CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204886Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 204886
Submission date: 5/10/2013
Drug: vorapaxar
Applicant: Merck Sharp and Dohme Corp
Indication: reduction of atherothrombotic events in patients with a history of myocardial infarction

Reviewing Division: Division of Cardiovascular and Renal Products

Discussion:
The primary pharm/tox reviewer and supervisor concluded that the information submitted was adequate to support approval of vorapaxar for the indications listed above.

Vorapaxar was associated with some effects on sensory function and neurobehavioral development in rats exposed in utero and during lactation. Vorapaxar is excreted in rat milk. These findings occurred at relatively high multiples of the human exposure. The findings are described in proposed labeling.

Carcinogenicity studies were conducted with vorapaxar in rats and mice. The Executive Carcinogenicity Assessment Committee concluded that no drug-related neoplasms were noted in either species.

Vorapaxar is an inhibitor of the protease activated receptor-1 (PAR-1). An acceptable Established Pharmacologic Class could be “Protease Activated Receptor-1 Antagonist”.

Conclusions:
The pharmacology/toxicology reviewer conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. I agree that this NDA may be approved for the above indications from a pharm/tox perspective. I have provided comments on labeling separately.

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

/s/

PAUL C BROWN
05/06/2014

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 204886
Supporting document/s:	75
Applicant's letter date:	2/6/2014
CDER stamp date:	2/6/2014
Product:	Vorapaxar (SCH 530348)
Indication:	Reduction of atherothrombotic events in patients with a history of myocardial infarction
Applicant:	Merck (previously Schering-Plough)
Review Division:	Cardiovascular and Renal Products (DCRP)
Reviewer:	Patricia P. Harlow, Ph.D.
Supervisor/Team Leader:	Thomas Papoian, Ph.D., D.A.B.T.
Division Director:	Norman Stockbridge, M.D., Ph.D.
Project Manager:	Alison Blaus

Template Version: September 1, 2010 (Modified by DCRP: Feb. 6, 2013)

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204886 are owned by Merck or are data for which Merck has obtained a written right of reference. Any information or data necessary for approval of NDA 204886 that Merck does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204886.

TABLE OF CONTENTS

Table of Tables

Table of Figures

Table of Appendices

1 Executive Summary

Vorapaxar (SCH 530848), an inhibitor of the protease activated receptor-1 (PAR-1), is being developed as an anti-platelet agent. Under NDA 204886, vorapaxar at 2.5 mg once a day is proposed for the prevention of atherothrombotic events in patients with a history of myocardial infarction.

Supporting document (SD) 75 was the sponsor's response to a paragraph in Section 4.3 of the background document provided by the FDA for the meeting of the Cardiovascular and Renal Drugs Advisory Committee on January 15, 2014. The sponsor's comments focused on the pre- and post-natal development (PPND) findings in studies 02148 and 07358. These studies were previously reviewed in detail under IND 71384 and were summarized in the nonclinical review of NDA 204886. These documents form the basis of the reviewer's response below to the sponsor's comments.

1.3 Recommendations

1.3.1 Non Clinical Recommendations

The reviewer recommends that the reviewer's response below in this document and the reviewer's recommendations concerning labeling (Appendix 1) be sent to the sponsor. The nonclinical review for NDA 204886 and the IND 71384 review dated 5/17/13 can be made available to the sponsor, if requested.

2 Drug Information

2.1 Drug

CAS Registry Number: 705260-08-8

Generic Name: Vorapaxar

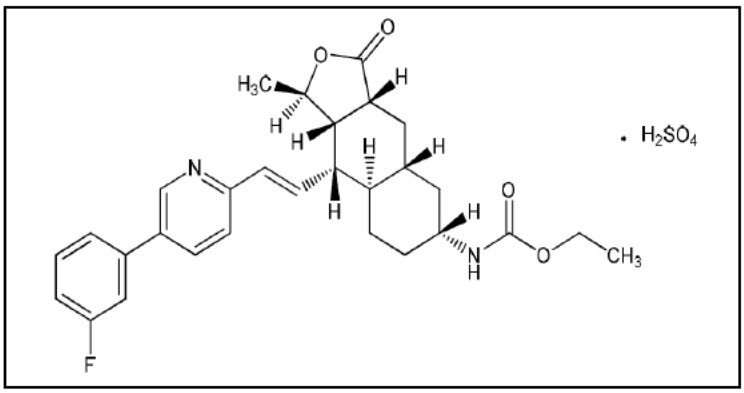
Code Names: SCH 530348 bisulfate, L-002409410, MK-5348, SCH 530348

