg/kg/day. However, there were no treatment-related adverse effects on early embryonic development at 10 mg/kg/day in the investigative study.

Mating and fertility indices and cesarean section data are presented below (from page 128 and 135 of the report).

FERTILITY AND EARLY EMBRYONIC DEVELOPMENTAL TOXICITY STUDY OF SCH 619734 ADMINISTERED ORALLY BY GAVAGE IN FEMALE RATS

SUMMARY OF MATING AND FERTILITY DATA

		GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 619734 1 MG/KG	GROUP 3 SCH 619734 5 MG/KG	GROUP 4 SCH 619734 10 MG/KG
Females paired with males	N	25	25	24	25
females mated	N	25	25	24	25
female mating index	%	100.0	100.0	100.0	100.0
females pregnant	N	25	25	24	24
female fertility index	%	100.0	100.0	100.0	96.0
Males placed with females	N	25	25	24	25
males mated	N	25	25	24	25
male mating index	%	100.0	100.0	100.0	100.0
with females pregnant	N	25	25	24	24
male fertility index	%	100.0	100.0	100.0	96.0
Females with defined day 0 of Gestation	N	25	25	24	25
No. of days until Mating	MEAN	2.1	1.7	2.2	2.4
	S.D.	1.00	0.98	1.50	1.63

Female mating index = no. of females with evidence of mating / total number of females placed for mating
Female fertility index = no. of females with confirmed pregnancy / total number of females with evidence of mating
Male mating index = no. of males with evidence of mating / total number of males placed for mating
Male fertility index = no. of males siring at least one litter / total number of males with evidence of mating

FERTILITY AND EARLY EMBRYONIC DEVELOPMENTAL TOXICITY STUDY OF
SCH 619734 ADMINISTERED ORALLY BY GAVAGE IN FEMALE RATS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 619734 1 MG/KG	GROUP 3 SCH 619734 5 MG/KG	GROUP 4 SCH 619734 10 MG/KG
Pregnant	N	25	25	24	24
Dams with Viable Fetuses	N	25	25	24	22
Corpora Lutea	TOTAL	440	409	358	347
No. per animal	MEAN	17.6 d	16.4	14.9*	14.5*
	S.D.	2.93	3.00	2.67	2.60
Implantation Sites	TOTAL	388	373	315	272
No. per animal	MEAN	15.5 d	14.9	13.1*	11.3*
	S.D.	2.69	1.71	2.29	3.95
Preimplantation Loss	TOTAL	52	36	43	75
No. per animal	MEAN	2.1	1.4	1.8	3.1
	S.D.	1.93	1.85	1.96	3.94
% per animal	MEAN%	11.5 k	7.6	11.3	21.1
	S.D.	10.39	8.44	11.23	24.39
Live Fetuses	TOTAL	364	364	291	237
left horn		174	181	149	101
right horn		190	183	142	136
No. per animal	MEAN	14.6	14.6	12.1	9.9
	S.D.	2.62	2.00	2.36	4.59

Statistics performed: d=ANOVA +/- Dunnett-test k=Kruskal Wallis +/- Dunn * = p<0.05

FERTILITY AND EARLY EMBRYONIC DEVELOPMENTAL TOXICITY STUDY OF
SCH 619734 ADMINISTERED ORALLY BY GAVAGE IN FEMALE RATS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 619734 1 MG/KG	GROUP 3 SCH 619734 5 MG/KG	GROUP 4 SCH 619734 10 MG/KG
Postimplantation Loss	TOTAL	24	9	24	35
No. per animal	MEAN	1.0	0.4	1.0	1.5
	S.D.	1.49	0.86	1.32	1.50
% implants per animal	MEAN%	5.9 k	2.5	7.4	20.3
	S.D.	7.83	6.12	9.80	29.30
Dead Fetuses	TOTAL	0	0	0	0
No. per animal	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
% of implants per animal	MEAN%	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
Resorptions: early+late	TOTAL	24	9	24	35
No. per animal	MEAN	1.0	0.4	1.0	1.5
	S.D.	1.49	0.86	1.32	1.50
% of implants per animal	MEAN%	5.9 k	2.5	7.4	20.3
	S.D.	7.83	6.12	9.80	29.30
Resorptions: Early	TOTAL	23	9	24	35
No. per animal	MEAN	0.9	0.4	1.0	1.5
	S.D.	1.50	0.86	1.32	1.50
% of implants per animal	MEAN%	5.7	2.5	7.4	20.3
	S.D.	7.92	6.12	9.80	29.30
Resorptions: Late	TOTAL	1	0	0	0
No. per animal	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.20	0.00	0.00	0.00
% of implants per animal	MEAN%	0.2	0.0	0.0	0.0
	S.D.	1.11	0.00	0.00	0.00

Statistics performed: k=Kruskal Wallis +/- Dunn No statistically significant differences

Summary: In an oral fertility and early embryonic development study in female rats, animals were treated with SCH 619734 at 1, 5 and 10 mg/kg/day. Females were dosed once daily for at least two weeks prior to and during the cohabitation period, and on gestation Days 0 through 7. Females were dosed for a total dosing period of 23 to 30 days. At 10 mg/kg, SCH 619734 caused increases in pre- and post-implantation losses. At 5 and 10 mg/kg, SCH 619734 decreased the number of corpora lutea. In addition, a decrease in the number of implantation sites was also observed at 5 and 10 mg/kg.

Study title: Oral Fertility and Early Embryonic Development Study in Male Rats

Study no.:	05078
Study report location:	EDR 4.2.3.5.1
Conducting laboratory and location:	Safety Evaluation Center, Schering-Plough Research Institute (SPRI), Lafayette, NJ
Date of study initiation:	July 25, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734, SZ-03-PHG-TX-001, 99.8%

Key Study Findings:

- In an oral fertility and early embryonic development study in male rats, animals were treated with SCH 619734 at 5, 25 and 100 mg/kg/day.
- The mean absolute weights of the prostate gland and seminal vesicles were decreased at 100 mg/kg/day.
- Male mating and fertility indices and early embryonic development were not affected by administration of SCH 619734 at doses up to 100 mg/kg/day.

Methods:

Doses:	5, 25, 100 mg/kg/day
Frequency of dosing:	Daily. Male rats were dosed once daily for four weeks prior to the cohabitation period through the day prior to scheduled sacrifice (total dosing period of 62 days).
Dose volume:	5 mL/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose (pH 4)
Species/Strain:	SD rats
Number/Sex/Group:	22/sex/dose
Satellite groups:	None
Study design:	Shown below
Deviation from study protocol:	The protocol deviations did not adversely affect either the quality or integrity of the study or the interpretation of the results.

The study design is shown below (from page 11 of the report).

Fertility and Early Embryonic Developmental Toxicity Study of SCH 619734 Administered Orally by Gavage in Male Rats (SN 05078): **Study Design**

Group	Test/Control Article	Total Daily Dose (mg/kg)[a]	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Rats	
					Males[b]	Females[c]
1	Control (Methylcellulose)	0	5	0	22	22
2	Low-Dose (SCH 619734)	5	5	1	22	22
3	Mid-Dose (SCH 619734)	25	5	5	22	22
4	High-Dose (SCH 619734)	100	5	20	22	22

a: Total daily dose is expressed as the hydrochloride monohydrate salt. When expressed as the free base, daily doses equal 4.5, 22.5 and 90 mg/kg for Groups 2, 3 and 4, respectively.

b: Male rats were dosed once daily for four weeks prior to and during the cohabitation period through the day prior to scheduled sacrifice (total dosing period of 62 days).

c: Non-dosed mating partners

Observations and Results:

Mortality: Mortality was checked daily. There was no test article-related mortality.

Clinical Signs: Clinical signs were observed on a daily basis. Peri-oral substance (red or tan) was observed in 4 of 22 animals at 25 mg/kg/day and 18 of 22 rats at 100 mg/kg/day.

Body Weight: Body weights were recorded twice weekly. The mean initial (Day 0) and final (Day 59) body weight of control animals were 351 and 523 g, respectively. There were no significant treatment-related effects.

Food Consumption: Food consumption was measured weekly. The mean initial (Day 0-6) and final (Day 20-27) food consumption in control males were 26 and 25 g/animal/day, respectively. Food consumption was decreased (92% of control) at 100 mg/kg between study Days 0 and 27.

Toxicokinetics: Not conducted

Dosing Solution Analysis: Not provided

Necropsy: Male rats were sacrificed within three weeks after the end of the cohabitation period. One male at 100 mg/kg/day had a small prostate gland, and this animal had low weights of the prostate gland and seminal vesicles. This was consistent with the treatment-related organ weight findings at 100 mg/kg/day.

Organ Weights: The following organs were weighed for all male rats sacrificed at the scheduled necropsy: epididymides, prostate gland (ventral), seminal Vesicles, and testes. The mean absolute weights of the prostate gland and seminal vesicles were

decreased by 18.0% and 20.5%, respectively, at 100 mg/kg/day, compared to the control group.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.): The numbers and distribution of corpora lutea, implantation sites, live fetuses, and early and late resorptions, mating index and fertility index were determined. There were no significant treatment-related effects on mating and fertility index or reproductive parameters. Mating and fertility indices and reproductive parameters are presented below (from page 112, 119 and 120 of the report).

