CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202258Orig1s000

PHARMACOLOGY REVIEW(S)

MEMO **FOOD AND DRUG ADMINISTRATION**

Division of Antiviral Products
Center for Drug Evaluation and Research

Date:	April 15, 2011
Reviewer:	Hanan Ghantous, PhD, DABT Supervisory Interdisciplinary Scientist
NDA #/SS#/date:	202-258/000/11/15/2010
Sponsor:	Schering-Plough
Drug Product:	Boceprevir (SCH 503034)
Indication:	Treatment of Chronic hepatitis
Recommended Action:	Nonclinical data support approval

Boceprevir (SCH 503034) is the first direct-acting antiviral agents for the treatment of chronic hepatitis C to be submitted for marketing approval in combination with a pegylated interferon and ribavirin. Boceprevir is an HCV NS3/4a serine protease inhibitors in the ketoamide class.

The safety of boceprevir was investigated in a number of toxicology studies including repeat-dose nonclinical toxicity studies (mice, rats and cynomolgus monkeys), genetic toxicity, carcinogenicity studies and reproductive, developmental, and neonatal/juvenile toxicity studies.

The primary toxicity findings in nonclinical studies were liver and testicular toxicity.

Liver toxicity was observed in mice, rats and monkeys at exposures similar to those attained in patients receiving boceprevir (800 mg TID). Higher liver weights with minimal Kupffer cell hypertrophy and neutrophil infiltration associated with mild elevations of AST and ALT, focal/multifocal single cell necrosis, pigment accumulation and macrophage infiltration of the liver were observed in mice. ALT elevations and scattered foci of greatly enlarged multinucleated hepatocytes were observed in rats. In cynomolgus monkeys, higher liver weights in the absence of histopathology findings were observed at doses providing a ~1.6-fold monkey to human AUC exposure multiple.

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In clinical trials, increases in liver enzymes have been mild and infrequent in infected patients, minimizing the risk of adverse liver-related effects.

Testicular toxicity findings were observed in rats at boceprevir exposures less than those attained in patients receiving the clinical dose (800 mg TID). Testicular findings were not observed in mice or cynomolgus monkeys administered boceprevir for 3 months at doses of up to 900 or 1000 mg/kg, respectively. At these doses, boceprevir AUC exposures are ~7- and 4-fold higher in mice and monkeys, respectively, than those in humans at the clinical dose (800 mg TID). Limited analysis of inhibin B and semen were evaluated clinically without any apparent adverse effects. Thus testicular toxicity, which is associated with reduced fertility, may be limited to rats.

In female rats, fertility and early embryonic development were affected adversely at boceprevir doses ≥150 mg/kg. These effects were reversible, not due to alterations in serum hormone levels (LH, FSH, progesterone and estradiol) and not observed at 75 mg/kg, providing a ~1.4-fold rat to human AUC exposure multiple.

Boceprevir was not mutagenic or clastogenic. In addition, two-year mouse and rat carcinogenicity studies were negative for boceprevir-related tumors at AUC exposures either similar to (rats) or ~2 to 6-fold greater (for male and female mice, respectively) than human exposure at the recommended dose (800 mg TID).

No adverse findings regarding embryo-fetal development or teratogenicity were observed in rats or rabbits at boceprevir doses of up to 600 and 300 mg/kg, respectively. Additionally, no test article-related effects on pregnancy, parturition and lactation of maternal animals or on the growth, viability, development or reproductive performance of the first generation, or survivability of the second generation were reported in a prenatal and postnatal development study in rats. The animal to human AUC exposure ratio at the high dose in this study is 6.5.

Adverse testicular and thyroid findings were observed in neonatal/juvenile rats. The testicular findings were consistent with those in adult rats; however, minimal follicular hyperplasia of the thyroid has not been observed in adults. Thyroid function will be monitored in pediatric clinical trials since boceprevir is given in combination with ribavirin and peginterferon-alpha that already has measureable effects on thyroid function in this population.

Conclusion: I concur with the primary nonclinical reviewer, Dr. Christopher Ellis that the nonclinical data support an approval action for boceprevir.

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/s/

HANAN N GHANTOUS
04/14/2011

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	202,258
Supporting document/s:	001
Applicant's letter date:	November 10, 2010
CDER stamp date:	November 15, 2010
Product:	Boceprevir (SCH 503034)
Indication:	Treatment of chronic hepatitis C (HCV genotype 1) in combination with peginterferon alpha and ribavirin in adults (for treatment naive patients and those that have failed previous interferon therapy)
Applicant:	Schering Corporation
Review Division:	Division of Antiviral Products
Reviewer:	Christopher Ellis, Ph.D.
Supervisor/Team Leader:	Hanan Ghantous, Ph.D., DABT
Division Director:	Debra Birnkrant, M.D.
Project Manager:	Sherly Abraham, R.Ph

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1 Executive Summary

1.1 Introduction

Boceprevir (SCH 503034) is an orally active, serine protease inhibitor for HCV NS3/4A (non-structural protein 3/4A) protease that inhibits viral replication by reversibly binding to the active site within the NS3/4A protease. The nonclinical safety profile of boceprevir has been evaluated in: safety pharmacology studies in rats, dogs and monkeys; single- and repeat-dose toxicology studies in mice, rats and cynomolgus monkeys for up to 3, 6 and 12 months duration, respectively; fertility and pre- and post-natal developmental studies in rats and embryo-fetal developmental studies in rats and rabbits; neonatal/juvenile toxicology studies in rats for up to 3 months; various investigational toxicology studies; genetic toxicology studies (Ames, *in vitro* chromosomal aberration and *in vivo* mouse micronucleus assays) with impurities/degradants; 1-month repeat-dose toxicology studies to qualify impurities/degradants; 2-year carcinogenicity studies in rats and mice; and combination toxicology studies with ribavirin and PEG-intron in rats and/or monkeys. In addition, numerous *in vitro* and *in vivo* nonclinical pharmacokinetic studies, evaluating the absorption, distribution, excretion, and metabolism of boceprevir, have been performed.

1.2 Brief Discussion of Nonclinical Findings

The oral bioavailability of the diastereomers (SCH 534128 and SCH 534129) that comprise boceprevir (SCH 503034) is 7 to 18% in monkeys, 27 to 34% in rats and ~35% in mice. These diastereomers are present at approximately a 1:1 ratio in boceprevir but are interconverted *in vivo* to varying extents by keto-enol tautomerization. This interconversion results in equilibrium AUC ratios of SCH 534128 to SCH 534129 of ~1.2:1 in mice, 1:1 in rats and 0.17:1 in monkeys, compared to ~2.2:1 in humans. Safety evaluation of both of these diastereomers is acceptable.

Boceprevir is metabolized extensively in all species with greater than 79% eliminated in feces and only ~14% excreted unchanged. AUC exposure ratios of SCH 629144, the predominant circulating human metabolite, to boceprevir vary widely between species with rats, mice, humans and monkeys having ~0.07:1, 0.8:1, 4:1 and 7.5:1 ratios, respectively. Although the safety of SCH 629144 could not be characterized sufficiently in rats, safety was established in both mice and monkeys. SCH 503034-K is the only other circulating human metabolite that exceeded 3% of the administered dose. Although low, the exposure in animal models to support safety of SCH 503034-K appears acceptable since exposure to this metabolite does not exceed 10% of the total circulating drug related material in humans.

Boceprevir distributes predominantly to the liver in rats and could not be detected in brain or spinal cord. In monkeys, extensive extravascular distribution was observed with liver to plasma ratios ranging from ~3 to 9 for the diastereomers (SCH 534128 and SCH 534129), indicating distribution to the site of action.

Placental transfer of boceprevir was assessed in pregnant rats. Transient exposure was observed in the fetus with an estimated maternal to fetal AUC plasma ratio of ~6. Most fetal tissues had boceprevir concentrations similar to or lower than maternal blood concentrations and did not contain measurable concentrations at 24 hours post-dose.

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Transfer of boceprevir into milk was assessed in lactating rats. Although milk concentrations of boceprevir were slightly higher than maternal plasma concentrations, plasma concentrations in the pups were low indicating that pups are not exposed to appreciable levels of boceprevir through milk consumption.

In a cardiovascular safety study in cynomolgus monkeys, boceprevir produced no adverse effects on cardiovascular function, with only a minor increase in heart rate observed at the 200 mg/kg dose level. No effects on blood pressure or ECG intervals or morphology were observed at this dose, providing a ~2.1-fold monkey to human exposure multiple (based on C_{max}). Cardiovascular safety signals have also not been identified in clinical trials. Additionally, no significant boceprevir-related effects on behavioral, neurologic or autonomic function or on respiratory parameters (respiratory rate, tidal or minute volumes) were observed in rats at doses of up to 200 mg/kg, providing a ~7-fold rat to human exposure multiple (based on C_{max}).

Liver toxicity was observed in mice, rats and monkeys at boceprevir exposures similar to those attained in patients receiving boceprevir (800 mg TID). In mice, higher liver weights with minimal Kupffer cell hypertrophy and neutrophil infiltration was associated with mild elevations of AST and ALT. In the 2-year mouse study, focal/multifocal single cell necrosis, pigment accumulation and macrophage infiltration of the liver was observed. In rats, liver findings were characterized by ALT elevations and scattered foci of multinucleated enlarged hepatocytes. In cynomolgus monkeys, liver findings were limited to higher liver weights in the absence of histopathology findings at doses ≥300 mg/kg. These effects were not observed at a 200 mg/kg dose level, providing a ~1.6-fold monkey to human AUC exposure multiple. The specific liver findings observed in each species were quite different and so a consistent mechanism for liver toxicity was not identified. Given that increases in liver enzymes have been mild and infrequent in clinical trials with boceprevir, and the likely benefit of boceprevir in preventing liver abnormalities in HCV infected patients, the risk of adverse liver-related effects in humans appear to be of limited concern.

Testicular toxicity was observed in rats administered doses ≥50 mg/kg at boceprevir exposures less than those attained in patients at the recommended dose of 800 mg TID, while no effects were observed at a 15 mg/kg dose level. Signs of reversibility of testicular toxicity were observed following a 2-month treatment-free (*i.e.*, recovery) period in a 3-month rat study. Testicular toxicity was not observed in mice or in immature or sexually mature cynomolgus monkeys administered boceprevir for 3 months at doses of up to 900 or 1000 mg/kg, respectively. At these doses, boceprevir AUC exposures are ~ 7- and 4-fold higher in mice and monkeys, respectively, than those in humans at the recommended dose of 800 mg TID. In addition, limited analysis of inhibin B and semen were evaluated clinically without any apparent adverse effects. Thus testicular toxicity, which is associated with reduced fertility, may be limited to rats. Initiation of testicular toxicity in rats most likely occurs after the first dose with continual progression following daily dosing. Testicular findings were not associated with alterations in FSH, LH or testosterone and generally consisted of lower epididymides, prostate and testis weights. In the epididymides, findings included luminal cellular debris and/or hypospermia, while in the testes, Sertoli cell vacuolation, depletion and/or degeneration of spermatocytes and spermatids and atrophy of seminiferous tubules were observed. Although the possibility of direct test-article effects on germ cell

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maturation cannot be totally excluded, the Sertoli cell appears to be the primary target of toxicity.

Decreases in red blood cell count, hemoglobin and hematocrit were observed in cynomolgus monkeys administered boceprevir at doses ≥300 mg/kg, at a ~1.9-fold monkey to human AUC exposure multiple. These values were reduced ~10% and were associated with increases in reticulocytes (up to ~100%). These mild effects did not progress over the duration of the 3 month study and were not considered to be adverse. Although the mechanism is uncertain, this mild anemia may be due to transient bone marrow suppression since no acute boceprevir-related effects have been observed on the osmotic fragility of red blood cells. The regenerative response, detected by 5 weeks of dosing, likely prevented any exacerbation of the effects upon longer drug exposure durations. Additionally, boceprevir, when administered in combination with ribavirin and PEG-intron in monkeys, did not exacerbate the hematological toxicity of ribavirin and PEG-intron alone at boceprevir AUC exposures up to 1.6-fold greater than exposures attained in patients receiving boceprevir (800 mg TID). However, this study was not capable of measuring subtle additive effects of combination drug treatment on hematology parameters due to the limited number of animals used, the limited duration of the study (1-month) and since higher doses of ribavirin were not evaluated. Therefore, it is not surprising that the additive hematological effects of boceprevir when given in combination with ribavirin and peginterferon-alpha, as has been detected after 6 weeks of combination treatment in clinical trials, were not observed in this study. It is also feasible that humans may be slightly more sensitive to boceprevir-induced reductions in red blood cell count than monkeys.

In female rats, fertility and early embryonic development were affected adversely at boceprevir doses ≥150 mg/kg. These effects were reversible and were not due to alterations in serum hormone levels (LH, FSH, progesterone and estradiol). Effects were not observed at 75 mg/kg, providing a ~1.4-fold rat to human AUC exposure multiple.

No adverse findings regarding embryo-fetal development or teratogenicity were observed in rats or rabbits at boceprevir doses of up to 600 and 300 mg/kg, respectively. These dose levels, which produced maternal toxicity, result in animal to human AUC exposure ratios of approximately 10 and 2, respectively. Although the safety of SCH 629144 to the developing fetus has not been established clearly, since the presence of this metabolite has not been demonstrated in rabbits and is at very low levels in rats, this is not of clinical safety concern given that boceprevir must be administered in combination with peginterferon alpha (abortifacient) and ribavirin (teratogenic and embryocidal). Additionally, no test article-related effects on pregnancy, parturition and lactation of maternal animals (F0) or on the growth, viability, development or reproductive performance of the F1 generation, or survivability of the F2 generation were reported in a prenatal and postnatal development study in rats. The animal to human AUC exposure ratio at the high dose in this study is 6.5.

Adverse testicular and thyroid findings were observed in a 3 month study in neonatal/juvenile rats at doses ≥ 75 mg/kg. Testicular findings were consistent with those in adult rats; however, minimal follicular hyperplasia of the thyroid has not been observed in adults. Additionally, femur length was reduced up to 3.3%. The sponsor theorized that thyroid findings could be due to liver enzyme (UGT1A1/6 & UGT2B2)

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induction that increases thyroid hormone clearance and TSH production leading to follicular hyperplasia. Although it is possible that reduced thyroid hormone exposure could cause these reductions in longitudinal bone growth, they are more likely the result of a secondary effect due to body weight gain reductions. In addition, although a small tendency for liver enzyme induction (in the absence of clear thyroid hormone changes) was observed in neonatal/juvenile rats, clear evidence to support the sponsor's theory is lacking. Nonetheless, further nonclinical thyroid toxicity assessment is not necessary, since the effect is minor and reversible, and because thyroid function will be monitored in pediatric clinical trials given that boceprevir is given in combination with ribavirin and peginterferon-alpha that already has measureable effects on thyroid function in this population.

Boceprevir was not mutagenic or clastogenic as tested in the Ames assay, the *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes and the *in vivo* mouse micronucleus assay. Additionally, two-year mouse and rat carcinogenicity studies were performed with boceprevir. Mice were administered doses of up to 500 mg/kg in males and 650 mg/kg in females, while rats were administered doses of up to 125 mg/kg in males and 100 mg/kg in females. Mice and rats were negative for drug-related neoplasms at boceprevir AUC exposures either similar to (rats) or ~2 to 6-fold greater (for male and female mice, respectively) than those in humans at the recommended dose of 800 mg TID.

1.3 Recommendations

1.3.1 Approvability

Yes, the sponsor provided sufficient nonclinical safety information on boceprevir in support of approval for marketing in the U.S.

1.3.2 Additional Non Clinical Recommendations

In the event that boceprevir is indicated for treatment of HCV infected patients in a future regimen without ribavirin and peginterferon alpha, the safety of the main human metabolite (SCH 629144) to the developing fetus must be established clearly. This could possibly be accomplished by determining whether SCH 629144 was present at sufficient levels in the rabbit embryo-fetal developmental study already submitted.

Labeling

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Pharmacologic Class

HCV NS3/4A protease inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 69,027

2.3 Drug Formulation

Boceprevir is a white to off-white powder and is supplied for clinical use as 200 mg strength capsules (400 mg total fill weight). Boceprevir containing hard gelatin capsules (b) (4) also contain the following excipients (% wt/wt): pregelatinized starch (b) (4) lactose monohydrate (b) (4), microcrystalline cellulose (b) (4), croscarmellose sodium (b) (4) sodium lauryl sulfate (b) (4) and magnesium stearate (b) (4)

2.4 Comments on Novel Excipients

Although the total daily amount of several excipients is slightly higher than amounts in drug products approved previously, all are compendial excipients with no safety concerns.

2.5 Comments on Impurities/Degradants of Concern

Bacterial mutagenicity assays, chromosomal aberration assays using human peripheral blood lymphocytes and 1-month repeat-dose toxicology studies in rats were performed using batches containing high levels of impurities or degradants. All batches tested were negative for mutagenicity and clastogenicity and there was no indication that impurities or degradants altered the toxicity profile of boceprevir. Given these results, the seriousness of the disease to be treated, the fact that boceprevir will be given in combination with ribavirin and peginterferon-alpha and since no structural alerts have been identified, evaluation of these impurities/degradants appears acceptable.

2.6 Proposed Clinical Population and Dosing Regimen

Boceprevir is to be indicated for the treatment of adult patients infected with chronic hepatitis C (HCV genotype 1) in combination with peginterferon alpha and ribavirin. Boceprevir is to be administered orally (TID) in either treatment naive patients or those that have failed previous interferon-based therapies.

2.7 Regulatory Background

IND 69,027 was opened in DAVP on May 19, 2005.

3 Studies Submitted

3.1 Studies Reviewed

Reference ID: 2933010

Study Title	Study #
Safety Pharmacology	
ANCILLARY PHARMACOLOGY STUDIES ON SCH 503034: EFFECTS ON CARDIOVASCULAR FUNCTION IN BEAGLE DOGS, IN VITRO EFFECTS ON hERG CURRENT AND EFFECTS ON CNS, RESPIRATORY, RENAL AND GASTROINTESTINAL FUNCTION IN RATS	44193
EFFECT OF SCH 503034 ON ACTION POTENTIAL PARAMETERS IN DOG ISOLATED CARDIAC PURKINJE FIBRES	2210
A SINGLE ORAL (GAVAGE) DOSE CARDIOVASCULAR SAFETY STUDY OF SCH 503034 IN MALE CYNOMOLGUS MONKEYS	1398
THE ACUTE CENTRAL NERVOUS SYSTEM PHARMACOLOGICAL PROFILE OF SCH 503034 FOLLOWING ORAL ADMINISTRATION IN RATS	1400
EFFECT OF SINGLE DOSE ORAL ADMINISTRATION OF SCH 503034 ON RESPIRATORY PARAMETERS OF RATS	1399
ADME/Pharmacokinetics	
EXPLORATORY NONCLINICAL PHARMACOKINETICS AND METABOLISM OF SCH 503034	3204
SCH 503034: PHARMACOKINETICS OF SCH 503034 AND SCH 503034-K METABOLITE FOLLOWING A SINGLE ORAL 900 MG SCH 503034/KG DOSE TO MALE AND FEMALE CD-1 MICE	DM27592
SCH 503034: PHARMACOKINETICS AND PLASMA METABOLITE PROFILING FOLLOWING A SINGLE ORAL OR INTRAVENOUS ADMINISTRATION OF ^{14}C-SCH 503034 OR SCH 503034 TO MALE AND FEMALE RATS	DM27293
SCH 503034: PHARMACOKINETICS OF SCH 503034 AND SCH 503034-K FOLLOWING A SINGLE ORAL DOSE OF 300 MG SCH 503034/KG TO MALE RATS	DM27593
SCH 503034: PHARMACOKINETICS OF SCH 503034 FOLLOWING A SINGLE ORAL OR INTRAVENOUS DOSE TO MALE CYNOMOLGUS MONKEYS	DM27278
SCH 503034: PHARMACOKINETICS OF SCH 503034 FOLLOWING A SINGLE ORAL DOSE OF 1000 MG/KG TO MALE CYNOMOLGUS MONKEYS	DM27594
TWO-WEEK TOXICOKINETIC STUDY OF SCH 503034 ADMINISTERED IN COMBINATION WITH SCH 54031 AND SCH 18908 IN CYNOMOLGUS MONKEYS	3321

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SCH 503034: PHARMACOKINETICS OF SCH 503034, SCH 629144 AND SCH 503034 STEREOISOMERS FOLLOWING MULTIPLE ORAL ADMINISTRATION OF 200 MG SCH 503034 CAPSULES (b) (4) DOLOBID, AND RITONAVIR TO MALE CYNOMOLGUS MONKEYS	DM27335
SCH 503034: PHARMACOKINETICS OF SCH 503034 AND SCH 629144 FOLLOWING MULTIPLE DOSE ORAL ADMINISTRATION OF 200 MG SCH 503034 CAPSULES (b) (4) AND DOLOBID TO MALE CYNOMOLGUS MONKEYS	DM27306
SCH 503034: TISSUE DISTRIBUTION AND EXCRETION PATTERN OF $_{14}$C-SCH 503034-DERIVED RADIOCARBON AFTER A SINGLE ORAL DOSE TO MALE AND FEMALE, ALBINO AND PIGMENTED RATS	DM27192
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SCH 503034: BILIARY EXCRETION, ENTEROHEPATIC CIRCULATION AND METABOLISM OF $_{14}$C-SCH 503034-DERIVED RADIOACTIVITY AFTER A SINGLE 25 MG/KG ORAL SUSPENSION ADMINISTRATION TO MALE AND FEMALE RATS	1551
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3.2 Studies Not Reviewed

Study Title	Study #
(b) (4)	

3.3 Previous Reviews Referenced

Many nonclinical studies, including safety pharmacology, ADME, single and repeat-dose toxicology, genetic toxicology and reproductive toxicology studies have been reviewed by Dr. Wu and carcinogenicity studies by Dr. Powley to support the NDA, and will be summarized in the appropriate sections of this review with complete reviews of pivotal studies also included within the review or as appendices.

4 Pharmacology

4.1 Primary Pharmacology

Boceprevir (SCH 503034) is an orally active, serine protease inhibitor for HCV NS3/4A (non-structural protein 3/4A) protease. The mechanism of inhibition of viral replication in infected host cells involves boceprevir reversibly binding to the NS3 protease active site serine using a ketoamide functional group. The IC_{90} for boceprevir in the HCV replicon assay is ~400 nM. Please refer to the clinical virology review for a

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more detailed description and review of the primary pharmacology data of boceprevir submitted with this NDA.

4.2 Secondary Pharmacology

Please refer to the clinical virology review.

4.3 Safety Pharmacology

Neurological effects: A GLP functional observational battery (FOB) test in CD®(SD)IGS BR rats (6/sex/group), given single oral doses of 0, 25, 75, 200 mg/kg, produced no significant effects on behavioral, neurologic or autonomic function at 60 minutes post-dose (Study #1400). Thus, the NOAEL was considered to be 200 mg/kg. Evaluations included home cage, handling, open field, sensory, neuromuscular and physiological observations and locomotor activity.

Cardiovascular effects: A GLP cardiovascular study in telemeterized male cynomolgus monkeys (6/group), given single oral doses of 0, 75 or 200 mg/kg, produced no adverse effects on cardiovascular function (Study #1398). A 16 to 22% increase in heart rate was observed at the 200 mg/kg dose level (C_{max}= 4270 ng/ml) at 4 to 5 hours post-dose. However, no effects on blood pressure or ECG intervals or morphology were observed at this dose. Thus, the NOAEL was considered to be 200 mg/kg.

Respiratory effects: A GLP respiratory study in CD®(SD)IGS BR rats (6/sex/group), given single oral doses of 0, 25, 75, 200 mg/kg, produced no significant effects on respiratory rate, tidal or minute volumes during the 5 hour post-dose evaluation period (Study #1399). Thus, the NOAEL was considered to be 200 mg/kg.

In addition to the GLP studies summarized above, the safety pharmacological profile of SCH 503034 was also evaluated in several non-GLP safety pharmacology studies. The results of these studies are included in the tabulated summary below.

Table 1: Safety Pharmacology Summary

Study	Dose	Summary
PO Male Monkey	75, 200 mg/kg	NOAEL = 200 mg/kg for BP, PR, QRS, QT intervals and ECG morphology. 200 mg/kg -↑HR 16% to 22% over baseline values 4 to 5 hours after administration.
PO Male Dog	3, 50 mg/kg	NOAEL =50 mg/kg for HR, BP, ECG intervals and morphology.
Dog cardiac Purkinje fibers	84, 218, 813 nM	NOEL = 218 nM for resting membrane potential, maximum rate of depolarization, upstroke amplitude, and action potential duration at 60 and 90% repolarization. At 813 nM less than 10% increase in action potential duration at 60% and 90% repolarization.
hERG assay in mouse L-929 cells	1000 nM	NOAEL =1000 nM for amplitude of hERG channel current.
PO Male Rat	10, 30, 100 mg/kg	NOAEL =100 mg/kg for respiratory rate, tidal volume, minute volume, arterial pH, PaCO2, PaO2, and bicarbonate levels.

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PO Male and Female Rat	25, 75, 200 mg/kg	NOAEL =200 mg/kg for changes in respiratory rate, tidal volume, and minute volume.
PO Male Rat	10, 30, 100 mg/kg	NOAEL =100 mg/kg for neurologic function, including sensory modalities, sensorimotor integration, locomotion, body temperature, and spontaneous motor activity.
PO Male and Female Rat	25, 75, 200 mg/kg	NOAEL =200 mg/kg for neurologic function, including sensory modalities, sensorimotor integration, locomotion, body temperature, and spontaneous motor activity.
PO Male Rat	10, 30, 100 mg/kg	NOAEL =100 mg/kg for gastric emptying or intestinal transit.
PO Male Rat	10, 30, 100 mg/kg	NOAEL =100 mg/kg for urine volume, electrolyte excretion, or 24-hour creatinine clearance.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The absorption, distribution, excretion, and metabolism of boceprevir (SCH 503034) have been studied in numerous *in vitro* and *in vivo* studies. A brief summary of the significant findings from studies in mice, rats and cynomolgus monkeys is presented below.

Absorption:

The oral bioavailability of SCH 503034 administered by gavage in vehicle [0.4% (w/v) aqueous methylcellulose] was 7 to 18% in monkeys, 27 to 34% in rats and ~35% in mice. SCH 503034 bioavailability was sufficient to achieve adequate circulating product exposure levels in the toxicology studies submitted in these species. T_{max} values in mice and rats were approximately 1 and 2 hours, respectively, while values in monkeys varied from approximately 1 hour at lower doses (≤75 mg/kg) to 4 hours at higher doses (≥200 mg/kg).

Exposure to the diastereomers (SCH 534128 and SCH 534129) that comprise SCH 503034 was determined after oral administration of SCH 503034 to mice, rats and monkeys. These diastereomers are present at approximately a 1:1 ratio in all batches of SCH 503034 administered non-clinically but can be interconverted *in vivo* to varying extents by keto-enol tautomerization. Although SCH 534128 is a much more potent inhibitor of the HCV NS3 protease, this interconversion results in an equilibrium mixture with potent activity. The equilibrium AUC ratio of SCH 534128 to SCH 534129 was approximately 1.2:1 in mice, 1:1 in rats and 0.17:1 in monkeys, compared to around 2.2:1 for humans.

Metabolism:

Boceprevir and metabolites formed by oxidation, reduction, hydroxylation etc. of boceprevir were evaluated *in vivo* in rodents (plasma, urine, feces and bile) and in monkeys (plasma, urine and bile) and in numerous *in vitro* studies using hepatocytes, liver microsomes, cytosol and S9 fractions (refer to sponsor's figure below). Boceprevir was metabolized extensively in all species with greater than 79% of the oral dose eliminated in feces and only ~14% excreted unchanged.

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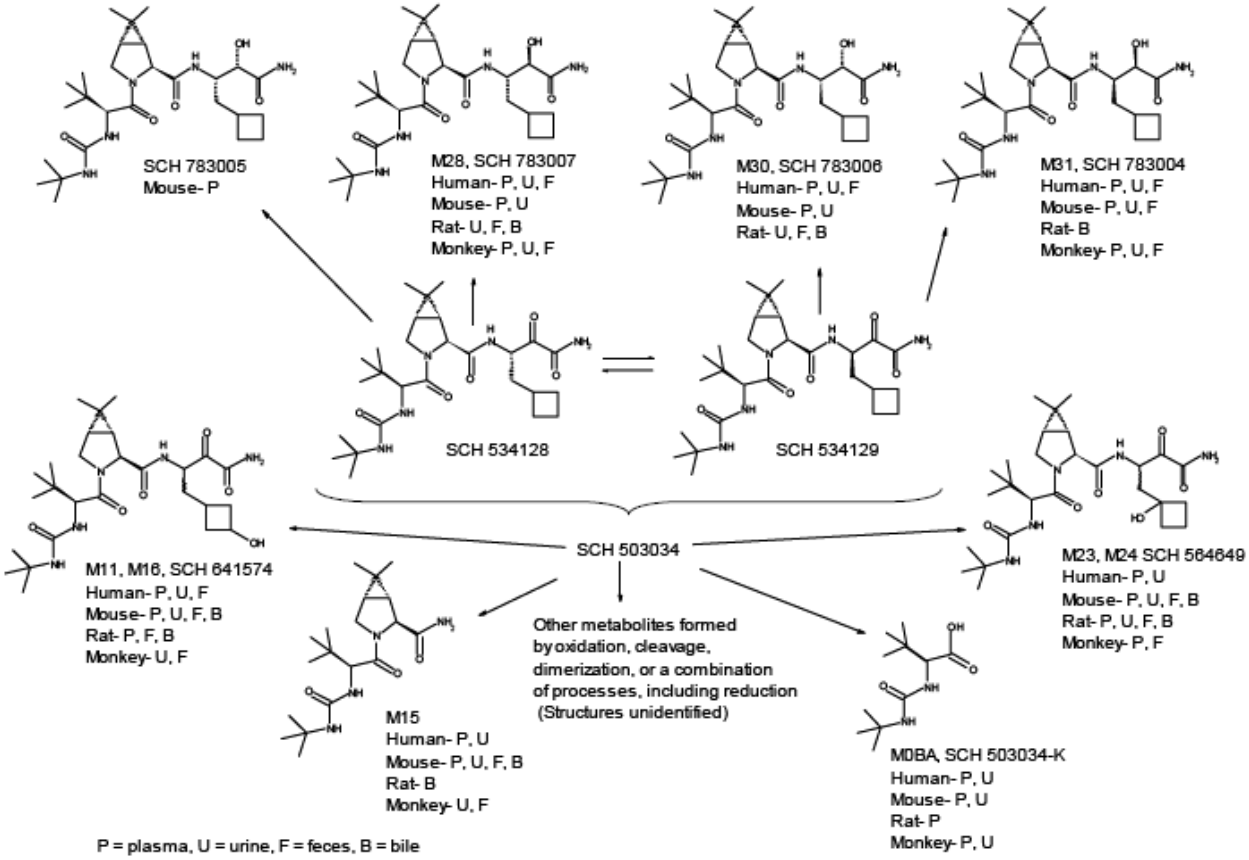

Figure 1: Possible Pathways for Boceprevir Metabolism

Metabolite profiling of human plasma revealed the presence of a prominent inactive circulating metabolite (SCH 629144), which was also present in urine, and was determined to be the most abundant circulating human metabolite, making up approximately 70% of circulating radioactivity at 6 hours post-dose in the clinical PK mass balance trial (P03588). SCH 629144 is a mixture of four stereoisomers (SCH 783004, 783005, 783006 and 783007) formed by reduction of the second carbonyl group at the carboxamide terminus of SCH 503034. SCH 629144 represented 18 and 22% of the total dose in feces in humans and monkeys, respectively, and was also present in mice and rats. AUC exposure ratios of SCH 629144 to SCH 503034 varied widely between species with rats having the lowest ratio (0.07:1) and monkeys having the highest (7.5:1). Mice had intermediate exposure ratios of approximately 0.8:1, while humans had ratios of approximately 4:1 (see sponsor's table below).