Chemical Name:
Ethyl[(1R,3aR,4aR,6R,8aR,9S,9aS)-9-[(E)-2-[5-(3-fluorophenyl)-2-pyridinyl]ethenyl] -dodecahydro-1-methyl-3-oxonaphtho[2,3-c]furan-6-yl]carbamate bisulfate

Molecular Formula/Molecular Weight: $C_{29}H_{33}FN_2O_4 \bullet H_2SO_4$/590.7

Structure or Biochemical Description:

Figure 1: Structure of Vorapaxar



Pharmacologic Class: proteinase-activated receptor-1 (PAR-1) antagonist; an anti-platelet drug that inhibits a G protein-coupled receptor activated by thrombin .

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 71384 (Schering-Plough, Merck)

(b) (4)

2.3 Drug Formulation

Vorapaxar tablets contain vorapaxar sulfate (2.5 mg) with lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, povidone (b) (4) USP, magnesium stearate NF (b) (4) The tablets are coated with (b) (4) which contains lactose monohydrate, (b) (4) hypromellose (b) (4), titanium dioxide, triacetin/glycerol triacetate, and iron oxide yellow.

2.4 Comments on Novel Excipients

No novel excipients are used in the manufacture of vorapaxar tablets.

2.5 Comments on Impurities/Degradants of Concern

See the discussion in the nonclinical review for NDA 204886.

2.6 Proposed Clinical Population and Dosing Regimen

In patients with a history of myocardial infarction (MI), vorapaxar 2.5 mg daily is proposed to reduce atherothrombotic events and to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization.

2.7 Regulatory Background

IND 71384 was originally submitted to this Division (DCRP) in 12/17/04. During the development of vorapaxar, two nonclinical issues resulted in action by the Division. The first issue involved the histopathologic finding of vacuolation of the inner nuclear layer of the retina in the eyes of rats. This issue resulted in several consults to the Division of Ophthalmology Products. The second issue involved the adverse effects found in rat offspring in the PPND study and resulted in modifications to the Informed Consent.

3 Studies Submitted

No additional nonclinical studies were submitted in SD 75

4 Reproductive and Developmental Toxicology

SD 75 was a response to a paragraph in Section 4.3 of the background document provided by the FDA for the meeting of the Cardiovascular and Renal Drugs Advisory Committee on January 15, 2014. The response focused on the PPND development findings in rats in studies 02148 and 07358, which were previously reviewed under IND 71384 (Table 1). The findings were summarized in the nonclinical review of NDA 204886 dated 12/17/2013. Please refer to these documents for more details concerning the PPND studies.

Table 1: Overview of Reproductive and Developmental Studies

Study number	Study	SCH-530848 Lot number	GLP	IND 71384 review date in DARRTS
SN 02148	A Prenatal and Postnatal Developmental Toxicity and Maternal Function Study of SCH 530348 Administered Orally by Gavage in Rats	05-530348-X-301	Yes	5/7/2013
SN 07358	Cross Fostering Study of SCH 530348 Administered Orally by Gavage in Rats	05-530348-X-301	Yes	5/7/2013

In the following section, the sponsor's comments are in italic text and the reviewer's response is in normal text. Some of the sponsor's comments were repeated throughout the four page response. To reduce redundancy in this review, comments concerning the same issue highlighted in bold text have been grouped together and are addressed with one response from the reviewer.