FERTILITY AND EARLY EMBRYONIC DEVELOPMENTAL TOXICITY STUDY OF
SCH 619734 ADMINISTERED ORALLY BY GAVAGE IN MALE RATS

SUMMARY OF MATING AND FERTILITY DATA

		GROUP 1 NON-DOSED FEMALES	GROUP 2 NON-DOSED FEMALES	GROUP 3 NON-DOSED FEMALES	GROUP 4 NON-DOSED FEMALES
Females paired with males	N	22	22	22	21
females mated	N	22	22	22	21
female mating index	%	100.0	100.0	100.0	100.0
females pregnant	N	20	20	22	19
female fertility index	%	90.9	90.9	100.0	90.5
Males placed with females	N	22	22	22	21
males mated	N	22	22	22	21
male mating index	%	100.0	100.0	100.0	100.0
with females pregnant	N	20	20	22	19
male fertility index	%	90.9	90.9	100.0	90.5
Females with defined day 0 of Gestation	N	22	22	22	21
No. of days until Mating	MEAN	2.4	2.6	2.2	2.6
	S.D.	1.05	2.74	1.19	1.16

Female mating index = no. of females with evidence of mating / total number of females placed for mating
Female fertility index = no. of females with confirmed pregnancy / total number of females with evidence of mating
Male mating index = no. of males with evidence of mating / total number of males placed for mating
Male fertility index = no. of males siring at least one litter / total number of males with evidence of mating

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FERTILITY AND EARLY EMBRYONIC DEVELOPMENTAL TOXICITY STUDY OF
SCH 619734 ADMINISTERED ORALLY BY GAVAGE IN MALE RATS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 NON-DOSED FEMALES	GROUP 2 NON-DOSED FEMALES	GROUP 3 NON-DOSED FEMALES	GROUP 4 NON-DOSED FEMALES
Pregnant	N	20	20	22	19
Dams with Viable Fetuses	N	20	20	22	19
Corpora Lutea	TOTAL	340	355	382	345
No. per animal	MEAN	17.0 d	17.8	17.4	18.2
	S.D.	1.84	2.22	3.00	2.43
Implantation Sites	TOTAL	317	326	341	310
No. per animal	MEAN	15.9 d	16.3	15.5	16.3
	S.D.	2.80	2.58	2.91	1.70
Preimplantation Loss	TOTAL	23	29	41	35
No. per animal	MEAN	1.1	1.5	1.9	1.8
	S.D.	1.79	1.85	2.38	2.52
% per animal	MEAN%	7.1 k	8.1	10.4	9.2
	S.D.	11.99	10.58	12.26	11.76
Live Fetuses	TOTAL	297	314	322	291
left horn		164	153	157	137
right horn		133	161	165	154
No. per animal	MEAN	14.9	15.7	14.6	15.3
	S.D.	3.20	2.64	2.70	2.50

Statistics performed: d=ANOVA +/- Dunnett-test k=Kruskal Wallis +/- Dunn No statistically significant differences

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FERTILITY AND EARLY EMBRYONIC DEVELOPMENTAL TOXICITY STUDY OF
SCH 619734 ADMINISTERED ORALLY BY GAVAGE IN MALE RATS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 NON-DOSED FEMALES	GROUP 2 NON-DOSED FEMALES	GROUP 3 NON-DOSED FEMALES	GROUP 4 NON-DOSED FEMALES
Postimplantation Loss	TOTAL	20	12	19	19
No. per animal	MEAN	1.0	0.6	0.9	1.0
	S.D.	0.86	0.82	0.89	1.37
% implants per animal	MEAN%	6.9 k	3.7	5.2	6.5
	S.D.	6.35	4.84	5.41	9.00
Dead Fetuses	TOTAL	0	0	0	0
No. per animal	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
% of implants per animal	MEAN%	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
Resorptions: early+late	TOTAL	20	12	19	19
No. per animal	MEAN	1.0	0.6	0.9	1.0
	S.D.	0.86	0.82	0.89	1.37
% of implants per animal	MEAN%	6.9	3.7	5.2	6.5
	S.D.	6.35	4.84	5.41	9.00
Resorptions: Early	TOTAL	20	12	19	19
No. per animal	MEAN	1.0	0.6	0.9	1.0
	S.D.	0.86	0.82	0.89	1.37
% of implants per animal	MEAN%	6.9	3.7	5.2	6.5
	S.D.	6.35	4.84	5.41	9.00
Resorptions: Late	TOTAL	0	0	0	0
No. per animal	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
% of implants per animal	MEAN%	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00

Statistics performed: k=Kruskal Wallis +/- Dunn No statistically significant differences

Summary: In an oral fertility and early embryonic development study in male rats, animals were treated with SCH 619734 at 5, 25 and 100 mg/kg/day. Male rats were dosed once daily for four weeks prior to the cohabitation period through the day prior to scheduled sacrifice (total dosing period of 62 days). The mean absolute weights of the prostate gland and seminal vesicles were decreased at 100 mg/kg/day. Male mating and fertility indices and early embryonic development were not affected by SCH 619734 treatment up to 100 mg/kg/day.

9.2 Embryonic Fetal Development

Review of Study Nos. 03118 and 03119 are incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP). Dr. Chakraborti's reviews of Studies 03118 and 03119 also summarize two exploratory, non-GLP studies (Study Nos. 03109 and 03110, respectively). While not discussed in Dr. Chakraborti's review, it is noted that in Study No. 03118, there was a decrement in body weight gain (compared to controls) over the gestation day (GD) 6 to 9 interval in female rats dosed at 15 mg/kg/day SCH 619734. In addition, there was a slight decrease in food consumption over the GD 6 to 12 interval in females dosed at 15 mg/kg/day SCH 619734.

Study title: Embryo-Fetal Developmental Toxicity Study of SCH 619734 Administered Orally by Gavage in Rats

Study no.:	03118
Study report location:	EDR 4.2.3.5.2
Conducting laboratory and location:	Safety Evaluation Center, Schering-Plough Research Institute (SPRI), Lafayette, NJ
Date of study initiation:	February 7, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734, SZ-03-PHG-TX-001, 99.8%

Key Study Findings:

- In an oral embryofetal development study in rats, animals were treated with SCH 619734 at 5, 15 and 25 mg/kg/day from GD 6 through GD 17.
- There were no significant treatment-related effects on reproductive parameters.
- There were no significant treatment-related fetal external, visceral or skeletal malformations.

Methods:

Doses:	5, 15, 25 mg/kg/day
Frequency of dosing:	Once daily from GD 6 through 17
Dose volume:	5 mL/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	SD rats (pregnant females)
Number/Sex/Group:	25/dose
Satellite groups:	None
Study design:	Shown in the table below
Deviation from study protocol:	The protocol deviations did not adversely affect either the quality or integrity of the study or the interpretation of the results.

Basis of dose selection: Doses were selected based on the results of the pilot embryofetal development study (SN 03109) in rats. In this study, animals (n = 6/dose) were treated with SCH 619734 orally (gavage) at 25, 50 and 75 mg/kg/day (5 mL/kg) from GD 6 through GD 17. The 50 and 75 mg/kg dose groups were sacrificed on GD 14 due to excessive maternal toxicity including body weight loss and decreased food consumption. Red material in the cage pan and/or red perivaginal substance was also noted. These dose levels were considered too high for the definitive embryo-fetal developmental toxicity study. However, there were no clinical observations or effects on food consumption, reproductive parameters, fetal weight and fetal external findings. Based on the results of this study, 5, 15 and 25 mg/kg/day doses were selected for the definitive embryo-fetal developmental toxicity study.

The study design is shown below (from page 11 of the report).

Embryo-Fetal Developmental Toxicity Study of SCH 619734 Administered Orally by Gavage in Rats (SN 03118): **Study Design**					
Group	Test/Control Article	Total Daily Dose[a] (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Females
1	Control (Methylcellulose)	0	5	0	25
2	Low-Dose (SCH 619734)	5	5	1	25
3	Mid-Dose (SCH 619734)	15	5	3	25
4	High-Dose (SCH 619734)	25	5	5	25
a: Total daily dose is expressed as the hydrochloride monohydrate salt. When expressed as the free base, daily doses equal 4.5, 13.5 and 22.5 mg/kg for Groups 2, 3 and 4, respectively.					

Observations and Results:

Mortality: Mortality was checked once daily. There was no treatment-related mortality.

Clinical Signs: Clinical signs were observed on a daily basis. There were no test article-related clinical observations.

Body Weight: Body weight was recorded on gestation Days 0, 6, 9, 12, 15, 17 and 21. The mean initial (Day 0) and final (Day 21) body weights of control animals were 214 and 401 g, respectively. Body weight gain was decreased by 10% at 25 mg/kg/day compared to control weight gain.

Food Consumption: Food consumption was recorded on gestation Days 0 to 6, 6 to 12, 12 to 17, and 17 to 21. The mean initial (Day 0-6) and final (Day 17-21) food consumption of control animals were 22 and 28 g/animal/day, respectively. At 25 mg/kg/day, food consumption was decreased by 8% compared to control.

Toxicokinetics: Not conducted

Dosing Solution Analysis: Not provided

Necropsy: Necropsy was conducted at GD 21. There were no significant necropsy findings attributed to SCH 619734.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.): For all rats at scheduled sacrifice, the uteri of pregnant females with at least one viable fetus were removed and weighed. The numbers and distribution of corpora lutea, implantation sites, fetuses (live and dead), and resorptions (early and late) were determined. The uteri of non-pregnant rats were examined for evidence of implantation sites. Placental observations were also performed. There were no significant treatment-related effects on reproductive parameters. The following tables (from page 99-100 of the report) show the cesarean section data.