Table 2: Pharmacokinetic Parameters for SCH 629144 after Administration of Boceprevir to Mice, Rats, Monkeys and Humans.

Species	Dose (mg/kg)	Sex[a] (n)	Cmax (ng/mL)	Tmax (hr)	AUC (0-t) (ng·hr/mL)	t (hr)	Study Number
Mouse	600	M	5320	4	23400	24	04320[8]
		F	22800	2	62900	24	
	750	M	21000	2	66200	24	
		F	18100	4	82300	8	
	900	M	18200	4	71500	24	
		F	22400	4	114000	8	
Rat	100	M	344	2	1080	24	04124[26]
	300	M	1170	2	4850	24	04124[26]
		M	378	4	1760	8	05023[17]
Juvenile Rat	150	M	101	4	375	24	09238[23]
		F	141	1	285	24	
Monkey	300	M/F (8)	26400 (34)	4[b]	226000 (24)	24	04080[38]
	500		37000 (39)	4[b]	364000 (46)	24	
	1000		44500 (29)	4[b]	457000 (20)	24	
Human	800 mg TID	M/F (71)	5380 (31)	4[b]	25300 (35)	8	P04489[83] P05880[81]

a: M = Male; F = Female; n = number of animals when serial blood samples were collected from individual animals

b: Median

The only other circulating metabolite that exceeded 3 % of the administered dose was SCH 503034-K, a hydrolytic cleavage product which accounted for ~19 % of the circulating radioactivity in plasma at 6 hours post-dose in the clinical PK mass balance trial. *In vitro* studies and clinical data suggest that SCH 503034-K may be formed by sodium lauryl sulfate (SLS) dependent hydrolysis in the stomach. Circulating levels of SCH 503034-K relative to parent drug were less than 8% in a clinical PK trial with the current capsule formulation (P05880). The sponsor attributed this difference (8% versus 19%) to the fact that the mass balance trial used an oral suspension containing (b) (4) (b) (4) SLS than that in the capsule. (b) (4) an impurity, was measured in mice, rats and monkeys. However, the amount of exposure measured in these studies was low, likely due to the fact that SLS was not present in the formulation. It should also be noted that even though two monkey PK studies were performed with the capsule formulation containing SLS, these single dose studies did not measure SCH 503034-K. (b) (4)
In addition, the amount of exposure in animal models to support safety of this hydrolysis product (although low) appears acceptable since exposure to this metabolite does not exceed 10% of the total circulating drug related material.

Numerous *in vitro* and *in vivo* studies suggest that boceprevir is metabolized primarily through aldo-ketoreductase (AKR) pathways, to produce the major circulating metabolite (SCH 629144), and CYP3A4/5 enzymes. Boceprevir was also shown to be a

moderate inhibitor but not an inducer of CYP3A4/5 and is also a P-glycoprotein substrate and inhibitor.

Distribution:

Tissue distribution of SCH 503034 was examined using quantitative whole body autoradiography in pigmented and non-pigmented rats, with no remarkable differences identified. Concentrations of SCH 503034 in the liver were ~50 times that in plasma at 4 hours post-dose and were below the level of detection by 24 hours. SCH 503034 concentrations were not measurable in brain or spinal cord at any time point. In addition to liver, the highest radiocarbon concentrations were measured in bladder, kidneys, various glandular tissues (adrenal, harderian, salivary, and prostate glands) and bone marrow. At 24 hours post-dose, boceprevir could only be detected in bone marrow (refer to sponsor's table below).

Table 3: Tissue distribution in Male Rats Following a Single 25 mg/kg Oral Dose of ^{14}C-Boceprevir.

Sampling Time	0.5 hr		2 hr		4 hr		8 hr		24 hr		168 hr	
Tissues	C[a]	T/B[b]	C	T/B	C	T/B	C	T/B	C	T/B	C	T/B
Blood	1430	1.00	743	1.00	148	1.00	BQL	NC	BQL	NC	BQL	NC
Lymph Node	1760	1.23	1470	1.98	502	3.39	387	NC	BQL	NC	BQL	NC
Bladder	1170[c]	0.818	3540	4.76	22300	151	1300[c]	NC	BQL	NC	BQL[c]	NC
Kidney	5120	3.58	3090	4.16	1640	11.1	290	NC	BQL[c]	NC	BQL	NC
Liver	16700	11.7	12800	17.2	7250	49.0	1410	NC	BQL	NC	BQL	NC
Adrenal Gland	4060[d]	2.84	1640[c]	2.21	922[c]	6.23	BQL[c]	NC	BQL[d]	NC	BQL[c]	NC
Pituitary Gland	1890[d]	1.32	1050[c]	1.41	972[c]	6.57	695[c]	NC	BQL[c]	NC	BQL[d]	NC
Thyroid Gland	1830[c]	1.28	1070[c]	1.44	1240[d]	8.38	BQL[d]	NC	BQL[c]	NC	BQL[d]	NC
Harderian Gland	1600[c]	1.12	1640[c]	2.21	791[c]	5.34	BQL[c]	NC	BQL[c]	NC	BQL[c]	NC
Salivary Gland	2300	1.61	1230	1.66	759	5.13	BQL	NC	BQL	NC	BQL	NC
Epididymis	616[d]	0.431	1480	1.99	661	4.47	BQL	NC	BQL	NC	BQL	NC
Prostate Gland	BQL[d]	NC	25900[c]	34.9	6220[c]	42.0	BQL	NC	BQL	NC	BQL[c]	NC
Seminal Vesicles	1160[d]	0.811	765	1.03	391	2.64	BQL	NC	BQL[c]	NC	BQL	NC
Testis	BQL[c]	NC	645	0.868	198	1.34	BQL	NC	BQL	NC	BQL	NC
Bone Marrow	1740	1.22	1460	1.97	913	6.17	826	NC	163	NC	BQL	NC
Pancreas	2080	1.45	1090	1.47	1090	7.36	BQL	NC	BQL[c]	NC	BQL	NC
Spleen	2320	1.62	1280	1.72	869	5.87	BQL	NC	BQL[c]	NC	BQL	NC

a: C = Mean concentration in ng equiv/g; n = 3 sections from a single rat
b: T/B = Tissue:blood ratio (concentration in tissue/concentration in blood)
c: n = 2
d: n = 1
BQL = Below quantifiable limit (412 ng equiv/g)
NC = Ratio could not be calculated since the blood or tissue concentration had no associated value.

In monkeys, the estimated volume of distribution of boceprevir was ~60-fold greater than plasma volume indicating significant extravascular distribution. Mean liver to plasma ratios ranged from ~3 to 9 for SCH 534128 and SCH 534129 indicating distribution to the site of action. In addition, trough liver concentrations (24 hours post-dose) following oral doses of 200 mg/kg for 6 months were 45 ng/g for SCH 534128 and 105 ng/g for SCH 534129.

Placental transfer of boceprevir was assessed in pregnant rats administered a single oral dose (~150 mg/kg) of ^{14}C-boceprevir on gestation day 18 and sacrificed at various post-dose time points (0.5 to 48 hr) (Study # 01556). Transient exposure was observed in the fetus with an estimated AUC ratio of maternal to fetal plasma of ~6.

Fetal tissues examined had boceprevir concentrations similar to or lower than maternal blood concentrations with the only exceptions being the liver (~2-fold higher concentrations at 2 to 4 hours post-dose) and embryonic sac (13-fold higher concentrations at 4 hours post-dose). No fetal tissues contained measurable concentrations of boceprevir by 24 hours post-dose, with the exception of the embryonic sac.

Plasma protein binding of SCH 503034 was determined in mouse, rat, monkey, and human plasma (among others). The percent binding to plasma protein in mouse, rat, monkey and human was approximately 72%, 55%, 56% and 68%, respectively, when boceprevir was incubated in plasma at a 5 μg/ml concentration.

Excretion:

Elimination of boceprevir and metabolites occurred primarily through the feces (greater than 79% recovery) due to unabsorbed drug and biliary excretion with less than 10% recovered in urine. Additionally, only ~3% of an oral dose undergoes enterohepatic circulation in rats.

Transfer of boceprevir into milk was assessed in lactating rats (refer to sponsor's table below). Although milk concentrations of boceprevir were slightly higher than plasma concentrations in the dam, plasma concentrations in the pups remained quite low indicating that pups are not exposed to appreciable levels of boceprevir through milk consumption.

Table 4: Boceprevir Concentrations in Plasma, Blood and Milk of Lactating Rats and Plasma and Blood of Nursing Pups.

Sample Time (hr)	Mean Concentration (ng equiv/g)					Mean Dam Milk:Plasma Ratio
	Dam[a]			Pup[b]		
	Blood	Plasma	Milk	Blood	Plasma	
1	5960	7530	6370	0	0	0.848
2	2840	3420	4200	0	0	1.29
4	1550	1780	2280	2.13	0	1.87
8	62.9	80.9	157	10.2	10.8	1.96
12	37.6	37.8	55.5	5.72	6.07	1.57
24	18.8	2.15	0	0	0	NC
48	10.9	0	0	0	0	NC
AUC(tf) (ng equiv·hr/g)	15900	18600	20200	NC	NC	1.09
tf	48	24	12	10	10	-

a: Thirty minutes prior to blood and milk collection, each dam was administered oxytocin (5 units/dam) via subcutaneous injection.

b: Immediately after dosing, dams (except for those in the 1- and 2-hr time point groups) were returned to their pups and allowed to nurse until 2 hr prior to dam blood and milk collection, when pup blood was sampled.

NC = Not calculated

Pharmacokinetic drug interactions:

Boceprevir (25, 75 & 200 mg/kg) did not alter significantly the overall exposure of ribavirin (50 mg/kg) or PEG-intron (1414 $\mu g/m^2$) when administered in combination to cynomolgus monkeys (Study # 3321).

5.2 Toxicokinetics

Refer to specific toxicology sections within this review for TK data and summaries.

Study title: TOXICOKINETIC STUDY OF SCH 503034 ADMINISTERED ORALLY BY GAVAGE IN PREGNANT RATS

Study no.:	08259
Study report location:	4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute, Summit, NJ
Date of study initiation:	10-20-2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 05-503034-Y-110B & 98.0%

Key Study Findings: The toxicokinetics of SCH 503034 were assessed in pregnant rats administered oral (gavage) doses of 150, 300, 600 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] from GD 7 to 19. Serum concentrations of SCH 503034 were determined on GD 17. This study used the same doses as the pivotal embryo-fetal development study (Study # 1307), which did not perform TK analysis. Therefore, the results of this study were used to determine exposures at the NOAEL for the pivotal embryo-fetal and prenatal and postnatal developmental studies.

Table 5: TK Summary for SCH 503034 Following Administration of Boceprevir from Gestation Day 7 to 19 to Pregnant Rats

SCH 503034 Dose (mg/kg)	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)
150	8370	4	110000
300	15700	4	192000
600	11200	8	170000

Table from sponsor

6 General Toxicology

Reference ID: 2933010

6.1 Single-Dose Toxicity

Several single-dose toxicology studies in rats, dogs and cynomolgus monkeys were included in the NDA submission as summarized briefly below. The acute toxicity of SCH 503034 was evaluated in rats (3/sex/group) administered a single oral (gavage) dose of 1000 (♂ only), 2000 mg/kg or vehicle control [0.4% (w/v) aqueous methylcellulose] (Study # 1286). No mortality was observed. Clinical signs in males were limited to transient excessive salivation in one rat at each dose. Clinical signs in females at 2000 mg/kg were limited to urogenital staining in two rats. Compared to control, administration of SCH 503034 resulted in a decrease in mean body weight gain for Days 0 to 7 in males dosed at 2000 mg/kg. The NOAEL was 2000 mg/kg in females and 1000 mg/kg in males, based on a reduction in body weight gain.

The acute toxicity of SCH 503034 was evaluated in rats (3/sex/group) administered as a single intraperitoneal dose of 100, 500, 1000 mg/kg or vehicle control [0.4% (w/v) aqueous methylcellulose] (Study # 1287). Mortality was reported in a male and female at 1000 mg/kg. Clinical signs of toxicity in rats at 1000 mg/kg were abnormal stool, cool to touch, hunched appearance, hypoactivity, urogenital staining, weakness (in ♂&♀), and tremors (♂ only). Clinical signs of toxicity at 500 mg/kg were urogenital staining (♂&♀), and weakness (♀ only). There were no clinical signs of toxicity in rats administered 100 mg/kg. Mean body weight gain for Days 0 to 7 was lower in males in the 500 and 1000 mg/kg dose groups and in females in the 100, 500 and 1000 mg/kg dose groups. The NOAEL was 100 mg/kg in males and <100 mg/kg in females, based on minimally lower body weight gain in females dosed at 100 mg/kg.

One group of cynomolgus monkeys (1/sex) received a single oral (gavage) dose of 500 mg/kg SCH 503034 (Study # 1298). A second group of monkeys (1/sex) received a single oral (gavage) dose of 250 mg/kg followed four days later with a dose of 1000 mg/kg. Each group was observed for 14 days after their final dose. There was no mortality. Clinical signs of toxicity in monkeys dosed at 500 mg/kg consisted of emesis (♂ only) and loose stool (♂&♀). Clinical signs of toxicity in monkeys dosed at 1000 mg/kg consisted of emesis (♂&♀), and soft stool (♂ only). There were no SCH 503034-related clinical signs effects on body weights in monkeys dosed at 250 mg/kg. The NOAEL of SCH 503034 was 250 mg/kg in cynomolgus monkeys.

The acute toxicity of SCH 503034 was evaluated in dogs (2♂/group) administered as a single oral (gavage) dose of 50, 100, 200 and 300 mg/kg (Study # 6568). Clinical signs of toxicity in dogs dosed at 200 and 300 mg/kg consisted of emesis and abnormal stool findings, while only emesis was observed at 100 mg/kg. It should be noted that body weight and food consumption parameters were not evaluated in this study.

6.2 Repeat-Dose Toxicity

Reference ID: 2933010

Study title: TWO-WEEK ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 IN MICE

Study no.:	5131
Study report location:	4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	8-31-2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 03-503034-Y-102 & 96.0%

Key Study Findings: The toxicity of SCH 503034 (2000 mg/kg) and toxicokinetics of SCH 503034 stereoisomers and metabolites (900 or 2000 mg/kg) were assessed in mice administered SCH 503034 orally (gavage). The NOAEL was not determined due to clinical signs of toxicity, clinical pathology and necropsy observations. No histopathology was performed in this study.

Systemic exposure to SCH 534128, SCH 534129 and SCH 503034 was dose-related and sex-dependent, with exposure generally greater in female mice. Systemic exposure to SCH 534128 was slightly greater than systemic exposure to SCH 534129. Systemic exposure to SCH 629144 (Peaks 2, 3, 4 and Total) was sex-dependent, dose-related, decreased over time, and was lower than systemic exposure to SCH 503034 (see table below). All mice at 2000 mg/kg were sacrificed on Day 1 following dosing due to clinical observations of severe toxicity which included dehydration, weakness, cyanosis, coolness to the touch, hypoactivity, tremors, urogenital staining, scant stool, lacrimation and bilateral ptosis. Mice at 2000 mg/kg demonstrated higher mean, BUN bilirubin concentrations. One female at 2000 mg/kg also had higher BUN, alanine aminotransferase and aspartate aminotransferase values. Other alterations in hematology and serum chemistry parameters along with small thymuses and spleens in the 2000 mg/kg dose group were consistent with dehydration and/or stress associated with poor or moribund condition.

Table 6: TK Summary for SCH 503034 Following Administration of Boceprevir for 2-Weeks in Mice

Dose(mg/kg)	Day	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng· hr/mL)	AUC(0-24 hr) (ng· hr/mL)
900	0	Female	37500	2	24	104000	104000
		Male	30500	1	8	125000	213000
	13	Female	35300	1	24	278000	278000
		Male	32300	1	8	114000	161000
2000	0	Female	48600	1	24	552000	552000
		Male	38600	1	24	320000	320000

Study title: THREE-MONTH ORAL (GAVAGE) DOSE RANGE-FINDING STUDY OF SCH 503034 IN MICE

Reference ID: 2933010

Study no.:	1303
Study report location:	4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	1-9-2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 03-503034-Y-102 & 95.8%

Key Study Findings: Toxicity of SCH 503034 was evaluated in CD-1(ICR)BR VAF/Plus mice (10/sex/group) administered oral (gavage) doses of 125, 250, 500 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] for 3 months. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, clinical pathology and gross and histopathology. Target organs of toxicity of SCH 503034 identified in this mouse study were the liver, kidneys and spleen. A NOAEL was not identified in females based on the increased food consumption at all doses. The NOAEL in males was 250 mg/kg based on organ weight and histopathologic changes at 500 mg/kg. Study results were used as part of dose range-finding efforts for the mouse carcinogenicity study.

Mean body weights and body weight gains were 4% and 17% higher, respectively, in females in the 500 mg/kg dose group compared to controls at Week 14. This effect was considered related to the increases in food consumption (up 16%) in this dose group. For females in the 500 mg/kg dose group, the mean absolute and relative weights for the liver and spleen were higher than in concurrent controls. Mild vacuolation of the renal cortical tubular cells and minimal hypertrophy of the Kupffer cells (RE cells) in the liver were observed in males in the 500 mg/kg dose group.

Table 7: TK Summary for SCH 503034 Following Administration of Boceprevir for 3-Months in Mice

Parameter (Units)	125 mg/kg		250 mg/kg		500 mg/kg	
	Females	Males	Females	Males	Females	Males
Day 0 Cmax (ng/mL)	6590	2750	15400	7270	34400	19500
Tmax (hr)	1	1	1	2	1	1
tf (hr)	8	8	24	8	24	24
AUC(tf) (ng.hr/mL)	9660	4320	53600	19400	120000	92300
AUC(0-24 hr) (ng hr/mL)	10700	4540	53600	22500	120000	92300
Female:Male[a]	2.36	NA[b]	2.38	NA	1.30	NA
Day 80 Cmax (ng/mL)	6950	1290	12300	3910	7170	9010
Tmax (hr)	1	1	1	1	1	2
tf (hr)	8	8	8	8	24	24
AUC(tf) (ng.hr/mL)	9720	2080	28100	9600	47500	23200
AUC(0-24 hr) (ng hr/mL)	9860	2240	29400	10400	47500	23200
Female:Male	4.39	NA	2.84	NA	2.05	NA

Reference ID: 2933010

R[c]	0.918	0.494	0.548	0.460	0.394	0.251

a:Female:Male = AUC(0-24 hr) Female ÷AUC(0-24 hr) Male; b:NA = Not applicable; c:R = AUC(0-24 hr) Day 80 ÷AUC(0-24 hr) Day 0; tf=Time to final quantifiable sample.

Study title: THREE-MONTH ORAL (GAVAGE) DOSE RANGE-FINDING STUDY OF SCH 503034 IN MICE

Study no.:	4320
Study report location:	4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	4-19-2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 03-503034-Y-102 & 96.0%

Key Study Findings: Toxicity of SCH 503034 was evaluated in CD-1(ICR)BR VAF/Plus mice (10/sex/main group, 30/sex/TK group) administered oral (gavage) doses of 600, 750, 900 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] for 3 months. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, clinical pathology and gross and histopathology. No NOAEL was identified due primarily to increased absolute and relative liver weights with mild elevations of AST and ALT at all dose levels associated with neutrophil infiltration and Kupffer cell hypertrophy (♂ all doses, ♀ high-dose only). Although mean body weight gains were decreased in males at all dose levels (from 17 to 36%), an MTD was not determined for females since mean body weight gains were decreased 10% at 600 mg/kg but were actually higher by 4 and 21% in mid- and high-dose animals (likely due to increased food consumption). Study results were used as part of dose range-finding efforts for the mouse carcinogenicity study.

Reference ID: 2933010

Table 8: TK Summary for SCH 503034 Following Administration of Higher Doses of Boceprevir for 3-Months in Mice

Toxicokinetics Parameters for SCH 503034										
Dose[a] (mg/kg)	Day	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(0-8 hr) (ng·hr/mL)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	R[b]	F:M[c]
600	0	Female	22500	1	8	85600	85600	130000[d]	NA[e]	1.62
		Male	16000	1	8	64300	64300	79900	NA	NA
	82	Female	16900	2	8	68400	68400	80500	0.621	1.63
		Male	11200	1	8	44200	44200	49400	0.619	NA
750	0	Female	24500	1	8	99500	99500	181000[f]	NA	1.14
		Male	24900	1	24	91700	159000	159000	NA	NA
	82	Female	19400	1	8	90700	90700	152000[g]	0.839	1.77
		Male	16900	2	8	80200	80200	85800	0.539	NA
900	0	Female	35400	1	24	131000	187000	187000	NA	1.05
		Male	30600	1	24	87600	178000	178000	NA	NA
	82	Female	24400	1	8	123000	123000	205000[g]	1.09	1.87
		Male	15600	4	24	82500	110000	110000	0.617	NA

a: SCH 503034
b: R = AUC(0-24 hr)$_{Day\ 82}$ ÷ AUC(0-24 hr)$_{Day\ 0}$
c: Female:Male = AUC(0-24 hr)$_{Female}$ ÷ AUC(0-24 hr)$_{Male}$
d: % AUC Extrap = 34%
e: NA = Not applicable
f: % AUC Extrap = 45%
g: % AUC Extrap = 40%

Table 9: TK Summary for SCH 629144 Following Administration of Boceprevir for 3-Months in Mice

Day	Dose (mg/kg)	Cmax (ng/mL)		Tmax (hr)		AUC (0-24 hr) (ng·hr/mL)		Accumulation Ratio	
		Male	Female	Male	Female	Male	Female	Male	Female
0	600	23500	26400	2	2	97600	NR	NA	NA
	750	27200	32800	2	2	144000	NR	NA	NA
	900	31300	27000	2	1	242000	168000	NA	NA
82	600	5320	22800	4	2	23400	62900	0.255	0.642
	750	21000	18100	2	4	66200	NR	0.569	0.641
	900	18200	22400	4	4	71500	NR	NC	NC

NA = Not applicable, NR = Not reportable, NC = Not calculated

Study title: THREE-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 IN RATS

Study no.:	1290
Study report location:	4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	9-27-2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 02-503034-Y-001 & 101.2%

Key Study Findings: Toxicity of SCH 503034 was evaluated in CD(SD)IGS BR VAF/Plus rats (10/sex/main group, 18/sex/group TK group) administered oral (gavage) doses of 25, 75, 200 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] for 3 months. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, clinical pathology and gross and histopathology. Target organs/tissues of toxicity identified in this study were the testes, epididymides, prostate gland and liver in male rats. Based on the prostate gland weight changes, a NOAEL was not determined for males. Based on mortality, associated observations, and body weight effects, the NOAEL in females was 75 mg/kg.

Mortality occurred in 4 females (2 main study & 2 satellite group rats) dosed with 200 mg/kg SCH 503034, and each was preceded by a period of body weight loss (24% to 32%). The cause of death of these animals was not determined by the sponsor. At the time of unscheduled sacrifice, rats were in moribund condition (dehydration, a hunched or abnormally thin appearance, coolness to touch, weakness and/or urogenital staining.) Several histopathologic changes were noted in the 2 main study group females subjected to unscheduled sacrifice, as well as a third female in the 200 mg/kg dose group that was considered by the sponsor to be in a debilitated condition (stress) at study termination (based on depletion of body fat.) Hypertrophy in the adrenal cortex, hypocellularity and/or hemorrhage of the bone marrow, lymphoid atrophy and/or necrosis in several lymphoid tissues, ovarian follicular atresia, uterine and vaginal atrophy, and/or decreased size and single cell necrosis of hepatocytes were evident in these 3 female rats. Female rats in the 200 mg/kg dose group (4/10) showed depletion of body fat. These findings were attributed to stress or the debilitated condition rather than a direct effect of SCH 503034. Additionally, minimally lower mean corpuscular volume, minimally higher mean corpuscular hemoglobin concentration, mildly higher platelet count, moderately elevated ALT/AST, and hypoproteinemia (consisting of proportional decreases in total protein, albumin and globulin) were observed in females given 200 mg/kg dose and were considered to be drug-related.

Decrements in body weight gain relative to controls at study termination occurred in both males (-18.1%) and females (-20.1%) dosed with 200 mg/kg SCH 503034, and were associated with decreased absolute body weight relative to controls at study termination (-10.7% and -7.6%, respectively). Decreases in body weight values

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occurred concomitantly with decreases in absolute food consumption (-7.2% and -6.2% g/animal/day, respectively).

Mean absolute and relative prostate gland weights were lower in all dose groups. In addition, the mean absolute and relative weights of the epididymides were lower in the 200 mg/kg dose group. These findings were drug-related. Degeneration of the seminiferous tubular epithelium of the testes, with or without atrophy, was seen in all male rats at 200 mg/kg. In the epididymides, luminal debris was increased in all male rats at 200 mg/kg, while hypospermia was seen in 4/10 male rats at 200 mg/kg. Multinucleated hepatocytes were present in 2/10 male rats at 200 mg/kg. Mean ALT was also higher during Week 12 in males administered 200 mg/kg SCH 503034.

Table 10: TK Summary for SCH 503034 Following Administration of Boceprevir for 3-Months in Rats

Day	Dose (mg/kg)	Cmax (ng/mL)		Tmax (hr)		AUC (0-24 hr) (ng·hr/mL)		Accumulation Ratio	
		Male	Female	Male	Female	Male	Female	Male	Female
0	25	1140	2140	0.50	1.00	1770	5040	NA	NA
	75	6800	6880	0.50	2.00	9480	27100	NA	NA
	200	ND	ND	ND	ND	ND	ND	NA	NA
78	25	1060	3210	0.50	0.50	1610	7110	0.910	1.41
	75	3850	8370	1.00	1.00	7310	16100	0.771	0.594
	200	11500	20200	1.00	2.00	34200	148000	ND	ND

NA = Not applicable ND = Not determined. Toxicokinetic parameters could not be reliably determined due to the absence of the 1-hr mean concentration data for the 200 mg/kg-dosed males and females on Day 0.

Study title: THREE-MONTH ORAL (GAVAGE) DOSE RANGE-FINDING AND TOXICOKINETIC STUDY OF SCH 503034 IN RATS

Study no.:	1302
Study report location:	4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	11-5-2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 03-503034-Y-002 & 95.8%

Key Study Findings: Toxicity of SCH 503034 was evaluated in CD(SD)IGS BR VAF/Plus rats (10/sex/group-main group, 15/sex/group TK group) administered oral (gavage) doses of 100, 150(125), 300(150) mg/kg ♂(♀) or vehicle [0.4% (w/v) aqueous methylcellulose] for 3 months. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, clinical pathology and gross and histopathology. Target organs/tissues identified in this study in males were the adrenal glands and thymus (based on organ weight changes only), and the liver, testes and epididymides. Based on the histopathologic findings in the testes and epididymides, a NOAEL was not established in males. However, the NOAEL for

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females was determined to be 125 mg/kg based upon the reduction in body weight gain at 150 mg/kg.

Test article-related decrements in mean body weight gain relative to controls were observed on Day 90 in males (-16.6%, 300 mg/kg) and females (-9.6%, 150 mg/kg). Mean body weight was 8.6% lower in males administered 300 mg/kg. Mean ALT activity was minimally higher during Week 12 in males administered 300 mg/kg SCH 503034 and was associated with multinucleated hepatocytes in males in both the 150 and 300 mg/kg dose groups. Slightly higher adrenal gland weights and lower epididymides weights in males in all dose groups, and lower testes and thymus weights in males in the 300 mg/kg dose group were observed. The thymus and adrenal gland weight changes were considered to be secondary to stress. SCH 503034-related macroscopic findings were limited to small testes and small epididymides in males in the 150 and 300 mg/kg dose groups. SCH 503034-related histopathologic findings included; Sertoli cell vacuolation, spermatid degeneration and atrophy of seminiferous tubules of the testes, and hypospermia and luminal cellular debris of the epididymides in males in all dose groups.

Table 11: TK Summary for SCH 503034 Following Administration of Boceprevir for 3-Months in Rats

Sex	Day	Dose (mg/kg)	Cmax (ng/mL)	Tmax (hr)	AUC (0-24 hr) (ng·hr/mL)	Accumulation Ratio
Male	0	100	14400	2.00	38700	NA
		150	14100	2.00	40200	NA
		300	24900	2.00	99400	NA
	77	100	4140	2.00	14400	0.372
		150	10500	2.00	30700	0.763
		300	22900	2.00	95900	0.965
Female	0	100	15500	2.00	48500	NA
		125	14600	2.00	49900	NA
		150	18600	2.00	75300	NA
	77	100	10100	2.00	52600	1.08
		125	13800	2.00	38600	0.775
		150	8000	4.00	46200	0.613

NA: Not applicable

Study title: THREE-MONTH ORAL (GAVAGE) STUDY OF SCH 503034 IN MALE RATS WITH A TWO-MONTH POSTDOSE PERIOD

Study no.:	3209
Study report location:	4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	6-17-2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 02-503034-Y-001 & 100.9%

Key Study Findings: Toxicity of SCH 503034 was evaluated in 6 week old CD(SD)IGS BR VAF/Plus male rats (20 ♂/group-main group, 18/sex/group TK group) administered oral (gavage) doses of 3, 10, 75 mg/kg, and 10 week old rats given 75 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] for 3 months. Only clinical signs, body weight, food consumption, organ weights (epididymides, prostate gland & testes) and gross and histopathology on the prostate gland only was performed. The results of this study indicate that the NOAEL for the limited parameters examined in 6- and 10-week-old male rats is ≥ 75 mg/kg based on the lack of test article-related changes. The expected prostate gland weight changes were not observed so animals in the post-dose period group were not examined.

Table 12: TK Summary for SCH 503034 Following Administration of Boceprevir for 3-Months in Male Rats

Day 83 Dose (mg/kg)	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)
3a	58.7	0.50	113
10a	441	0.50	942
75a	4020	2.00	10397
75b	8267	2.00	19639
a: 6-week-old rats at initiation of dosing; b: 10-week-old rats at initiation of dosing			

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE:	**SIX-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 IN RATS**
STUDY NO.:	01299
VOLUME/PAGE:	01299.pdf
LABORATORY:	Schering-Plough Research Institute (SPRI)
STUDY INITIATION:	8/20/2003
GLP:	yes (x) no ()
QA REPORT:	Yes (x) no ()

Reference ID: 2933010

DRUG LOT/VEHICLE: 03-503034-Y-102; 0.4% (w/v) aqueous methylcellulose

METHODS:

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)
		Toxicity Portion	Satellite Portion[a]				
C1	Control (Methylcellulose)	15	3	0	5	0	183 - 185
T1	Low-Dose (SCH 503034)	15	15	15	3	5	183 - 185
T2	Mid-Dose (SCH 503034)	15	15	75	5	15	183 - 185
T3	High-Dose (SCH 503034)	15	15	125	5	25	183 - 185

a: These animals were designated for toxicokinetic analysis only.

DOSING: See above.

SPECIES/STRAIN: Rat/Crl:CD(SD)IGS BR VAF/Plus

#/SEX/GROUP: See above

ROUTE Oral gavage for 183-185 days

OBSERVATIONS AND TIMES:

CLINICAL SIGNS: At least once daily beginning Week -1

BODY WEIGHTS: Weekly beginning Week -1; day of randomization; prior to first day of terminal sacrifice; and terminal sacrifice

FOOD CONSUMPTION: Weekly beginning Week -1; prior to first day of terminal sacrifice

OPHTHALMOLOGY: Once pretest, Week 44 and 25

COAGULATION: Week 27

HEMATOLOGY: Week 13 and 26

SERUM/ URINE CHEMISTRY: Week 13 and 26

HISTOPATHOLOGY The following organs/tissues from toxicity portion rats were examined microscopically: all organs/tissues collected from rats in the control and high-dose groups, as well as rats that were sacrificed prior to scheduled necropsy; all collected gross findings; testes, epididymides and prostate gland from males in the low- and mid-dose groups; and liver and seminal vesicles from males in the mid-dose group.