*The sponsor does not agree with some FDA interpretations of the PPND and cross-foster study data (most significantly the F1 and F2 generation **survival decrements***

*The sponsor does not agree with the interpretation that the survival results in the F1 and F2 generation were attributable to vorapaxar administration, based on the **small magnitude of the decrements***

In Study 02149, F1 survival for the postnatal period birth to PND 4 (pre-selection) was 97.2%, 97.3%, 94.8% and 84.7% in the 0, 5, 25, and 50 mg/kg groups, respectively (Table 2). Therefore, perinatal survival in the control and low dose groups were similar, whereas perinatal survival in the higher dose groups showed reduced survival with increasing dose. Given that the historical control data for birth to PND 4 (pre-cull) indicate a maximum of 98.7% and a minimum of 86.6%, the survival in the high dose group is notable, because it is below the minimum in the historical control data from birth to PND 4.

Table 2: Sponsor's F1 Postnatal Survival from Table 29 – Study 02148

TABLE 29 (F1)
PROJECT NO.:WIL-370062 ORAL PRE/POSTNATAL DEV & MATERNAL FUNCTION OF SCH 530348 IN RATS
SPONSOR:SCHERING-PLOUGH SUMMARY OF POSTNATAL SURVIVAL [% PER LITTER]
SPONSOR NO.:SN 02148

GROUP :	1	2	3	4
PND 0 TO PND 1				
MEAN	99.5	98.6	99.3	96.0+
S.D.	1.80	3.40	2.74	8.15
S.E.	0.38	0.69	0.55	1.63
N	23	24	25	25
PND 1 TO PND 4 (PRE-SELECTION)				
MEAN	98.5	98.9	97.4	89.1
S.D.	2.83	2.62	4.22	19.14
S.E.	0.59	0.53	0.84	3.83
N	23	24	25	25
PND 4 (POST-SELECTION) TO PND 7				
MEAN	98.9	99.0	99.0	94.5
S.D.	3.60	3.53	3.46	12.54
S.E.	0.75	0.72	0.69	2.51
N	23	24	25	25
BIRTH TO PND 4 (PRE-SELECTION)				
MEAN	97.2	97.3	94.8	84.7
S.D.	4.31	5.14	5.39	21.21
S.E.	0.90	1.05	1.08	4.24
N	23	24	25	25
PND 4 (POST-SELECTION) TO PND 21				
MEAN	94.6	98.4	98.5	93.0
S.D.	20.93	4.22	5.50	16.57
S.E.	4.36	0.86	1.10	3.31
N	23	24	25	25

1- 0 MG/KG/DAY 2- 5 MG/KG/DAY 3- 25 MG/KG/DAY 4- 50 MG/KG/DAY

In Study 02148, the lower survival in the high dose group indicated in Table 2 is supported by calculations for the number of dead or missing pups per litter (Table 3). For the perinatal period from PND 0 to PND 7, a total of 70 pups (2.8 pups/liter) were dead or missing in the high dose group compared with 12 pups (0.52 pups/liter) in the control group. The number of dead or missing pups/litter increased over 5-fold in the high dose group compared with the control group.

Table 3: Reviewer's Summary - Dead/Missing Pups - Study 02148

Dose	**0**	**5**	**25**	**50**
Dams with viable pups	23 (22[1])	24	25	25
	# pups found dead or missing			
PND 0	3	1	7	5
PND 1-3	7	7	9	41
Dead/missing pups/liter	0.30	0.29	0.36	1.64
PND 4-7	2	4	5	24
PND 8-21	8[1]	1	1	2
PND 0-7	12	12	21	70
Dead/missing pups/liter	0.52	0.50	0.84	2.8
PND 0-21 Total F1 pups dead or missing/litter	20 (0.87) [12 (0.54)][1]	13 (0.54)	22 (0.88)	72 (2.88)

Based on Table 30 (p 552) [1]All 8 pups from F45693 were found dead or missing between PND 8 and 15

The reviewer agrees that the results on the F2 generation in Study 02148 were not clearly reproduced in Study 07538. Therefore, the reviewer has NOT recommended inclusion of the F2 results in the label.