03118

EMBRYO-FETAL DEVELOPMENTAL TOXICITY STUDY OF SCH 619734
ADMINISTERED ORALLY BY GAVAGE IN RATS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 619734 5 MG/KG	GROUP 3 SCH 619734 15 MG/KG	GROUP 4 SCH 619734 25 MG/KG
Pregnant	N	24	25	24	25
Dams with Viable Fetuses	N	24	25	23	24
Corpora Lutea	TOTAL	334	327	317	349
No. per animal	MEAN	13.9	13.1	13.2	14.0
	S.D.	1.77	1.78	3.18	1.40
Implantation Sites	TOTAL	312	307	298	330
No. per animal	MEAN	13.0	12.3	12.4	13.2
	S.D.	2.25	1.97	3.01	1.19
Preimplantation Loss	TOTAL	22	20	19	19
No. per animal	MEAN	0.9	0.8	0.8	0.8
	S.D.	1.38	0.96	0.98	1.05
% per animal	MEAN%	6.8	6.3	6.8	5.1
	S.D.	11.57	7.67	10.95	6.75
Live Fetuses	TOTAL	303	296	284	311
left horn		148	143	141	143
right horn		155	153	143	168
No. per animal	MEAN	12.6	11.8	11.8	12.4
	S.D.	2.45	2.03	3.17	2.90
Males	TOTAL	128	151	142	150
	MEAN%	41.7	50.2	50.3	47.9
	S.D.	12.69	13.69	11.29	12.37
Females	TOTAL	175	145	142	161
	MEAN%	58.3	49.8	49.7	52.1
	S.D.	12.69	13.69	11.29	12.37

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03118

EMBRYO-FETAL DEVELOPMENTAL TOXICITY STUDY OF SCH 619734
ADMINISTERED ORALLY BY GAVAGE IN RATS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 619734 5 MG/KG	GROUP 3 SCH 619734 15 MG/KG	GROUP 4 SCH 619734 25 MG/KG
Postimplantation Loss	TOTAL	9	11	14	19
No. per animal	MEAN	0.4	0.4	0.6	0.8
	S.D.	0.77	1.08	0.88	2.40
% implants per animal	MEAN%	3.3 k	3.4	7.9	6.2
	S.D.	6.47	7.97	20.73	20.04
Dead Fetuses	TOTAL	0	0	1	0
No. per animal	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.20	0.00
% of implants per animal	MEAN%	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.70	0.00
Resorptions: early+late	TOTAL	9	11	13	19
No. per animal	MEAN	0.4	0.4	0.5	0.8
	S.D.	0.77	1.08	0.88	2.40
% of implants per animal	MEAN%	3.3	3.4	7.6	6.2
	S.D.	6.47	7.97	20.79	20.04
Resorptions: Early	TOTAL	9	8	13	18
No. per animal	MEAN	0.4	0.3	0.5	0.7
	S.D.	0.77	1.03	0.88	2.39
% of implants per animal	MEAN%	3.3	2.3	7.6	5.8
	S.D.	6.47	7.39	20.79	19.90
Resorptions: Late	TOTAL	0	3	0	1
No. per animal	MEAN	0.0	0.1	0.0	0.0
	S.D.	0.00	0.33	0.00	0.20
% of implants per animal	MEAN%	0.0	1.0	0.0	0.4
	S.D.	0.00	2.85	0.00	1.82

Statistics performed: k-Kruskal Wallis +/- Dunn No statistically significant differences

Offspring (Malformations, Variations, etc.): Fetuses were examined for external, visceral and skeletal aberrations. There were no test article-related effects on fetal body weight.

There were no significant treatment-related fetal external, visceral or skeletal malformations.

Summary: In an oral embryofetal development study in rats, animals were treated with SCH 619734 at 5, 15 and 25 mg/kg/day from GD 6 through GD 17. There were no significant treatment-related effects on reproductive parameters. There were no significant treatment-related fetal external, visceral or skeletal malformations.

Study title: Embryo-Fetal Developmental Toxicity Study of SCH 619734 Administered Orally by Gavage in Rabbits

Study no.:	03119
Study report location:	EDR 4.2.3.5.2
Conducting laboratory and location:	Safety Evaluation Center, Schering-Plough Research Institute (SPRI), Lafayette, NJ
Date of study initiation:	February 23, 2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734, SZ-03-PHG-TX-001, 99.8%

Key Study Findings:

- In an oral embryofetal development study in New Zealand white rabbits, animals were treated with SCH 619734 at 5, 15 and 30 mg/kg/day from GD 7 through GD 19.
- There were no significant treatment-related effects on reproductive parameters.
- There were no significant treatment-related fetal external, visceral or skeletal malformations.

Methods:

Doses:	5, 15, 30 mg/kg/day
Frequency of dosing:	Once daily from GD 7 through 19
Dose volume:	2 mL/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose (pH = 4.0)
Species/Strain:	New Zealand white rabbits (pregnant females)
Number/Sex/Group:	20/dose
Satellite groups:	None
Study design:	Shown in the table below
Deviation from study protocol:	The protocol deviations did not adversely affect either the quality or integrity of the study or the interpretation of the results.

Basis of dose selection: Doses were selected based on the results of the oral dose ranging and pilot embryofetal development study (SN 03110) in rabbits. This study consisted of two phases. In Phase 1, animals (n = 6/dose) were treated with SCH 619734 orally (gavage) at 25, 100, 200 or 400 mg/kg/day from days 0 through 9. One rabbit at 100 mg/kg/day and all rabbits at 200 and 400 mg/kg/day were sacrificed on study Day 5, 6 or 8 due to decreased food consumption in conjunction with body weight loss and stool findings. In addition, one rabbit at 400 mg/kg/day exhibited abnormal posture and tremors. There was a slight decrease in food consumption in the remaining rabbit at 100 mg/kg/day. There were no treatment-related effects at 25 mg/kg/day. In Phase II, the potential maternal, embryofetal toxicity of SCH 619734 was assessed in pregnant rabbits administered single daily oral (gavage) doses of 25, 50 or 100 mg/kg on GD 7 through GD 19. One rabbit at 50 mg/kg/day and all rabbits at 100 mg/kg/day were sacrificed without reproductive or fetal evaluation on GD 11, 14 or 18 due to poor food consumption, body weight loss and related stool findings,. In the remaining rabbits at 50 mg/kg/day, there was a slight decrease in food consumption and body weight. At 25 and 50 mg/kg/day, there were no significant treatment-related effects on reproductive parameters, fetal weight or fetal external findings. The NOAEL for maternal toxicity was considered as 25 mg/kg/day and the NOAEL for embryo-fetal toxicity was considered as 50 mg/kg/day. Based on the results of this dose ranging study, the low, mid and high doses were selected as 5, 15 and 30 mg/kg/day, respectively, for the definitive embryo-fetal developmental study.

The study design is shown below (from page 11 of the report).

Embryo-Fetal Developmental Toxicity and Toxicokinetic Study of SCH 619734 Administered Orally by Gavage in Rabbits (SN 03119): **Study Design**

Group	Test/Control Article	Total Daily Dose (mg/kg)[a]	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Females[b]
1	Control (Methylcellulose)	0	2	0	20
2	Low-Dose (SCH 619734)	5	2	2.5	20
3	Mid-Dose (SCH 619734)	15	2	7.5	20
4	High-Dose (SCH 619734)	30	2	15	20

a: Total daily doses are expressed as the hydrochloride monohydrate salt. When expressed as the free base, daily doses were 4.5, 13.5 and 27.0 mg/kg for Groups 2, 3 and 4, respectively.

b: Four rabbits were selected from each group for toxicokinetic analysis.

Observations and Results:

Mortality: Mortality was checked once daily. Two rabbits (animal Nos. 2773 and 2792) at 30 mg/kg/day were euthanized on GD 12 and 14, respectively, due to poor food consumption for several days. This finding was associated with scant stool.

Clinical Signs: Clinical signs were observed twice daily. There were no test article-related clinical observations.

Body Weight: Body weight was recorded on gestation Days 0, 7, 10, 13, 16, 19, 22, 25 and 29. The mean initial (Day 0) and final (Day 29) body weights of control animals were 3.61 and 3.91 Kg, respectively. There were no significant treatment-related effects.

Food Consumption: Food consumption was recorded daily basis. The data were not provided. There were no significant treatment-related effects.

Toxicokinetics: Blood samples were collected on GD 19 at 1, 2, 4, 8 and 24 hr post-dose. Peak SCH 619734 plasma concentrations were achieved between 1 and 4 hr post-dose on GD 19. Systemic exposure to SCH 619734 increased with increasing dose; however, the increase was greater between 5 and 15 mg/kg/day than between 15 and 30 mg/kg/day, where the mean increase was less than dose-proportional. Toxicokinetic parameters for SCH 619734 are shown in the table below (from page 24 of the report).

Mean (CV) SCH 619734 Toxicokinetic Parameters on Gestation Day 19 Following Oral (Gavage) Administration of 5, 15 or 30 mg/kg SCH 619734 on Gestation Days 7 through 19 to Female Rabbits

SCH 619734 Dose (mg/kg)[a]	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)
5[b]	94.2 (78)	3 (38)	8 (0)	470 (61)	NR[c]
15[b]	640 (11)	3 (38)	24 (0)	7120 (21)	7120 (21)
30[d]	863 (31)	2 (35)	24 (0)	11000 (48)	11000 (48)

a: Expressed as the hydrochloride monohydrate salt. When expressed as the free base, daily doses were 4.5, 13.5 and 27.0 mg/kg for the 5, 15 and 30 mg/kg groups, respectively.
b: N = 4
c: NR = Not reportable. $AUC_{Extrapolated}$ >25% for all animals.
d: N = 3

Dosing Solution Analysis: Not provided

Necropsy: Necropsy was conducted at GD 29. There were no significant treatment-related necropsy findings.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.): For all rabbits at scheduled sacrifice, the uteri of pregnant females with at least one viable fetus were removed and weighed. The numbers and distribution of corpora lutea, implantation sites, fetuses (live and dead), and resorptions (early and late) were determined. The uteri of non-pregnant rats were examined for evidence of implantation sites. Placental observations were also performed. There were no significant treatment-related effects on reproductive parameters. The following tables (from page 100-101 of the report) show the cesarean section data.