SPONSOR'S TISSUE LIST

Tissues Collecteda	
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 – Sternumb	Seminal Vesicles

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Brain	Skeletal Muscle - Biceps Femoris
Epididymides	Skin
Esophagus	Small Intestine – (Duodenum, Jejunum, Ileum)
Eyesc	Spinal Cord – Thoracolumbar
Harderian Glandsc	Spleen
Headd	Stomach
Heart	Testesf
Kidneys	Thymus
Large Intestine – (Cecum and Colon)	Thyroid Gland
Liver	Tongued
Lungs	Trachea
Lymph Nodes - Mandibular and Mesenteric	Urinary Bladder
Mammary Glande	Uterus (plus Cervix)
Ovaries	Vagina
Pancreas	Animal Identificationd
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 except those found dead during the morning viability check 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

ORGANS WEIGHTED

Organs Weighed	
Adrenal Glands	Pituitary Gland
Brain	Prostate Gland (ventral)
Epididymides	Spleen
Heart	Testes
Kidneys	Thymus
Liver	Thyroid Gland/Parathyroid Glandsa
Lungs	Uterus (plus Cervix)
Ovaries	

a: Thyroid gland/parathyroid glands were weighed post-fixation.

RESULTS:

CLINICAL SIGNS: Unremarkable (no drug-related deaths).

BODY WEIGHTS: Decreases in mean body weight (-7.9% and -5.7% for males and females, respectively) and mean body weight gain (-11.6% and -11.5% for males and females, respectively) relative to controls were observed at the conclusion of the study in the 125 mg/kg SCH 503034 dose group. These decreases did not correlate with decreases in mean food consumption.

FOOD CONSUMPTION: Unremarkable.

OPHTHALMO- Unremarkable.

Reference ID: 2933010

LOGY:

HEMATOLOGY: Unremarkable except the two females sacrificed in moribund condition.

COAGULATIONS: Unremarkable

SERUM/ URINE CHEMISTRY: One male at 125 mg/kg SCH 503034 had minimally higher ALT activity during Week 26. This rat also had microscopic evidence of multinucleated hepatocytes (see below).

Mean urine osmolality was minimally lower at Weeks 13 and 26 in rats administered 75 or 125 mg/kg SCH 503034. Correspondingly, mean urine volumes were higher in the same groups (see below).

SCH 503034-Related Differences in Mean Urine Chemistry Values

Finding (Units)	Week	Dose Group (mg/kg)		
		0 (Control)	75 (SCH 503034)	125 (SCH 503034)
Male Osmolality (mOsm/kg)	13	2255.1	1703.3	1760.1
	26	1799.9	1439.6	1514.7
Volume (mL/kg/24 hr)	13	23.94	35.05	32.16
	26	24.15	34.52	32.76
Female Osmolality (mOsm/kg)	13	2132.1	1691.3	1584.5
	26	1637.0	1421.7	1029.6
Volume (mL/kg/24 hr)	13	27.26	44.89	43.58
	26	26.30	40.57	63.42

ORGAN WEIGHTS: Unremarkable.

HISTO-PATHOLOGY: SCH 503034-related necropsy findings were limited to the testes and epididymides of one high-dose rat (No. 3014M). In rat No. 3014M, bilaterally small epididymides correlated histologically with hypospermia. Bilaterally small and (altered texture) soft testes correlated histologically with atrophy of seminiferous tubules.

SCH 503034-related histopathologic findings occurred in the liver, testes and epididymides of males in the mid- and high-dose groups. Liver findings were characterized by scattered foci of multinucleated hepatocytes. Affected hepatocytes were slightly to greatly enlarged and contained from five to nine variably-sized nuclei. Multinucleated hepatocytes have been reported previously in rats given ≥ 150 mg/kg SCH 503034 daily for three months. Testicular findings consisted of minimal bilateral spermatid degeneration; and minimal to moderate bilateral Sertoli cell vacuolation and atrophy of seminiferous tubules. In the epididymides, minimal bilateral luminal cellular debris was present as a consequence of the spermatid degeneration noted in the testes. A moderate bilateral hypospermia was present in one high-dose rat (No. 3014M) and considered a consequence of the moderate atrophy of seminiferous tubules also present in the testes of this animal. The histopathologic findings are presented in the following table.

Dose Group (mg/kg):	Control (Methylcellulose)	Low-Dose (SCH 503034)	Mid-Dose (SCH 503034)	High-Dose (SCH 503034)

	0		15		75		125	
Sex:	M	F	M	F	M	F	M	F
Organ/Finding/Severity				Incidence[a]				
Liver								
-multinucleated hepatocytes								
minimal	0/15	0/15	0/15	NA	1/15*	0/15	4/15*	0/16b
Testes								
-Degeneration, spermatid								
minimal	0/15	NA	0/15	NA	7/15*	NA	15/15*	NA
-Vacuolation, Ser toli cell								
minimal	0/15	NA	0/15	NA	3/15*	NA	8/15*	NA
mild	0/15	NA	0/15	NA	1/15*	NA	1/15*	NA
moderate	0/15	NA	0/15	NA	0/15	NA	1/15*	NA
-Atrophy, seminif erous tubule								
minimal	1/15	NA	1/15	NA	1/15*	NA	1/15*	NA
moderate	0/15	NA	0/15	NA	0/15	NA	1/15*	NA
Epididymides								
-Hypospermia								
moderate	0/15	NA	0/15	NA	0/15	NA	1/15*	NA
-Cellular debris, luminal								
minimal	0/15	NA	0/15	NA	5/15*	NA	13/15*	NA

a: Incidence = Number affected/Number examined.

b: Includes one rat that was sacrificed on Day 13 due to traumatic injury and was subsequently replaced

* = Test article-related finding

NA = Not applicable

TOXICOKINETICS: Peak drug concentrations were observed by 1 or 2 hr post-dose. Exposures to SCH 503034 were sex-dependent, with greater exposure in females, and were dose-related. SCH 503034 did not accumulate in plasma. Plasma drug concentrations sowed high inter-animal variability.

Sex	Day	Dose (mg/kg)	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)	R[a]
Female	0	15	391	1	1450	NAb
		75	12800	2	39300	NA
		125	19900	2	85000	NA
	167	15	1470	1	3770	2.60
		75	10000	1	31600	0.804
		125	16000	1	53500	0.629
Male	0	15	426	1	NCc	NA
		75	5730	1	14400	NA
		125	12500	1	37500	NA
	167	15	1160	1	NC	NC
		75	9600	1	16700	1.16
		125	16400	2	37000	0.987

a: R = AUC(0-24 hr)Day 167 ÷AUC(0-24 hr)Day 0

b: NA = Not applicable

:

c: NC =Not calculated due to insufficient plasma concentration-time profile

CONCLUSION: Target organs identified in this study were the liver, testes and epididymides in males. The results of this study indicate that NOEL is 15 mg/kg based on test article-related changes in urine chemistry (males and females) and histopathology observations (males) at 75 mg/kg.

Study title: ONE-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 IN CYNOMOLGUS MONKEYS

Study no.:	1291
Study report location:	4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute, Summit, NJ
Date of study initiation:	10-16-2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 02-503034-Y-001 & 97.4%

Key Study Findings: Toxicity of SCH 503034 was evaluated in cynomolgus monkeys [4/sex/group-main group, 2/sex/group recovery group (1 month)-control & high-dose only] administered oral (gavage) doses of 25, 75, 200 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] for 1 month. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, electrocardiograms, urinalysis, clinical pathology and gross and histopathology. The results of this study indicate that the NOEL in cynomolgus monkeys is 25 mg/kg based on drug-related changes in APTT and cholesterol parameters.

Compared to pretest values, minimal to mild increases in serum cholesterol were observed in all high-dose males, 1/4 high-dose females and 1/4 mid-dose males. These monkeys had increases in Week 4 serum cholesterol of 25% or greater (range 25.1%-44.5%) compared to their pretest values. Although increases in serum cholesterol relative to pretest values were seen in all groups, including controls, these increases were of a smaller magnitude than those seen in the noted animals. Additionally, compared to pretest and/or concurrent control data, all high-dose males and females had minimal increases in APTT. Week 4 values were over 28 seconds in duration, 2.1-9.2 seconds longer than the longest pretest value for the individual. No changes in prothrombin time were evident. Although these increases were not observed with all instrument/reagent systems, SCH 503034 may have a marginal effect on some step(s) of the intrinsic clotting cascade.

Table 13: TK Summary for SCH 503034 Following Administration of Boceprevir for 1-Month in Cynomolgus Monkeys

Day	Dose (mg/kg)	Cmax (ng/mL)		Tmax (hr)		AUC (0-24 hr) (ng·hr/mL)		Accumulation ratio	
		Mean	(CV)	Median	(Min, Max)	Mean	(CV)	Mean	(CV)

Reference ID: 2933010

0	25	764	(39)	0.50	(0.50, 1.00)	2850	(19)	NA	(NA)
	75	1910	(25)	0.50	(0.50, 4.00)	11800	(29)	NA	(NA)
	200	6720	(15)	4.00	(1.00, 4.00)	55300	(30)	NA	(NA)
29	25	467	(70)	0.75	(0.50, 4.00)	2960	(13)	1.03	(16)
	75	1240	(80)	0.75	(0.50, 4.00)	9230	(41)	0.804	(39)
	200	3560	(49)	4.00	(0.50, 8.00)	30900	(40)	0.617	(37)
NA = Not applicable									

Study title: THREE-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 IN CYNOMOLGUS MONKEYS

Study no.: 2605
Study report location: 4.2.3.2
Conducting laboratory and location: (b) (4)
Date of study initiation: 1-13-2003
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: SCH 503034, 02-503034-Y-001 & 97.4%

Key Study Findings: Toxicity of SCH 503034 was evaluated in cynomolgus monkeys (4/sex/group) administered oral (gavage) doses of 25, 75, 200 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] for 3 months. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, electrocardiograms, urinalysis, clinical pathology and gross and histopathology. The NOEL was 25 mg/kg/day based on minor changes in cholesterol, triglycerides, APTT and alanine aminotransferase parameters. The NOAEL was considered to be 200 mg/kg/day based on lack of adverse findings in the high-dose group.

Administration of SCH 503034 was associated with mildly to moderately higher activated partial thromboplastin time for males given 200 mg/kg/day (at Week 12, approximately 2.2-fold higher than control mean) and females given 75 or 200 mg/kg/day (at Week 12, approximately 1.5- and 2.1-fold higher, respectively, than control mean). These increases appeared to be highly dependent on particular APTT reagent/detection instrument combinations with clear increases in APTT only observed with optical detection methods, while mechanical methods demonstrated formation of actual clots. Additionally, there were no test article-related effects on intrinsic and contact factor coagulant activities (Factors VIII, IX, XI and XII; prekallikrein and high molecular weight kininogen). Thus, it appears unlikely that hemostasis through the intrinsic coagulation cascade was impaired in a clinically significant manner.

A few modest differences at Week 12 between control and SCH 503034-dosed animals were somewhat similar to baseline differences and affected parameters that normally exhibit high variability. These included higher cholesterol and triglycerides for males and females given 200 mg/kg/day and lower alanine aminotransferase for males and females given 75 or 200 mg/kg/day.

Table 14: TK Summary for SCH 503034 Following Administration of Boceprevir for 3-Months in Cynomolgus Monkeys

Day	Dose (mg/kg)	Cmax (ng/mL)		Tmax (hr)		AUC (0-24 hr) (ng·hr/mL)		Accumulation ratio	
		Mean	(CV)	Median	(Min, Max)	Mean	(CV)	Mean	(CV)
1	25	223	(66)	1.00	(0.50, 8.00)	2560a	(42)	NA	(NA)
	75	1050	(31)	1.00	(0.50, 8.00)	9380	(33)	NA	(NA)
	200	2980	(52)	6.00	(1.00, 8.00)	34200	(58)	NA	(NA)
83	25	649	(35)	0.50	(0.50, 1.00)	3480	(36)	1.66a	(42)
	75	1140	(48)	1.00	(0.50, 1.00)	9750	(28)	1.10	(27)
	200	2850	(54)	4.00	(0.50, 8.00)	26400	(69)	0.918	(50)

a: n=6; AUC(0-24 hr) and R could not be reliably determined in two animals. NA: Not applicable

Study title: THREE-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 AT ELEVATED DOSES IN CYNOMOLGUS MONKEYS

Study no.:	4080
Study report location:	4.2.3.2
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	5-12-2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 02-503034-Y-103 & 97.2%

Key Study Findings: Toxicity of SCH 503034 was evaluated in cynomolgus monkeys (4/sex/group) administered oral (gavage) doses of 300, 500, 1000 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] for 3 months. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, urinalysis, clinical pathology and gross and histopathology. The NOEL was not identified due to minor decreases in red blood cell count, hemoglobin and hematocrit and increases in APTT, cholesterol and liver weights in all dose groups.

During the first 5 weeks of dosing (Week -2/-1 to Week 5), decreases in mean red blood cell count, hemoglobin and hematocrit were observed in both males and females in all SCH 503034 dose groups. These values were reduced 14 to 18% and 8 to 10% relative to pre-dose levels and to control values, respectively. These findings were associated with mild (40 to ~100%) increases in reticulocytes during this time period. These effects were seen to a lesser extent at 12 weeks and so did not progress

Reference ID: 2933010

over the duration of the study. Although significant, these reductions were small and are not considered to be adverse.

Compared to pretest values, minimal to mild increases in serum cholesterol were observed at Week 5 in most monkeys administered SCH 503034. However, the effect appeared to be transient. Cholesterol values declined, with similar magnitude, between Weeks 5 and 12 in most individuals in all groups, including controls. By Week 12, only a minority of monkeys were affected. Two males dosed with 300 mg/kg and all other individuals in all dose groups also had minimal to mild increases in APTT during Week 12. Most were similarly affected during Week 5 and, in the majority of those affected, APTT was slightly longer during Week 12 than Week 5. SCH 503034 related organ weight changes were also observed and were limited to higher mean liver weights (increased 42 to 67%) in males in the 500 and 1000 mg/kg dose groups and in females in all dose groups.

Table 15: TK Summary for SCH 503034 Following Administration of Boceprevir for 3-Months at Higher Doses in Cynomolgus Monkeys

Dose (mg/kg)	Day	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng · hr/mL)
300	25	3630 (32)	3.06 (80)	30500 (15)
	84	3840 (32)	4.13 (46)	32300 (30)
500	25	7240 (51)	3.44 (67)	79800 (25)
	84	5260 (33)	3.25 (43)	54500 (36)
1000	25	8540 (20)	4.00 (0)	84700 (33)
	84	6050 (23)	4.50 (31)	63800 (30)

Table 16: TK Summary for SCH 629144 Following Administration of Boceprevir for 3-Months at Higher Doses in Cynomolgus Monkeys

Dose[a] (mg/kg)	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)
SCH 629144			
300	26400 (34)	4.0 (0)	226000 (24)
500	37000 (39)	5.0 (37)	364000 (46)
1000	44500 (29)	5.0 (37)	457000 (20)
SCH 629144 Peak 2			
300	19000 (39)	4.0 (0)	152000 (26)
500	24800 (41)	4.5 (31)	238000 (47)
1000	29600 (33)	4.5 (31)	295000 (23)
SCH 629144 Peak 3			
300	285 (34)	7.0 (26)	3250 (37)
500	583 (74)	5.6 (48)	5760 (72)
1000	598 (34)	6.5 (32)	6090 (41)
SCH 629144 Peak 4			
300	7210 (28)	4.5 (31)	70400 (20)
500	11800 (37)	5.0 (37)	121000 (44)
1000	14800 (21)	5.5 (38)	155000 (18)
a: SCH 503034; N=8/dose group			

Table from Sponsor

Study title: 6-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 IN CYNOMOLGUS MONKEYS

Study no.: 1300
Study report location: 4.2.3.2
Conducting laboratory and location: (b) (4)
Date of study initiation: 8-20-2003
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: SCH 503034, 03-503034-Y-102 & 95.8%

Key Study Findings: Toxicity of SCH 503034 was evaluated in cynomolgus monkeys (4/sex/group) administered oral (gavage) doses of 25, 75, 200 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] for 6 months. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, electrocardiograms, urinalysis, clinical pathology and gross and histopathology. Higher cholesterol levels in males and females at 200 mg/kg/day (approximately 12 and 31% higher than control means, respectively, at Week 24) were reported. The mechanism was not apparent. Higher APTTs for males at 200 mg/kg/day were reported (approximately 26 and 18% higher than control means at Weeks 12 and 24, respectively). The NOEL of this cynomolgus monkeys study was considered to be 75 mg/kg based on minor changes in cholesterol and APTT observed at 200 mg/kg.

Reference ID: 2933010

Table 17: TK Summary for SCH 503034 Following Administration of Boceprevir for 6-Months in Cynomolgus Monkeys

Day	Dose (mg/kg)	Cmax (ng/mL)		Tmax (hr)		AUC(tf) (ng·hr/mL)		AUC(0-24 hr) (ng·hr/mL)		Accumulation ratio	
		Mean	(CV)	Median	(Min, Max)	Mean	(CV)	Mean	(CV)	Mean	(CV)
1	25	389	(66)	0.8	(0.5, 8.0)	1750	(51)	21606	(42)	NA	(NA)
	75	1180	(49)	1.0	(1.0, 4.0)	6860	(21)	860	(21)	NA	(NA)
	200	4910	(36)	4.0	(1.0, 4.0)	32800	(29)	32800	(29)	NA	(NA)
177	25	256	(45)	1.0	(0.5, 8.0)	1870	(62)	2070	(54)	1.20	(42)
	75	716	(75)	1.0	(0.5, 8.0)	5640	(18)	5790	(21)	0.884	(34)
	200	3430	(36)	4.0	(1.0, 8.0)	26700	(30)	26700	(30)	0.851	(30)
NA = Not applicable											

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE: **12-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 IN CYNOMOLGUS MONKEYS**

STUDY NO.: 01301

VOLUME/PAGE: Pdf file

LABORATORY: (b) (4)

STUDY INITIATION: 3/2004

GLP: yes (x) no ()

QA REPORT: Yes (x) no ()

DRUG LOT/VEHICLE: 03-503034-Y-102 (98%); 0.4% (w/v) aqueous methylcellulose

METHODS:

DOSING:

Group	No. of Animals		Dose Level[a]	Dose Concentration [a]
	Male	Female	(mg/kg/day)	(mg/mL)
1 (Control)b	4	4	0	0
2 (Low)	4	4	25	5
3 (Mid)	4	4	75	15
4 (High)	4	4	200	40
a: The dose volume was 5 mL/kg. b: The control group received 0.4% methylcellulose only.				

SPECIES/STRAIN: Cynomolgus monkeys

NO./SEX/GROUP see table above

ROUTE Oral gavage 1/day, 365 days

OBSERVATIONS:

Clinical Observations	Daily	**Coagulation**	Twice pretest and once during Weeks 4 and 12
Ophthalmic Examinations	Once pretest and once during Weeks 4 and 12	**Clinical Chemistry**	During Weeks -3, -1, 12, 24, and 52
Body Weights	Weekly	**Urinalysis**	During Weeks -3, -1, 12, 24, and 52
Food Consumption	Daily	**Intrinsic Blood Coagulation Factor Analysis**	During Weeks -3, -1, 12, 24, and 52

Physical Examination	Weeks -4, -2, 5, 25, and 53	**Organ Weights**	Terminal sacrifice
ECG, BP, and Body Temperature Examinations	Twice prior to initiation of dosing and at a target time of 0.5 to 2 hours postdose during Weeks 5, 25, and 53	**Necropsy (Macroscopic Observations)**	All animals
Toxicokinetics	Day 1 and Week52 (0.5, 1, 4, 8, and 24 hours postdose)		
Hematology	During Weeks -3, -1, 12, 24, and 52		

HISTOPATHOLOGY:

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

a: Collected but not processed. b: Both eyes were carefully removed with a segment of the optic nerve. Using a 27-gauge needle inserted approximately 5 mm posterior to the limbus into the vitreous chamber just posterior to the ciliary process and lens, the eyes were injected with freshly prepared phosphate-buffered 3% glutaraldehyde (pH 6.9 to 7.1) until there was a minimal increase in turgidity of the globe. Each eye was placed in a separate container filled with the same glutaraldehyde fixative (labeled separately for the right and left eye). The eyes were fixed in 3% glutaraldehyde for at least 48 hours (but no longer than 72 hours). They were then rinsed briefly in tap water and placed in 10% neutral-buffered formalin.

ORGANS WEIGHTED

Adrenal Glands	Pituitary Gland
Brain	Prostate Gland
Epididymides	Spleen
Heart	Testes
Kidneys	Thymus
Liver	Thyroid Gland/ Parathyroid Glands
Lungs	Uterus (plus Cervix)
Ovaries	

RESULTS:

MORTALITY: None

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CLINICAL SIGNS: Unremarkable
BODY WEIGHT: Unremarkable
FOOD CONSUMPTION: Unremarkable
OPHTHALMOLOGY: Unremarkable
EKG Unremarkable
SERUM CHEMISTRY: Unremarkable
HEMATOLOGY: Unremarkable
URINANALYSIS: Unremarkable
SERUM CHEMISTRY: Unremarkable; minimally to mildly higher cholesterol for males in the 200 mg/kg dose group during Week 24 only.
COAGULATION: Unremarkable
ORGAN WEIGHTS: Unremarkable
HISTO-PATHOLOGY: Unremarkable
TOXICOKINETICS Systemic exposure to SCH 503034, SCH 534128 and SCH 534129 was independent of sex and increased in a dose-related manner from 25 to 200 mg/kg. SCH 534128:SCH 534129 AUC(0-24 hr) ratios were similar across all dose levels on Day 1 and Day 360; systemic exposure to SCH 534129 was approximately six-fold greater than exposure to SCH 534128.

SCH 503034

SCH 503034a Dose (mg/kg)	Day	Cmax (ng/mL)	Tmax (hr)	AUC(tf) (ng · hr/mL)	AUC(0-24 hr) (ng · hr/mL)
25	1	352 (83)	0.9 (132)	1740 (99)	2450 (79)d
	360	357 (61)	0.6 (31)	1480 (27)	1480 (27)
75	1	904 (63)	1.2 (98)	6030 (57)	6030 (57)
	360g	1220 (66)	1.6 (171)	8880 (67)	8880 (67)
200	1	3020 (77)	2.6 (102)	18900 (49)	18900 (49)
	360	2070 (73)	2.9 (113)	21900 (105)	21900 (105)

SCH 534129

SCH 503034a Dose (mg/kg)	Day	Cmax (ng/mL)	Tmax (hr)	AUC(tf) (ng · hr/mL)	AUC(0-24 hr) (ng · hr/mL)
25	1	297 (87)	1.0 (122)	1500 (105)	2130 (83)d
	360	292 (57)	0.6 (37)	1210 (28)	1210 (28)
75	1	733 (67)	1.3 (91)	5030 (61)	5030 (61)
	360g	1030 (75)	1.7 (162)	7530 (73)	7530 (73)
200	1	2510 (77)	2.9 (87)	16300 (51)	16300 (51)
	360	1770 (80)	3.1 (106)	19100 (112)	19100 (112)

SCH 534128

SCH 503034a Dose (mg/kg)	Day	Cmax (ng/mL)	Tmax (hr)	AUC(tf) (ng · hr/mL)	AUC(0-24 hr) (ng · hr/mL)

25	1	54.9 (68)	0.9 (132)	199 (81)	428 (NC)d,e
	360	66.0 (80)	0.6 (31)	210 (31)	297 (15)g
75	1	187 (56)	0.6 (37)	830 (58)	1170 (35)j
	360h	217 (42)	1.6 (180)	1350 (53)	1350 (53)
200	1	532 (78)	2.2 (118)	2220 (55)	2640 (48)l
	360	336 (44)	1.6 (167)	2850 (61)	2850 (61)

CONCLUSION The NOAEL was ≥200 mg/kg [AUC(0-24 hr) = 21900 ng·hr/mL], based upon transient cholesterol increases in males at 200 mg/kg that were not considered to be toxicologically significant by the sponsor. Please note that APTT increases seen in previous 3- and 6-month monkey studies are not reported in this study.

7 Genetic Toxicology

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

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE: **Mutagenicity Testing of SCH503034 with *Salmonella typhimurium* TA1535, TA97a, TA98, TA102 and TA100 and *Escherichia coli* WP2 uvrA.**

STUDY NO: 1292

VOLUME: 1292.pdf

LABORATORY: Sponsor

LABORATORY: Sponsor

GLP: Yes

INITIATION DATE: 11/02

BATCH NO. 02-503034-Y-001

METHODS: SCH503034 was tested in Salmonella typhimurium and Escherichia coli (see below), with and without S9 metabolic activation.

Bacterial Strains	Nonactivation Assays	(µg/plate)	Activation Assays	(µg/plate)
Salmonella typhimurium				
TA1535/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 WP2uvrA	N-Ethyl-N'-nitro- N-nitrosoguanidine	(2)	2-Aminoanthracene	(20)

STRAINS: Salmonella typhimurium TA1535, TA97a, TA98, TA102 and TA100 and Escherichia coli WP2 uvrA.

DOSAGE 3, 10, 33, 100, 333, 1000, 3333, 5000 µg/plate.

RESULTS: Over a dose range of 312.5 to 5000 µg/plate, SCH 503034 did not induce any increase in revertant colony counts in any of the strains tested, with or without metabolic activation in two independent trials. All solvent controls were within their respective historical control range, except for the solvent control for TA98 in the activation phase of Trial 2, which was slightly lower than the historical control

	range. This finding does not affect the integrity or the interpretation of the results of this study.
CONCLUSION:	SCH 503034 was not mutagenic in the bacterial mutagenicity assay, with or without metabolic activation, under the conditions of this study.

7.2 *In Vitro* Assays in Mammalian Cells

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE:	**CHROMOSOME ABERRATION STUDY OF SCH 503034 IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES**
STUDY NO:	1293 1293.pdf
LABORATORY:	(b) (4)
GLP:	yes
INITIATION DATE:	11/2002
BATCH NO.	SCH 503034 (Batch No.: 02-503034-Y-001) in DMSO
METHODS:	The potential clastogenicity of SCH 503034 was assessed in a human peripheral blood lymphocyte chromosome aberration assay. The dose levels scored for chromosome aberrations without metabolic activation ranged from 53.5 to 425 ug/mL - in the first valid trial and from 50 to 150 ug/mL in the confirmatory trial. The dose levels scored for chromosome aberrations with metabolic activation ranged from 150 to 650 ug/mL in the first valid trial, and from 300 to 550 ug/mL in the confirmatory trial (positive controls: non-activation: mitomycin c activation: cyclophosphamide).
RESULTS:	SCH 503034 did not induce an increase in chromosome aberrations over dose ranges of 53.5 to 425 ug/mL (first valid trial) and 50 to 150 ug/mL (confirmatory trial) without metabolic activation, and 150 to 650 ug/mL (first valid trial) and 300 to 550 ug/ml (confirmatory trial) with metabolic activation. All vehicle controls were within their respective historical vehicle control range.
Conclusions:	SCH 503034, was negative for inducing chromosome aberrations in cultured whole blood human lymphocytes in the presence or absence of an exogenous metabolic activation system under the conditions of this study.
OVERALL CONCLUSIONS:	Overall, SCH 503034 was shown not to be mutagenic or clastogenic in the three tests presented above.

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

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

Reference ID: 2933010

STUDY TITLE:	**MOUSE BONE MARROW ERYTHROCYTE MICRONUCLEUS STUDY OF SCH 503034**
STUDY NO:	1310
VOLUME:	1310.pdf
LABORATORY:	(b) (4)
GLP:	yes
INITIATION DATE:	12/2003
BATCH NO.	SCH 503034 (Batch No.: 02-503034-Y-001) in DMSO
METHODS:	The genotoxicity of SCH 503034 was evaluated in a mouse bone marrow erythrocyte micronucleus assay in CD-1® mice. The doses were 500, 1000, and 2000 mg/kg/day in male and female mice.
RESULTS:	No bone marrow toxicity was observed in the males or females dosed at 500, 1000, or 2000 mg/kg/day at the 24-hour or 48-hour harvest. Administration of SCH 503034 did not induce an increase in micronucleated polychromatic erythrocytes (PCE) relative to the vehicle controls at a dose range of 500 to 2000 mg/kg/day in either males or females. The positive control, cyclophosphamide, induced statistically significant increases in micronucleated PCE in both sexes.
Conclusions:	Administration of SCH 503034 did not induce micronuclei in bone marrow polychromatic erythrocytes in male or female mice under the conditions of this study.

7.4 Other Genetic Toxicity Studies

Study title: BACTERIAL MUTAGENICITY STUDY OF SCH 503034 CONTAINING IMPURITIES (BATCH NO. 56783-31-22) (Study # 5113)

Key Study Findings: The potential mutagenicity of SCH 503034 containing impurities (Batch No. 56783-31-22) was assessed in the *Salmonella*/mammalian microsome (Ames test) and *Escherichia*/mammalian microsome plate incorporation reverse mutation assays over a dose range of 78 to 5000 µg/plate. SCH 503034 containing impurities did not induce an increase in revertant colony counts in any strain tested, with or without metabolic activation.

Study title: CHROMOSOME ABERRATION STUDY OF SCH 503034 CONTAINING IMPURITIES (BATCH NO. 56783-31-22) IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES (Study # 5114)

Key Study Findings: Cultured human peripheral blood lymphocytes were tested with SCH 503034 containing impurities (Batch No. 56783-31-22) at a dose range of 62.5 to 500 µg/mL in an initial trial and at 50 to 200 µg/mL in a confirmatory trial with and without metabolic activation. The high doses reached acceptable levels of cytotoxicity or the limit of solubility and all positive controls induced acceptable increases of chromosome aberrations above their respective vehicle controls. SCH 503034 containing impurities did not induce chromosome aberrations in cultured human

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peripheral blood lymphocytes in the presence or absence of an exogenous metabolic activation system under the conditions of this study.

Study title: BACTERIAL MUTAGENICITY STUDY OF SCH 503034 CONTAINING IMPURITIES (BATCH NO SI-07HCVY202A) (Study # 7359)

Key Study Findings: SCH 503034 containing impurities (Batch No. SI-07HCVY202A) was assessed in the Salmonella/mammalian microsome (Ames test) and Escherichia/mammalian microsome plate incorporation reverse mutation assays. When corrected for purity, doses of SCH 503034 ranged from 78 to 5000 µg/plate for strains TA1535, TA97a, TA98, TA100 and WP2uvrA, and from 78 to 2500 µg/plate for strain TA102, with and without metabolic activation. These dose ranges were equivalent to 83.6 to 5348.0 µg/plate of SCH 503034 with impurities for strains TA1535, TA97a, TA98, TA100 and WP2uvrA, and 83.6 to 2674.0 µg/plate of SCH 503034 with impurities for strain TA102, with and without metabolic activation. All solvent controls were within their respective historical solvent control ranges. Additionally, all positive controls induced an acceptable increase in revertant colony counts above their respective solvent controls. Thus it was concluded that this batch of SCH 503034 did not induce an increase in revertant colony counts in any strain tested and was not mutagenic in the bacterial mutagenicity assay, with or without metabolic activation, under the conditions of this study.

Study title: CHROMOSOME ABERRATION STUDY OF SCH 503034 CONTAINING IMPURITIES (BATCH NO SI-07HCVY202A) IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES (Study # 7360)

Key Study Findings: Cultured human peripheral blood lymphocytes were tested with SCH 503034 containing impurities (Batch # SI-07HCVY202A) at a dose range of 60 to 500 µg/mL with metabolic activation for 4 hours, 400 to 700 µg/mL without metabolic activation for 4 hours, and 20 to 150 µg/mL without metabolic activation for 19 hours. All positive controls induced acceptable increases of chromosome aberrations above their respective vehicle controls, while the high doses reached acceptable levels of cytotoxicity or the limit of solubility. No statistically significant increases in cells with chromosome aberrations, polyploidy or endoreduplication were observed in test article groups at any dose. Thus it was concluded that this batch did not induce an increase in chromosome aberrations and thus was negative for clastogenicity.