*The sponsor does not agree with the interpretation that the survival results in the F1 and F2 generation were attributable to vorapaxar administration, based on … t**he high survival in control group,***

*The mean **concurrent control survival** from birth to PND 4 was at the high end of the historical control value range for this laboratory.*

In Study 02148, postnatal F1 survival for the period birth to PND 4 (pre-selection) was 97.2%, 97.3%, 94.8% and 84.7% in the 0, 5, 25, and 50 mg/kg groups, respectively. Therefore, percent survival in the control group was similar to that in the low dose group. Both percentages were within the historical control range, although both were above the historical mean of 95.8% (Table 4). In contrast, F1 survival from birth to PND 4 in the high dose group was lower than the survival in the control and low dose groups. Importantly, survival in the mid- and high-dose groups decreased with increasing dose, and high dose group from birth to PND 4 was below the minimum of 86.6% in the historical control range.

Table 4: Historical Control Data in SN 02148

(b) (4) - Developmental and Reproductive Toxicology

Historical Control Summary of Pup Survival Indices (%)

Sex: Male/Female | Species: Rat | Number of Studies/Data Sets: 62 / 96

Study Type: All | Strain: Crl:CD(SD) | Range of Study Dates: 08/00 - 09/05

Age Range: 0 - 21 Days

	Mean	S.D.	N	Mean -/+ 2 S.D.	Mean -/+ 3 S.D.	Observed Low/High Value
Mean Number of Pups Born	14.3	0.91	46	12.48 / 16.12	11.57 / 17.03	12.2 / 16.0
Survival (%)						
PND 0 (Relative to No. Born)	98.0	1.53	46	94.94 / 100.00	93.41 / 100.00	93.3 / 100.0
PND 0 to PND 1	99.1	0.89	46	97.32 / 100.00	96.43 / 100.00	95.8 / 100.0
PND 1 to PND 4 (Before Selection)	98.6	1.33	45	95.94 / 100.00	94.61 / 100.00	94.1 / 100.0
PND 4 (After Selection) to PND 7	98.9	1.76	44	95.38 / 100.00	93.62 / 100.00	91.7 / 100.0
PND 7 to PND 14	99.3	1.46	41	96.38 / 100.00	94.92 / 100.00	93.5 / 100.0
PND 14 to PND 21	99.5	1.11	41	97.28 / 100.00	96.17 / 100.00	94.7 / 100.0
Birth to PND 4 (Before Selection)	95.8	2.26	43	91.28 / 100.00	89.02 / 100.00	86.6 / 98.7
PND 4 (After Selection) to PND 21	97.8	2.50	40	92.80 / 100.00	90.30 / 100.00	91.1 / 100.0

*The sponsor does not agree with the interpretation that the survival results in the F1 and F2 generation were attributable to vorapaxar administration, based on … **the limited number of litters impacted,**…..*

*The apparent survival decrements from birth to PND 4 in the 50 mg/kg/day F1 and F2 groups was unlikely test article-related since it resulted from decreased postnatal survival i**n only 1-2 litters** (out of 25) in this narrow window,*

In Study 02148, 9 dams (39%) in the control group and 17 dams (72%) in the high dose group had a dead or missing F1 pup from birth to PND 7. From PND 1 to PND 3, 6 dams (26%) in the control group, but 15 dams (60%) in the high dose group had a dead

or missing pup. In the perinatal period, the number of litters with a dead or missing pup in the perinatal period was higher in the high dose group than in the control group. The reviewer disagrees that only 1-2 litters were involved in the decreased survival in the high dose group in Study 02148.

Table 5: Reviewer's Summary – Dams with Dead/Missing Pups - Study 02148

Dose	**0**	**5**	**25**	**50**
Dams with viable pups	23	24	25	25
	# Dams with pups found dead or missing			
	# dams	# dams	# dams	# dams
PND 0	2	1	6	4
PND 1-3	6	4	7	15
% dams	26	17	28	60
PND 4-7	1	4	4	7
PND 8-21	1	1	1	2
PND 0-7	9	8	13	17
% dams	39	33	52	72
Based on Table 30 (p 552)				

The sponsor considers that the F1 and F2 survival decrements are not vorapaxar-related, and a description of the data in the label is not warranted.