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EMBRYO-FETAL DEVELOPMENTAL TOXICITY AND TOXICOKINETIC STUDY
OF SCH 619734 ADMINISTERED ORALLY BY GAVAGE IN RABBITS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 619734 5 MG/KG	GROUP 3 SCH 619734 15 MG/KG	GROUP 4 SCH 619734 30 MG/KG
Pregnant	N	19	20	17	17
Dams with Viable Fetuses	N	19	20	17	17
Corpora Lutea	TOTAL	188	201	170	176
No. per animal	MEAN	9.9	10.1	10.0	10.4
	S.D.	1.49	2.09	2.32	1.77
Implantation Sites	TOTAL	176	173	148	165
No. per animal	MEAN	9.3	8.6	8.7	9.7
	S.D.	2.02	2.94	3.00	1.99
Preimplantation Loss	TOTAL	12	28	22	11
No. per animal	MEAN	0.6	1.4	1.3	0.6
	S.D.	1.21	1.47	1.65	0.70
% per animal	MEAN%	6.7	15.8	14.1	6.6
	S.D.	12.80	19.26	19.85	7.45
Live Fetuses	TOTAL	171	164	144	154
left horn		82	68	72	73
right horn		89	96	72	81
No. per animal	MEAN	9.0	8.2	8.5	9.1
	S.D.	2.05	2.80	2.98	1.98
Males	TOTAL	92	86	75	80
	MEAN%	54.9	52.5	52.4	52.6
	S.D.	18.83	18.14	16.02	19.68
Females	TOTAL	79	78	69	74
	MEAN%	45.1	47.5	47.6	47.4
	S.D.	18.83	18.14	16.02	19.68

EMBRYO-FETAL DEVELOPMENTAL TOXICITY AND TOXICOKINETIC STUDY
OF SCH 619734 ADMINISTERED ORALLY BY GAVAGE IN RABBITS

SUMMARY OF CESAREAN SECTION DATA

		GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 619734 5 MG/KG	GROUP 3 SCH 619734 15 MG/KG	GROUP 4 SCH 619734 30 MG/KG
Postimplantation Loss	TOTAL	5	9	4	11
No. per animal	MEAN	0.3	0.4	0.2	0.6
	S.D.	0.56	0.51	0.44	0.86
% implants per animal	MEAN%	2.8 k	4.9	2.9	6.4
	S.D.	5.85	5.87	5.89	8.58
Dead Fetuses	TOTAL	0	0	1	0
No. per animal	MEAN	0.0	0.0	0.1	0.0
	S.D.	0.00	0.00	0.24	0.00
% of implants per animal	MEAN%	0.0	0.0	0.7	0.0
	S.D.	0.00	0.00	2.69	0.00
Resorptions: early+late	TOTAL	5	9	3	11
No. per animal	MEAN	0.3	0.4	0.2	0.6
	S.D.	0.56	0.51	0.39	0.86
% of implants per animal	MEAN%	2.8	4.9	2.3	6.4
	S.D.	5.85	5.87	5.52	8.58
Resorptions: Early	TOTAL	4	3	2	7
No. per animal	MEAN	0.2	0.2	0.1	0.4
	S.D.	0.42	0.37	0.33	0.87
% of implants per animal	MEAN%	2.2	1.5	1.8	4.2
	S.D.	4.51	3.83	5.40	8.72
Resorptions: Late	TOTAL	1	6	1	4
No. per animal	MEAN	0.1	0.3	0.1	0.2
	S.D.	0.23	0.47	0.24	0.44
% of implants per animal	MEAN%	0.5	3.4	0.4	2.2
	S.D.	2.29	5.53	1.73	4.19

Statistics performed: k=Kruskal Wallis +/- Dunn No statistically significant differences

Offspring (Malformations, Variations, etc.): Fetuses were examined for external, visceral and skeletal aberrations. There were no significant treatment-related fetal external, visceral or skeletal malformations.

Summary: In an oral embryofetal development study in New Zealand white rabbits, animals were treated with SCH 619734 at 5, 15 and 30 mg/kg/day from GD 7 through

GD 19. There were no significant treatment-related effects on reproductive parameters. There were no significant treatment-related fetal external, visceral or skeletal malformations.

9.3 Prenatal and Postnatal Development

The review of Study No. 03120 is incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP). While not discussed in Dr. Chakraborti's review, it is noted that in Study No. 03120, there were decreased body weights (compared to controls) in F1 pups in the 10 and 25 mg/kg/day SCH 619734 groups on postnatal day 1 (PND 1). Body weight gain in F1 pups was reduced (compared to controls) in the 25 mg/kg/day group during the pre-weaning period (PND 1-21).

Study title: Prenatal and Postnatal Developmental Toxicity and Maternal Function Study of SCH 619734 Administered Orally by Gavage in Rats

Study no.:	03120
Study report location:	EDR 4.2.3.5.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	February 5, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 619734, SZ-03-PHG-TX-001, 99.8%

Key Study Findings:

- In an oral (gavage) pre and postnatal development study in rats, animals (F0) were treated with SCH 619734 at 2.5, 10 and 25 mg/kg/day from GD 6 through LD 20.

F0:

- Mortality was observed at 25 mg/kg/day.
- Reductions of body weight and food consumption were observed at the high dose.
- At 25 mg/kg/day, a shorter mean gestation length was observed. In addition, 12 females at 25 mg/kg/day had prolonged parturition. Moreover, an increase in the number of unaccounted-for implantation sites was seen at 25 mg/kg/day.

F1:

- At 25 mg/kg/day, there were decreases in the mean number of pups born, live litter size on PND 0 and postnatal survival from birth to PND 0, PND 0 to 1, and PND 1 to 4 and birth to PND 4. Increases in the numbers of pups that did not have milk present in the stomach when examined internally during PND 0 through 4 and stillborn pups were noted at 25 mg/kg/day compared to the control group.
- For moribund pups (prior to weaning), clinical findings consisted of cyanosis, gasping, labored respiration and/or subcutaneous hemorrhage (ventral neck, dorsal head or mouth). Due to effects on pup survival to PND 4, all surviving pups at 25 mg/kg/day were euthanized on PND 21 (early group termination).
- There were no significant treatment-related effects on locomotor activity. In females, on PND 22, mean times to escape the maze and numbers of errors committed at 10 mg/kg/day were higher compared to control.

F2:

- There were no SCH 619734-related effects on litter size, pre- and postnatal survival or body weights at 2.5 and 10 mg/kg/day.

Methods: Females (F0) were administered single daily oral (gavage) doses at 2.5, 10 or 25 mg/kg/day on GD 6 through LD 20. The females were allowed to deliver naturally and rear their offspring until LD 21, at which time the F0 females were euthanized. One male and one female from each litter in the control, 2.5 and 10 mg/kg groups were randomly selected (F1) and retained for post-weaning measurements (neurobehavioral assessments and non-sibling matings to produce an F2 generation). The remaining rats from each litter and all pups at 25 mg/kg/day were euthanized on postnatal Day (PND) 21. Reproductive and offspring parameters were evaluated for the F1 and F2 generations. F1 females and F2 pups were euthanized on lactation day/PND 7.

Doses:	2.5, 10 and 25 mg/kg/day
Frequency of dosing:	Orally (gavage), once daily on GD 6 through lactation Day 20 (LD 20). Females that failed to deliver were dosed through post-mating Day 24.
Dose volume:	5 mL/kg
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose (pH 3.98 to 4.12)
Species/Strain:	New Zealand white rabbits
Number/Sex/Group:	25/dose
Satellite groups:	None
Study design:	Shown in the table below
Deviation from study protocol:	The protocol deviations did not adversely affect either the quality or integrity of the study or the interpretation of the results.

The following table (from page 21 of the report) shows the study design.

A Prenatal and Postnatal Developmental Toxicity and Maternal Function Study of SCH 619734 Administered Orally by Gavage in Rats (SN 03120): **Study Design**

Group	Test/Control Article	Daily Dose (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	Number of Females
1	Control (Methylcellulose)	0	0	5	25
2	Low-Dose (SCH 619734)	2.5	0.5	5	25
3	Mid-Dose (SCH 619734)	10	2	5	25
4	High-Dose (SCH 619734)	25	5	5	25

Observations and Measurements: The following table (from pages 22-23 of the report) shows the observations and measurements.