Study title: BACTERIAL MUTAGENICITY STUDY OF SCH 503034 WITH DEGRADANTS (BATCH NO 04-503034-Y-101) (Study # 4044)

Key Study Findings: The potential mutagenicity of SCH 503034 containing degradants (Batch No. 04-503034-Y-101) was assessed in the *Salmonella*/mammalian microsome (Ames test) and *Escherichia*/mammalian microsome plate incorporation reverse mutation assays in TA1535, TA97a, TA98, TA100, TA102 and WP2uvrA strains for 48 hours over a dose range of 274 to 5000 µg/plate (corrected for purity) or 313 to 5700 µg/plate (not corrected for purity). Solvent control values were acceptable, while the

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positive controls induced an acceptable increase in revertant colony counts above their respective solvent controls. SCH 503034 containing degradants did not induce an increase in revertant colony counts in any strain tested, with or without metabolic activation and thus was not mutagenic under the study conditions tested.

Study title: CHROMOSOME ABERRATION STUDY OF SCH 503034 WITH DEGRADANTS (BATCH NO 04-503034-Y-101) IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES (Study # 4043)

Key Study Findings: Cultured human peripheral blood lymphocytes were tested with SCH 503034 containing degradants (Batch # 04-503034-Y-101) without metabolic activation at a dose range of 62.5 to 500 µg/mL for 4 hours and 19 to 150 µg/mL for 19 hours, and with metabolic activation at a dose range of 62.5 to 500 µg/mL (initial) and 150 to 500 µg/mL (confirmatory) for 4 hours. All positive controls induced acceptable increases of chromosome aberrations above their respective vehicle controls, while the high doses reached acceptable levels of cytotoxicity or the limit of solubility. No statistically significant increases in cells with chromosome aberrations were observed in test article groups at any dose. Thus it was concluded that this batch did not induce an increase in chromosome aberrations and thus was negative for clastogenicity.

Study title: BACTERIAL MUTAGENICITY STUDY OF SCH 503034 WITH IMPURITIES (BATCH NO. 68771-16) (Study # 10064)

Key Study Findings: The potential mutagenicity of SCH 503034 containing impurities (Batch No. 68771-16) was assessed in the *Salmonella*/mammalian microsome (Ames test) and *Escherichia*/mammalian microsome plate incorporation reverse mutation assays in TA1535, TA97a, TA98, TA100, TA102 and WP2uvrA strains for 44 hours over a dose range of 78 to 5000 µg/plate. Solvent control values were within their historical control range, while the positive controls induced an acceptable increase in revertant colony counts above their respective solvent controls. SCH 503034 containing degradants did not induce an increase in revertant colony counts in any strain tested, with or without metabolic activation and thus was not mutagenic under the study conditions tested.

Study title: CHROMOSOME ABERRATION STUDY OF SCH 503034 WITH IMPURITIES (BATCH NO. 68771-16) IN HUMAN PERIPHERAL BLOOD LYMPHOCYTES (Study # 10065)

Key Study Findings: Cultured human peripheral blood lymphocytes were tested with SCH 503034 containing impurities (Batch # 68771-16) without metabolic activation at a dose range of 500 to 700 µg/mL for 4 hours and 31.3 to 125 µg/mL for 19 hours, and with metabolic activation at a dose range of 500 to 700 µg/mL for 4 hours. All positive controls induced acceptable increases of chromosome aberrations above their

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respective vehicle controls, while the high doses reached acceptable levels of cytotoxicity or the limit of solubility. No statistically significant increases in cells with chromosome aberrations were observed in test article groups at any dose. Thus it was concluded that this batch did not induce an increase in chromosome aberrations and thus was negative for clastogenicity.

8 Carcinogenicity

NOTE: The following study summaries were taken from the original IND review by Dr. Mark Powley. The complete reviews for these studies can be found in section 12.1 Carcinogenicity Studies.

Study title: 24-MONTH CARCINOGENICITY STUDY OF SCH 503034 in RATS

Study no.:	1304
Study report location:	4.2.3.4.1
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	3-2-2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 05-503034-Y-110B & 94.6%
CAC concurrence:	Yes (11-30-2010)

Key Study Findings: Based on criteria for common tumors (i.e., p-value ≤ 0.005 for trend-test and p-value ≤ 0.01 for pair-wise comparison), there were no SCH503034-related neoplastic lesions in rat. Drug-related effects included decreased body weight parameters as well as changes in pathology. Testicular effects were noted during both macroscopic evaluation (small; altered texture) and microscopic evaluation (atrophy; degeneration, seminiferous tubule). Macroscopic changes in epididymides (small) correlated with microscopic lesions (hypospermia; cellular debris, luminal). Additional non-neoplastic histopathological lesions were observed in liver (multinucleated hepatocytes, multifocal). Similar SCH503034-related effects were observed in the 6-month toxicity study.

Reference ID: 2933010

Study title: A 104-WEEK ORAL GAVAGE CARCINOGENICITY STUDY IN THE ALBINO MOUSE

Study no.:	1305
Study report location:	4.2.3.4.1
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	3-22-2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 05-503034-Y-110A & 97.2%
CAC concurrence:	Yes (11-30-2010)

Key Study Findings: Based on criteria for common tumors (i.e., p-value ≤ 0.005 for trend-test and p-value ≤ 0.01 for pair-wise comparison), there were no SCH503034-related neoplastic lesions in the mouse. Drug-related effects were limited to gross changes in the gallbladder (dark material) and microscopic lesions in the liver (single cell necrosis, focal/multifocal; pigment accumulation, macrophage). The liver was previously identified as a target organ in the 3-month range-finding study.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Key Study Findings for Pilot (non-GLP) Studies: SCH 503034 was evaluated in 9 to 13 week old rats (8/sex/group) administered once daily oral (gavage) doses of 250, 500 or 1000 mg/kg or vehicle control [0.4% (w/v) aqueous methylcellulose] (Study # 1295). Males were dosed for 3 weeks prior to cohabitation through the day prior to scheduled sacrifice, while females were dosed for 2 weeks prior to and during cohabitation, and on gestation days 0 through 7. Clinical signs, body weights, food consumption, gross pathology, estrous cycle determinations, mating and fertility indices and reproductive parameters were evaluated. Reduced body weight gain (associated with decreased food consumption) was observed in males at all doses and females at 1000 mg/kg. Several males had small and/or flaccid testes or small epididymides. The paternal and maternal NOELs were <250 mg/kg and 500 mg/kg, respectively. Virtually all dams were not pregnant in the 500 and 1000 mg/kg dose groups, while post-implantation loss was increased and associated with a decrease in the number of live fetuses in the 250 mg/kg group. Thus, decreases in fertility were observed at all doses; however, separate NOELs for male and female fertility could not determined because the effects could be due to male and/or female effects. Due to increases in both post-implantation loss and the incidence of dams that were not pregnant, the NOEL for combined male and female fertility was <250 mg/kg.

SCH 503034 was evaluated in 9 to 10 week old rats (8/sex/group) administered once daily oral (gavage) doses of 25, 75 or 250 mg/kg or vehicle control [0.4% (w/v) aqueous methylcellulose] (Study # 3011). Males were dosed for 20 days prior to

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cohabitation through the day prior to scheduled sacrifice, while females were dosed for 13 days prior to and during cohabitation, and on gestation days 0 through 7. Dosed males and females were cohabited with non-dosed mating partners. Clinical signs, body weights, food consumption, gross pathology, estrous cycle determinations, mating and fertility indices and reproductive parameters were evaluated. Several males in the 250 mg/kg group had small and/or flaccid testes, so the NOEL for paternal toxicity was 75 mg/kg. The NOEL for embryo-fetal toxicity in both females and males administered SCH 503034 and cohabited with non-dosed animals was 75 mg/kg, due to increases in both pre- and post-implantation losses observed in the 250 mg/kg groups.

SCH 503034 was evaluated in female rats (8/group) administered once daily oral (gavage) doses of 250 mg/kg or vehicle control [0.4% (w/v) aqueous methylcellulose] on gestation days 0 through 7 (Study # 3417). Clinical signs, body weights, food consumption, gross pathology, estrous cycle determinations, mating and fertility indices and reproductive parameters were evaluated. Four dams had total resorptions, 3 were not pregnant and only 1 had a viable litter containing one fetus in SCH 503034 treated females. Of the dams with implantations, there were fewer implantation sites and corpora lutea, and greater pre- and post-implantation losses, compared to the control group. It was concluded that dosing females on gestation days 0 through 7 with 250 mg/kg doses of SCH 503034 was toxic to female fertility.

SCH 503034 was evaluated in female mice (8/group) administered once daily oral (gavage) doses of 250, 500, 1000 or 2000 mg/kg or vehicle control [0.4% (w/v) aqueous methylcellulose] on gestation days 0 through 6 (Study # 3418). Clinical signs, body weights, food consumption, gross pathology and reproductive parameters were evaluated. Due to the high number of mice with mortality and poor health (some due to test-article inhalation), it was not possible to determine whether the 1000 and 2000 mg/kg doses affected reproductive parameters. The NOEL for maternal toxicity and for early embryonic development in mice was ≥500 mg/kg.

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE: **FERTILITY AND EARLY EMBRYONIC DEVELOPMENTAL TOXICITY STUDY OF SCH 503034 ADMINISTERED ORALLY BY GAVAGE IN FEMALE RATS**

STUDY NO.: 3194

VOLUME/PAGE: 3194.pdf

LABORATORY: Sponsor

STUDY INITIATION: 12/15/2003

GLP: Yes (x) no ( )

QA REPORT: Yes (x) no ( )

LOT # 02-503034-Y-01

FORMULATION/ VEHICLE: SCH 503034 in 0.4% (w/v) aqueous methylcellulose

METHODS:

Test/Control Articles	Dose (mg/kg/day)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Rats	
				Males[a]	Females[b]
Control (Methylcellulose)	0	5	0	25	25

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Low-Dose (SCH 503034)	25	5	5	25	25
Mid-Dose (SCH 503034)	75	5	15	25	25
High-Dose (SCH 503034)	150	5	30	25	25

a: Non-dosed mating partners 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. b:Females were dosed for a total dosing period of 23 to 36 days.

DOSING: See above.

SPECIES/STRAIN: Crl:CD[SD]IGS BR VAF/Plus Rats

NO./SEX/GROUP See above.

ROUTE Oral (gavage)

OBSERVATIONS:

CLINICAL SIGNS: Male Breeders: On the first day of cohabitation and then at least once weekly until the completion of the cohabitation period Females: At least once daily on the day of randomization and after the completion of dosing through the day of sacrifice; twice daily during the dosing period

BODY WEIGHTS: Male Breeders: On the first day of cohabitation only
Females: On the day of randomization and on the first day of dosing then twice weekly until mated or scheduled necropsy to include the first day of the cohabitation period and day of sacrifice; Gestation Days 0, 4, 7 and 14

FOOD CONSUMPTION: Male Breeders: Not measured
Females: Weekly prior to cohabitation and for gestation Days 0 to 7 and 7 to 14

NECROPSY Yes

MACROSCOPIC OBSERVATIONS

ESTROUS CYCLE Measured.

HISTOPATHOLOGY No

MATING/FERTILITY INDICES AND REPRODUCTION PARAMETERS Yes

TOXICOKINETICS None

RESULTS:

MORTALITY None.

CLINICAL SIGNS Unremarkable.

BODY WEIGHTS: Unremarkable.

FOOD CONSUMPTION Unremarkable.

NECROPSY: Unremarkable.

MATING AND FERTILITY INDICES Unremarkable.

REPRODUCTIVE PARAMETERS: There was a test article-related increase in pre-implantation loss observed in the 150 mg/kg dose group. The mean percent of pre-implantation loss per animal in this group was 10.0 versus 4.2 in the control. There was also a test article-related and statistically significant increase in post-implantation loss observed in the 150 mg/kg dose group. The mean percent of post-implantation loss per

animal in this group was 18.3 versus 6.2 in the control. This increase in post-implantation loss was due to an increase in early resorptions (16.8% versus 5.9% in control). However, these effects on implantation were not sufficient to affect the total number of implantation sites.

CONCLUSION Mating and fertility indices in female rats were not affected by administration of SCH 503034 at doses up to 150 mg/kg. Female rats administered 150 mg/kg of SCH 503034 exhibited a slight increase in pre-implantation loss and a significant increase in post-implantation loss. However, these effects did not result in a decrease in implants. The no-effect level (NOEL) for maternal toxicity and mating is ≥150 mg/kg and the NOEL for female fertility and early embryo developmental toxicity in rats is 75 mg/kg.

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE: **INVESTIGATIVE FERTILITY AND EARLY EMBRYONIC DEVELOPMENTAL TOXICITY STUDY OF SCH 503034 ADMINISTERED ORALLY BY GAVAGE IN FEMALE RATS**

STUDY NO.: 1306

VOLUME/PAGE: 1306.pdf

LABORATORY: Sponsor

STUDY INITIATION: 5/12/03

GLP: Yes (x) no ( )

QA REPORT: Yes (x) no ( )

LOT # 02-503034-Y-01

FORMULATION/ VEHICLE: SCH 503034 in 0.4% (w/v) aqueous methylcellulose

METHODS:

Group	Test/Control Articles	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Rats		
					Non-Recovery Females[a]	Recovery Females[b]	Non-dosed Males[c]
1	Control (Methylcellulose)	0	5	0	8	8	8
2	High-Dose (SCH 503034)	250	5	50	8	8	8

a: Dosed daily for 14 days prior to cohabitation, during the cohabitation period with non-dosed male mating partners, and from Gestation Days 0 through 7 (total dosing period of 22 to 35 days).

b: Dosed daily for 21 days after which dosing ceased for a recovery period of four weeks. Females were then cohabited with non-dosed male partners (total dosing period of 21 days).

c: Non-dosed mating partners

DOSING: See above.

SPECIES/STRAIN: Crl:CD[SD]IGS BR VAF/Plus Rats

NO./SEX/GROUP 8

ROUTE Oral (gavage)

OBSERVATIONS:

CLINICAL SIGNS: Males: At least once weekly to include the day of randomization, first day of each cohabitation period, and the day of sacrifice
Females: At least once daily starting on the day of randomization and then twice daily during the dosing period

BODY WEIGHTS:	Males: At least once weekly until day of sacrifice, day of randomization and first day of each cohabitation period. Females: On day of randomization and first day of dosing, at least twice weekly until mated or scheduled sacrifice; first day of cohabitation period; and gestation Days 0, 4, 7 and 14 (if confirmed mated)
FOOD CONSUMPTION:	Males: Not measured Females: Weekly prior to cohabitation period and during recovery period (recovery females only) and on gestation Days 0 to 7 and 7 to 14
NECROPSY MACROSCOPIC OBSERVATIONS	Yes
ESTROUS CYCLE	Measured.
HISTOPATHOLOGY	No
MATING/FERTILITY INDICES AND REPRODUCTION PARAMETERS	Yes
TOXICOKINETICS	None
RESULTS:	
MORTALITY	None
CLINICAL SIGNS	There were no test article-related clinical observations.
BODY WEIGHTS:	In the non-recovery portion of the study, there was a 95.2% decrease in body weight gain for the pre-cohabitation dosing period (Days 0 to 13), representing +1g at 250 mg/kg compared to +21g for the vehicle control group. Body weight gain at 250 mg/kg was also decreased by 25.0% during the gestation period (+54g compared to +72g in the vehicle control group). In the recovery portion of the study, there was a decrease in the premating (Days 0 to 20) body weight gain of -21% at 250 mg/kg (+22g versus +28g in the control group). There was no test article-related effect on body weight during gestation.
FOOD CONSUMPTION	In the non-recovery portion of the study, food consumption during the pre-cohabitation dosing period (Days 0 to 13) was 11.1% lower than the vehicle control group. This decrease was not considered related to the test article because there were no food consumption effects during the gestation period or in the recovery portion of the study.
NECROPSY:	There were no necropsy findings. Mating and Fertility Indices: In the non-recovery portion of the study, the female fertility index was reduced to 50% in the 250 mg/kg dose group compared to 100% in the vehicle control group. There was no effect on the female mating index. In the recovery portion of the study, there were no effects on mating or fertility indices. The time-to-mating was not affected by SCH 503034 in either portion of the study.
REPRODUCTIVE PARAMETERS:	Similar findings at 250 mg/kg were seen in the non-recovery portion of this study as those observed in previous fertility studies with SCH 503034. These findings included an increased number of non-pregnant females (4/8 rats), a decrease in the numbers of implantation sites and live fetuses, which were associated with

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	increases in pre- and postimplantation losses. In addition, the mean number of corpora lutea was decreased in these females (5.5 versus 17.1 in control), but it is not possible to discern whether this is a primary effect of SCH 503034 or secondary to the decrease in number of live fetuses. In the recovery portion of the study, there were no effects on reproductive parameters.
CONCLUSION	SCH 503034 decreased female fertility and affected uterine reproductive parameters at 250 mg/kg. Three weeks of dosing at 250 mg/kg, followed by a four-week recovery period, demonstrated normal female fertility and uterine reproductive parameters and indicates that the effect on female fertility is reversible.

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE:	**INVESTIGATIVE STUDY OF THE EFFECT OF SCH 503034 ADMINISTERED ORALLY BY GAVAGE ON HORMONE LEVELS DURING PREGNANCY IN FEMALE RATS**
STUDY NO.:	3379
VOLUME/PAGE:	3379.PDF
LABORATORY:	Sponsor
STUDY INITIATION:	12/2003
GLP:	Yes (x) no ()
QA REPORT:	Yes (x) no ()
LOT #	03-503034-Y-102
FORMULATION/ VEHICLE:	SCH 503034 in 0.4% (w/v) aqueous methylcellulose/Vehicle, 0.4% (w/v) aqueous methylcellulose
METHODS:	The potential effects of SCH 503034 on serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2) and progesterone (P4) were assessed in female pregnant rats at daily oral (gavage) doses of 250 mg/kg on gestation Days 0-1, 0-3, 0-5 or 0-7.
RESULTS:	There was no mortality, and no test article-related clinical or necropsy observations. On gestation Days 5 and 7, only one female was pregnant in the 250 mg/kg dose group compared with all females in the control group. This finding is consistent with the SCH 503034-related decrease in the number of pregnancies observed in previous female fertility studies in rats. Serum LH, FSH, P4 and E2 were not affected when dosed from gestation Days 0-7 with 250 mg/kg of SCH 503034. The no-effect level (NOEL) for SCH 503034 on pregnancy was <250 mg/kg. The NOEL for SCH 503034 on LH, FSH, P4 and E2 was ≥250 mg/kg.

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE:	**FERTILITY AND EARLY EMBRYONIC DEVELOPMENTAL TOXICITY STUDY OF SCH 503034 ADMINISTERED ORALLY BY GAVAGE IN MALE RATS**
STUDY NO.:	3195

Reference ID: 2933010

VOLUME/PAGE: 3195.pdf
LABORATORY: Sponsor
STUDY INITIATION: 8/03
GLP: Yes (x) no ( )
QA REPORT: Yes (x) no ( )
LOT # 02-503034-Y-01
FORMULATION/ VEHICLE: SCH 503034 in 0.4% (w/v) aqueous methylcellulose
METHODS:

Test/Control Articles	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Rats	
				Males[a]	Females[b]
Control (Methylcellulose)	0	5	0	25	25
Low-Dose (SCH 503034)	25	5	5	25	25
Mid-Dose (SCH 503034)	75	5	15	25	25
High-Dose (SCH 503034)	150	5	30	25	25

a:Male rats were dosed once daily for ten weeks prior to and during the cohabitation period b: through the day prior to scheduled sacrifice (total dosing period of 97 days). Female rats were non-dosed mating partners.

DOSING: See above.
SPECIES/STRAIN: Crl:CD[SD]IGS BR VAF/Plus Rats
NO./SEX/GROUP See above.
ROUTE Oral (gavage)
OBSERVATIONS:
CLINICAL SIGNS: On the day of randomization:
Males: At least twice daily during the dosing period and once on the day of sacrifice.
Females: At least once weekly until mated or scheduled necropsy to include the first day of the cohabitation period and day of sacrifice; Gestation Days 0, 7 and 14 (if confirmed mated).
BODY WEIGHTS: On the day of randomization:
Males: On the first day of dosing, at least twice weekly to include the first day of the cohabitation period and the day of sacrifice.
Females: At least once weekly until mated or scheduled necropsy to include the first day of the cohabitation period and day of sacrifice; Gestation Days 0, 7 and 14 (if confirmed mated).
FOOD CONSUMPTION: Weekly prior to the cohabitation period Females: Not measured
NECROPSY MACROSCOPIC OBSERVATIONS Male only.
ESTROUS CYCLE Measured.
HISTOPATHOLOGY No

Reference ID: 2933010

MATING/FERTILITY INDICES AND REPRODUCTION PARAMETERS	Yes
TOXICOKINETICS	None
RESULTS:	
MORTALITY	None.
CLINICAL SIGNS	Unremarkable.
BODY WEIGHTS:	There was a 16% decrease in the mean body weight gain (80 g versus 95 g in control) observed during the early premating period (0-17 days) in the 150 mg/kg dose group compared to the control group. However, the body weight or body weight gain was not significantly affected during the entire premating period (0-69 days) at this dose level. There were no changes in the mean gestation body weights or gestation body weight gain in the non-dosed females.
FOOD CONSUMPTION	Unremarkable.
NECROPSY:	Absolute epididymal and testes weights were decreased by approximately 23% and 11.5%, respectively, in the 150 mg/kg dose group compared to the control group. Macroscopic findings of small epididymides, small and flaccid testes and a soft yellow material in the bladder were observed in the 150 mg/kg dose group. Mating and Fertility Indices: The male mating index was not affected but the male fertility index was decreased (76% versus 88% in control) in the 150 mg/kg dose group.
REPRODUCTIVE PARAMETERS:	Unremarkable.
CONCLUSION	SCH 503034 decreased the mean weights of epididymides and testes at 150 mg/kg. Macroscopic findings of small epididymides, small and flaccid testes and a soft yellow material in the bladder were also observed at this dose. SCH 503034 did not affect the male mating index but decreased the male fertility index at 150 mg/kg. The NOEL for paternal toxicity, male fertility, reproductive and early embryonic developmental toxicity in rats is 75 mg/kg. (Reviewer's Comments: This study was basically similar to previous ones except that the dosage was lowered to find a NOAEL that was not successfully identified before.)

Study title: INVESTIGATIVE ONE-MONTH HORMONE, TESTICULAR TOXICITY, AND TOXICOKINETIC STUDY OF SCH 503034 IN MALE RATS

Reference ID: 2933010

Study no.:	5023
Study report location:	4.2.3.7.7
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	4-1-2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 03-503034-Y-103 & 98.4%

Key Study Findings: Testicular toxicity of SCH 503034 and it's effects on hormones were evaluated in 14-week old CD(SD) VAF/Plus male rats (60/group-main group, 30/group TK group) administered oral (gavage) doses of 50, 300 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] for 4, 8, 15 or 29 days. Toxicity endpoints evaluated in this study included clinical signs, body weights, hormone analysis (serum LH, FSH & testosterone), and limited organ weights and gross and histopathology. Staging of the seminiferous tubules was also conducted. The results of this study indicate that NOAEL in rats is <50 mg/kg based on histopathological findings in the testes and epididymides. Although the NOAEL was not identified in this study, it was previously determined to be 15 mg/kg, based on testicular toxicity findings in the 6-month repeat-dose study.

Small epididymides, small testes and/or soft testes were present in rats in the 300 mg/kg dose group at day 28 only and correlated with lower mean epididymidis and testis weights. Dose- and time-dependent histopathological findings were present in the epididymides and testes of rats at 300 mg/kg from day 4 to day 29 and of rats at 50 mg/kg from day 15 to day 29. In the epididymides, these findings were luminal cellular debris and/or hypospermia. In the testes, these findings were sloughed spermatids, Sertoli cell vacuolation, degeneration of spermatocytes and spermatids, depletion of spermatocytes and spermatids, spermatid retention, atrophy of seminiferous tubules and/or debris. The sequence of occurrence of testicular and epididymal findings suggests initiation of testicular toxicity on the first dose and continual progression of SCH 503034-induced toxicity following daily dosing. These testicular findings were not associated with alterations in FSH, LH or testosterone. The earliest signs of testicular toxicity in 300 mg/kg animals (at day 4) are germ cell sloughing and Sertoli cell vacuolation, while there appeared to be an absence of targeting of a specific germ cell population, as would typically occur with a germ cell toxicant. Although this study cannot totally exclude the possibility of direct test-article effects on germ cell maturation, the Sertoli cell appears to be the primary target of toxicity.

Reference ID: 2933010

Table 18: TK Summary for SCH 503034, SCH 534128 and SCH 534129 Following Administration of Boceprevir for 1-Month in Male Rats

SCH 534128, SCH 534129 and SCH 503034 Toxicokinetic Parameters on Day 0 and Day 24 Following Oral (Gavage) Administration of 50 or 300 mg/kg SCH 503034 to Male Rats							
Dose[a] (mg/kg)	Day	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	R[b]
SCH 534128							
50	0	2880	2	8	9090	9430	NA[c]
	24	1500	1	8	4680	4910	0.520
300	0	7950	2	24	93200	93200	NA
	24	8900	2	24	58900	58900	0.632
SCH 534129							
50	0	2680	1	8	8340	8590	NA
	24	1360	1	8	4150	4320	0.503
300	0	6860	4	24	81100	81100	NA
	24	7300	2	24	47400	47400	0.584
SCH 503034[d]							
50	0	5530	2	8	17400	18000	NA
	24	2850	1	8	8830	9220	0.512
300	0	14500	2	24	174000	174000	NA
	24	16200	2	24	106000	106000	0.610

a: SCH 503034 Dose
b: R (Accumulation Ratio) = $AUC(0\text{-}24\ hr)_{Day\ 24} \div AUC(0\text{-}24\ hr)_{Day\ 0}$
c: NA = Not Applicable
d: SCH 503034 = SCH 534128 + SCH 534129

Table from sponsor

9.2 Embryonic Fetal Development

Key Study Findings for Pilot (non-GLP) Studies: SCH 503034 was evaluated in female rats (6/group) administered once daily oral (gavage) doses of 250, 500 or 1000 mg/kg or vehicle control [0.4% (w/v) aqueous methylcellulose] on gestation days 6 through 17 (Study # 1296). Clinical signs, body weights, food consumption, gross pathology, reproductive parameters and fetal body weights, sex and external examinations were evaluated. Dams administered 1000 mg/kg of SCH 503034 had alopecia and exhibited decreases in body weight gain and food consumption, while dams administered ≥500 mg/kg exhibited salivation. Thus, the NOEL for maternal toxicity was 250 mg/kg. The number of litters (and total fetuses) was insufficient to allow proper evaluation of potential SCH 503034 effects on fetal body weight. Due to the absence of fetal external examination findings and sex ratio differences in dams from all treated groups, the NOEL for embryo-fetal toxicity was ≥1000 mg/kg.

SCH 503034 was evaluated in female rabbits administered once daily oral (gavage) doses of either 20, 50, 200, 500 or 1000 mg/kg or vehicle control [0.4% (w/v) aqueous methylcellulose] on days 0 through 9 (2 non-pregnant animals/group), or 200, 500 or 1000 mg/kg or vehicle control on gestation days 7 through 19 (4/group) (Study # 1297). Clinical signs, body weights, food consumption and gross pathology were evaluated in all animals, while reproductive parameters, fetal body weights and external examinations (in pregnant animals) and clinical pathology (non-pregnant animals) were

examined in the designated groups only. SCH 503034 was not toxic to non-pregnant animals when administered at doses of up to 1000 mg/kg for 10 days. For pregnant animals, all rabbits in the 1000 mg/kg dose group and 2 animals in the 500 mg/kg dose group were sacrificed due to test article-related toxicity (decreased food consumption and body weight gain). Based on maternal toxicity observed at 500 and 1000 mg/kg doses and the lack of adverse maternal or fetal observations at the 200 mg/kg dose, the NOELs for maternal toxicity and embryo-fetal toxicity were 200 mg/kg and ≥ 200 mg/kg, respectively.

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE: **EMBRYO-FETAL DEVELOPMENTALTOXICITY STUDY OF SCH 503034 ADMINISTERED ORALLY BY GAVAGE IN RATS**

STUDY NO.: 1307

VOLUME/PAGE: 1307

LABORATORY: Sponsor

STUDY INITIATION: 10/03

GLP: Yes (x) no ()

QA REPORT: Yes (x) no ()

LOT # 03-503034-Y-102

FORMULATION/ VEHICLE: SCH 503034 in 0.4% (w/v) aqueous methylcellulose

METHODS & DOSING:

Group	Test/Control Articles	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Females
1	Control (Methylcellulose)	0	5	0	25
2	Low-Dose (SCH 503034)	150	5	30	25
3	Mid-Dose (SCH 503034)	300	5	60	25
4	High-Dose (SCH 503034)	600	5	120	25

SPECIES/STRAIN: Rat (Crl :CDS[SD]IGS BR), females

NO./SEX/GROUP 25 females

ROUTE Once daily from Days 6 to 17 of gestation, inclusive

OBSERVATIONS:

CLINICAL SIGNS: 1-2/day

BODY WEIGHTS: Gestation Days 0 (provided by supplier), 6, 9, 12, 15, 17 and 21

FOOD CONSUMPTION: Gestation Days 4 to 6, 6 to 12, 12 to 17, and 17 to 21

MATING WITH PROVEN BREEDER MALE RATS Yes

UTERINE EXAMINATION Yes

NECROPSY MACROSCOPIC Yes (day 21)

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OBSERVATIONS	
ORGAN WEIGHTS	No
HISTOPATHOLOGY	No
REPRODUCTION PARAMETERS	Yes
FETAL WEIGHTS	Yes
FETAL EXAMINATION (EXTERNAL)	Yes
TOXICOKINETICS	None
RESULTS:	
MORTALITY	None
CLINICAL SIGNS	Salivation prior to dosing and excessive salivation after dosing was observed in the 300 and 600 mg/kg dose groups.
BODY WEIGHTS:	Rats in the 150, 300 and 600 mg/kg dose groups exhibited statistically significant decreases of 15, 19 and 24%, respectively (relative to control) in body weight gain over the gestation Days 6 to 17 dosing interval.
FOOD CONSUMPTION	Rats in the 600 mg/kg dose group exhibited a biologically significant decrease (21%, relative to controls) in food consumption over the gestation Days 6 to 12 interval.
NECROPSY:	Unremarkable
REPRODUCTIVE PARAMETERS:	Unremarkable
FETAL EXAMINATION	Unremarkable (body weight, sex, external, visceral, skeletal).
SUMMARY	This study show that pregnant female rats administered: • 300 or 600 mg/kg of SCH 503034 exhibited salivation prior to dosing and/or excessive salivation after dosing. • 150, 300 or 600 mg/kg of SCH 503034 displayed dose-responsive decreases in body weight gain over the dosing period. • 600 mg/kg of SCH 503034 exhibited decreased food consumption. There were no SCH 503034-mediated toxicities on reproductive parameters (e.g. resorptions, fetal viability), or fetal weight, nor were there any drug-related malformations or variations.
CONCLUSION	The no-effect level NOEL for maternal toxicity in rats is <150 mg/kg (based on the decrement in gestational body weight gain) and the NOEL for embryo-fetal toxicity in rats is ≥600 mg/kg.

NOTE: The following study was taken from the original IND review by Dr. KM Wu.