The apparent survival decrements from birth to PND 4 in the 50 mg/kg/day F1 and F2 groups was unlikely test article-related since it ……. was ***not associated with an overall decrease in offspring survival*** *for the study.*

For the whole pre-weaning period (PND 0-21) in Study 02148, a total of 72 pups (2.88 pups/liter) were found dead or missing in the high dose group compared with 20 (0.87 pups/litter) in the control group (Table 3). If control female F45693, who lost almost 5% of her body weight from PND 10 to 14 and consequently all of her pups between PND 8 to PND 15, is excluded, the control group had a total of 12 dead or missing pups (0.52 pups/liter) for the whole pre-weaning period. In particular, for the perinatal period from PND 0 to PND 7, a total of 70 pups (2.8 pups/liter) were dead or missing in the high dose group compared with 12 pups (0.52 pups/liter) in the control group.

Although the reviewer agrees that F1 survival beyond PND 7 was not affected by vorapaxar administration to the F0 dams, the reviewer considers the perinatal increases in the total number of dead or missing pups/liter particularly for the perinatal period to be vorapaxar-related. Given the relatively high excretion of vorapaxar into milk, the high dose F1 neonatal rats, who weighed 6 to 9 gm, were exposed to the highest postnatal vorapaxar doses on a mg/kg basis (10-20 mg/kg) on PND 0-4. Thus, the perinatal period is more likely to show adverse effects than later in development.

The sponsor and reviewer estimated exposure to SCH 530348 and/or its metabolites in a human infant via milk consumption to be approximately 6% to 7% of the orally administered dose to the mother. The adult maintenance dose of SCH 530348 in the Phase 3 trial was 2.5 mg/day or 42 µg/kg, when based on a 60 kg individual. If the transfer of SCH 530348 and/or its metabolites in humans is similar to that in rats, then a nursing mother would transfer 7% of the administered dose or 175 µg of SCH 530348

and/or its metabolites to her infant. Given body weight ranges for neonates and 1 year old infants of 2-5 kg and 7-11 kg, respectively, neonates and 1 year old infants would receive SCH 530348 doses of 35-88 µg/kg and 16-25 µg/kg, respectively, if all drug-related material in milk is in the form of the parent. The sponsor has shown that repeated doses of 1 mg SCH 530348 to adult humans (1000 µg/60 kg = 16.6 µg/kg) results in inhibition of platelet aggregation by 50%. The reviewer is concerned that infants up to 1 year of age, who consume milk from mothers being treated with SCH 530348, could likely have significantly decreased platelet aggregation.

*The Sponsor strongly believes that the results of the cross fostering study (with a much **more robust study design)** do negate the findings in the initial PPND study.*

*……a **robust repeat PPND (effectively 2-fold larger** than the first PPND) was conducted to determine if the findings were reproducible,*

*….(**robustly designed t**o confirm or refute the observations made in the PPND study) strongly indicates that the previously observed effects on pup survival and F2 body weight gain was a random/incidental finding and not related to administration of vorapaxar.*

The number of litters per group in Study 02148 was 23 to 25. The number of litters per group in Study 07358 was 25 to 27. Although Studies 02148 and 07358 had different designs and purposes, they had similar robustness (number of litters evaluated per group). Study 07358 was not 2-fold larger than the first PPND study in terms of litters evaluated per group. Therefore, the reviewer does not consider Study 07358 a more robust study.

*The sponsor does not agree with the interpretation that the survival results in the F1 and F2 generation were attributable to vorapaxar administration, based on …. **lack of reproducibility** in either generation, with and without cross-fostering in the robust follow up study.*

*The overall conclusion from these studies was that the only vorapaxar-related effect was a lower mean body weight and body weight gain in pups in the F1 generation. Survival decrements in both the F1 and F2 generations observed in SN 02148 **were not repeated i**n the follow up study (SN 07358).*

*The results of this study again demonstrated a decrease in body weight for F1 pups nursing from vorapaxar-treated dams; however, the decreased F1 and F2 survival noted in the PPND **was not repeated**. There was no effect on F1 postnatal survival with or without cross-fostering, and no effect on F2 pup growth or survival.*

Table 6 compares Study 02148 and Study 07358. As previously indicated in Table 3, the high dose group (50 mg/kg) in Study 02148 had at least a 5 fold increase in the number of dead or missing F1 pups/liter compared to the control group for the periods PND 1-3 and PND 1-7. The reviewer's analysis of the number of F1 dead or missing pups/liter in Study 07358 indicates that the A2 (F0-50/F1-50) group had an approximately 2 fold increase in the number of F1 dead or missing pups/liter compared

to the control A1 (F0-0/F1-0) group for the periods PND 1-3 and PND 1-7. Although the fold increase was different, F1 pup mortality increased in both studies.