A Prenatal and Postnatal Developmental Toxicity and Maternal Function Study of SCH 619734 Administered Orally by Gavage in Rats (SN 03120): **Observations and Measurements**			
Investigation	F_0 Generation	F_1 Generation	F_2 Generation
Viability	Twice daily	Twice daily	Twice daily
Clinical Observations	Daily from gestation Day 0 through euthanasia. On days of dose administration, daily observations were performed prior to dose administration. Animals were also observed approximately 3 hours following dose administration.	Detailed physical examinations for each surviving pup were conducted on PND 1, 4, 7, 10, 14, 17 and 21 and weekly until euthanasia.	Detailed physical examinations for each surviving pup were conducted on PND 1, 4 and 7.
Body Weight	Gestation Days 0, 6, 9, 12, 15, 18 and 20; gestation Day 25 for females that failed to deliver Lactation Days 1, 4, 7, 10, 14, 17 and 21.	PND 1, 4, 7, 10, 14, 17 and 21 and weekly until euthanasia. Mated F_1 females weighed on gestation Days 0, 6, 9, 12, 15, 18 and 20 and lactation Days 1, 4 and 7. Females that failed to deliver were also weighed on gestation Day 25.	PND 1, 4 and 7.
Food Consumption	Gestation Days 0, 6, 9, 12, 15, 18 and 20; gestation Day 25 for females that failed to deliver Lactation Days 1, 4, 7, 10, 14, 17 and 21.	Weekly from PND 28 until euthanasia. Mated F_1 females also had food consumption recorded on gestation Days 0, 6, 9, 12, 15, 18 and 20 and lactation Days 1, 4 and 7. Females that failed to deliver also had food consumption recorded on gestation Day 25.	No
Parturition	Yes	Yes	No
Sex Determination	NA	PND 0, 4, 7, 14 and 21	PND 0, 4 and 7
Necropsy Observations	Lactation Day 21, post-mating Day 25 or within 24 hours of total litter loss	Nonselected pups: PND 21 Males: After last day of parturition of F_1 females Females: Lactation Day 7 or post-mating Day 25.	PND 7
Litter Size	NA	Yes	Yes
NA = Not Applicable PND = postnatal Day			

Investigation	F_0 Generation	F_1 Generation	F_2 Generation
Maturational and Behavioral Evaluations	No	Startle Response: Evaluated on PND 20 and 60 Locomotor Activity: Evaluated on PND 21 and 61 Learning and Memory: Evaluated on PND 22-28 (7 consecutive days) Vaginal Perforation: Evaluated daily beginning on PND 25 Balanopreputial Separation: Evaluated daily beginning on PND 35	No
Estrous Cycle Determination	No	Yes	No
PND = postnatal Day			

Results:

F0 Generation:

Mortality: Treatment-related mortality and moribundity were seen in five F0 females at 25 mg/kg/day on LD 2, 4 and 6. Female No. 54754 was found dead on LD 4, and female No. 54718 was euthanized *in extremis* on LD 2. Additionally, female Nos. 54711, 54670 and 54745 had total litter loss on LD 4, 0 and 4, respectively, and were euthanized on LD 6.

Clinical Signs: Clinical signs in the decedent/moribund animals included hunched posture, a pale and/or cool (to the touch) body, pale and/or cool (to the touch) limbs, red vaginal discharge and/or red material around the mouth and/or urogenital area and increased respiration and swollen limbs. There were no significant treatment-related clinical signs in surviving animals.

Body Weight: The mean initial (Day 0) and final (Day 20) body weights of control females were 254 and 390 g, respectively. Final body weights at low, mid and high dose were 98%, 100% and 93% of control, respectively.

Food consumption: The mean initial (Day 0) and final (Day 18) food consumption of control females were 19 and 25 g/animal/day, respectively. Final food consumption values at low, mid and high dose were 100%, 96% and 83 of control, respectively.

Uterine content: Eight females at 25 mg/kg/day delivered early on GD 20. Mean gestation length at 25 mg/kg/day (20.8 days) was shorter than the control (21.7 days) and the minimum mean value in the (b) (4) historical control data (21.5 days). An additional seven females at 25 mg/kg/day (Nos. 54670, 54677, 54715, 54722, 54725, 54738 and 54757) showed early signs of imminent delivery on GD 20 (e.g., vaginal discharge/material, enlarged vaginal opening and/or a pup in the birth canal). Test article-related signs of dystocia were also noted at 25 mg/kg/day. In addition, twelve females at the high dose had prolonged parturition (palpable fetuses were present approximately 17 hours or longer following the first observation of pups, parturition lengths were greater than 20 hours and/or retained fetuses or placentae were present at necropsy). Nine of the 12 females with prolonged parturition delivered or had signs of imminent delivery on GD 20, while the three remaining females delivered on GD 21. In addition, 5 of the 12 females with prolonged parturition were found dead or euthanized *in extremis*. The following table (from page 57 of the report) summarizes the varied relationship between gestation length, prolonged parturition and/or moribundity, abnormal nesting and nursing behaviors and pup survival.

RELATIONSHIP BETWEEN GESTATION LENGTH, PROLONGED PARTURITION AND/OR MORIBUNDITY, ABNORMAL NESTING AND NURSING BEHAVIORS AND PUP SURVIVAL

Delivery Day	8 females delivered on gestation Day 20			7 females had early signs of imminent delivery on gestation Day 20, but delivered or were presumed to have delivered after gestation Day 20			10 females did not have early signs of imminent delivery and delivered after gestation Day 20		
Prolonged Parturition[a]/ Moribundity	6 of 8 females had prolonged parturition; 2 of these 6 had signs of moribundity		2 of 8 females did not have prolonged parturition	3 of 7 females had prolonged parturition; 1 of these 3 had signs of moribundity		4 of 7 females did not have conclusive evidence of prolonged parturition	3 of 10 females had prolonged parturition; 2 of these 3 had signs of moribundity	7 of 10 females did not have prolonged parturition	
Litter Outcome	5 of 6 females had total litter loss or decreased pup survival from birth to PND 4; 3 of 5 females had abnormal nursing/ nesting findings	1 of 6 females did not have decreased pup survival	2 of 2 females had total litter loss; 2 of 2 females had indications of abnormal nursing/ nesting findings	2 of 3 females had total litter loss; 1 of 3 females had abnormal nursing/ nesting findings	1 of 3 females did not have decreased pup survival	4 of 4 females had total litter loss or decreased pup survival from birth to PND 4	3 of 3 females had total litter loss or decreased pup survival from PND 0-1; 1 of 3 females had abnormal nursing/ nesting findings	5 of 7 females had total litter loss or decreased pup survival from birth to PND 4; 1 of 5 females had abnormal nursing/ nesting findings	2 of 7 females did not have decreased pup survival

a: Prolonged parturition was defined as the presence of palpable fetuses approximately 17 hours or longer following the first observation of pups present in the nesting box, parturition lengths greater than 20 hours and/or retained fetuses or placentae present at necropsy

Necropsy observation: A statistically significant increase in the mean number of unaccounted-for implantation sites (difference between the number of implantation sites and number of pups born) was observed at 25 mg/kg/day compared to the control and the value was also higher than the maximum mean value in the (b) (4) historical control data. Female No. 54722 at 25 mg/kg/day that failed to deliver had 11 implantation sites,

10 of which were noted in the absence of identifiable resorptions or fetuses and one was noted with one late resorption. The following table (from page 518 of the report) shows the summary of implantation sites.

(b) (4)370063 TABLE 28 (F0) PAGE 1
PROJECT NO.
SPONSOR:SCHERING-PLOUGH ORAL PRE/POSTNATAL DEV & MATERNAL FUNCTION OF SCH 619734 IN RATS
SPONSOR NO.:SN 03120 SUMMARY OF IMPLANTATION SITES

GROUP:	0 MG/KG/DAY	2.5 MG/KG/DAY	10 MG/KG/DAY	25 MG/KG/DAY
IMPLANTATION SITES				
MEAN	15.0	15.1	15.6	14.2
S.D.	2.46	1.36	1.62	1.47
S.E.	0.51	0.30	0.34	0.32
N	23	20	23-A	21-A
NUMBER BORN				
MEAN	14.3	14.2	14.4	11.5*
S.D.	2.12	1.57	2.02	3.98
S.E.	0.44	0.35	0.41	0.81
N	23	20	24-B	24
UNACCOUNTED SITES				
MEAN	0.7	0.9	1.3	2.5*
S.D.	1.29	1.02	1.39	3.17
S.E.	0.27	0.23	0.29	0.69
N	23	20	23-A	21-A

IMPLANTATION SITES, NUMBER BORN AND UNACCOUNTED SITES WERE STATISTICALLY ANALYZED AS SPECIFIED IN THE PROTOCOL
* - SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP AT 0.05 USING DUNNETT'S TEST
NOTE: ONLY DAMS THAT HAVE DELIVERED ONE OR MORE PUPS ARE INCLUDED IN CALCULATION OF MEAN.
A - THE NUMBER OF PUPS BORN, RETAINED FETUSES AND/OR RESORPTIONS EXCEEDED THE NUMBER OF IMPLANTATION SITES FOR 2 FEMALES EACH (INCLUDING FEMALE NO. 54746 THAT WAS FOUND DEAD ON LACTATION DAY 0) IN THE 10 MG/KG/DAY AND 25 MG/KG/DAY GROUPS; THE NUMBER OF IMPLANTATION SITES EXCEEDED THE NUMBER OF CORPORA LUTEA FOR 1 FEMALE IN THE 25 MG/KG/DAY GROUP EXAMINED ON LACTATION DAY 2. VALUES FOR THESE FEMALES NOT INCLUDED IN CALCULATION OF MEAN.
B - FEMALE NO. 54746 WAS FOUND DEAD ON LACTATION DAY 0 WITH RETAINED FETUSES IN UTERO; NOT INCLUDED IN CALCULATION OF MEAN.

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F1 Generation:

Survival: There was no test article-related mortality.

Clinical signs: In moribund pups, clinical sings included cyanosis, gasping, labored respiration and/or subcutaneous hemorrhage (ventral neck, dorsal head or mouth). All surviving pups at 25 mg/kg/day were euthanized on PND 21 (early group termination). There was no significant treatment-related clinical sings in surviving pups.

Body weight: The mean initial (PND 28) and final (PND 126) body weights of control males were 88 and 577 g, respectively. The mean initial (PND 28) and final (PND 84) body weights of control females were 79 and 271 g, respectively. There were no significant treatment-related effects on mean F1 body weights or body weight gains in either sex.