STUDY TITLE:	**EMBRYO-FETAL DEVELOPMENTALTOXICITY STUDY OF SCH 503034 ADMINISTERED ORALLY BY GAVAGE IN RABBITS**
STUDY NO.:	1308
VOLUME/PAGE:	1308.pdf

Reference ID: 2933010

LABORATORY: Sponsor
STUDY INITIATION: 2/04
GLP: Yes (x) no ()
QA REPORT: Yes (x) no ()
LOT # 03-503034-Y-102
FORMULATION/ VEHICLE: SCH 503034 in 0.4% (w/v) aqueous methylcellulose

METHODS:

Group	Test/Control Articles	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Females
1	Control	0	5	0	20
	(Methylcellulose)				
2	Low-Dose	50	5	10	20
	(SCH 503034)				
3	Mid-Dose	150	5	30	20
	(SCH 503034)				
4	High-Dose (SCH 503034)	300	5	60	20

DOSING:
SPECIES/STRAIN: Hra:[NZW]SPF female rabbits
NO./SEX/GROUP 20 females
ROUTE Once daily from Days 7 to 19 of gestation, inclusive
OBSERVATIONS:
CLINICAL SIGNS: 1-2/day
BODY WEIGHTS: Gestation Days 0 (provided by supplier), 7, 10, 13, 16, 19, 22, 25 and 29
FOOD CONSUMPTION: Daily, from two days after arrival through gestation Day 29
MATING WITH PROVEN BREEDER MALE RATS Yes
UTERINE EXAMINATION Yes
NECROPSY Yes (day 29)
MACROSCOPIC OBSERVATIONS
ORGAN WEIGHTS No
HISTOPATHOLOGY No
REPRODUCTION PARAMETERS Yes
FETAL WEIGHTS Yes
FETAL EXAMINATION (EXTERNAL) Yes
TOXICOKINETICS yes [Gestation Day 19 (0.5, 1, 2, 6 and 24 hr post-dose)]

Reference ID: 2933010

RESULTS:

MORTALITY Rabbits administered SCH 503034 exhibited dose-related increases in maternal toxicity. Two rabbits in the 50 mg/kg dose group exhibited decreases in food consumption. This finding was associated with either scant or no stool. These rabbits were subsequently euthanized for humane reasons on gestation Days 15 and 23, respectively. Three rabbits in the 150 mg/kg dose group exhibited similar findings and was euthanized on gestation Day 16. Similarly, six rabbits in the 300 mg/kg dose group exhibited decreases in food consumption and stool findings. These rabbits were euthanized on gestation Days 16, 20, 15, 20, 15 and 16, respectively.

CLINICAL SIGNS Two rabbits in the 50 mg/kg dose group and one rabbit in the 150 mg/kg dose group exhibited multiple observations of scant stool. These findings were associated with a decrease in the amount of food consumed.

BODY WEIGHTS: Unremarkable

FOOD CONSUMPTION In addition to the test article-related effects on food consumption noted in the mortality section, four rabbits in the 50 mg/kg dose group exhibited multiple days of decreased food consumption that was concomitant with dosing. Similarly, three rabbits in the 150 and one rabbit in the 300 mg/kg dose groups displayed decreased food consumption during the dosing period.

TOXICOKINETICS Peak drug concentrations were achieved by 2 hr post-dose. Systemic exposure to SCH 503034 increased in a dose-proportional manner on gestation Day 19 at 50, 150 and 300 mg/kg SCH 503034 on gestation Days 7 through 19.

Time	Unit	50 mg/kga, [b]	150 mg/kg[c]	300 mg/kg[b]
0.5 1 2 6 24	hr	1000 (60) 900 (64) 610 (50) 180 (89) 35 (49)	2200 (16) 2000 (18) 1900 (19) 650 (18) 200 (12)	3300 (42) 3100 (40) 3900 (48) 1400 (58) 420 (52)
Cmax Tmax AUC (0-24 hr) AUC/D	ng/mL hr ng hr/mL (ng hr/mL)/ (mg/kg)	1000 (60) 0.500 (0) 4990 (59) 99.8 (59)	2200 (16) 0.667 (43) 16400 (16) 109 (16)	4350 (30) 1.38 (55) 32800 (48) 109 (48)

a: SCH 503034 plasma concentration units are ng/mL b: n = 4 c: n = 3

NECROPSY: Unremarkable

REPRODUCTIVE PARAMETERS: Unremarkable

FETAL EXAM Unremarkable (body weight, sex, external, visceral, skeletal).

SUMMARY This study shows that pregnant rabbits administered ≥50 mg/kg of SCH 503034 exhibited dose-related increases in maternal toxicity as evidenced by decreased food consumption and concomitant decreases in fecal output. These findings reached a severity in some animals that warranted euthanasia for humane reasons. Oral absorption of SCH 503034 in pregnant rabbits was rapid and peak SCH 503034 plasma concentrations were achieved by 2 hr post-dose.

CONCLUSION The NOEL for maternal toxicity in rabbits is <50 mg/kg and the NOEL for embryo-fetal toxicity in rabbits is ≥300 mg/kg. Embryo-fetal toxicity or teratogenicity was not observed at the dose levels examined.

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9.3 Prenatal and Postnatal Development

NOTE: The following study summary was taken from the original IND review by Dr. KM Wu. The complete review for this study can be found in section 12.2 Prenatal and Postnatal Development Study.

Study title: PERINATAL AND POSTNATAL DEVELOPMENTAL TOXICITY AND MATERNAL FUNCTION STUDY OF SCH 503034 ADMINISTERED ORALLY BY GAVAGE IN RATS

Study no.:	1309
Study report location:	4.2.3.5.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	8-4-2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 06-503034-YY-106A & 93.7%

Key Study Findings: No boceprevir-related effects on pregnancy, parturition and lactation of maternal animals (F0) or on the growth, viability, development or reproductive performance of the F1 generation, or survivability of the F2 generation were reported. The NOAEL for the F0, F1 and F2 generations was ≥150 mg/kg. No exposure information was included in this study. The exposures at 150 mg/kg from 3-month rat studies were 34 (male)-40 (female) ug.h/ml. These exposures were in the range of NOAELs used in the risk assessment of the original IND. These results did not produce new safety concerns, in regard to reproductive toxicity risk of Boceprevir in humans.

10 Special Toxicology Studies

10.1 Nonclinical safety studies of impurities and degradants

To qualify impurities that may result from scale-up of the synthetic process, bacterial mutagenicity assays, chromosomal aberration assay using human peripheral blood lymphocytes, and 1-month repeat-dose toxicology studies (see below) in rats were performed using batches containing high levels of impurities or degradants (up to ~12% total SCH 503034 related compounds). There was no indication that impurities or degradants elicited any novel toxicity or altered the toxicity profile of boceprevir. Additionally, all batches of SCH 503034 were negative for mutagenicity and clastogenicity as tested in various genotoxicity assays (refer to section 7.4). Given these results and since no structural alerts have been identified [w/DEREK (v 11.0.0) & MC4PC (V.2.0)], evaluation of these impurities appears acceptable (see sponsor's summary table below). Despite many of the impurities having small safety margins,

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based on calculations using adverse effects of SCH 503034 and/or its metabolites, the presence of these impurities in the final drug product are not of significant clinical concern particularly given the seriousness of the disease to be treated and the fact that boceprevir will be given in combination with ribavirin and peginterferon-alpha.

Table 19: Impurity Qualification Summary

Compound	Acceptance Criteria (%)	Justification			
		Repeat-dose general toxicology study ≥ 1 month duration Impurity (%) batch no. study no. (SN)	Genotoxicity studies[a] impurity (%) batch no. study no. (SN)	Human equivalent dose[b] impurity (%)	Compound is a metabolite of SCH 503034
(b) (4)		(b) (4)		(b) (4)	
		03-503034-Y-102 05087	56783-31-22 05113 and 05114		Yes
		(b) (4)			
		SI-07HCVY202A 07357	SI-07HCVY202A 07359 and 07360		Yes
		(b) (4)			
		03-503034-Y-102 05087	68771-16 10064 and 10065		Yes
		(b) (4)			
		SI-07HCVY202A 07357	SI-07HCVY202A 07359 and 07360		No
		(b) (4)			
		56783-31-22 05087	56783-31-22 05113 and 05114		Yes
		(b) (4)			
		SI-07HCVY202A 07357	SI-07HCVY202A 07359 and 07360		Yes
		(b) (4)			
		56783-31-22 05087	56783-31-22 05113 and 05114		Yes
		(b) (4)			
		56783-31-22 05087	56783-31-22 05113 and 05114		Yes
		(b) (4)			
		SI-07HCVY202A and 68771-16 07357 and 10080	SI-07HCVY202A and 68771-16 07359, 07360, 10064, and 10065		Yes

(b) (4)	(b) (4)		(b) (4)	Yes
	SI-07HCVY202A and 68771-16 07357 and 10080	SI-07HCVY202A and 68771-16 07359, 07360, 10064, and 10065		
	(b) (4)			No
	56783-31-22 05087	56783-31-22 05113 and 05114		
	(b) (4)			No
	68771-16 10080	68771-16 10064 and 10065		
	(b) (4)			No
	68771-16 10080	68771-16 10064 and 10065		
	(b) (4)			No
	68771-16 10080	68771-16 10064 and 10065		
	(b) (4)			No
	56783-31-22 05087	56783-31-22 05113 and 05114		
	(b) (4)			No
	56783-31-22 05087	56783-31-22 05113 and 05114		
	(b) (4)			No
	SI-07HCVY202A 07357	SI-07HCVY202A 07359 and 07360		
	(b) (4)			No
	56783-31-22 05087	56783-31-22 05113 and 05114		
	(b) (4)			Yes
	04-503034-Y-101 04032	04-503034-Y-101 04044 and 04043		
	(b) (4)			Yes
	04-503034-Y-101 04032	04-503034-Y-101 04044 and 04043		
	(b) (4)			Yes
	56783-31-22 05087	56783-31-22 05113 and 05114		

a: Genotoxicity evaluation included bacterial mutagenicity (Ames) and chromosome aberration (HPBL) studies.

b: Calculated based on the total daily human dose of the impurity, relative to the total daily dose of the impurity in the most appropriate non-clinical species at the NOAEL or based on the endpoints most relevant to human risk assessment. (Assumption = representative human weights 50 kg.)

Table from sponsor

Study title: ONE-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 CONTAINING IMPURITIES IN RATS

Study no.:	5087
Study report location:	4.2.3.7.6
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	9-1-2005
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 5678-31-22 & 88.2%; SCH 503034, 03-503034-Y-102 & 96.0%

Key Study Findings: The objectives of this study were to assess the systemic toxicity and toxicokinetics of SCH 503034 containing impurities (Batch # 5678-31-22) compared to a SCH 503034 control batch (Batch # 03-503034-Y-102) when administered orally by gavage to rats at 30 and 150 mg/kg for 1 month. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, clinical pathology and gross and histopathology. Toxicities observed in this study were similar to previous 1 month studies with SCH 503034 (increases in

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cholesterol, testicular findings and lower urine osmolality). However, there were no meaningful toxicological differences between the SCH 503034 comparative control and SCH 503034 containing impurities.

Study title: ONE-MONTH ORAL (GAVAGE) TOXICITY STUDY OF SCH 503034 CONTAINING HIGH LEVELS OF DEGRADANTS IN RATS

Study no.:	4032
Study report location:	4.2.3.7.6
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	3-31-2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 04-503034-Y-101 & 89.9%; SCH 503034, 03-503034-Y-102 & 95.8%

Key Study Findings: The objectives of this study were to assess the systemic toxicity and toxicokinetics of SCH 503034 containing degradants (Batch # 04-503034-Y-101) compared to a SCH 503034 control batch (Batch # 03-503034-Y-102) when administered orally by gavage to rats at 75, 150 and 200 mg/kg or 200 mg/kg of the control batch for 1 month. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, clinical pathology and gross and histopathology. The NOAEL in female rats was 75 mg/kg due to minimally decreased urine osmolality observed at higher doses, while a NOAEL was not identified in male rats, based on histopathologic findings in the epididymides and testes (mild luminal cellular debris in the epididymides, minimal Sertoli cell vacuolation, spermatid degeneration and/or atrophy of the seminiferous tubules in the testes of all treated groups). However, similar systemic exposures with no meaningful toxicological differences were observed between rats receiving the SCH 503034 comparative control batch and SCH 503034 containing degradants batch.

Study title: ONE-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 (BATCH SI-07HCVY202A) IN RATS

Study no.:	7357
Study report location:	4.2.3.7.6
Conducting laboratory and location:	Schering-Plough Research Institute, Summit, NJ
Date of study initiation:	10-29-2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, SI-07HCVY202A & 95.1%; SCH 503034, SI-06HCVY204A & 97.7%

Key Study Findings: The objectives of this study were to perform a batch comparison to assess the systemic toxicity and toxicokinetics of SCH 503034 (Batch # SI-07HCVY202A) compared to SCH 503034 (Batch # SI-06HCVY204A) when

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administered orally by gavage to rats at 75, 150 and 200 mg/kg or 200 mg/kg of batch # SI-06HCVY204A for 1 month. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, clinical pathology and gross and histopathology. Dose-dependent histopathology findings (similar to those observed in previous studies with SCH 503034) were observed in males at all dose levels, consisting of diffuse to multifocal, minimal to moderate degeneration of seminiferous tubules in the testes and minimal to moderate hypospermia with cellular debris accumulations in the epididymides. Thus, the NOAEL was 200 mg/kg in females but was not identified for males. The results indicate that there were no differences in toxicity findings between the two different batches of SCH 503034 and no new target organ of toxicity emerged from this study.

Study title: ONE-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 WITH IMPURITIES IN RATS

Study no.:	10080
Study report location:	4.2.3.7.6
Conducting laboratory and location:	Schering-Plough Research Institute, Summit, NJ
Date of study initiation:	5-19-2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 68771-16 & 96.3%; SCH 503034, 08HCVY103 & 97.9%

Key Study Findings: The objectives of this study were to assess the systemic toxicity and toxicokinetics of SCH 503034 containing added impurities (Batch # 68771-16) compared to a SCH 503034 control batch (Batch # 08HCVY103) when administered orally by gavage to rats at 75, 150 and 200 mg/kg or 200 mg/kg of the control batch for 1 month. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, clinical pathology and gross and histopathology. A NOAEL was not identified for males in this study based on the expected histopathological findings in the testes and epididymides in all SCH 503034 dose groups, consisting of minimal degeneration of seminiferous tubules in the testes; and in the epididymides, minimal hypospermia with minimal to mild cellular debris accumulations. For the females, the NOAEL was 200 mg/kg. No toxicologically significant difference between the two batches tested in this study was identified. In addition, there were no new findings in rats administered either of the batches tested in this study as compared to previous studies with other batches of SCH 503034.

10.2 Nonclinical safety studies in neonatal and juvenile rats

Study title: AN ORAL (GAVAGE) DOSE RANGE-FINDING 14-DAY TOXICITY STUDY OF THE EFFECTS OF SCH 503034 ON NEONATAL RATS

Reference ID: 2933010

Study no.:	6483
Study report location:	4.2.3.5.4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	5-23-2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 05-503034-Y-110B & 95.6%

Key Study Findings: The toxicity of SCH 503034 was evaluated in post-natal day (PND) 7 rats (12 or 24/sex/group) administered once daily oral (gavage) doses of 75, 125, 200/250 or 500 mg/kg or vehicle control [0.4% (w/v) aqueous methylcellulose] for 14 days. Mortality, clinical signs and body weights were evaluated in this study. The 500 mg/kg dose group (12/sex) was terminated early due to excessive mortality following the first dose. Twelve animals/sex of the 200/250 mg/kg dose group were administered 200 mg/kg for their first dose only. These 12 animals were then administered 250 mg/kg for the remainder of the study, while the other 12 animals/sex of this group received 250 mg/kg for the entire duration of the study. One male animal of the 200/250 mg/kg group was found dead on PND 9 and was considered to be test-article related. Additionally, reduced body weight and body weight gain (primarily due to reduced body weight gain from PND 7 and 10) were observed in the 200/250 mg/kg dose group. Thus, the NOAEL in neonatal rats was considered to be 125 mg/kg in this study based on mortality and reduced body weight gain at higher dose levels.

Study title: THREE MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY WITH A FOUR-WEEK RECOVERY PERIOD OF SCH 503034 IN NEONATAL AND JUVENILE RATS

Study no.:	6484
Study report location:	4.2.3.5.4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	7-15-2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 05-503034-Y-110B & 98.0%

Key Study Findings: The NOAEL is 25 mg/kg (AUC= 3.0 µg·h/ml at 21d) in males and females due primarily to adverse testicular and thyroid findings in mid- and high-dose animals. Testicular findings consisted of hypospermia in epididymides, vacuolation of seminiferous epithelium and degeneration of seminiferous tubules that were associated with reductions in testes and epididymides organ weights. In general, these findings did

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not show any significant degree of recovery over the 4-week post-dose period, which is not unexpected given this short duration.

Minimal hyperplasia of follicular cells of the thyroid was also observed in both males and females but was not present following the post-dose period. Additionally, femur length was reduced up to 3.3%. Although it is possible that reduced thyroid hormone exposure [due to increased clearance via liver enzyme induction (liver weights were increased) and leading to follicular hyperplasia of the thyroid] could cause these reductions in longitudinal bone growth, they are more likely the result of a secondary effect due to body weight gain reductions observed during this time period.

A small test-article related effect on the age of attainment of balanopreputial separation was observed at 150 mg/kg. Although significant statistically, this effect is not likely of clinical significance due, in part, to anatomical and developmental differences between male rats and humans, the small magnitude of the effect and due to the fact that the effect may be indirect (due to testicular toxicity).

Methods

Doses:	0, 25, 75, 150 mg/kg/day
Frequency of dosing:	once/day
Route of administration:	oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Neonatal Crl:CD(SD) rats
Number/Sex/Group:	48/sex/group originated from 16 litters/group (3/sex) with 15 (main study), 15 (recovery) & 18 (TK)
Age:	PND 7
Weight:	8.3 to 20.9 (♂) & 11.0 to 19.8 (♀) g
Satellite groups:	4-week recovery and TK groups
Unique study design:	None
Deviation from study protocol:	None that affected the integrity or conclusions of the study.

Observations and Results

Mortality (1x/day): No test-article related mortalities observed. There were 2 unscheduled deaths the causes of which were not entirely clear (1 ♂ in 75 mg/kg group at PND 88 & 1 ♀ in 25 mg/kg group at PND 85).

Clinical Signs (1x/day): Note: Animals also observed ~1 hour post-dose and detailed exams conducted on PND 1, 4, 7, 10, 14, 17, 21 & weekly thereafter.

- ↑ incidence of red material around eyes at all doses (♂) (total observations/number of animals: control: 0/0; 25 mg/kg: 5/1; 75 mg/kg: 7/2; 150 mg/kg: 10/3). Finding of little toxicological significance.
- ↑ incidence of salivation at 1 hour post-dose at 150 mg/kg only

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Body Weights: Note: Conducted on PND 1, 4, 7, 10, 14, 17, 21, 24, 28 & weekly thereafter.

- mean body weights ↓11.8% (♂) and 9.9% (♀) starting on PND 10 at 150 mg/kg due primarily to reduced body weight gain (↓~36%) from PND 7 to 10.
- Body weights in the 150 mg/kg group recovered to control levels by PND 42 (♂) and PND 98 (♀).
- Body weights also ↓3-4% (♀) from PND 35 to 98 at 75 mg/kg.

Feed Consumption: Note: Conducted on PND 21 to 28 (litter means) & weekly (individual measurements) thereafter. It should be noted that consumption could not be evaluated during the time period that body weight changes were observed, since the animals were not yet weened. No test-article related changes noted.

Hematology (PND 92 or 120):

- APTT ↑10 & 14% at 75 & 150 mg/kg (♂) at PND 92 (not present at PND 120).
- RBC's and Hct ↓~5% at 75 & 150 mg/kg (♂) at PND 92 (not reduced at PND 120).
- These findings are not considered adverse.

Clinical Chemistry (PND 92 or 120): No test-article related changes noted.

Urinalysis (PND 92 or 120): No test-article related changes noted.

Gross Pathology: No test-article related changes noted.

Organ Weights:

- Liver weight (relative to body weight) ↑11 & 15% at 75 & 150 mg/kg (♂) and ↑9 & 20% at 75 & 150 mg/kg (♀) at PND 92. No significant differences were observed at PND 120.
- Absolute testes weight ↓11% at PND 92 and 15% at PND 120 (150 mg/kg). Also ↓10% at PND 120 (75 mg/kg).
- Absolute epididymides weight ↓25% at PND 92 and 18% at PND 120 (150 mg/kg). Also ↓11% at PND 120 (75 mg/kg).

Histopathology

Adequate Battery: Yes

Peer Review: No

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Histological Findings:

- Hypospermia observed in epididymides that was minimal (9/15) to mild (2/15) at PND 92 and moderate (2/15) to severe (1/15) at PND 120 (150 mg/kg). Hypospermia also observed at 75 mg/kg that was moderate (1/15) to severe (1/15) at PND 92 and moderate (3/15) at PND 120.
- Vacuolation of seminiferous epithelium observed in testes that was minimal (13/15) to mild (1/15) at PND 92 and minimal (4/15) at PND 120 (150 mg/kg). Finding also present at 75 mg/kg that was minimal (2/14) at PND 92 and not observed at PND 120 at this dose level.
- Degeneration of seminiferous tubules observed in testes that was minimal (3/15) to moderate (2/15) at PND 92 and minimal (3/15), mild (2/15), moderate (1/15) or severe (1/15) at PND 120 (150 mg/kg). Finding also present at 75 mg/kg that was minimal (1/15) to severe (2/15) at PND 92 and minimal (1/15) to severe (3/15) at PND 120.
- Minimal hyperplasia of follicular cells of the thyroid in 5/14 (♂) at 75 mg/kg and 9/15 (♂) & 5/15 (♀) at 150 mg/kg at PND 92. Finding not observed in animals sacrificed at PND 120.

Special Evaluation: Maturational/behavioral evaluations (age at attainment of vaginal patency and balanopreputial separation, and femur measurements) were performed.

- Minimal test-article related effect on age of attainment of balanopreputial separation observed at 150 mg/kg (<u>controls</u>: PND 44.4+/-2.4; <u>150 mg/kg dose group</u>: PND 46.1+/-2.7).
- Mean femur length ↓2.6 % (♀) at PND 92 (75 mg/kg) and ↓1.1 (♀) & 3.3 (♂)% at PND 21, ↓3.4 (♀) & 1.3 (♂)% at PND 92, and ↓1.7 (♀) & 3.2 (♂)% at PND 120 (150 mg/kg). At PND 21, the ↓3.3% (♂, 150 mg/kg) equates to 18.4 +/-0.56 mm (control) versus 17.8 +/-0.63 mm.

Toxicokinetics: Note: Plasma measurements performed on PND 21 (0.5, 1, 2, 4, 8 & 24 hours post-dose). SCH534128:SCH534129 exposure ratios ranged from ~0.85-0.96 and did not change with increasing SCH 503034 dose.

Table 20: TK Summary for SCH 503034 Following Administration of Boceprevir for 3-Months in Neonatal/Juvenile Rats

SCH 503034 Toxicokinetic Parameters Following Oral (Gavage) Administration of 25, 50 or 150 mg/kg SCH 503034 to Rats (Males and Females Combined)						
Dose (mg/kg)[a]	Day	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)
25	PND 21	944	2	8	2780	3030
75		8300	1	8	22900	23500
150		9090	2	8	45900	48500
a: SCH 503034						

<u>Table from sponsor</u>

Dosing Solution Analysis: Formulations used for test-article administration were analyzed sufficiently and determined to be within acceptable limits (85-115% of target concentration).

Study title: A ONE-MONTH HORMONE EVALUATION STUDY OF SCH 503034 IN JUVENILE RATS

Study no.:	9238
Study report location:	4.2.3.5.4
Conducting laboratory and location:	(b) (4)
Date of study initiation:	11-23-2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 08HCVY105 & 97.9%

Key Study Findings: This study was designed to test the hypothesis that the thyroid effect (follicular hyperplasia) observed previously when administering SCH 503034 to neonatal/juvenile rats (Study # 6484) was not due to a direct test-article effect but an indirect effect due to induction of liver enzymes (UGT1A1/6 & UGT2B2) that increase thyroid hormone clearance thereby resulting in increased production of TSH that ultimately leads to follicular hyperplasia. It is thought that rats may be more sensitive than humans to liver enzyme induction and thus the follicular hyperplasia observed would be less of a concern for administering SCH 503034 to the pediatric human population. However, the data collected from this study failed to deliver clear evidence to support this hypothesis, due in part to the lack of compelling data obtained in positive control animals administered phenobarbital.

Minimal to mild follicular hyperplasia of the thyroid was observed in SCH 503034 treated animals, despite achieving only about one third the exposure of the previous study at the same dose (Study # 6484), and in positive control animals from PND 14 to 35. This effect could not be associated confidently with increases in TSH, since only SCH 503034 treated females at PND 35 demonstrated a small increase.

No effects on liver weight or histopathology were noted in SCH 503034 treated animals, while minimal to mild cytoplasmic alterations of the liver were observed in positive control animals. In the positive control group, it should be noted that only 3 males and 1 female remained in the study at PND 35 due to significant mortality. Thus, this time point (and the original 80 mg/kg dose level) could not be evaluated since it appears that neonatal/juvenile rats are more sensitive to the CNS effects of phenobarbital than adult rats.

There was a small tendency for liver enzyme induction in this study (in the absence of clear thyroid hormone changes). In SCH 503034 treated animals, there were inconsistent small increases in UGT2B2 and/or UGT1A1/6 observed at PND 14 & PND 35, with ~2-fold increase in both enzymes compared to control values in female animals at PND 14 being the most significant. In positive control animals, small inconsistent

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increases (<2-fold) in UGT1A1/6 & UGT2B2 activity compared to control values were observed at PND 14 and/or PND 21.

Methods

Doses:	0, 150 mg/kg/day (also 80/60/40 Phenobarbital-positive control group)
Frequency of dosing:	once/day
Route of administration:	oral gavage
Dose volume:	5 ml/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Neonatal Crl:CD(SD) rats
Number/Sex/Group:	86/sex/group, 68 (main study) & 18 (TK), (24 Phenobarbital treated TK animals)
Age:	PND 7
Weight:	9.6 to 21.9 (♂) & 8.7 to 20.4 (♀) g
Satellite groups:	TK group
Unique study design:	Animals sacrificed on PND 21 (TK) or PND 14 or 35 (main study)
Deviation from study protocol:	None that affected the integrity or conclusions of the study.

Observations and Results

Mortality (1x/day): No test-article related mortalities observed. Phenobarbital (positive control)-related mortalities were observed in 18 males and 23 females during PND 8 to 13 (see sponsor table below).

Table 21: Summary of Phenobarbital-Related Mortality in Neonatal/Juvenile Rats

Day of PND 7	Total No. of Animals	No. Found Dead or Missing	No. Euthanized *in extremis*	Total % Mortality
Males				
PND 7 on first day of dose admin.[a]	11	3	3	55%
PND 7 on second day of dose admin.[b]	36	3	8	31%
PND 7 on third day of dose admin.[c]	21	2[d]	0	10%[d]
Females				
PND 7 on first day of dose admin.[a]	11	2	6	73%
PND 7 on second day of dose admin.[b]	36	6	6	33%
PND 7 on third day of dose admin.[c]	21	1	2	14%

[a]: Animals in the first replicate received up to two doses at 80 mg/kg PB and 40 mg/kg PB thereafter.
[b]: Animals in the second replicate received one dose at 60 mg/kg PB and 40 mg/kg PB thereafter.
[c]: Animals in the third replicate received doses at 40 mg/kg PB only.
[d]: Includes male no. 60288-02 that was missing and presumed cannibalized on PND 10

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Clinical Signs (1x/day): No test-article related changes noted. Cool body, decreased/labored/shallow respiration and hypoactivity observed primarily in positive control animals that were found dead or euthanized.

Body Weights: Note: Conducted on PND 4, 7, 10, 14, 17, 21 (main study & TK groups) & 24, 28, 31 & 35 (main study group only).

- In SCH 503034 treated animals: mean body weights ↓~6% (♂ & ♀) at PND 10 and ↓7.9% (♂) and 2.9% (♀) at PND 35 due primarily to reduced body weight gain (↓~19%) from PND 7 to 10.
- In positive control animals: mean body weights ↓19% (♂) & 20% (♀) at PND 10 and ↓14.6% (♂) & 3.5% (♀) at PND 35 due primarily to reduced body weight gain (↓~34%) from PND 7 to 10. It should be noted that only 3 ♂ & 1 ♀ remained in the study at PND 35 due to mortality.

Feed Consumption: Not performed.

Hematology: Not performed.

Clinical Chemistry: Not performed.

Urinalysis: Not performed.

Gross Pathology: No test-article related changes noted.

Organ Weights: Note: Only liver and thyroids/parathyroids weighed. No test-article related changes noted.

Histopathology

Adequate Battery: Yes, only liver, thyroid, parathyroids, pituitary and gross lesions were examined.

Peer Review: No

Histological Findings:

In SCH 503034 treated animals:

- Hyperplasia of follicular cells of the thyroid was observed as follows: minimal in 2/24 (♂) at PND 14; minimal in 11/24 (♂) & 7/24 (♀) or mild in 1/24 (♀) at PND 21; and minimal in 10/18 (♂) & 7/20 (♀) or mild in 1/20 (♀) at PND 35.

In positive control animals:

- Minimal follicular hyperplasia of the thyroid was observed in 8/21 (♂) & 12/19 (♀) at PND 21 and in 2/4 (♂) at PND 35.
- Minimal heptocellular vacuolation of the liver observed in 2/24 (♀) at PND 14.
- Minimal to mild cytoplasmic alteration of the liver in 16/21 & 1/21 (♂) and 16/19 & 1/19 (♀) at PND 21, and in 3/4 & 1/4 (♂) and 1/2 & 1/2 (♀) at PND 35.

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Special Evaluation: Hormone (TSH, T_4, T_3) and liver enzyme (UGT1A1/6 & UGT2B2) analysis was performed. Note: UGT1A1/6 is thyroxine glucuronosyltransferase which metabolizes T_4, while UGT2B2 is triiodothyronine glucuronosyltransferase which metabolizes T_3.

Hormone analysis:

- In SCH 503034 treated animals (♂): T_4 ↑~12% & T_3 ↑~22% at PND 14 but TSH was not different significantly from control values.
- In SCH 503034 treated animals (♀): T_3 ↑~23% at PND 14 but T_4 and TSH were not different significantly from control values. Additionally, TSH ↑~25% at PND 35 only in the absence of significant changes in T_4 & T_3.
- In positive control animals (♂): T_4 ↑~34%, TSH ↑~16% but T_3 ↓~9% at PND 21.
- In positive control animals (♀): T_4 ↑~33% but T_3 ↓~17% & TSH ↓~11% at PND 21.
- It should be noted that only 3 ♂ & 1 ♀ remained in the study at PND 35 in the positive control group due to mortality. Thus, this time point could not be evaluated sufficiently.

Liver enzyme analysis:

- In SCH 503034 treated animals (♂): UGT2B2 was ↑53% at PND 14 & ↑74% at PND 35 compared to control values.
- In SCH 503034 treated animals (♀): UGT1A1/6 & UGT2B2 were ↑93% & ↑~2.1-fold at PND 14 only compared to control values.
- In positive control animals (♂): UGT2B2 were ↑65% at PND 14 & ↑51% at PND 21 compared to control values.
- In positive control animals (♀):UGT1A1/6 & UGT2B2 were ↑67% & ↑86% at PND 14 only compared to control values.

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Toxicokinetics: Note: Plasma measurements performed on PND 21 (0.5, 1, 2, 4, 8 & 24 hours post-dose).