Table 6: Reviewer's Comparison – Pup Mortality in Studies 02148 and 07358

	Study 02148				Study 07358			
Dose	**0**		**50**		**A1: F_0-0/F_1-0**		**A2: F_0-50/F_1-50**	
Dams with viable pups	23		25		26 (25)		27	
	# Dams with pups found dead or missing/# pups found dead or missing							
	# dams	# pups	# dams	# pups	# dams	# pups	# dams	# pups
PND 0	2	3	4	5				
PND 1-3	6	7	15	41	9 (8†)	17 (12†)	13	32
% dams	26		60		35 (32†)		48	
Dead/missing pups/liter		0.30		1.64		0.65 (0.48†)		1.19
PND 4-7	1	2	7	24	4	5	6	12
PND 8-21	1	8	2	2	4	7	1	3
PND 1-7	8	9	16	65	9 (8†)	22 (17†)	13	44
% dams	35		64		35 (32†)		48	
Dead/missing pups/liter		0.39		2.6 (6.6)		0.85 (0.68†)		1.63

† Excluded litters that lost all pups in the indicated group by PND 1.

In Study 07358, the higher mortality in the A2 group indicated in Table 6 is supported by calculations for percent survival. Table 7 presents both the sponsor's (S) and reviewer's (R) values for percent survival for Study 07358. The sponsor calculated a percent survival for each litter and then determined a mean for each group. However, this mean, particularly for the percentage alive on PND 4 precull versus PND 0 at cross-fostering, is greatly affected by the inclusion of litters in which all pups were lost by PND 1. When these litters are excluded, the mean percentage survival calculated using the sponsor's method is comparable to the percentage overall survival calculated by the reviewer using the total number of F1 pups alive at the various timepoints.

Both sponsor's and reviewer's methods of calculation result in Group A2 having the lowest percentage of live pups on PND 4 pre-cull versus the number on PND 0 at cross-fostering. The percentages of live pups in Groups A3 and A4 on PND 4 pre-cull versus the number on PND 0 at cross-fostering also decreased and are in-between the percentages for Groups A2 and A1. However, these differences are not statistically significant and historical data was not provided to impart context.

The sponsor did provide historical control values for the percentage of F1 pups alive on PND 4 pre-cull versus the number born based on standard PPND studies. In addition to percentages based on total pup numbers, the reviewer also calculated percentage of F1 pups alive on PND 4 pre-cull versus the number born for Groups A1 and A2 using the sponsor's method. The values using either method are almost identical. Group A2 had a lower percentage of F1 pups alive on PND 4 pre-cull versus the number born compared to the percentage in the control group. This percentage in Group A2 was lower than the minimum reported in the historical data range from standard PPND studies.

Table 7: Selected Rows from Reviewer's Table – F_1 Survival – Study 07358

Group	A1		A2		A3		A4	
Dam/pup	F_0-0/F_1-0		F_0-50/F_1-50		F_0-0XF_1-50		F_0-50XF_1-0	
F_1 Exposure period	None		Pre & post-natal		Pre-natal		Post-natal	
Number of litters on PND 0	26		27		25		25	
Post-cross-fostering (CF)								
	S	**R**	**S**	**R**	**S**	**R**	**S**	**R**
% alive PND 4 pre-cull vs. PND 1/ # litters [HC = 94.1, 100][3]	**97.5/25**		**93.0/26**		**93.3/25**		**96.3/24**	
% alive PND 4 pre-cull vs. PND 0 at CF/ # litters	**92.1/26** (96.0/25‡)	95.2 (96.4†)	**88.4/27** (91.7/26‡)	91.2 (91.5†)	**92.2/25** (92.2/25)	92.3 92.3	**89.8/25** (93.5/24‡)	89.3 (93.0†)
% alive PND 4 pre-cull vs. # born/ # litters [HC = 86.6, 100][1]	89.0/26	89.1	84.4/27	84.4		89.1		85.8