Food consumption: The mean initial (PND 28-35) and final (PND 119-126) food consumption of control males were 19 and 31 g/animal/day, respectively. The mean initial (PND 28-35) and final (PND 77-84) body weights of control females were 16 and 21 g/animal/day, respectively. There were no significant treatment-related effects.

Physical development: There were no significant treatment-related effects on balanopreputial separation and vaginal patency.

Neurological assessment: There were no significant treatment-related effects on acoustic startle response and locomotor activity. A test article-related effect on memory was noted for the females at 10 mg/kg/day on PND 22. Mean times to escape the maze during trial No. 11 and 12 (79.36 and 76.65 seconds, respectively) were higher than the control group values (60.38 and 34.18 seconds for the respective trials) and the mean value in the (b) (4) historical control data for trial No. 12 (58.2 seconds). Additionally, the number of errors committed for these females during the same trials (22 and 20 errors for trial Nos. 11 and 12, respectively) were also higher than the control group values (17 and 7 errors for the respective trials) and the mean value in the (b) (4) historical control data for trial No. 12 (13.7 errors). The higher mean times to escape and numbers of errors committed during the memory probe (particularly for trial No. 12) at 10 mg/kg/day were considered treatment-related.

Reproduction: There were no significant treatment-related effects on reproductive performance parameters including gestational length and parturition. The following table (from page 1160 of the report) shows the summary of reproductive performance data.

TABLE 62 (F1)

PROJECT NO.: (b) (4)370063D — ORAL PRE/POSTNATAL DEV & MATERNAL FUNCTION OF SCH 619734 IN RATS — PAGE 1
SPONSOR:SCHERING-PLOUGH
SPONSOR NO.:SN 03120
SUMMARY OF REPRODUCTIVE PERFORMANCE

DOSE GROUP :	1		2		3		4	
	NO.	%	NO.	%	NO.	%	NO.	%
FEMALES ON STUDY	22		20		24		0	
FEMALES THAT DIED DURING STUDY	0		0		0		NA	
FEMALES SELECTED TO DELIVER	22		20		24		NA	
NONGRAVID	2	9.1	1	5.0	0	0.0	NA	NA
GRAVID	20	90.9	19	95.0	24	100.0	NA	NA
DELIVERED	20	100.0	19	100.0	24	100.0	NA	NA
FEMALES WITH TOTAL LITTER LOSS	0	0.0	0	0.0	0	0.0	NA	NA
FEMALES WITH VIABLE PUPS	20	100.0	19	100.0	24	100.0	NA	NA
FAILED TO DELIVER	0	0.0	0	0.0	0	0.0	NA	NA
FEMALES WITH EVIDENCE OF MATING	21	95.5	20	100.0	24	100.0	NA	NA
NUMBER THAT DELIVERED	19	90.5	19	95.0	24	100.0	NA	NA
NUMBER THAT DID NOT DELIVER	2	9.5	1	5.0	0	0.0	NA	NA
FEMALES WITH NO EVIDENCE OF MATING	1	4.5	0	0.0	0	0.0	NA	NA
NUMBER THAT DELIVERED	1	100.0	0	NA	0	NA	NA	NA
NUMBER THAT DID NOT DELIVER	0	0.0	0	NA	0	NA	NA	NA
TOTAL FEMALES GRAVID	20	90.9	19	95.0	24	100.0	NA	NA

1- 0 MG/KG/DAY 2- 2.5 MG/KG/DAY 3- 10 MG/KG/DAY 4- 25 MG/KG/DAY

NOTE: POSITIVE EVIDENCE OF MATING DURING THE BREEDING PERIOD WAS CONFIRMED BY THE PRESENCE OF SPERM IN A VAGINAL LAVAGE OR A VAGINAL COPULATORY PLUG.
NA = NOT APPLICABLE

(b) (4)

PROJECT NO.: 370063D — TABLE 62 (F1) — PAGE 2
SPONSOR:SCHERING-PLOUGH — ORAL PRE/POSTNATAL DEV & MATERNAL FUNCTION OF SCH 619734 IN RATS
SPONSOR NO.:SN 03120 — SUMMARY OF REPRODUCTIVE PERFORMANCE

DOSE GROUP :	1		2		3		4	
	NO.	%	NO.	%	NO.	%	NO.	%
MALES ON STUDY	22		20		24		0	
MALES THAT DIED DURING STUDY	0		0		1-A		NA	
MALES WITH EVIDENCE OF MATING	21	95.5	18	90.0	24	100.0	NA	NA
NO. THAT SIRED A LITTER	19	90.5	17	94.4	24	100.0	NA	NA
NO. THAT DID NOT SIRE A LITTER	2	9.5	1	5.6	0	0.0	NA	NA
MALES WITH NO EVIDENCE OF MATING	1	4.5	2	10.0	0	0.0	NA	NA
NO. THAT SIRED A LITTER	1	100.0	0	0.0	0	NA	NA	NA
NO. THAT DID NOT SIRE A LITTER	0	0.0	2	100.0	0	NA	NA	NA
MALES THAT SIRED MORE THAN ONE LITTER	0	NA	2	NA	0	NA	NA	NA

1- 0 MG/KG/DAY 2- 2.5 MG/KG/DAY 3- 10 MG/KG/DAY 4- 25 MG/KG/DAY

NOTE: MALES WERE CONSIDERED TO HAVE SIRED A LITTER IF THE PAIRED FEMALE WAS GRAVID
NOTE: POSITIVE EVIDENCE OF MATING DURING THE BREEDING PERIOD WAS CONFIRMED BY THE PRESENCE OF SPERM IN A VAGINAL LAVAGE OR A VAGINAL COPULATORY PLUG
NA = NOT APPLICABLE
A = MALE NO. 54669-14 WAS EUTHANIZED IN EXTREMIS FOLLOWING THE MATING PERIOD; INCLUDED IN CALCULATIONS

(b) (4)

PROJECT NO.: 370063D — TABLE 62 (F1) — PAGE 3
SPONSOR:SCHERING-PLOUGH — ORAL PRE/POSTNATAL DEV & MATERNAL FUNCTION OF SCH 619734 IN RATS
SPONSOR NO.:SN 03120 — SUMMARY OF REPRODUCTIVE PERFORMANCE

DOSE GROUP :	1		2		3		4	
	NO.	%	NO.	%	NO.	%	NO.	%
MALE MATING INDEX	22/22	100.0	18/20	90.0	24/24	100.0	NA	NA
FEMALE MATING INDEX	22/22	100.0	20/20	100.0	24/24	100.0	NA	NA
MALE FERTILITY INDEX	20/22	90.9	17/20	85.0	24/24	100.0	NA	NA
FEMALE FERTILITY INDEX	20/22	90.9	19/20	95.0	24/24	100.0	NA	NA
MALE COPULATION INDEX	20/22	90.9	17/18	94.4	24/24	100.0	NA	NA
FEMALE CONCEPTION INDEX	20/22	90.9	19/20	95.0	24/24	100.0	NA	NA
MEAN PRE-COITAL INTERVALS (DAYS)	3.0	NA	3.9	NA	3.3	NA	NA	NA
S.D.	1.86	NA	4.06	NA	1.46	NA	NA	NA
S.E.	0.41	NA	0.91	NA	0.30	NA	NA	NA
N	21	NA	20	NA	25	NA	NA	NA

$$\text{MALE (FEMALE) MATING INDEX (\%)} = \frac{\text{NO. OF MALES (FEMALES) WITH EVIDENCE OF MATING (OR CONFIRMED PREGNANCY)}}{\text{TOTAL NO. OF MALES (FEMALES) USED FOR MATING}} \times 100$$

$$\text{MALE FERTILITY INDEX (\%)} = \frac{\text{NO. OF MALES SIRING A LITTER}}{\text{TOTAL NO. OF MALES USED FOR MATING}} \times 100$$

$$\text{MALE COPULATION INDEX (\%)} = \frac{\text{NO. OF MALES SIRING A LITTER}}{\text{NO. OF MALES WITH EVIDENCE OF MATING (OR FEMALES CONFIRMED PREGNANT)}} \times 100$$

$$\text{FEMALE FERTILITY INDEX (\%)} = \frac{\text{NO. OF FEMALES WITH CONFIRMED PREGNANCY}}{\text{TOTAL NO. OF FEMALES USED FOR MATING}} \times 100$$

$$\text{FEMALE CONCEPTION INDEX (\%)} = \frac{\text{NO. OF FEMALES WITH CONFIRMED PREGNANCY}}{\text{NO. OF FEMALES WITH EVIDENCE OF MATING (OR CONFIRMED PREGNANCY)}} \times 100$$

1- 0 MG/KG/DAY 2- 2.5 MG/KG/DAY 3- 10 MG/KG/DAY 4- 25 MG/KG/DAY

PRE-COITAL INTERVALS AND MATING, FERTILITY, COPULATION AND CONCEPTION INDICES STATISTICALLY ANALYZED AS SPECIFIED IN THE PROTOCOL BUT WERE NOT SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP
NA = NOT APPLICABLE

Necropsy: There were no significant treatment-related necropsy findings.

F2 Generation:

Survival: The mean number of pups born, live litter size, percentage of males per litter at birth and postnatal survival from birth to PND 0 (relative to number born), PND 0 to 1, 1 to 4, 4 to 7, birth to PND 7 and PND 1 to 7 were unaffected by the F0 maternal treatment with SCH 619734.

Body weight: The mean initial (PND 1) and final (PND 7) body weights of control males were 7.3 and 14.9 g, respectively. The mean initial (PND 1) and final (PND 7) body weights of control females were 7.0 and 14.3 g, respectively. There were no significant treatment-related effects on mean F2 body weights in either sex.

Necropsy: There were no significant treatment-related necropsy findings.