Table 22: TK Summary for SCH 503034, SCH 534128 and SCH 534129 Following Administration of Boceprevir for 1-Month in Neonatal/Juvenile Rats

Group	Dose[a] (mg/kg)	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	F:M[b]	SCH 534128: SCH 534129[c]
SCH 534128									
3	150	Female	3440	0.5	8	6960	7180	0.870	0.890
		Male	2030	4	8	8050	8260	NA[d]	0.886
SCH 534129									
3	150	Female	3810	0.5	8	7840	8070	0.866	NA
		Male	2260	4	8	9100	9320	NA	NA
SCH 503034									
3	150	Female	7250	0.5	8	14800	15300	0.868	NA
		Male	4300	4	8	17100	17600	NA	NA

a: SCH 503034
b: F:M = $AUC(0\text{-}24\ hr)_{Female} \div AUC(0\text{-}24\ hr)_{Male}$
c: SCH 534128:SCH 534129 = $AUC(0\text{-}24\ hr)_{SCH\ 534128} \div AUC(0\text{-}24\ hr)_{SCH\ 534129}$
d: NA = Not applicable

Table from sponsor

Table 23: TK Summary for SCH 629144 Following Administration of Boceprevir for 1-Month in Neonatal/Juvenile Rats

Group	Dose[a] (mg/kg)	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	F:M[b]	SCH 629144: SCH 503034[c]
SCH 783004									
3	150	Female	15.8	0.5	4	27.4	31.9	NA[d]	NA
		Male	11.6	4	4	19.3	NR[e]	NA	NA
SCH 783006									
3	150	Female	62.8	1	8	126	128	0.779	NA
		Male	43.0	4	8	162	164	NA	NA
SCH 783007									
3	150	Female	62.0	1	8	121	124	0.737	NA
		Male	46.1	4	8	164	168	NA	NA
SCH 629144									
3	150	Female	141	1	8	280	285	0.758	0.0186
		Male	101	4	8	370	375	NA	0.0213

a: SCH 503034
b: F:M = $AUC(0\text{-}24\ hr)_{Female} \div AUC(0\text{-}24\ hr)_{Male}$
c: SCH 629144:SCH 503034 = $AUC(0\text{-}24\ hr)_{SCH\ 629144} \div AUC(0\text{-}24\ hr)_{SCH\ 503034}$
d: NA = Not applicable
e: NR = Not reported. AUC(0-24 hr) not reported when % AUC extrapolated > 25%.

Table from sponsor

Reference ID: 2933010

Dosing Solution Analysis: Formulations used for test-article administration were analyzed sufficiently and determined to be within acceptable limits (85-115% of target concentration).

10.3 Combination toxicology studies

Study title: THREE-MONTH ORAL (GAVAGE) REPRODUCTIVE TOXICITY/ TOXICOKINETIC STUDY OF SCH 503034 AND RIBAVIRIN (SCH 18908) IN MALE RATS WITH A POST-DOSE PERIOD

Study no.:	4124
Study report location:	4.2.3.7.7
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	6-11-2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 03-503034-Y-104 & 97.8% and 02-503034-Y-001 & 94.7%; SCH 18908, 020709947 & 100.3%

Key Study Findings: Toxicity of SCH 503034 was evaluated in male CD®(SD) IGS BR VAF/Plus® rats (20/group-main group; 15/group-TK group) administered oral (gavage) doses of 100 and 300 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] with or without 80 mg/kg ribavirin for 3 months with a 2 month post-dose “recovery” period. Standard reproductive toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, sperm analysis, clinical chemistry and gross and histopathology. The study indicated that ribavirin did not increase the toxicity of SCH 503034, despite increasing the systemic exposures of SCH 503034, the stereoisomers (SCH 534128, SCH 534129) and a metabolite (SCH 629144). Systemic exposures to SCH 503034, SCH 534128, SCH 534129 and SCH 629144 were dose-related and both isomers had similar blood levels to each other. Additionally, ribavirin alone did not have significant effects on reproductive tissues.

Excessive salivation and/or peri-oral substance were noted in all groups dosed with SCH 503034 during the dosing period. Transient decrease in body weight gain was observed in all dose groups during the first week of dosing that was sustained in the 300 mg/kg dose group. Decreased mean epididymal weights were observed in all SCH 503034 dose groups and remained reduced following the 2-month post-dose “recovery” period in the 300 mg/kg dose group. Testicular weights were lower in the 300 mg/kg SCH 503034 dose group at the end of the dosing period and following the post-dose period. Sperm motility and count were reduced in the 100 mg/kg dose group but recovered following the post-dose period, while this reduction was of higher incidence in the 300 mg/kg SCH 503034 dose group. Following the 2-month post-dose period, the majority of the 300 mg/kg dose SCH 503034 group animals had normal sperm motility

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and counts. Hypospermia was present in the 100 and 300 mg/kg dose groups during the dosing period and in the 300 mg/kg dose group following the post-dose period. Vacuolation of Sertoli cells were observed in all SCH 503034 dose groups. Epididymal cellular debris and spermatid degeneration was observed in all SCH 503034 dose groups (not present following the post-dose period). These findings were of lower incidence but still present following the post-dose period.

In the 300 mg/kg dose group, multinucleated hepatocytes and Kupffer cell hypertrophy were present in the liver during dosing and following the post-dose period associated with minimal increases in AST and ALT. A low incidence of multinucleated hepatocytes in the 100 mg/kg group was observed following the post-dose period. Mean ALT and AST were higher in the 300 mg/kg dose group at the end of the dosing period and post-dose period.

Table 24: TK Summary for SCH 503034 and SCH 629144 Following Administration of Boceprevir with and without Ribavirin for 3-Months in Male Rats

Group	Dose (mg/kg)[a]	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)
SCH 503034						
T2	100/0	4890	2	24	15300	15300
T3	300/0	14300	2	24	57200	57200
T4	100/80	6530	4	8	27300	34700
SCH 629144						
T2	100/0	344	2	8	1030	1080
T3	300/0	1170	2	8	3960	4850
T4	100/80	597	4	8	2370	2990

a: SCH 503034/SCH 18908

Table from sponsor

Table 25: TK Summary for Ribavirin Following Administration of Boceprevir with and without Ribavirin for 3-Months in Male Rats

Group	Dose (mg/kg)[a]	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)
T1	0/80	1150	2	16800
T4	100/80	1650	2	24400

a: SCH 503034/SCH 18908

Table from sponsor

Study title: THREE-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 ADMINISTERED IN COMBINATION WITH SCH 18908 AND EITHER DIFLUNISAL OR RITONAVIR IN RATS

Study no.:	6320
Study report location:	4.2.3.7.7
Conducting laboratory and location:	Schering-Plough Research Institute, Summit, NJ
Date of study initiation:	7-24-2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 06-503034-YY-106A & 93.7%; SCH 18908, 889176 & 99.6%; diflunisal, K-H07297 & 98.8%; ritonavir, RV0010405 & 99.1%

Key Study Findings: Toxicity and toxicokinetics of SCH 503034 was evaluated in rats (10/group-main group; 18/group-TK group) administered oral (gavage) doses of 1.25 & 7.5 mg/kg SCH 503034 in combination with 80 mg/kg ribavirin (SCH 18908) and 25 mg/kg ritonavir or 25 & 150 mg/kg SCH 503034 in combination with 80 mg/kg ribavirin and 40 mg/kg diflunisal for 3 months. The study also included control groups administered vehicle [0.4% (w/v) aqueous methylcellulose], diflunisal (40 mg/kg) or ritonavir (25 mg/kg) alone, but not groups administered SCH 503034 and ribavirin either alone or in combination (without diflunisal or ritonavir). Standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, urinalysis, clinical pathology and gross and histopathology. Due to poor study design, the effect of CYP 3A4/5 inhibition (by ritonavir) and aldo-keto-reductase (AKR) inhibition (by diflunisal) on SCH 503034 exposure could not be determined with any certainty. Additionally, the contribution of diflunisal and ritonavir on the toxicity of the combination of SCH 503034 and ribavirin could not be established clearly, making the study of limited value. Although not a stated objective of the study, the combination of SCH 503034 and ribavirin did not appear to significantly affect the PK profiles of diflunisal or ritonavir but did result in increased toxicity. The toxicities observed appear to be due to the added toxic effects of the 3 drug combinations studied.

Target organs/tissues identified for SCH 503034 in combination with ribavirin and diflunisal were the thymus, adrenal gland, kidneys and thyroid glands. A NOAEL was not identified due to findings such as renal pathology (degeneration of outer medulla in ♀), thymus weight decreases, thyroid gland weight increases (♀), lower mean body weight parameters, and lower mean food consumption (♂). Target organs/tissues identified for SCH 503034 in combination with ribavirin and ritonavir were the thymus, liver, and thyroid glands. A NOAEL was not identified due to findings such as thymus weight decreases; liver weight increases associated with multinucleated hepatocytes (♀), clinical signs of toxicity, and lower mean body weight gain.

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Study title: ONE-MONTH ORAL (GAVAGE) TOXICITY AND TOXICOKINETIC STUDY OF SCH 503034 ADMINISTERED IN COMBINATION WITH SCH 54031 (PEG-Intron) AND SCH 18908 (ribavirin) IN CYNOMOLGUS MONKEYS

Study no.:	1532
Study report location:	4.2.3.7.7
Conducting laboratory and location:	Schering-Plough Research Institute, Lafayette, NJ
Date of study initiation:	6-30-2003
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	SCH 503034, 02-503034-Y-001 & 101.2%; SCH 18908, 020709947 & 100.3%; SCH 54031, 1-IQD-901 & 105% (HPSEC)

Key Study Findings: Toxicity of SCH 503034 was evaluated in cynomolgus monkeys (4/sex/group) administered oral (gavage) doses of 25, 75, 200 mg/kg or vehicle [0.4% (w/v) aqueous methylcellulose] with 1414 ug/m^2 PEG-intron and 50 mg/kg ribavirin for 1 month. All standard toxicity endpoints were evaluated in this study including clinical signs, body weights, food consumption, ophthalmology, electrocardiograms, urinalysis, clinical pathology and gross and histopathology. Based on clinical pathology, organ weight and histopathology findings in all groups administered PEG-intron and ribavirin alone or in combination with SCH 503034, a NOAEL was not determined under the conditions of this study. With the exception of reduced food consumption, findings in this study were attributed to the administration of 1414 µg/m^2 PEG-intron and 50 mg/kg ribavirin alone (such as a mild reduction in RBCs, HCT & HGB) and were not exacerbated by the concurrent administration of SCH 503034 at doses of up to 200 mg/kg.

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Table 26: TK Summary for SCH 503034 Following Administration of Boceprevir in Combination with PEG-Intron (SCH 54031) and Ribavirin (SCH 18908) for 1-Month in Cynomolgus Monkeys

Mean SCH 503034 Toxicokinetic Parameters									
Day	SCH 503034 Dose (mg/kg)/ Group[a]	Cmax (ng/mL)[b]		Tmax (hr)[c]		AUC(0-24 hr) (ng·hr/mL)[b]		R[b]	
		Male	Female	Male	Female	Male	Female	Male	Female
0	25/ T1	302 (39)	440 (69)	2.00 (2.00-4.00)	1.50 (1.00-4.00)	2620 (22)	3160 (33)	NA	NA
	75/ T2	949 (45)	1500 (28)	3.00 (1.00-8.00)	2.50 (1.00-4.00)	11200 (57)	10100 (41)	NA	NA
	200/ T3	3930 (43)	3060 (15)	3.00 (2.00-8.00)	2.00 (1.00-8.00)	42600 (28)	31900 (41)	NA	NA
28	25/ T1	823 (42)	587 (68)	1.00 (1.00-1.00)	1.00 (1.00-2.00)	4800 (38)	3440 (49)	1.99 (58)	1.10 (26)
	75/ T2	2400 (73)	1990 (29)	1.00 (1.00-2.00)	1.00 (1.00-1.00)	19800 (113)	11900 (26)	2.45 (139)	1.30 (44)
	200/ T3	5830 (64)	8460 (43)	2.00 (1.00-4.00)	1.50 (1.00-2.00)	55800 (56)	64000 (49)	1.30 (40)	2.48 (76)

a: T1 = Oral (gavage): 25 mg/kg/day SCH 503034, 50 mg/kg/day SCH 18908; Subcutaneous injection: 1414 μg/m^2/every other day SCH 54031
T2 = Oral (gavage): 75 mg/kg/day SCH 503034, 50 mg/kg/day SCH 18908; Subcutaneous injection: 1414 μg/m^2/every other day SCH 54031
T3 = Oral (gavage): 200 mg/kg/day SCH 503034, 50 mg/kg/day SCH 18908; Subcutaneous injection: 1414 μg/m^2/every other day SCH 54031
b: Mean (CV%)
c: Median (range)
NA = Not Applicable

Table from sponsor

11 Integrated Summary and Safety Evaluation

Boceprevir (SCH 503034) is an orally active, serine protease inhibitor for HCV NS3/4A (non-structural protein 3/4A) protease that inhibits viral replication by reversibly binding to the active site within the NS3/4A protease.

Safety Pharmacology:

In a cardiovascular safety study in telemeterized male cynomolgus monkeys, a single dose of boceprevir produced no adverse effects on cardiovascular function, with only a minor increase in heart rate (16 to 22%) observed at the 200 mg/kg dose level (C_{max}= 4.3 μg/ml). No effects on blood pressure or ECG intervals or morphology were observed at this dose, providing a ~2.1-fold monkey to human exposure multiple (based on C_{max}). Cardiovascular safety signals have also not been observed in clinical trials. Additionally, no significant effects on behavioral, neurologic or autonomic function or on respiratory parameters (respiratory rate, tidal or minute volumes) were observed in rats following single doses of up to 200 mg/kg (C_{max}= 15.2 μg/ml), providing a ~7-fold rat to human exposure multiple (based on C_{max}). Exposure estimates are based on TK data obtained in a different study (Study # 4032).

Pharmacokinetics:

The oral bioavailability of the diastereomers (SCH 534128 and SCH 534129) that comprise SCH 503034 is 7 to 18% in monkeys, 27 to 34% in rats and ~35% in mice. These diastereomers are present at approximately a 1:1 ratio in SCH 503034 but are interconverted *in vivo* to varying extents by keto-enol tautomerization. Although SCH 534128 is a much more potent inhibitor of the HCV NS3/4 protease, this interconversion results in equilibrium mixtures with potent activity. The equilibrium AUC ratio of SCH 534128 to SCH 534129 is ~1.2:1 in mice, 1:1 in rats and 0.17:1 in monkeys, compared to around 2.2:1 in humans. Despite some species specific differences in this ratio, particularly in monkeys, safety evaluation of these diastereomers is acceptable, given that exaggerated pharmacology is not a safety concern for boceprevir.

Boceprevir is metabolized extensively in all species with greater than 79% of the oral dose eliminated in feces and only ~14% excreted unchanged. By far the most abundant circulating human metabolite (SCH 629144), produced by aldo-ketoreductase (AKR) activity, is a mixture of four stereoisomers (SCH 783004, 783005, 783006 and 783007). Boceprevir can also be metabolized by CYP3A4/5, is a moderate inhibitor but not an inducer of CYP3A4/5, and is a P-glycoprotein substrate and inhibitor. AUC exposure ratios of SCH 629144 to SCH 503034 vary widely between species with rats, mice, humans and monkeys having ~0.07:1, 0.8:1, 4:1 and 7.5:1 ratios, respectively. Although the safety of SCH 629144 could not be characterized sufficiently in rats, safety was established in both mice and monkeys. The only other circulating human metabolite (SCH 503034-K) that exceeded 3 % of the administered dose appears to be formed by sodium lauryl sulfate (SLS) dependent hydrolysis in the stomach. Circulating levels of SCH 503034-K relative to parent drug were less than 8% in humans administered the "to be marketed" capsule formulation. SCH 503034-K (b) (4) has been qualified in nonclinical safety studies. The amount of exposure in animal models to support safety of this hydrolysis product (although low) appears acceptable since exposure to this metabolite does not exceed 10% of the total circulating drug related material.

Boceprevir distributed predominantly to the liver in rats, while boceprevir was below the level of detection in brain and spinal cord. In monkeys, extensive extravascular distribution of SCH 503034 was observed with liver to plasma ratios ranging from ~3 to 9 for SCH 534128 and SCH 534129, indicating distribution to the site of action. Moderate plasma protein binding of ~72%, 55%, 56% and 68% was observed in mice, rats, monkeys and humans, respectively, when 5 μg/ml of SCH 503034 was incubated in plasma.

Placental transfer of boceprevir was assessed in pregnant rats administered a single oral dose on gestation day 18. Transient exposure was observed in the fetus with an estimated maternal to fetal AUC plasma ratio of ~6. Fetal tissues examined had boceprevir concentrations similar to or lower than maternal blood concentrations with the only exceptions being the liver and embryonic sac. No fetal tissues contained measurable concentrations of boceprevir by 24 hours post-dose, with the exception of the embryonic sac.

Transfer of boceprevir into milk was assessed in lactating rats. Although milk concentrations of boceprevir were slightly higher than maternal plasma concentrations,

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plasma concentrations in the pups were low indicating that pups are not exposed to appreciable levels of boceprevir through milk consumption.

Repeat-Dose Toxicology Studies:

Liver toxicity:

In mice, the NOAEL for liver toxicity was 250 mg/kg [$AUC_{0\text{-}24\ hr}$ = 29.4 (♀) & 10.4 (♂) μg·hr/ml at 80d] in 3 month studies. Higher liver weights with minimal Kupffer cell hypertrophy were observed in animals receiving ≥500 mg/kg for 3 months. Kupffer cell hypertrophy with neutrophil infiltration was associated with mild elevations of AST and ALT in males and females receiving ≥600 mg/kg and 900 mg/kg for 3 months, respectively. In the 2-year study, focal/multifocal single cell necrosis in the liver was noted in animals receiving a dose of 500 (♂)/650 (♀) mg/kg, while pigment (lipofuscin) accumulation and macrophage infiltration occurred at doses ≥250 mg/kg (♂) and 650 mg/kg (♀).

In rats, the NOAEL for liver toxicity was 75 mg/kg [$AUC_{0\text{-}24\ hr}$ = 31.6 (♀) & 16.7 (♂) μg·hr/ml at 167d] in the 6 month study. Findings were characterized by scattered foci of multinucleated hepatocytes that were slightly to greatly enlarged, containing 5 to 9 variably-sized nuclei. Multinucleated hepatocytes and ALT elevations were also observed at doses ≥150 mg/kg and ≥200 mg/kg (♂) for 3 months. In the 2-year study, multinucleated hepatocytes were observed in males and females at doses ≥ 50 mg/kg.

In cynomolgus monkeys, liver findings were limited to higher liver weights in the absence of histopathology findings at doses ≥300 mg/kg for 3 months. These effects were not observed at a 200 mg/kg dose level, providing a ~1.6-fold monkey to human AUC exposure multiple.

The specific liver findings observed in each species were quite different and so a consistent mechanism for liver toxicity was not identified. Given that increases in liver enzymes have been mild and infrequent in clinical trials with boceprevir, and the likely benefit of boceprevir in preventing liver abnormalities in HCV infected patients, the risk of adverse liver-related effects in humans appear to be of limited concern.

Testicular toxicity:

Testicular toxicity was observed at doses ≥50 mg/kg ($AUC_{0\text{-}24\ hr}$ =18 μg·hr/ml at 1d & 9.2 μg·hr/ml at 24d from Study # 5023) in male rat studies at boceprevir exposures less than those in humans at the recommended dose of 800 mg TID. The NOAEL was determined to be 15 mg/kg in the rat 6-month repeat-dose study, resulting in boceprevir exposures much lower than those in humans at the recommended dose. Signs of reversibility of testicular toxicity were observed in a 3-month study (Study # 4124) following a 2-month treatment-free (*i.e.*, recovery) period. Findings generally consisted of small epididymides, small testes and/or soft testes correlating with lower epididymidis, prostate and testis weights. In the epididymides, findings were luminal cellular debris and/or hypospermia. In the testes, findings were sloughed spermatids, Sertoli cell vacuolation, degeneration of spermatocytes and spermatids, depletion of spermatocytes and spermatids, spermatid retention, atrophy of seminiferous tubules and/or debris. In a 1-month investigative study, dose- and time-dependent histopathological findings were present in the epididymides and testes of rats beginning

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by 4 days after initiation of dosing. The sequence of occurrence of these findings suggested initiation of testicular toxicity on the first dose and continual progression of SCH 503034-induced toxicity following daily dosing. Testicular findings were not associated with alterations in FSH, LH or testosterone. Additionally, no antagonistic activity towards the androgen receptor was demonstrated in transfected CHO cells at up to ~5 μM concentrations of boceprevir. The earliest signs of testicular toxicity were germ cell sloughing and Sertoli cell vacuolation, while there appeared to be an absence of targeting of a specific germ cell population, as would typically occur with a germ cell toxicant. Although this study cannot totally exclude the possibility of direct test-article effects on germ cell maturation, the Sertoli cell appears to be the primary target of toxicity.

Testicular toxicity was not observed in mice or in immature and sexually mature cynomolgus monkeys administered boceprevir for 3 months at doses of up to 900 or 1000 mg/kg, respectively. At these doses, boceprevir AUC exposures are ~7- and 4-fold higher in mice and monkeys, respectively, than those in humans at the recommended dose of 800 mg TID. In addition, limited analysis of inhibin B and semen were evaluated clinically without any apparent adverse effects. Thus testicular toxicity, which is associated with male fertility effects, may be limited to rats.

Testicular toxicity has also been observed in mice and Wistar rats administered ribavirin. Although ribavirin did not exacerbate the testicular toxicity observed in boceprevir treated rats when administered in combination, the Sprague-Dawley rats used in this study also did not show signs of testicular toxicity when ribavirin was administered alone (Study # 4124). So this may not be the ideal strain of rats to study potential testicular effects of the combination of boceprevir and ribavirin. Since ribavirin is known to have effects on functional sperm parameters in human patients, the potential of additive effects of combination treatment of boceprevir and ribavirin on germ cell function in humans cannot be totally ruled out.

Other toxicities:

In cynomolgus monkeys administered boceprevir, the NOEL is 25 mg/kg based on increases in cholesterol and activated partial thromboplastin time (APTT) observed at doses ≥75 mg/kg, while the NOAEL was considered to be 200 mg/kg ($AUC_{0\text{-}24\ hr}$ = 26.4 μg·h/ml at 83d), providing a ~1.6-fold monkey to human AUC exposure multiple. Increases in cholesterol were minimal to mild, did not progress with increasing duration of SCH 503034 exposure and were not considered adverse. The mechanism for these consistent cholesterol increases was not apparent.

Mild to moderately higher APTT was observed in animals administered doses of ≥75 mg/kg. These increases appeared to be highly dependent on the particular APTT reagent/detection instrument combinations with clear increases in APTT only observed with optical detection methods. No changes in prothrombin time were evident. Additionally, there were no test article-related effects on intrinsic and contact factor coagulant activities. Since increases in APTT have not been observed clinically, impairment of hemostasis through the intrinsic coagulation cascade does not appear to be of clinical concern.

Decreases in red blood cell count, hemoglobin and hematocrit were observed in cynomolgus monkeys administered doses ≥300 mg/kg ($AUC_{0\text{-}24\ hr}$ = 32.3 μg·h/ml at 84d)

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at a ~1.9-fold monkey to human AUC exposure multiple. These values were reduced 8 to 10% relative to control values at boceprevir dose levels from 300 to 1000 mg/kg and were associated with mild (40 to ~100%) increases in reticulocytes. These minor effects did not progress over the duration of the study and are not considered to be adverse. Although the mechanism is uncertain, this mild anemia may be due to transient bone marrow suppression since no acute boceprevir-related effects have been observed on the osmotic fragility of red blood cells. The regenerative response, detected by 5 weeks of dosing, likely prevented any exacerbation of the effects upon longer drug exposure durations. Humans may be slightly more sensitive to boceprevir-induced reductions in red blood cell count than monkeys given the reductions observed clinically when boceprevir is given in combination with ribavirin and peginterferon-alpha.

Reproductive and Developmental Toxicology:

In female rats administered boceprevir, the NOEL is ≥150 mg/kg for maternal toxicity and mating and 75 mg/kg for fertility and early embryo developmental toxicity. The rat to human AUC exposure multiple at this 75 mg/kg dose level was estimated to be ~1.4-fold. Since TK was not performed in the pivotal female fertility study, exposures at the 75 mg/kg dose level were estimated based on TK data from other studies (Study # 04032, 01290, 01299 & 10080). The data from these studies revealed a great deal of variability in AUC values at this dose level resulting in exposure multiples that may range from ~1 up to 2.2. At a 150 mg/kg dose, a slight increase in pre-implantation loss and a significant increase in post-implantation loss were observed without significant effects on mating and fertility indices. At a 250 mg/kg dose, female fertility was reduced and uterine reproductive parameters were affected adversely. However, female fertility and uterine reproductive parameters were unaffected following a 4-week recovery period, indicating that the effect on female fertility at 250 mg/kg dose is reversible. No agonistic activity towards the estrogen receptor alpha was demonstrated in transfected CHO cells at up to ~5 μM concentrations of boceprevir. Additionally, serum hormone levels (LH, FSH, progesterone and estradiol) were not affected at the 250 mg/kg dose when administered from gestation day 0 to 7, making it unlikely that the affect on female fertility is due to hormonal disruptions.

In male rats administered boceprevir, the NOEL for paternal toxicity, fertility and reproductive and early embryonic developmental toxicity is 75 mg/kg. The mating index was not affected, but the fertility index was reduced at the 150 mg/kg dose level. The effect on male fertility was due to testicular toxicity and was observed at a 75 mg/kg dose in the 6 month repeat-dose toxicology study (see “Testicular toxicity” summary).

In rats, the NOEL for maternal toxicity is <150 mg/kg, based on reduction in gestational body weight gain, and for embryo-fetal toxicity is ≥600 mg/kg ($AUC_{0\text{-}24\ hr}$ = 170 μg·h/ml at 17d). Although TK was not performed in this study, exposures at the 600 mg/kg dose level can be reasonably inferred from a TK study in pregnant rats (Study # 08259) and are included above. In rabbits, the NOEL for maternal toxicity is <50 mg/kg, based on reduction in food consumption and fecal output warranting euthanasia in some animals, and for embryo-fetal toxicity is ≥300 mg/kg ($AUC_{0\text{-}24\ hr}$ = 32.8 μg·h/ml at 19d). Thus, no adverse findings regarding embryo-fetal development or teratogenicity were observed in rats and rabbits at dose levels that produced maternal toxicity and boceprevir AUC exposures ~10- and 2-fold higher, respectively, than those in humans

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at the recommended dose of 800 mg TID. However, since the presence of the main human metabolite (SCH 629144) has not been demonstrated in rabbits and is at only very low levels in rats, it is unclear whether the safety of SCH 629144 to the developing fetus has been evaluated adequately. Currently, this is not of clinical safety concern given that boceprevir must be administered in combination with peginterferon alpha, which is abortifacient, and ribavirin, which is teratogenic and embryocidal.

Regarding prenatal and postnatal development in rats administered boceprevir, the NOAEL for the F0, F1 and F2 generations was ≥150 mg/kg ($AUC_{0\text{-}24\ hr}$ = 110 μg·h/ml at 17d). Although TK was not performed in this study, exposures at the 150 mg/kg dose level can be reasonably inferred from a TK study in pregnant rats (Study # 08259) and are included above. No test article-related effects on pregnancy, parturition and lactation of maternal animals (F0) or on the growth, viability, development or reproductive performance of the F1 generation, or survivability of the F2 generation were reported at boceprevir AUC exposures 6.5-fold higher than those in humans at the recommended dose of 800 mg TID.

Neonatal/Juvenile Toxicology:

In a 3 month repeat-dose study with dosing initiated in PND 7 rat pups, the NOAEL is 25 mg/kg ($AUC_{0\text{-}24\ hr}$ = 3.0 μg·h/ml at 21d) due primarily to adverse testicular and thyroid findings at doses ≥ 75 mg/kg. Testicular findings were consistent with respect to incidence and severity as those described previously in adult rats. However, minimal follicular hyperplasia of the thyroid, although not present following the post-dose period, has not been observed in adult animals. Additionally, femur length was reduced up to 3.3%. The sponsor theorized that the thyroid findings may result from an indirect effect due to induction of liver enzymes (UGT1A1/6 & UGT2B2) that increase thyroid hormone clearance thereby resulting in increased production of TSH that ultimately leads to follicular hyperplasia. It is thought that rats may be more sensitive than humans to liver enzyme induction and thus the follicular hyperplasia observed would be less of a concern for administering SCH 503034 to the pediatric human population. Although it is possible that reduced thyroid hormone exposure could cause these reductions in longitudinal bone growth, they are more likely the result of a secondary effect due to body weight gain reductions. In addition, although a small tendency for liver enzyme induction (in the absence of clear thyroid hormone changes) was observed in an investigative study in neonatal/juvenile rats, clear evidence to support the sponsor's theory is lacking. Nonetheless, further nonclinical thyroid toxicity assessment is not necessary, since the effect seen is minor and reversible, and because thyroid function will be monitored in pediatric clinical trials given that boceprevir is given in combination with ribavirin and peginterferon-alpha that already has measureable effects on thyroid function in this population.

Genetic Toxicology and Carcinogenicity:

Boceprevir was not mutagenic or clastogenic as tested in the Ames assay, the *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes and the *in vivo* mouse micronucleus assay. Additionally, two-year mouse and rat carcinogenicity studies were performed with boceprevir. Mice were administered doses of up to 500 mg/kg in males and 650 mg/kg in females, while rats were administered doses of

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up to 125 mg/kg in males and 100 mg/kg in females. Mice and rats were negative for drug-related neoplasms at boceprevir AUC exposures either similar to (rats) or ~2 to 6-fold greater (for male and female mice, respectively) than those in humans at the recommended dose of 800 mg TID. The dose levels examined were consistent with recommendations of the executive Carcinogenicity Assessment Committee with the high dose based on an MTD. Additionally, excessive mortality did not occur during the 24-month dosing period.

The main human metabolite (SCH 629144) is present at only very low amounts in rats. Thus, carcinogenicity and mutagenicity (via metabolic activation in Ames assay with the S9 fraction from rat) of this metabolite could not be evaluated well in rats. However, this metabolite is present at clinically relevant amounts in mice, so the carcinogenicity of this metabolite was evaluated adequately.

Impurity/Degradant Qualification:

Bacterial mutagenicity assays, chromosomal aberration assays using human peripheral blood lymphocytes and 1-month repeat-dose toxicology studies in rats were performed using batches containing high levels of impurities or degradants. All batches tested were negative for mutagenicity and clastogenicity and there was no indication that impurities or degradants altered the toxicity profile of boceprevir. Given these results, the seriousness of the disease to be treated, the fact that boceprevir will be given in combination with ribavirin and peginterferon-alpha and since no structural alerts have been identified, evaluation of these impurities/degradants appears acceptable.

Combination Toxicology (with ribavirin and PEG-intron):

Boceprevir did not exacerbate the hematological toxicity of ribavirin and PEG-intron in monkeys at boceprevir AUC exposures ~1.6-fold greater than clinical exposures attained in patients receiving boceprevir (800 mg TID). This study was not capable of measuring subtle additive effects of combination drug treatment on hematology parameters due to: the limited number of animals used, the limited duration of the study (1-month) and since higher doses of ribavirin were not evaluated. Therefore, it is not surprising that the additive hematological effects of boceprevir when given in combination with ribavirin and peginterferon-alpha, as has been detected after 6 weeks of combination treatment in clinical trials, were not observed in this study.

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Table 27: Summary of Systemic Exposure Multiples for Boceprevir Toxicology Studies

Species	Study Type/Duration	Dose (mg/kg)	Exposure Multiple Based on SCH 503034 AUC*	Exposure Multiple Based on SCH 629144 AUC^
Mouse	3-month	250 (NOAEL)	0.6 (♂), 1.7 (♀)	NA
	carcinogenicity	500(♂), 650(♀)	2.3 (♂), 5.8 (♀)	NA (♂), 0.8 (♀)
Rat	6-month	15(♂), 75(♀) (NOAEL)	<0.1 (♂), 1.9 (♀)	NA
	carcinogenicity	125(♂), 100(♀)	0.8 (♂), 0.7 (♀)	<0.1 (♂), NA (♀)
Rat (pregnant)	PPND	150 (NOAEL)	6.5	NA
	EFD	600 (NOEL)	10.1	NA
Rabbit (pregnant)	EFD	300 (NOEL)	1.9	NA
Cynomolgus monkey	3-month	300 (LOAEL)	1.9	3.0
	12-month	200 (NOAEL)	1.6	NA

*AUC in human: 16,900 ng.hr/ml at 800 mg TID; ^AUC in human: 76,000 ng.hr/ml at 800 mg TID; NA= not applicable

12 Appendix/Attachments

12.1 Carcinogenicity Studies

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

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number: IND#69,027

Supporting document/s: Rat – SDN#349

Mouse – SDN#367

Sponsor's letter date: Rat – September 10, 2009

Reference ID: 2933010

	Mouse – December 7, 2009
CDER stamp date:	Rat – September 10, 2009
	Mouse – December 7, 2009
Product:	Boceprevir (SCH503034)
Indication:	HCV
Sponsor:	Schering Corporation
Review Division:	DAVP
Reviewer:	Mark W. Powley, Ph.D.
Supervisor/Team Leader:	Hanan Ghantous, Ph.D.
Division Director:	Debra B. Birnkrant, M.D.
Project Manager:	Myung-Joo Patricia Hong, M.S.