Summary: In an oral (gavage) pre and postnatal development study in rats, animals (F0) were treated with SCH 619734 at 2.5, 10 and 25 mg/kg/day from GD 6 through LD 20. Mortality, reductions of body weight and food consumption were observed at the high dose. At 25 mg/kg/day, SCH 619734 caused shortened mean gestation length, prolonged parturition, increase in the number of unaccounted-for implantation sites, decreases in the mean number of pups born, live litter size and postnatal survival, increases in the numbers of stillborn pups when compared to respective control. In moribund pups (F1), clinical sings included cyanosis, gasping, labored respiration and/or subcutaneous hemorrhage (ventral neck, dorsal head or mouth). All surviving pups at 25 mg/kg/day were euthanized on PND 21 (early group termination). There were no significant treatment-related effects on locomotor activity in F1 pups. In F1 females, on PND 22, mean times to escape the maze and numbers of errors committed at 10 mg/kg/day were higher compared to control. For F2 pups, there were no SCH 619734-related effects on litter size, pre- and postnatal survival or body weights at 2.5 and 10 mg/kg/day. The NOAEL for F0 maternal toxicity was considered to be 10 mg/kg/day based on mortality/moribund condition, total litter loss, prolonged parturition, decreased gestation length, increased number of unaccounted-for implantation sites and effects on body weights and food consumption at 25 mg/kg/day. The NOAEL for offspring (F1) effects was considered as 2.5 mg/kg/day based on decreased postnatal survival at 25 mg/kg, decreased pup body weights at 10 and 25 mg/kg/day and effects on memory at 10 mg/kg/day. The NOAEL for the F2 generation was considered as ≥10 mg/kg/day, the highest tested dose.

10 Special Toxicology Studies

Local Tolerance (Intravenous, Intra-arterial, Intramuscular and Paravenous) Study of SCH 619734 in Male Rabbits (07398)

Methods: This study was conducted to evaluate the local irritation potential of SCH 619734 IV solution (2 mg/mL) following four routes of administration. IV injection was identified as the target route of administration, whereas the other routes (intra-arterial,

intramuscular, and paravenous) were considered as potential routes of mis-dosing. One group of male New Zealand white rabbits (n=9) was administered single IV and intramuscular injections (both 0.5 mL) of 1 mg SCH 619734. A second set of male rabbits (n=9) was administered a single intra-arterial dose of 1 mg SCH 619734 (0.5 mL dose volume) and a single paravenous dose of 0.4 mg SCH 619734 (0.2 mL dose volume). As a comparative control, contralateral sites were injected with 0.9% sodium chloride for injection. Animals were observed for viability, clinical signs, and local irritation at dosing sites at least twice daily, with the exception of a single evaluation on the day of sacrifice. Animals were sacrificed 1, 4, or 7 days after dosing and the injection sites and surrounding areas were examined histopathologically.

Results: There were no mortalities, treatment-related clinical signs, or observations of local tissue irritation at the dosing sites. At necropsy, there were no treatment-related macroscopic findings for any route of administration. Microscopic findings for the intra-arterial route of administration were similar for the test article and control. For the IV route of injection, minimal focal subcutaneous edema was observed in 2/3 SCH 619734 treated rabbits on Day 4, while findings for the test article and control were similar on Days 1 and 7. For the intramuscular route of administration, minimal acute (focal) necrosis and minimal hemorrhage were observed in 1/3 SCH 619734-injected rabbits on Day 1. On Day 4, minimal to mild mixed inflammatory cell infiltration, minimal focal edema, and minimal to mild necrosis occurred at SCH 619734 intramuscular injection sites. At the paravenous injection sites, SCH 619734-related findings included minimal mononuclear cell infiltration on Days 1 and 4 (3/3 and 2/3 rabbits, respectively), and mild or moderate focal edema on Day 4 (3/3 rabbits). On Day 7, mild fibrosis was observed in 1/3 rabbits. Limited findings for the IV and intramuscular routes of administration not observed in concurrent controls were considered common incidental findings, while findings for the paravenous route were concluded to be test-compound related. Changes observed at intramuscular injection sites were reported to be consistent with findings observed previously in control rabbits in a study of a similar study design. Thus, SCH 619734 was considered to be slightly more irritating when administered via paravenous injection, as compared to the concurrent saline control.

Review of Study No. 06533 is incorporated below from the pharmacology review of IND (b) (4) dated August 14, 2013 (Tamal Chakraborti, Ph.D., DGIEP).

Investigative Study of the Effects of SCH 619734 on Rat Hormone Levels During Pregnancy: Reversibility of Effects on Female Fertility and Early Embryonic Development (Study No. 06533)

Methods: This study was conducted in two phases. The objective of the first phase was to assess the effects of SCH 619734 on serum levels of prolactin (PRL), estradiol (E2), and progesterone (P4) in female rats when administered orally by gavage on GD 0 through GD 7. The objective of the second phase was to assess the reversibility of SCH 619734-mediated effects on female fertility, early embryonic development and potential alterations in hormone levels. This was assessed by examining the fertility and early

embryonic development of dams that have been previously dosed on GD 0 through GD 7, allowed to undergo parturition and re-mated once regular cyclicity was evidenced. Serum hormone levels of these dams were examined on GD 5 of the subsequent pregnancy. In both Phase 1 and 2 of the study, pregnant rats were treated with SCH 619734 at 25 mg/kg/day.

Results: SCH 619734 decreased body weight gain and food consumption when compared to control. However, after re-mating (Phase 2), previous administration of SCH 619734 did not affect subsequent gestation body weight gain or food consumption. In Phase 1, administration of SCH 619734 resulted in fewer pregnancies and decreased number of implantation sites and corpora lutea and increased pre-implantation loss. In addition, complete post-implantation loss was also observed in the SCH 61973 treated animals. In Phase 2, administration of SCH 619734 also resulted in fewer pregnancies (like Phase 1) and subsequently fewer litters. SCH 619734 also prolonged gestation by an average of eight days. These dams delivered normal pups; however, live litter size was lower at birth. Pup weights on lactation Day 1 were not affected by the treatment. When the dams were subsequently re-mated, there were no persistent effects on fertility and development. Prolactin, estradiol, and progesterone levels were unaffected by SCH 619734 on GD 5 during Phase 1 and after re-mating during Phase 2. These data suggested that the SCH 619734-mediated effects on fertility and early embryonic development in female rats were probably not mediated by changes in prolactin, estradiol, or progesterone. Administration of SCH 619734 during the first week of gestation increased implantation loss, delayed implantation and subsequently parturition.

Review of Study No. 6000033 (Audited Draft Report) is incorporated below from the pharmacology review of IND 72,754 dated December 5, 2012 (Tamal Chakraborti, Ph.D., DGIEP).

In Vitro Evaluation of the Influence of Rolapitant on Human Whole Blood Hemolysis (Study No. 6000033)

Methods: The objective of this study was to evaluate the hemolytic potential of rolapitant using whole human blood. In this study, blood samples were collected from 6 subjects (n = 3/sex). Prior to the incubation (37°C for 1 hour), blood samples were spiked with negative control (0.9% NaCl), positive control (20% saponin) or rolapitant at 0.01, 0.025 and 0.1 mg/mL (final concentration). At the end of the incubation period, hemolysis was evaluated by determination of whole blood hematocrit, whole blood hemoglobin concentration, plasma hemoglobin concentration, plasma hemolytic index and visual macroscopic hemolysis assessment.

Results: Results of positive and negative controls were considered acceptable for all the samples. No significant hemolysis was observed with rolapitant at any tested concentrations based on the released hemoglobin from red blood cells to the plasma.

11 Integrated Summary and Safety Evaluation

Tesaro, Inc. is seeking approval to market rolapitant tablets for use in adult patients in combination with other antiemetic agents for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. Rolapitant is a substance P / neurkokinin 1(NK-1) receptor antagonist, and the recommended dosage is 180 mg rolapitant (equivalent to 200 mg rolapitant hydrochloride) given orally. Rolapitant can be administered prior to the initiation of each chemotherapy cycle, but at no less than 2 week intervals. The Applicant has conducted pharmacology, pharmacokinetics/ADME/toxicokinetics, single- and repeat dose general toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicology, and special toxicology studies with rolapitant in support of the NDA.

In radioligand binding assays, rolapitant (also known as SCH 619734) and metabolite SCH 720881 bind with high affinity to the human NK-1 receptor, and there were no significant affinities for other receptors, transporters, enzymes, and channels tested. *In vitro*, rolapitant was shown to be a competitive antagonist as demonstrated through inhibition of NK-1 receptor agonist-mediated stimulation of calcium efflux. In vivo, SCH 619734 demonstrated antiemetic activity in an animal model of chemotherapy-induced emesis.

In safety pharmacology studies, SCH 619734 did not produce any effects on respiratory, CNS, renal, or gastrointestinal parameters. Although in vitro studies showed that SCH 619734 inhibited hERG channel current (IC50 = 1.05 µM) and shortened action potential duration in isolated canine cardiac purkinje fibers at 8.04 µM, the IC50 for hERG channel current inhibition represents at least a 278-fold exposure multiple over the free drug Cmax at the clinical dose. Furthermore, SCH 619734 produced no treatment-related changes in heart rate, blood pressure, ECG intervals, or ECG morphology in telemetered monkeys. The IC50 for inhibition of hERG channel current by metabolite 720881 (5.8 µM) was higher than that of SCH 619734.

SCH 619734 was rapidly absorbed, with oral bioavailability of 47-71% in rats and higher in monkeys. SCH 619734 and metabolite SCH 720881 exhibit high plasma protein binding (≥99%), and are distributed to the brain and highly brain tissue-bound in rats. SCH 619734 is extensively metabolized, with the primary routes of metabolism in rat and monkey being oxidation and glucuronidation. Metabolite SCH 720881 (formed by oxidation of SCH 619734) is a major circulating metabolite in humans, rats, and monkeys. Biliary excretion into the feces was the major route of elimination SCH 619734 in rats and monkeys, and the half-life in rats and Cynomolgus monkeys was approximately 6 and 8 h, respectively. In postpartum female rats dosed with radiolabelled drug, milk radioactivity concentrations were higher than the time point-paired concentrations in blood and plasma samples from dams. However, the Applicant estimated that based on an assumed average daily consumption of milk in nursing pups and the maximum milk radioactivity concentration, pup exposure was <1% of the orally administered dose. In cultured human hepatocytes, SCH 619734 caused a concentration-dependent increase in CYP1A2 and CYP3A4/6 activity. Evaluation of CYP3A4 induction through the PXR pathway showed maximum induction at 10 µM. SCH 619734 caused direct inhibition of CYP2B6, CYP2C9, CYP2C19, and CYP2D6 with IC50 values of 13, 9.6, 8.7, and 7.1 µM, respectively; and, SCH 619734 was a competitive inhibitor of CYP2D6 with a Ki value of 3.4 µM. SCH 619734 inhibited p-Glycoprotein (Pgp) with an IC50 of 7.4 µM, and also inhibited the breast cancer resistance protein (BCRP) transporter with an IC50 of 0.172 µM (applying the corrected efflux ratio) or 4.55 µM using the B-A permeability coefficient.

Comparison of exposures of rolapitant in animals relative to humans is complicated in several respects. The half-lives of rolapitant and its major metabolite (SCH 720881) are markedly longer in humans (169-183 h for rolapitant) than in Cynomolgus monkeys and rats (6-8 h for rolapitant). Furthermore, repeat-dose toxicology, carcinogenicity, and reproductive and developmental toxicity studies employed repeated daily dosing, whereas the recommended dosing regimen in humans is a single dose per treatment cycle. Given differences in half-lives, the Applicant considered direct comparison of steady-state $AUC_{0\text{-}24h}$ values in animals to $AUC_{0\text{-}\infty}$ values following a single dose in humans to be misleading. Thus, to allow for a comparison of cumulative total exposure in animals relative to the total exposure in humans over the same timeframe, the Applicant estimated animal “AUC Projected” values by multiplying the daily, steady-state $AUC_{0\text{-}24h}$ values for SCH 619734 and metabolite SCH 720881 in animals by a factor of 21 days (or the total number of days of animal exposure for the embryofetal development studies). The Applicant then compared “AUC Projected” values in animals to human $AUC_{0\text{-}\infty}$ values produced by the recommended single oral dose per treatment cycle for exposure comparisons. Rather than using the Applicant’s approach, exposure multiples estimated on a body surface area basis (mg/m^2) will be used for exposure comparison.

In single dose oral toxicity studies, 500 and 300 mg/kg rolapitant hydrochloride in rats and mice, respectively, produced lethality or moribund condition. A single intraperitoneal dose of 500 mg/kg rolapitant hydrochloride produced mortality in rats. In

a single dose oral toxicity study in monkeys, 200 mg/kg rolapitant hydrochloride produced moribund condition.

In rodents, rolapitant hydrochloride was tested in repeated dose oral toxicity studies up to 26-weeks in duration, and the liver and thyroid were identified as target organs. In 3-month toxicity studies in mice and rats, there were increased liver weights, hepatocellular hypertrophy, and increased CYP gene expression. In a 3-month toxicity study in rats, increased thyroid weights and follicular cell hyperplasia occurred. In the chronic 26-month oral toxicity study in which rats were treated with 25, 50, and 100 mg/kg/day, there were dose-dependent increases in liver weights, which correlated with histopathological findings such as hepatocellular hypertrophy. In the thyroid, the incidence of follicular cell hypertrophy was increased at all doses and relative thyroid weights were increased at the high dose. Although a NOAEL was established in the 26-week toxicity study, changes in the liver and thyroid appear to be related to the activation of drug metabolizing enzymes and may not be relevant to humans.

In rats, treatment-related minimal vacuolation in the epididymis was observed in two toxicity studies with rolapitant hydrochloride. In the 3-month toxicity study, the no observed effect level (NOEL) for this finding was 5 mg/kg/day; whereas this finding occurred at all dose levels in the 26-week study (≥25 mg/kg/day). Overall, the observed vacuolation was not considered adverse since the changes were minimal and did not increase in severity with longer duration treatment. In a reproductive and developmental toxicity study, male mating and fertility indices and early embryonic development were not affected by up to 100 mg/kg/day rolapitant hydrochloride (equivalent to 90 mg/kg/day rolapitant free base). This dose is about 4.9 times the recommended human dose on a body surface area basis.

Repeat-dose toxicity oral studies of rolapitant hydrochloride for up to 39-weeks in duration were conducted in monkeys. In a 1-month study, doses of 60 and 100 mg/kg/day produced severe toxicity which necessitated premature sacrifice of animals in these dose groups following 1-3 days of dosing. In a 3-month study, there were no significant treatment-related effects at up to 15 mg/kg/day (the highest dose tested). In the chronic 39-week oral toxicity study in Cynomolgus monkeys, the NOAEL was considered to be the highest dose tested (30 mg/kg/day rolapitant hydrochloride; equivalent to 27 mg/kg/day rolapitant free base). This NOAEL is approximately 2.9 times the recommended human dose on a body surface area basis.

Incidences of convulsions were observed following administration of rolapitant hydrochloride in multiple species. In mice, oral doses of ≥300 mg/kg/day and intraperitoneal doses of ≥125 mg/kg/day produced convulsions. In rats, convulsions occurred following a single IP dose of 1000 mg/kg and in a single animal given 125 mg/kg/day in a 3-month oral toxicity study. In monkeys, there were incidences of convulsions in animals given a single oral dose of ≥100 mg/kg, 3 oral doses of 60 mg/kg/day, and intravenous doses of 20 mg/kg/day. While this finding occurred in acute and subchronic studies, there were no incidences of convulsions in chronic oral toxicity studies in rats and monkeys, or in two additional single-dose studies in monkeys with

100 mg/kg/day conducted to further investigate this finding. In rats, there were no convulsions following treatment for 26-weeks at the highest dose tested (100 mg/kg/day rolapitant hydrochloride; equivalent to 90 mg/kg/day rolapitant free base). This dose is approximately 4.9 times the recommended human dose on a body surface area basis. In the 39-week toxicity study in monkeys, the highest dose tested was the NOAEL (30 mg/kg/day rolapitant hydrochloride, equivalent to 27 mg/kg/day free base). This NOAEL is approximately 2.9 times the recommended human dose on a body surface area basis.

Rolapitant hydrochloride was negative in the Ames test, chromosome aberration assay, and mouse bone marrow micronucleus assay. In addition, metabolite SCH 720881 was negative in the Ames test and chromosome aberration assay. In 2-year oral carcinogenicity studies in mice and rats, there were no statistically significant, treatment-related neoplastic findings at rolapitant hydrochloride doses up to 150 and 100 mg/kg/day, respectively (equivalent to 135 and 90 mg/kg/day rolapitant free base, respectively).

In an oral fertility and early embryonic development study in female rats, there was a transient decrease in body weight gain in maternal animals and increases in pre- and post-implantation losses at a rolapitant hydrochloride dose equivalent to 9 mg/kg/day rolapitant free base. At rolapitant hydrochloride doses equivalent to ≥4.5 mg/kg/day rolapitant free base, there was a slight decrease in the number of corpora lutea and implantation sites. In an oral fertility and early embryonic development study, male mating and fertility indices and early embryonic development were not affected at up to 100 mg/kg/day rolapitant hydrochloride (equivalent to 90 mg/kg/day rolapitant free base). In embryofetal development studies of rolapitant hydrochloride administered by oral gavage to rats and rabbits, there were no significant treatment-related effects on reproductive parameters or fetal external, visceral, or skeletal malformations at doses equivalent to up to 22.5 and 27 mg/kg/day rolapitant free base, respectively. In an oral pre- and postnatal development study in rats, the NOAEL for F0 maternal toxicity was 10 mg/kg/day rolapitant hydrochloride (equivalent to 9 mg/kg/day rolapitant free base) based on mortality/moribund condition, total litter loss, prolonged parturition, decreased gestation length, increased number of unaccounted-for implantation sites and effects on body weights and food consumption at 25 mg/kg/day. The NOAEL for offspring (F1) effects was 2.5 mg/kg/day rolapitant hydrochloride (equivalent to 2.25 mg/kg/day rolapitant free base) based on decreased postnatal survival and body weight gain at 25 mg/kg/day, decreased pup body weights at 10 and 25 mg/kg/day, and effects on memory at 10 mg/kg/day. The NOAEL for the F2 generation was ≥10 mg/kg/day rolapitant hydrochloride (equivalent to ≥9 mg/kg/day rolapitant free base).

In summary, rolapitant was adequately studied in nonclinical pharmacology and toxicology studies. From a nonclinical perspective, the NDA is approvable. Specific recommendations for the label are provided in Section 1.3.3 (Labeling).

12 Appendix/Attachments

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/s/

TRACY L BEHRSING
03/19/2015

SUSHANTA K CHAKDER
03/19/2015

Comments on N206500 Rolapitant

From A. Jacobs, AD

Date: 3/9/15

1. I concur that there are no pharm/tox approval issues.

2. I have discussed my comments with the reviewer and supervisor and they will address them as appropriate.

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/s/

ABIGAIL C JACOBS
03/09/2015