Template Version: December 7, 2009

Reference ID: 2933010

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1 Executive Summary

1.1 Brief Discussion of Nonclinical Findings

Carcinogenicity: *Based on criteria for common tumors (i.e., p-value ≤ 0.005 for trend-test and p-value ≤ 0.01 for pair-wise comparison), there were no SCH503034-related neoplastic lesions in rat or mouse.*

Other:

Rat - *Drug-related effects included decreased body weight parameters as well as changes in pathology. Testicular effects were noted during both macroscopic evaluation (small; altered texture) and microscopic evaluation (atrophy; degeneration, seminiferous tubule). Macroscopic changes in epididymides (small) correlated with microscopic lesions (hypospermia; cellular debris, luminal). Additional non-neoplastic histopathological lesions were observed in liver (multinucleated hepatocytes, multifocal). Similar SCH503034-related effects were observed in the 6-month toxicity study.*

Mouse - *Drug-related effects were limited to gross changes in the gallbladder (dark material) and microscopic lesions in the liver (single cell necrosis, focal/multifocal; pigment accumulation, macrophage). The liver was previously identified as a target organ in the 3-month range-finding study.*

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

394730-60-0

2.1.2 Generic Name

boceprevir

2.1.3 Code Name

SCH 503034

2.1.4 Chemical Name

(1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide

2.1.5 Molecular Formula/Molecular Weight

C27H45N5O5/519.7

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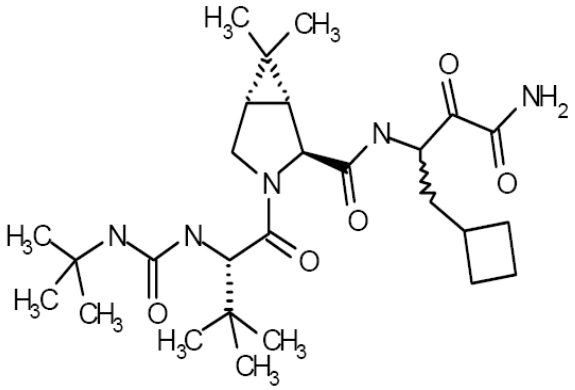
2.1.6 Structure



2.1.7 Pharmacologic class

NS3 protease inhibitor

3 Studies Submitted

3.1 Studies Reviewed

Carcinogenicity

Study no. 1304:	24-Month Carcinogenicity Study of SCH 503034 in Rats
Study no. 1305:	A 104-Week Oral Gavage Carcinogenicity Study in the Albino Mouse

4 Carcinogenicity

Study title: Study no. 1304: 24-Month Carcinogenicity Study of SCH 503034 in Rats

Study no.:	1304
Study report location:	electronic
Conducting laboratory and location:	Schering-Plough Research Institute (Lafayette, NJ)
Date of study initiation:	March 2, 2006
GLP compliance:	yes
QA statement:	included
Drug, lot #, and % purity:	SCH 503034, lot 05-503034-Y-110B, purity 94.6%
CAC concurrence	November 30, 2010

Key Study Findings: *An evaluation of mortality, clinical signs, body weights, food consumption, ophthalmoscopy, gross pathology, histopathology (i.e., neoplastic and non-neoplastic lesions), and toxicokinetics was conducted in Sprague-Dawley rats administered oral doses of 20, 50, and 100/125 mg/kg/day for 24 months (vehicle/control: 0.4% aqueous methylcellulose). Decreased body weight and body weight gain were observed in males at doses ≥ 50 mg/kg/day and females at 100 mg/kg/day. There were macroscopic changes in testes (small; altered texture) correlating with microscopic lesions (atrophy; degeneration, seminiferous tubule) at doses ≥ 50 mg/kg/day. Macroscopic effects in epididymides (small) were associated with microscopic lesions (hypospermia; cellular debris, luminal) at 125 mg/kg/day. Additional non-neoplastic histopathological lesions were limited to liver (multinucleated hepatocytes, multifocal) in males*

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and females at doses ≥ 50 mg/kg/day. Systemic exposure was confirmed on Days 22 and 164. $AUC_{0\text{-}24\ hr}$ and C_{max} values were slightly higher in females for the 20 and 50 mg/kg/day dose groups but were similar between sexes at the highest dose levels.

Adequacy of Carcinogenicity Study: *Overall, this was an adequate study. The dose-levels were consistent with recommendations of exec-CAC with a high dose based on MTD (i.e., >10% decrease in body weight gain at 125 mg/kg/day for both sexes in 6-month study; mortality at 200 mg/kg/day for females in 3-month study). Excessive mortality did not occur during the 24-months of dosing. $AUC_{0\text{-}24\ hr}$ values on Day 22 were between 0.7- and 0.8-fold of clinical exposure.*

Appropriateness of Test Model: *SCH503034 is extensively metabolized in humans with SCH629144 accounting for a majority of circulating drug-related material. In male rats administered 100 mg/kg/day of SCH503034 (separate study), systemic exposure to the major metabolite was only ~2.5% of that observed clinically. Therefore, while the rat is an appropriate model for evaluating the carcinogenicity of SCH503034, this is not the case for SCH629144.*

Evaluation of Tumor Findings: *Based on criteria for common tumors (i.e., p-value ≤ 0.005 for trend-test and p-value ≤ 0.01 for pair-wise comparison), there were no drug-related tumors in male or female rats.*

Reference ID: 2933010

Methods

Doses:

24-Month Carcinogenicity Study of SCH 503034 in Rats (SN 01304): **Study Design**

Group	Test/Control Article	No. of Rats/Sex		Total Daily Dose (mg/kg)		Dose Volume (mL/kg)	Dose Conc. (mg/mL)		Duration of Dosing (Weeks)
		Toxicity Portion	Satellite Portion[a]	Male	Female		Male	Female	
C1	Control (Methylcellulose)	50	9	0	0	5	0	0	104-106
C2	Control (Methylcellulose)	50	0	0	0	5	0	0	104-106
T1	Low-Dose (SCH 503034)	50	9	20	20	5	4	4	104-106
T2	Mid-Dose (SCH 503034)	50	9	50	50	5	10	10	104-106
T3	High-Dose (SCH 503034)	50	9	125	100	5	25	20	104-106

a: These animals were designated for toxicokinetic and/or plasma concentration analysis only.

Frequency of dosing: 1x daily
Route of administration: oral
Formulation/Vehicle: 0.4% (w/v) aqueous methylcellulose
Species/Strain: rat/Crl:CD®(SD) VAF/Plus® (b) (4)
Age at study start: 6 weeks
Weight at study start: males - 151.8 to 198.2 g
females – 128.3 to 169.1 g
Animal housing: individually housed in stainless-steel cages
Dual control 0.4% methylcellulose
Dietary Restriction: Certified Rodent LabDiet® 5002
males – 21 g/day
females – 17 g/day
Interim sacrifice: none
Deviations from study protocol: do not affect the quality of the study

Observations and Results

Mortality: Checked 1x daily.

No drug-related effects. There was a statistically significant decrease in mortality for 100 mg/kg/day females; however, this is not adverse. See summary table and figures below (figures taken from Sponsor report).

Table 28. Survival in rat

	Males				Females			
	Control ½	20 mg/kg	50 mg/kg	125 mg/kg	Control 1/2	20 mg/kg	50 mg/kg	100 mg/kg
% survival to scheduled sacrifice	54/62%	60%	54%	50%	36/42%	48%	44%	58%

Reference ID: 2933010

Figure 2. Survival in male rat

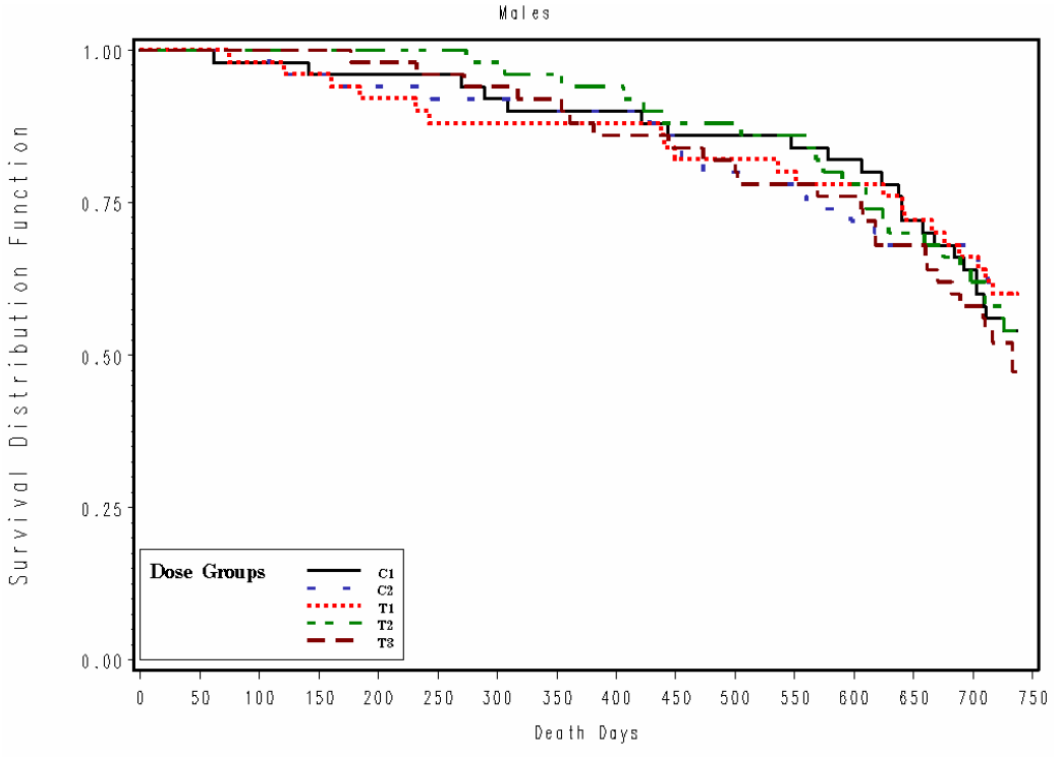
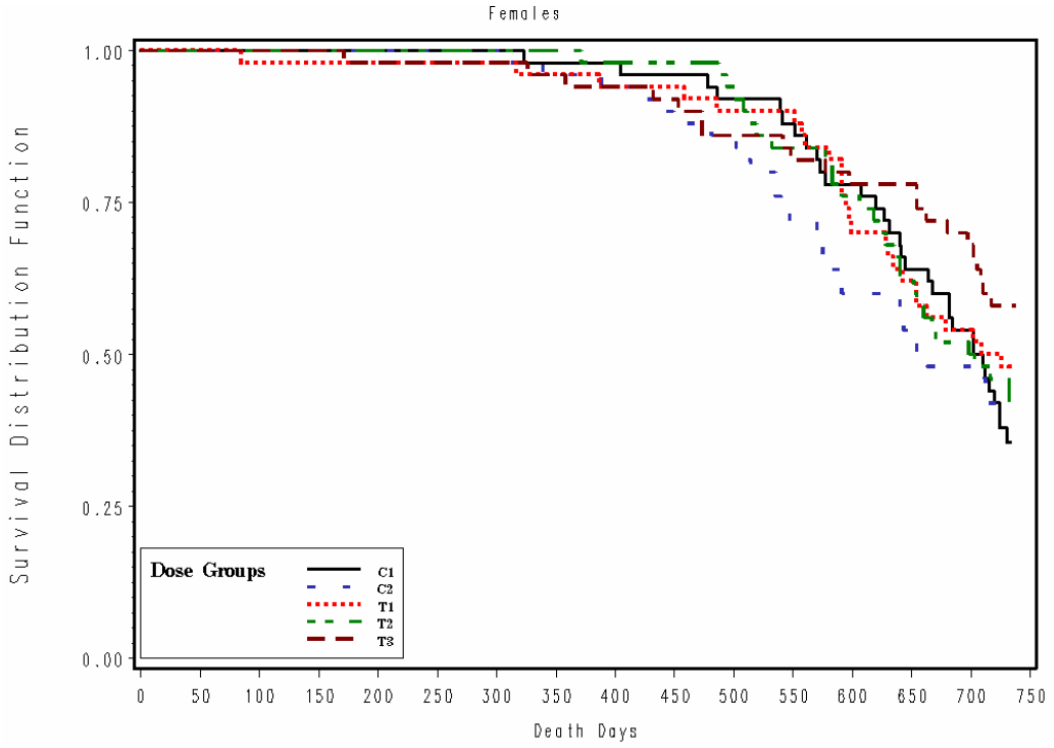


Figure 3. Survival in female rat



Clinical Signs: Checked 1x daily.

No drug-related effects in regards to both clinical signs and palpable masses. An apparent dose-related increase in the incidence of convulsions was noted in both male and female rats. The Sponsor indicates that convulsions are likely due to stress from repeat handling and are a common background finding in multiple strains of rat. Convulsions were not observed in 3-month and 6-month studies for doses ≥ those evaluated in the current study. Also, the timing of the convulsion did not correlate with T_{max}. Taking into account the totality of information, this effect seems unlikely related to SCH503034.

Body Weights: 1x weekly pre-test through Week 24, 1x every 2 weeks from Week 25 to 36, and every 4 weeks thereafter.

High dose males and females had decreased body weight and body weight gain (-4 to -6%) starting in Week 52. At the terminal necropsy decreased body weight parameters were noted in males at 50 and 125 mg/kg/day (-6 to -10%) and females at 100 mg/kg/day (-6 to -8%).

Food Consumption: 1x weekly pre-test through Week 24, 1x every 2 weeks from Week 25 to 36, and every 4 weeks thereafter.

No drug-related effects.

Ophthalmoscopy: Checked pre-test, Week 52, and Week 103.

No drug-related effects.

Gross Pathology

Macroscopic changes occurred in testes (small; altered texture) at doses ≥ 50 mg/kg/day and epididymides (small) at 125 mg/kg/day. The summary table below was taken from the Sponsor report.

Table 29. Macroscopic lesions in rat

Principal Necropsy Findings: Males										
	Survivors					Decedents				
Dose (mg/kg):	0	0	20	50	125	0	0	20	50	125
Organ/Finding	Incidence[a]									
Testes	(27)[b]	(31)	(30)	(27)	(25)	(23)	(19)	(20)	(23)	(25)
- small (soft)[c]	1	0	1	1*	3*	0	1	0	2*	3*
- altered texture (soft[d])	0	0	0	0	1*	0	0	0	0	0
Epididymides	(27)	(31)	(30)	(27)	(25)	(23)	(19)	(20)	(23)	(25)
- small	1	0	0	0	0	0	0	0	0	2*

* = Test article-related
a: Incidence = Number affected.
b: ( ) = Number examined.
c: Includes macroscopic findings of "small" and "small, soft."
d: Texture characterized as "soft" in the individual animal data.

Histopathology: Recorded at each scheduled sacrifice (see tissue list at end of review).

Adequate Battery: *yes*

Peer Review: *listed in protocol but not shown in report*

Neoplastic Findings: *No drug-related effects. The Sponsor's evaluation found no increase in any tumor type. However, the FDA analysis detected a statistically significant trend for thyroid gland follicular cell adenoma in high dose males (p-value = 0.013). A statistically significant difference, based on pair-wise comparison, was also found between combined control and high dose males (p-value = 0.032). Data for tumors with p-values ≤ 0.05 is summarized below (table taken from statistics review).*

Table 30. FDA statistical analysis of tumors in rat

	Organ Name	Tumor Name	combined control	Low	Med	High	P_Value Dos Resp	P_Value C vs L	P_Value C vs M	P_Value C vs H
Male	ADRENAL GLANDS	CORTICAL-CELL ADENOM	1	0	0	3	0 023	0 333	0 339	0 097
		PHEOCHROMOCYTOMA [B]	7	6	10	5	0 239	0 230	0 024	0 347
	THYROID GLAND	FOLLICULAR CELL ADEN	0	1	1	3	0 013	0 333	0 339	0 032
	THYROID_GLAND	FOLL_CARCINOMA+PAPIL	1	1	1	3	0 042	0 558	0 565	0 097

Based on 0% incidence of this tumor in concurrent controls, the FDA analysis used rare tumor criteria to determine statistical significance (i.e., p-value ≤ 0.025 for trend-test and p ≤ 0.05 for pair-wise comparison). In contrast, the Sponsor considered all tumors to be common and applied appropriate statistical criteria (i.e., p-value ≤ 0.005 for trend-test). Historical control incidence for thyroid follicular cell adenoma in the Sponsor's facility was 0.74% for all carcinogenicity studies conducted in the last 10 years and 1.34% when matched by diet and vehicle. Additional historical data from Merck Research Laboratories, (b) (4), and Registry of Industrial Toxicology Animal-data indicates that this tumor occurs at an incidence ≥ 1% in Sprague-Dawley rats. Using criteria for common tumors, the incidence of thyroid follicular cell adenoma does not achieve statistical significance.

See statistical review for additional details.

Non-Neoplastic Findings: *SCH505034-related lesions were observed in testis (atrophy; degeneration, seminiferous tubule), epididymides (hypospermia; cellular debris, luminal), and liver (multinucleated hepatocytes, multifocal). Findings in testes and epididymides correlated with gross observations. The summary table below was constructed from the Sponsor report.*

Reference ID: 2933010

Table 31. Non-neoplastic lesions in rat

Principal Non-Neoplastic Findings According to Tissue or Organ of Origin										
Sex:	Males					Females				
Dose (mg/kg):	0	0	20	50	125	0	0	20	50	100
Organ/Finding/Severity	Incidence[a]									
Testes	(50)[b]	(50)	(50)	(50)	(50)					
- atrophy[c]										
mild		1								
severe	3	2		1*	6*					
- degeneration, seminiferous tubule[c]										
minimal	2	3	2	9*	14*					
mild			2	3*	10*					
moderate		1	1	1*	7*					
severe		1		2*	1*					
Epididymides	(50)	(50)	(50)	(50)	(50)					
- hypospermia[c]										
minimal		1		2*	1*					
mild			3	1*	10*					
moderate			1	2*	4*					
severe	3	4		1*	8*					
- cellular debris, luminal										
minimal		2	2	15*	18*					
mild			4	3*	12*					
moderate					2*					
Liver	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- multinucleated hepatocytes, multifocal										
minimal				1*	5*	2	2	2	4*	8*
mild					1*					

* = Test article-related

a: Incidence = Number affected. The absence of a numeral indicates that the specified finding was not present in that group.

b: ( ) = Number examined.

c: Most control group males with histopathologic findings of the testes or epididymides graded > minimal were affected unilaterally.

Toxicokinetics: Blood was collected via jugular vein or abdominal aorta on Days 22 (drug-treated groups: 0.5, 2, 4, 8, 12, and 24 hr; control group: 0.5, 2, and 4 hr) and 164 (control and drug-treated groups: 0.5, 2, and 4 hr). Plasma concentrations of SCH503034 and SCH534128, were determined by LC-MS/MS. SCH534129 concentrations were determined by subtracting SC534128 from SCH503034 concentrations. Note that SCH503034 is a mixture of stereoisomers (SCH534128 and SCH534129).

Toxicokinetic profiles were similar for SCH503034, SCH534128, and SCH534129. Although the differences were not substantial, females had up to 2-fold greater systemic exposure for SCH503034 compared to males at 20 and 50 mg/kg/day. Exposures were similar between sexes at the highest dose levels. SCH503034 appeared rapidly in plasma followed by rapid elimination. Based on a limited subset of timepoints, mean plasma concentrations were generally higher on Day 164 compared to Day 22. However, the range of concentrations did not appear

substantially different and data confirms exposure in the later sampling period. Overall, $AUC_{0-24\ hr}$ and C_{max} values increased in a greater than dose-proportional manner across the dose range. Control contamination was not detected. The summary tables below were taken from the Sponsor report.

Table 32. Toxicokinetic data in rat

SCH 503034 Toxicokinetic Parameters on Day 22 Following Oral (Gavage) Administration of 20, 50 or 125 mg/kg SCH 503034 to Male Rats and 20, 50 or 100 mg/kg SCH 503034 to Female Rats

Group	SCH 503034 Dose (mg/kg)	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	F:M[a]
T1	20	Female	572	2.00	8.00	1430	1450	1.94
		Male	273	2.00	8.00	738	747	NA[b]
T2	50	Female	1410	2.00	12.00	4000	4240	1.58
		Male	1350	0.59	12.00	2590	2680	NA
T3F	100	Female	4390	0.50	12.00	11800	12200	NA
T3M	125	Male	4430	2.00	24.00	13200	13200	NA

a: Female:Male = $AUC(0\text{-}24\ hr)_{Female} \div AUC(0\text{-}24\ hr)_{Male}$
b: NA = Not applicable

SCH 534128 Toxicokinetic Parameters on Day 22 Following Oral (Gavage) Administration of 20, 50 or 125 mg/kg SCH 503034 to Male Rats and 20, 50 or 100 mg/kg SCH 503034 to Female Rats

Group	SCH 503034 Dose (mg/kg)	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	F:M[a]	SCH 534128: SCH 534129[b]
T1	20	Female	338	2.00	8.00	835	845	1.93	1.39
		Male	164	2.00	8.00	433	439	NA[c]	1.43
T2	50	Female	662	2.00	12.00	3080	3210	2.05	1.75
		Male	801	0.59	12.00	1510	1560	NA	1.39
T3F	100	Female	2430	0.50	12.00	7200	7500	NA	1.34
T3M	125	Male	3070	0.50	24.00	7850	7850	NA	1.18

a: Female:Male = $AUC(0\text{-}24\ hr)_{Female} \div AUC(0\text{-}24\ hr)_{Male}$
b: SCH 534128:SCH 534129 = $AUC(0\text{-}24\ hr)_{SCH\ 534128} \div AUC(0\text{-}24\ hr)_{SCH\ 534129}$
c: NA = Not applicable

SCH 534129 Toxicokinetic Parameters on Day 22 Following Oral (Gavage) Administration of 20, 50 or 125 mg/kg SCH 503034 to Male Rats and 20, 50 or 100 mg/kg SCH 503034 to Female Rats

Group	SCH 503034 Dose (mg/kg)	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	F:M[a]
T1	20	Female	234	2.00	8.00	599	606	1.97
		Male	109	2.00	8.00	304	308	NA[b]
T2	50	Female	527	2.00	12.00	1720	1830	1.63
		Male	551	0.59	12.00	1080	1120	NA
T3F	100	Female	1960	0.50	12.00	5410	5580	NA
T3M	125	Male	2270	0.50	24.00	6630	6630	NA

a: Female:Male = $AUC(0\text{-}24\ hr)_{Female} \div AUC(0\text{-}24\ hr)_{Male}$
b: NA = Not applicable

Stability: Dose formulation concentration and/or homogeneity were evaluated throughout the study.

Concentration measurements were within ± 15% of expected through Week 96. However, Week 100 samples were 54.5 to 74.5% of expected nominal concentration (corrected for purity). Analysis of back-up samples confirmed that concentrations were not in the acceptable ranges. This appears to be an isolated event and is unlikely to substantially impact on the study. Homogeneity analysis was within the acceptable range for all formulations sampled in Week 1.

Reference ID: 2933010

Study title: Study no. 1305: A 104-Week Oral Gavage Carcinogenicity Study in the Albino Mouse

Study no.:	1305
Study report location:	electronic
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 22, 2006
GLP compliance:	yes
QA statement:	included
Drug, lot #, and % purity:	SCH 503034, lot 05-503034-Y-110A, purity 97.2%
CAC concurrence	November 30, 2010

Key Study Findings: *An evaluation of mortality, clinical signs, body weights, food consumption, ophthalmoscopy, gross pathology, histopathology (i.e., neoplastic and non-neoplastic lesions), and toxicokinetics was conducted in CD-1 mice administered oral doses of 100, 250, and 500/650 mg/kg/day for 104 weeks (vehicle/control: 0.4% aqueous methylcellulose). Macroscopic changes were observed in the gallbladder (dark material) at all dose levels. Histopathological lesions were noted in the liver (single cell necrosis, focal/multifocal; pigment accumulation, macrophage). Single cell necrosis was limited to high dose animals while pigment accumulation occurred at 250 and 500 mg/kg/day in males and 650 mg/kg/day in females. Systemic exposure was confirmed on Day 27 and in Week 24. For comparable doses,* $AUC_{0\text{-}24\ hr}$ *and* C_{max} *values were slightly higher in females compared to males.*

Adequacy of Carcinogenicity Study: *Overall, this was an adequate study. The dose-levels were consistent with recommendations of exec-CAC with a high dose based on MTD (i.e., 1/3rd lethal dose of 2000 mg/kg/day in 2-week study). Excessive mortality was not observed during the 104 weeks of dosing.* $AUC_{0\text{-}24\ hr}$ *values on Day 27 were between 2.2- and 5.8-fold of clinical exposure.*

Appropriateness of Test Model: *SCH503034 is extensively metabolized in humans with SCH629144 accounting for a majority of circulating drug-related material. In female mice administered 600 mg/kg/day of SCH503034 (separate study), systemic exposure to the major metabolite was 0.8-fold of that observed clinically. Therefore, the mouse is an appropriate model for evaluating the carcinogenicity of both SCH503034 and SCH629144.*

Evaluation of Tumor Findings: *Based on criteria for common tumors (i.e., p-value ≤ 0.005 for trend-test and p-value ≤ 0.01 for pair-wise comparison), there were no drug-related tumors in male or female mice.*

Reference ID: 2933010

Methods

Doses:

SCH 503034 A 104 Week Oral Gavage Carcinogenicity Study in the Albino Mouse (SPRI 01305):
Study Design

Group	Dose (mg/kg/day)	Dose Concentration (mg/mL)	Number of Mice[a]			
			Main Study		Toxicokinetic Study[b]	
			Males	Females	Males	Females
1/ Control (Methylcellulose)	0	0	1001-1050	1501-1550	1051-1067; 1069	1551-1568
2/ Control (Methylcellulose)	0	0	2001-2050	2501-2550	NA	NA
3. SCH 503034	100	10	3001-3050	3501-3550	3051-3058; 3060-3078	3551-3561; 3563-3578
4/ SCH 503034	250	25	4001-4050	4501-4550	4051-4077	4551-4559; 4561-4578
5/ SCH 503034	500	50	5001-5050	NA	5051-5077	NA
6/ SCH 503034	650	65	NA	6501-6550	NA	6551-6577
7/ Health Screen[c]	-	-	7001-7036	7501-7536	NA	NA

NA: Not Applicable
Dose volume: 10 mL/kg
a: Up until the end of the replacement period, the following replacement were performed:
Animal No. 3059 was replaced by spare Animal No. 364 to become Animal No. 3078
Animal No. 1068 was replaced by spare Animal No. 68 to become Animal No. 1069
Animal No. 4560 was replaced by spare Animal No. 469 to become Animal No. 4578
Animal No. 3562 was replaced by spare Animal No. 514 to become Animal No. 3578.
b: Toxicokinetic animals were used for toxicokinetic evaluation only.
c: Health screen animals were used for health screen and serology evaluations during the predose period and every 3 months thereafter.

Frequency of dosing: 1x daily
Route of administration: oral
Formulation/Vehicle: 0.4% (w/v) aqueous methylcellulose (protected from light)
Species/Strain: mouse/Crl:CD1[ICR] VAF/Plus (b) (4)
Age at study start: 6 weeks
Weight at study start: males – 24.9 to 34.6 g
females – 19.2 to 27.9 g
Animal housing: individually housed in stainless-steel, wire-mesh bottomed cages
Dual control 0.4% methylcellulose
Dietary Restriction: Certified Rodent Laboratory Meal 5002
males – ad libitum
females – ad libitum
Interim sacrifice: none
Deviations from study protocol: do not affect the quality of the study

Observations and Results

Mortality: Checked 2x daily.

No drug related effects. The summary table and figures below were taken from the Sponsor report.

Reference ID: 2933010

Table 33. Survival in mouse

Mortality/Survival Data				
Group	Males		Females	
	Mortality	Survival	Mortality	Survival
1	22/50	56%	33/50	34%
2	30/50	40%	35/50	30%
3	23/50	54%	26/50	48%
4	25/50	50%	28/50	44%
5/6	33/50	34%	27/50	46%
Note: The values presented include animals that were found dead after the 104-week dosing period.				

Figure 4. Survival in male mouse

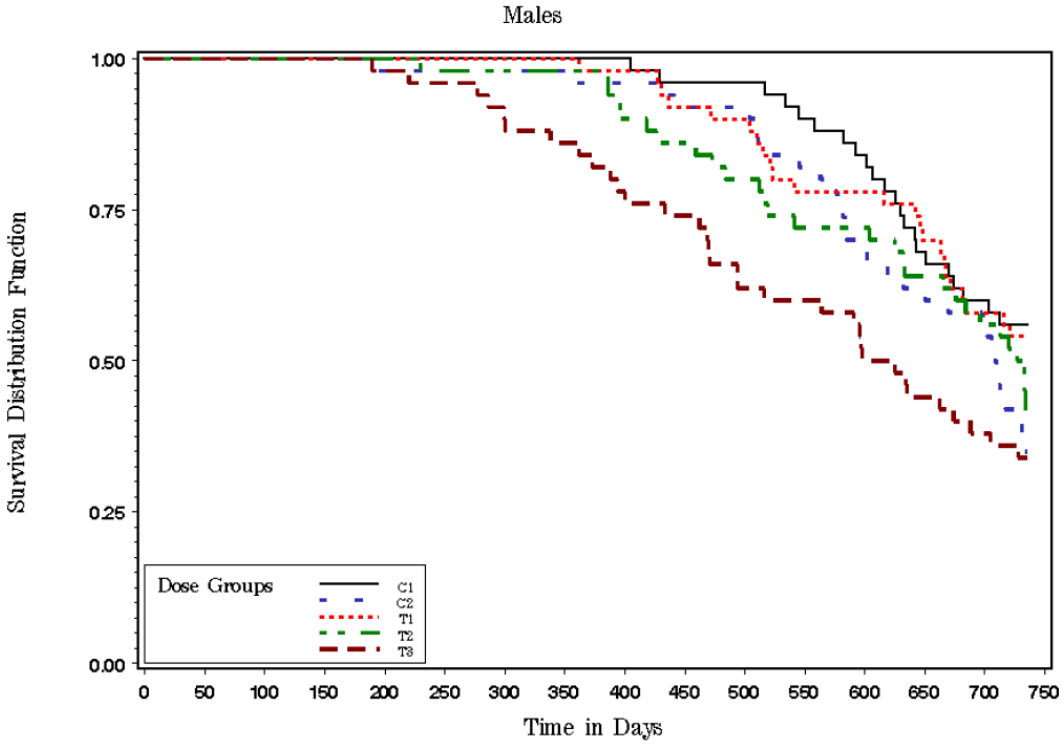
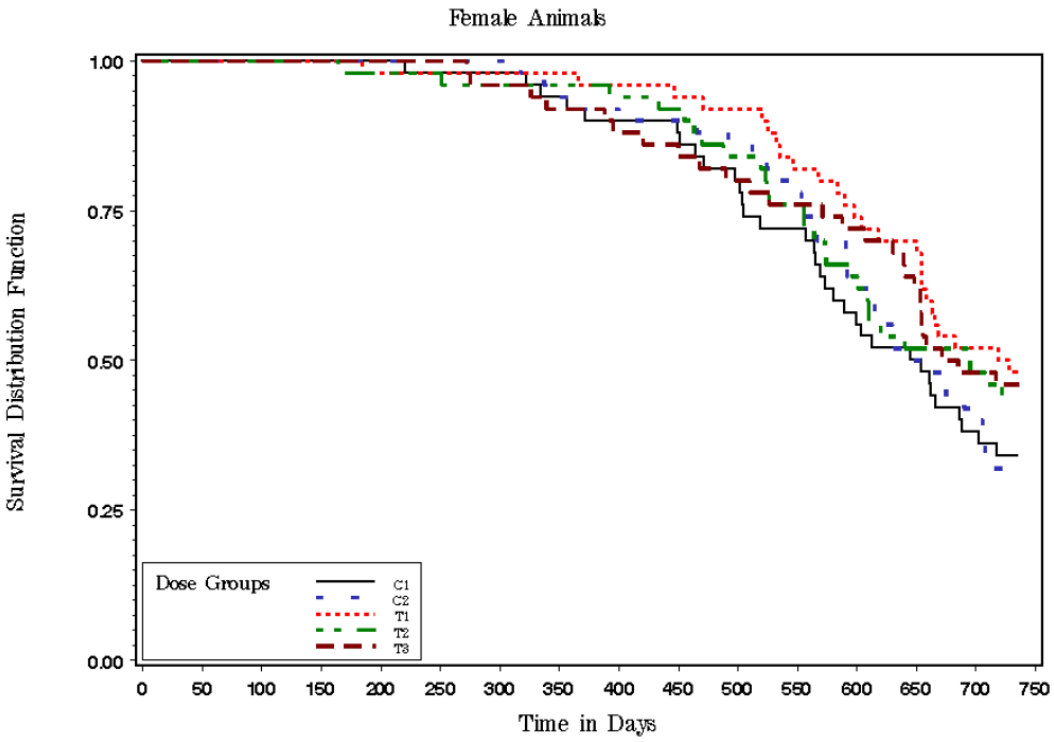


Figure 5. Survival in female mouse



Clinical Signs: Checked 2x daily. Detailed exams performed weekly. Palpable masses evaluated in Week 1, every 4 weeks from Weeks 4 to 24, every 2 weeks from Weeks 25 to 52, and weekly thereafter.

No drug-related effects.

Body Weights: Weekly pre-test through Week 24, every 2 weeks from Weeks 25 to 36, and monthly thereafter.

No drug-related effects.

Food Consumption: Measured weekly pre-test through Week 24, every 2 weeks from Weeks 25 to 36, and monthly thereafter.

No drug-related effects.

Ophthalmoscopy: Pre-test, Weeks 52 and Week 103.

No drug-related effects.

Gross Pathology

Macroscopic changes were observed in the gallbladder (dark material) at all dose levels. The table below was taken from the Sponsor report.

Table 34. Macroscopic lesions in mouse

Principal Necropsy Finding: Gallbladder - All Animals										
Sex	Male					Female				
Dose (mg/kg):	0	0	100	250	500	0	0	100	250	650
Organ/Finding	Incidence[a]									
Gallbladder	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- material dark	1		11*	10*	16*	2	1	14*	19*	23*

* = Test article-related

a: Incidence = Number affected. The absence of a numeral indicates that the specified finding was not present in that group.

b: ( ) = Number examined.

Histopathology: Recorded at each scheduled sacrifice (see tissue list at end of review).

Adequate Battery: *yes*

Peer Review: *listed in protocol but not shown in report*

Neoplastic Findings: *No drug-related effects. The Sponsor suggested a non-statistically significant increase in hepatocellular adenoma for females at 650 mg/kg/day. A summary table from the Sponsor's report is provided in Table 8. The FDA statistical analysis did not identify an increase in this tumor type. Furthermore, none of the tumors in the FDA analysis achieved statistical significance for both trend-test and pair-wise comparison. FDA data for tumors with p-values ≤ 0.05 is summarized in Table 9 (table taken from statistics review).*

Table 35. Neoplastic lesions in mouse

Principal Neoplastic Findings: Liver - All Animals										
	Males					Females				
Dose (mg/kg):	0	0	100	250	500	0	0	100	250	650
Organ/Finding/Severity	Incidence[a]									
Liver	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(49)
- hepatocellular adenoma [B]	14	12	13	17	8	4	2	2	4	9*

* = Test article-related

a: Incidence = Number affected.

b: ( ) = Number examined.

Table 36. FDA statistical analysis for tumors in mouse

			combined control	P_Value Low	P_Value Med	P_Value High	P_Value Dos Resp	P_Value C vs L	P_Value C vs M	P_Value C vs H
Male	KIDNEYS	HISTIOCYTIC SARCOMA	0	4	0	1	0 336	0 012		0 275

Reference ID: 2933010

	LIVER	HEPATOCELLULAR CARCI	9	4	7	7	0 045	0 439	0 209	0 108
	LYMPH NODES	HISTIOCYTIC SARCOMA	0	3	1	0	0 528	0 036	0 325	
	SPLEEN	HISTIOCYTIC SARCOMA	1	4	0	1	0 477	0 043	0 319	0 477
	STOMACH	HISTIOCYTIC SARCOMA	0	4	1	0	0 566	0 012	0 325	
	TESTES	INTERSTITIAL CELL AD	1	0	3	2	0 043	0 331	0 095	0 183
Female	LIVER	HEPATOCELLULAR ADENO	6	2	4	9	0 007	0 613	0 459	0 032
		HEP_ADENOMA+CARCINOM	8	2	4	11	0 004	0 781	0 383	0 023
	OVARIES	TUBULOSTROMAL ADENOM	0	0	1	2	0 033		0 343	0 120

Non-Neoplastic Findings: *SCH505034-related lesions were observed in liver (single cell necrosis, focal/multifocal; pigment accumulation, macrophage). Single cell necrosis was noted at the high dose in both sexes. Pigment accumulation occurred in males at 250 and 500 mg/kg/day and in females at 650 mg/kg/day. Special staining procedures indicated the pigment found in 500 mg/kg/day males contained lipofuscin and ferric iron but not bilirubin. The summary table below was taken from the Sponsor report.*

Table 37. Non-neoplastic lesions in mouse

Principal Non-Neoplastic Findings: Liver - All Animals										
	Males					Females				
Dose (mg/kg):	0	0	100	250	500	0	0	100	250	650
Organ/Finding/Severity	Incidence[a]									
Liver	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(49)
- single cell necrosis, focal/ multifocal	6	4	5	6	13*	2	4	2	5	8*
minimal	5	4	4	4	13	2	4	1	4	7
mild	1		1	2				1	1	1
- pigment accumulation, macrophage	13	8	9	36*	37*	17	12	13	14	22*
minimal	11	7	7	24	10	11	9	9	8	14
mild	2	1	2	10	25	5	3	4	5	8
moderate				2	2	1			1	

* = Test article-related

a: Incidence = Number affected. The absence of a numeral indicates that the specified finding was not present in that group.

b: ( ) = Number examined.

Toxicokinetics: Blood was collected via abdominal aorta in Weeks 4 (control: 1, 2, and 4 hr; drug-treated: 1, 2, 4, 8, 12, and 24 hr) and 24 (all groups: 1, 2, and 4 hr). Plasma concentrations of SCH534128 and SCH 534129, were determined by LC-MS/MS. SCH503034 concentrations were determined by adding SCH50304 and SC 5374128

concentrations. Note that SCH503034 is a mixture of stereoisomers (SCH534128 and SCH534129).

Toxicokinetic profiles were similar for SCH503034, SCH534128, and SCH534129. Females generally had greater systemic exposure for SCH503034 compared to males at 100 and 250 mg/kg/day. Females also had greater systemic exposure at 650 mg/kg/day compared to males at 500 mg/kg/day. SCH503034 appeared rapidly in plasma followed by rapid elimination. Based on a limited subset of timepoints, mean plasma concentrations were generally similar on Days 27 and 168. This data confirms systemic exposure on the later sampling period. Although limited data was available, increases in $AUC_{0\text{-}24\ hr}$ *appeared greater than dose-proportional across the range of doses. Increases in* C_{max} *values appeared to be greater than dose-proportional between 100 and 250 mg/kg/day but were less than dose-proportional between 250 mg/kg/day and the high dose groups. Control contamination was not detected. The summary tables below were taken from the Sponsor report.*

Table 38. Toxicokinetic data in mouse

SCH 503034 Toxicokinetic Parameters on Day 27 Following Oral (Gavage) Administration of 100, 250 or 500 mg/kg to Male Mice and 100, 250 or 650 mg/kg SCH 503034 to Female Mice

Dose Group	Dose[a] (mg/kg)	Day	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	F:M[b]
3	100	27	Female	1140	1	2	NC[c]	NC	NA[d]
			Male	507	1	8	789	807	NA
4	250	27	Female	11500	1	8	18900	18900	1.49
			Male	7910	1	8	12700	13100	NA
5	500	27	Male	12900	1	8	37300	38100	NA
6	650	27	Female	19400	1	12	97000	98000	NA

a: SCH 503034

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

c: NC = Not calculated; AUC was not determined due to insufficient plasma concentration-time profiles (N < 4 consecutive quantifiable time points).

d: NA = Not applicable

SCH 534128 Toxicokinetic Parameters on Day 27 Following Oral (Gavage) Administration of 100, 250 or 500 mg/kg to Male Mice and 100, 250 or 650 mg/kg SCH 503034 to Female Mice

Dose Group	Dose[a] (mg/kg)	Day	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)
3	100	27	Female	617	1	2	NC[b]	NC
			Male	305	1	8	505	523
4	250	27	Female	6410	1	4	NC	NC
			Male	4690	1	8	7560	7840
5	500	27	Male	7740	1	8	22000	22600
6	650	27	Female	10900	1	12	52400	52800

a: SCH 503034

b: NC = Not calculated; AUC was not determined due to insufficient plasma concentration-time profiles (N < 4 consecutive quantifiable time points).

SCH 534129 Toxicokinetic Parameters on Day 27 Following Oral (Gavage) Administration of 100, 250 or 500 mg/kg to Male Mice and 100, 250 or 650 mg/kg SCH 503034 to Female Mice

Dose Group	Dose[a] (mg/kg)	Day	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)	F:M[b]
3	100	27	Female	518	1	2	NC[c]	NC	NA[d]
			Male	202	1	2	NC	NC	NA
4	250	27	Female	5060	1	8	8720	8790	1.66
			Male	3230	1	8	5130	5290	NA
5	500	27	Male	5180	1	8	15300	15600	NA
6	650	27	Female	8540	1	12	42000	42500	NA

a: SCH 503034

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

c: NC = Not calculated; AUC was not determined due to insufficient plasma concentration-time profiles (N < 4 consecutive quantifiable time points).

d: NA = Not applicable

Stability: Dose formulation concentration and/or homogeneity were evaluated throughout the study.

Concentration measurements were within ± 15% of expected with few exceptions. In Week 26 the 100 mg/kg/day formulation was 76-77% of the expected nominal concentration and in Week 101 the 250 mg/kg/day formulation was 83.7% of the expected nominal concentration (corrected for purity). Neither of these out of specification results have a substantial impact on the study. Homogeneity analysis was within the acceptable range for all formulations in Week 1.

Appendix/Attachments

Histopathology

Tissue	Rat Study	Mouse Study
adrenal glands	x	x
aorta	x	x
bone (femur)	x	x
bone + marrow (sternum)	x	x
brain (mouse - forebrain, midbrain cerebellum, and medulla oblongata)	x	x
cecum	x	x
cervix	x	x
colon	x	x
duodenum	x	x
epididymides	x	x
esophagus	x	x
eyes	x	x
fallopian tube		
gallbladder		x
gross lesions	x	x
gut associated lymphoid tissue (Peyer's patch)		
Harderian glands	x	x
heart	x	x

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ileum	x	x
jejunum	x	x
kidneys	x	x
lacrimal gland		
liver	x	x
lungs	x	x
lymph node (mandibular)	x	x
lymph node (mesenteric)	x	x
mammary gland	x	x
muscle (skeletal)	x	x
nasal cavity/turbinates		
nerve (optic)		x
nerve (sciatic)	x	x
observed masses	x	
ovaries	x	x
pancreas	x	x
pharynx/larynx	x	x
pituitary gland	x	x
prostate		x
rectum		
salivary glands, mandibular	x	x
seminal vesicles	x	x
skin/subcutis		x
spinal cord (thoracolumbar)	x	x
spleen	x	x
stomach	x	x
testes	x	x
thymus	x	x
thyroid/parathyroid	x	x
tongue		
trachea	x	x
urinary bladder	x	x
uterus	x	x
vagina	x	x
Zymbal's gland		

Reference ID: 2933010

Table 39. PK summary (taken from Sponsor submission)

Species	Dose (mg/kg)	Sex	Boceprevir AUC(0-24 hr) (ng·hr/mL)	Boceprevir EM	SCH 534128 AUC(0-24 hr) (ng·hr/mL)	SCH 534128 EM	SCH 629144 AUC(0-24 hr) (ng·hr/mL)	SCH 629144 EM	Reference
Mouse	250[a]	F	26900	1.6	10100[b]	0.89	NA	NA	SN 01305,[10] SN 01303[7]
	500[a,c]	M	27400	1.6	22600	2.0	NA	NA	SN 01305,[10] SN 01303[7]
	600[c]	F	80500	4.8	40700	3.6	62900	0.83	SN 04320[8]
Rat	75[d]	F	21300	1.3	NA	NA	NA	NA	SN 04032,[15] SN 01290,[21] SN 01299[24]
	100	M	19700	1.2	12800	1.1	2040	0.03	SN 04124,[26] SN 01302[19]
	100[a]	F	15100	0.89	8310	0.74	NA	NA	SN 01304[25]
	125[a]	M	15000	0.89	8330	0.74	NA	NA	
Pregnant Rat	150[e]	F	110000	6.5	57500	5.1	NA	NA	SN 08259[28]
	600[e]		170000	10	91400	8.1	NA	NA	
Pregnant Rabbit	50[f]	F	4990	0.30	NA	NA	NA	NA	SN 01308[29]
	300[f]		32800	1.9	NA	NA	NA	NA	
Monkey	25[g]	M/F	2480	0.15	297	0.03	NA	NA	[g]
	300		31400	1.9	4460	0.39	226000	3.0	SN 04080[38]
Human	800 mg TID[h]	M/F	16900	-	11300	-	76000	-	P04489,[83] P05880[81]

a: Highest dose administered in the carcinogenicity studies; no boceprevir-related tumors were observed.

b: Due to a lack of 4 consecutive quantifiable time points for SCH 534128, the AUC was calculated by subtracting the AUC(0-24 hr) for SCH 534129 from that of boceprevir in SN 01305.[10]

c: NOAEL for mice based on neutrophilic infiltrates in the liver (SN 01303[7] [M], SN 04320[8] [F])

d: NOAEL for female rats based on mortality, decreases in body weight, body weight gain, and food consumption (SN 01290[21]). An AUC was not obtained at the NOAEL for male rats (15 mg/kg based on decreases in body weight gain and histopathological changes in the liver and male reproductive tissues [SN 01299[24]]) due to insufficient plasma concentration time points.

e: The NOAEL for maternal toxicity was <150 mg/kg based on decreases in gestational body weight gain; the NOAEL for embryo-fetal toxicity was ≥600 mg/kg (SN 01307[56]). Pregnant rats were fed ad libitum and obtained higher exposures than nonpregnant rats fed a restricted diet in other toxicity studies.

f: The NOAEL for maternal toxicity was <50 mg/kg based on decreased food consumption and fecal output; the NOAEL for embryo-fetal toxicity was ≥300 mg/kg (SN 01308[29]).

g: NOAEL for monkeys; boceprevir AUC value is the mean (n = 29) of individual AUC(0-24 hr) values from SN 01291,[36] SN 01300,[39] SN 01301,[40] and SN 02605;[37] SCH 534128 AUC value is from SN 01301.[40]

h: AUC values are the means of individual values from fed, healthy subjects from P04489[83] (n = 31) and P05880[81] (n = 40).

Executive CAC
Date of Meeting: November 30, 2010

Committee: David Jacobson-Kram, Ph.D., DABT, OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Adam Wasserman, Ph.D., DAAP, Rotating Member
Hanan Ghantous, Ph.D., DABT, DAVP, Team Leader
Mark W. Powley, Ph.D., DAVP, Presenting Reviewer

Author of Draft: Mark W. Powley, Ph.D.

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

IND #69,027
Drug Name: Boceprevir (SCH 503034)
Sponsor: Schering Corporation

Background:
Data from rodent carcinogenicity studies with boceprevir were reviewed. Boceprevir is a

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NS3 protease inhibitor indicated for the treatment of HCV.

Carcinogenicity Study of 104 weeks in Sprague-Dawley rats:
Dose Levels:
male = 20, 50, and 125 mg/kg/day by gavage in 0.4% methylcellulose
female = 20, 50, and 100 mg/kg/day by gavage in 0.4% methylcellulose

Statistical Analysis of Tumor Incidence – None of the tumors in the FDA analysis achieved statistical significance for both trend-test and pair-wise comparison.

TK - Systemic exposure for SCH 503034 was confirmed during the study. Females had slightly greater $AUC_{0\text{-}24\ hr}$ and C_{max} values at the low and mid doses.

Metabolite - It is worth noting that SCH 503034 is extensively metabolized in humans with SCH 629144 accounting for a majority of circulating drug-related material. In male rats administered 100 mg/kg/day of SCH 503034 (separate study), systemic exposure to the major metabolite was only ~2.5% of that observed clinically. Therefore, while the rat is an appropriate model for evaluating the carcinogenicity of SCH 503034, this is not the case for SCH 629144.

Summary - Overall, this was an adequate study. The dose-levels were consistent with recommendations of exec-CAC with a high dose based on MTD. Excessive mortality did not occur during the study. $AUC_{0\text{-}24\ hr}$ values on Day 22 were between 0.7- and 0.8-fold of clinical exposure. No drug-related tumors were observed.

Carcinogenicity Study of 104 weeks in CD-1 mice:
Dose Levels:
male = 100, 250, and 500 mg/kg/day by gavage in 0.4% methylcellulose

female = 100, 250, and 650 mg/kg/day by gavage in 0.4% methylcellulose

Statistical Analysis of Tumor Incidence – The FDA statistical evaluation did not identify an increase in any tumor based on trend-test and pair-wise comparison.

TK - Systemic exposure for SCH 503034 was confirmed during the study. Females had slightly greater $AUC_{0\text{-}24\ hr}$ and C_{max} values at the low and mid doses.

Metabolite - In female mice administered 600 mg/kg/day of SCH 503034 (separate study), systemic exposure to the major metabolite was 0.8-fold of that observed clinically. Therefore, the mouse is an appropriate model for evaluating the carcinogenicity of both SCH 503034 and SCH 629144.

Summary - Overall, this was an adequate study. The dose-levels were consistent with recommendations of exec-CAC with a high dose based on MTD. Excessive mortality was not observed during the study. $AUC_{0\text{-}24\ hr}$ values on Day 27 were between 2.2- and 5.8-fold of clinical exposure. No drug-related tumors were observed.

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Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agrees that the study is adequate, noting prior Exec CAC concurrence.
- The Committee concluded that the study is negative for drug related tumors.

Mouse:

- The Committee agrees that the study is adequate, noting prior Exec CAC concurrence.
- The Committee concluded that the study is negative for drug related tumors.

David Jacobson-Kram, Ph.D., DABT
Chair, Executive CAC

12.2 Prenatal and Postnatal Development Study

PHARMACOLOGY/TOXICOLOGY COVER SHEET

IND NUMBER:	69,027
SEQUENCE NUMBER/DATE:	129/Feb-1-2006
INFORMATION TO SPONSOR:	Yes () No (x)
SPONSOR:	Schering Corporation, NJ, USA
MANUFACTURER:	Same as above
REVIEWER NAME:	Kuei-Meng Wu
DIVISION NAME:	DAVDP
HFD NO.:	HFD-530
REVIEW COMPLETION:	1/18/08
DRUG:	SCH 503034
CHEMICAL NAME:	(1R,5S)-N-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide

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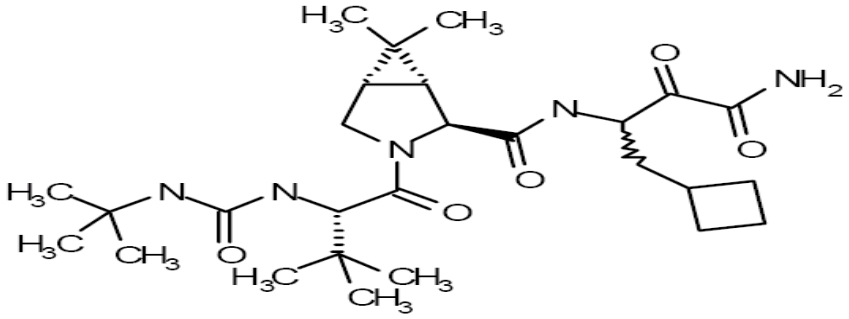
FORMULA/MW:	CAS Number: 394730-60-0; $C_{27}H_{45}N_5O_5$; MW: 519.7 Five chiral centers [redacted] (b) (4) drug substance is a white to off-white amorphous powder and has approximately equal mixture of two diastereomers, SCH 534128 and SCH 534129, with a ratio of approximately 1:1. Solubility: ethanol and isopropanol (>100 mg/mL); dimethyl sulfoxide (DMSO, >50 mg/mL); water (0.6 mg/mL); phosphate buffer at pH 7.4 (0.2 mg/mL).
STRUCTURE:	
RELATED INDS/NDAS:	Pre-IND 69027
DRUG CLASS:	Antiviral - HCV Protease Inhibitor
INDICATION:	Treatment of HCV Infection
CLINICAL FORMULATION:	Capsules [redacted] (b) (4) hard gelatin [redacted] (b) (4) capsule (excipients: lactose anhydrous, croscarmellose sodium, and magnesium stearate)
ROUTE OF ADMINISTRATION	Oral

DISCLAIMER: TABULAR AND GRAPHICAL INFORMATION IS MODIFIED FROM SPONSOR'S SUBMISSION UNLESS STATED OTHERWISE.

INTRODUCTION	This submission includes a reproductive toxicity study report on SCH 503034 performed in rats. It is reviewed below.

STUDY TITLE:	**PRENATAL AND POSTNATAL DEVELOPMENTAL TOXICITY AND MATERNAL FUNCTION STUDY OF SCH 503034 ADMINISTERED ORALLY BY GAVAGE IN RATS**
KEY FINDINGS:	No remarkable findings were reported from this prenatal/postnatal developmental toxicity study conducted in the rat (NOAEL = 150 mg/kg, which is the high dose). No toxicokinetics was performed. The reference exposure levels at 150 mg/kg from previous 3-month rat studies were 34 (male) – 40 (female) ug.h/ml. These levels were in the range of NOAELs used in the risk assessment of the original IND. In regard to reproductive toxicity risk of SCH 503034 in humans, the current results should not produce new safety concerns.
STUDY NO.:	1309
VOLUME/PAGE:	1309.PDF
LABORATORY:	[redacted] (b) (4)
STUDY	8/2006

Reference ID: 2933010

INITIATION:

GLP: Yes (x) no ()

QA REPORT: Yes (x) no ()

LOT # 06-503034-YY-106A

FORMULATION/ VEHICLE: SCH 503034 in 0.4% (w/v) aqueous methylcellulose/Vehicle, 0.4% (w/v) aqueous methylcellulose

METHODS & DOSING:: The effects of SCH 503034 on gestation, parturition, offspring development and survival during the perinatal and postnatal periods were assessed in mated female rats. Females (F0) were orally gavaged 15, 75 or 150 mg/kg/day from gestation Day 6 through lactation Day 20 or an estimated gestation Day 24 (for rats that did not deliver a litter). The females delivered and reared offspring until lactation Day 21 (F0 females sacrificed day). On postpartum Day 21, 1 male and female from each litter were used (F1 generation) for postweaning measurements including developmental/ neurobehavioral evaluation, assessment of fertility and their ability to produce a F2 generation (see table below). The remaining rats from each litter were euthanized.

F_0 Generation				
Dose Group	Test/Control Article	Dose (mg/kg)	Dose Volume (mL/kg)	Concentration (mg/mL)
1	Methylcellulose (Control)	0	5	0
2	SCH 503034	15	5	3
3	SCH 503034	75	5	15
4	SCH 503034	150	5	30

F_1		
Dose Group	Test/Control Article	Maternal (F_0) Dose (mg/kg)
1	Methylcellulose (Control)	0
2	SCH 503034	15
3	SCH 503034	75
4	SCH 503034	150

SPECIES/STRAIN: Rat (Crl :CDS[SD])

NO. /GROUP 25/group (F1), 25/group (F0)

ROUTE Once daily oral gavage

OBSERVATIONS:

Investigation	F_0 Generation	F_1 Generation (from F_0 dams)	F_2 Generation (from F_1 dams)
Viability	At least twice daily	At least twice daily	At least twice daily
Clinical Observations	At least weekly during acclimation, on DG[a] 0, daily before dosing and between one and three hours after dosing	Once daily during the preweaning period and at least once weekly during the postweaning period	Daily during the postpartum period
Maternal Behavior	DL[b]s 1, 4, 7, 14 and 21. Observed abnormal behavior recorded daily	DLs 1, 4 and 7. Observed abnormal behavior recorded daily	NA[c]
Body Weight	At least weekly during acclimation, on DGs 0, 6, 9, 12, 15, 17, 21 and 25 (if necessary) and DLs 1, 4, 7 and 14, and before sacrifice (DL 21)	Male Rats: Postpartum Days 1, 4, 7, 14 and 21, weekly during the postweaning period, day of preputial separation, day of sacrifice Female Rats: Postpartum Days 1, 4, 7, 14, 21 and 25 (if necessary), weekly during the postweaning period, day of vaginal patency, DGs 0, 6, 9, 12, 17, 21 and DLs 1, 4, 7, day of sacrifice	Postnatal Days 1, 4 and 7
Food Consumption	DGs 0, 6, 12, 17, 21 and 25 (if necessary) and DLs 1, 4, 7, 10 and 14	Weekly during the postweaning period except during cohabitation Female Rats: DGs 0, 6, 9, 12, 17, 21 and 25 (if necessary), DLs 1, 4 and 7	NA
Parturition	Yes	Yes	NA
Necropsy Observations	Yes	Yes	Yes
Litter Size	Yes	Yes	NA
Maturational and Behavioral Evaluations	NA	Postweaning: Preputial separation and vaginal patency, motor activity, acoustic startle habituation, passive avoidance test, reproductive capacity and natural delivery	NA
Estrous Cycle Determination	NA	Yes	NA

a. DG = Gestation Day
b. DL = Lactation Day
c. NA = Not applicable

TOXICOKINETICS None

RESULTS:

F0

MORTALITY None

CLINICAL SIGNS Unremarkable.

BODY WEIGHTS: Body weight gain in the 250 mg/kg dose group was affected during the interval of gestation Days 7-14 (36% lower than control, 33.4 g vs. 52.4 g). The sponsor indicated that it was attributed to increased resorptions, fewer implantations and/or fewer live fetuses (one gravid female).

FOOD CONSUMPTION Unremarkable.

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NECROPSY:	Unremarkable
PARTURITION:	Unremarkable. The duration of gestation and the length of parturition (number of dams delivering over two days) were comparable among the groups.
OFFSPRING SURVIVAL (F1):	All changes from control in survivability were unremarkable. Both the viability and lactation indices were comparable among groups.
F1 MORTALITY (POST WEANING):	Unremarkable
CLINICAL SIGNS	Unremarkable
BODY WEIGHTS:	Unremarkable
FOOD CONSUMPTION	Unremarkable
MATURATIONAL & BEHAVIORAL EVALUATIONS:	Unremarkable on sexual maturation (as measured by the average day of vaginal patency or day of preputial separation), motor activity (the number of movements and time spent in movement), acoustic startle habituation (a measure of learning), and memory or learning (measured by passive avoidance testing).
ESTROUS CYCLES, MATING AND FERTILITY:	Unremarkable on mating and fertility or estrous cycles. Unremarkable on parturition parameters. The duration of gestation was comparable among the groups.
NECROPSY:	Unremarkable. The terminal body weights, organ weights and ratios of organ weights to terminal body weights of F1 were unremarkable.
OFFSPRING SURVIVAL (F2):	Unremarkable.
F2 BODY WEIGHTS:	Unremarkable
CLINICAL SIGNS	Unremarkable
NECROPSY:	Unremarkable
SUMMARY AND CONCLUSION:	No SCH 503034-related effects on pregnancy, parturition and lactation of the maternal animals (F0) or on the growth, viability, development or reproductive performance of the F1 generation, survivability of the F2 generation were reported. The NOAEL for the F0, F1 and F2 generations was ≥150 mg/kg. No exposure information was available. The exposures at 150 mg/kg from 3-month rat studies were 34 (male) – 40 (female) ug.h/ml. These exposures were in the range of NOAELs used in the risk assessment of the original IND. The current results did not produce new safety concerns, in regard to reproductive toxicity risk of SCH 503034 in humans. No regulatory action is needed for this submission.

Kuei-Meng Wu, Ph.D.

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Reviewing Pharmacologist
DAVDP

Concurrences:
HFD-530/Dep Dir/PTL/HGhantous
Wu/Pharm/1/20/0

12.3 Histopathology inventory

Study	6484	9238
Species	rat	rat
Adrenals	*, X	
Aorta	X	
Bone Marrow smear	X	
Bone (femur)	X	
Brain	*, X	
Cecum	X	
Cervix	X	
Colon	X	
Duodenum	X	
Epididymis	*, X	
Esophagus	X	
Eye	X	
Fallopian tube		
Gall bladder		
Gross lesions	X	X
Harderian gland	X	
Heart	*, X	
Ileum	X	
Injection site		
Jejunum	X	
Kidneys	*, X	
Lachrymal gland		
Larynx	X	
Liver	*, X	*, X
Lungs	*, X	
Lymph nodes, cervical		
Lymph nodes mandibular	X	
Lymph nodes, mesenteric	X	

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Lymph nodes, popliteal		
Lymph nodes, unilateral		
Mammary Gland	X	
Nasal cavity		
Optic nerves		
Ovaries	*, X	
Pancreas	X	
Parathyroid	X	*, X
Peripheral nerve	X	
Pharynx		
Pituitary	*, X	X
Prostate	*, X	
Rectum	X	
Salivary gland	X	
Sciatic nerve	X	
Seminal vesicles	X	
Skeletal muscle	X	
Skin	X	
Spinal cord	X	
Spleen	*, X	
Sternum	X	
Stomach	X	
Testes	*, X	
Thymus	*, X	
Thyroid	*, X	*, X
Tongue	X	
Trachea	X	
Urinary bladder	X	
Uterus	*, X	
Vagina	X	
Zymbal gland		

X, histopathology performed
*, organ weight obtained
Note: some organs weighed together

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/s/

CHRISTOPHER E ELLIS
04/14/2011

HANAN N GHANTOUS
04/14/2011

Comments on NDA 202-258 boceprevir
From: Abigail Jacobs, AD
Date 4/8/11

1. I concur that there are no outstanding pharm/tox approval issues for this NDA.

2. Some other comments have been discussed with the reviewer and supervisor and will be addressed as appropriate

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABIGAIL ABBY C C JACOBS

04/11/2011

This replaces an erroneous document from about 30 minutes earlier, which will be deleted from Darrts

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202,258 **Applicant: Schering Corp.** **Stamp Date: 11-15-2010**

Drug Name: Boceprevir **NDA Type: Original**

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		Some minor issues identified including incorrect or missing links in PK and Toxicology tabulated summaries.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

Reference ID: 2877881

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Appropriateness of content will be determined upon review and discussed at labeling meetings.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Whether sponsor has addressed issues adequately is a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?		X	Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		X	Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Not applicable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

Reference ID: 2877881

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER E ELLIS
12/15/2010

HANAN N GHANTOUS
12/15/2010