S = sponsor's value from Report Table 29 in bold text, R = reviewer's analysis based on Report Table 31 (Individual litter viability), Values in red text are below the historical control range, † Excluded litters that lost all pups in the indicated group beginning PND 1, ‡ In blue text, reviewer used sponsor's calculation method, but excluded dams that lost all pups by PND 1,
Historical control (HC) ranges
[1] Birth to PND 4 (pre-cull), mean ± 2S.D.= 91.64, 100; mean ± 3S.D = 89.5, 100; minimum, maximum = 86.6, 98.7
[2] PND 4 post-cull to PND 21, mean ± 2S.D.= 92.18, 100; mean ± 3S.D = 89.4, 100; minimum, maximum = 86.7, 100
[3] PND 4 pre-cull to PND 1, mean ± 2S.D.= 95.9, 100; mean ± 3S.D = 94.55, 100; minimum, maximum = 94.1, 100

*In addition, the F2 generation findings are not considered to be **biologically implausible**. [The reviewer believes the sponsor meant to say "not considered to be biologically plausible" or "considered to be biologically implausible"]*

*…..the unusual and **biologically implausible** nature of the F2 survival findings*

Since only the F0 generation was treated, it is reasonable at first to arrive at a conclusion that the F2 findings are implausible. However, all PARs, including PAR-1, are widely expressed in the central and peripheral nervous systems throughout development (Luo et al. 2007) and multiple studies indicate the direct involvement of PARs, particularly PAR-1, in brain development and function. Given that the role for PAR-1 receptor in many systems, such as the nervous system, is not well understood, the reviewer believes that we may not yet have the knowledge to know how effects on the F1 generation could result in effects on the F2 generation.

However, the reviewer agrees that the results on the F2 generation in Study 02148 were not clearly reproduced in Study 07538. Therefore, the reviewer has NOT recommended inclusion of the F2 results in the label (Appendix 1).

*In regards to the "neurological effects", the sponsor agrees that there was a small, transient change in acoustic startle response observed at 38 x the RHD, however, there was no vorapaxar related **memory impairment** or other effects that could be considered neurological observed in this study.*

*sponsor does not agree with some FDA interpretations of the PPND and cross-foster study data (most significantly the ……**memory impairment**).*

There were some statistically significant decreases in motor activity and alterations in auditory startle response for certain, selected intervals but no overall biologically-meaningful change in either behavioral assessment was apparent due to these inconsistent and transient effects of small magnitude.

The reviewer agrees that treatment of F0 dams with SCH 530348 did not have a clear effect on learning in F1 off-spring. However, reviewer believes there is a potential effect on memory in F1 females. As summarized in Table 8, the mid and high dose F1 female groups in Trial 11 had dose-dependent increases of 37% and 45%, respectively, in the time to escape and increases of 39% and 44%, respectively, in number of errors/trial relative to the control means. In addition, the high dose F1 female group in Trial 12 had a 22% increase in the time to escape relative to the control group. However, most animals in each group displayed a decrease in the time to escape in Trial 12 compared to Trial 11, indicating learning ability (Figure 2).

The differences in mean values for time to escape and number of errors/trial for Trials 11 and 12 were not statistically significant as calculated by the sponsor. However, the reviewer noted highly aberrant values for control female 45649-11, whose values could be rejected based on a statistical Q-test (Dean and Dixon, 1951). When the values for this female are omitted, the differences between mean values for the high dose and control F1 females for Trial 11 are statistically significant. The mid and high dose F1 female groups in Trial 11 had dose-dependent increases of 63% and 73%, respectively, in the time to escape and increases of 77% and 84%, respectively, in number of errors/trial relative to the control means. Furthermore, the mean values in Trial 11 for the mid and high dose F1 females are above the maximum historical control values for time to escape and for number of errors/trial. Additionally, the number of F1 females with values above the maximum historical control value increased with dose (2, 4, 5 at 5, 25, 50 mg/kg).

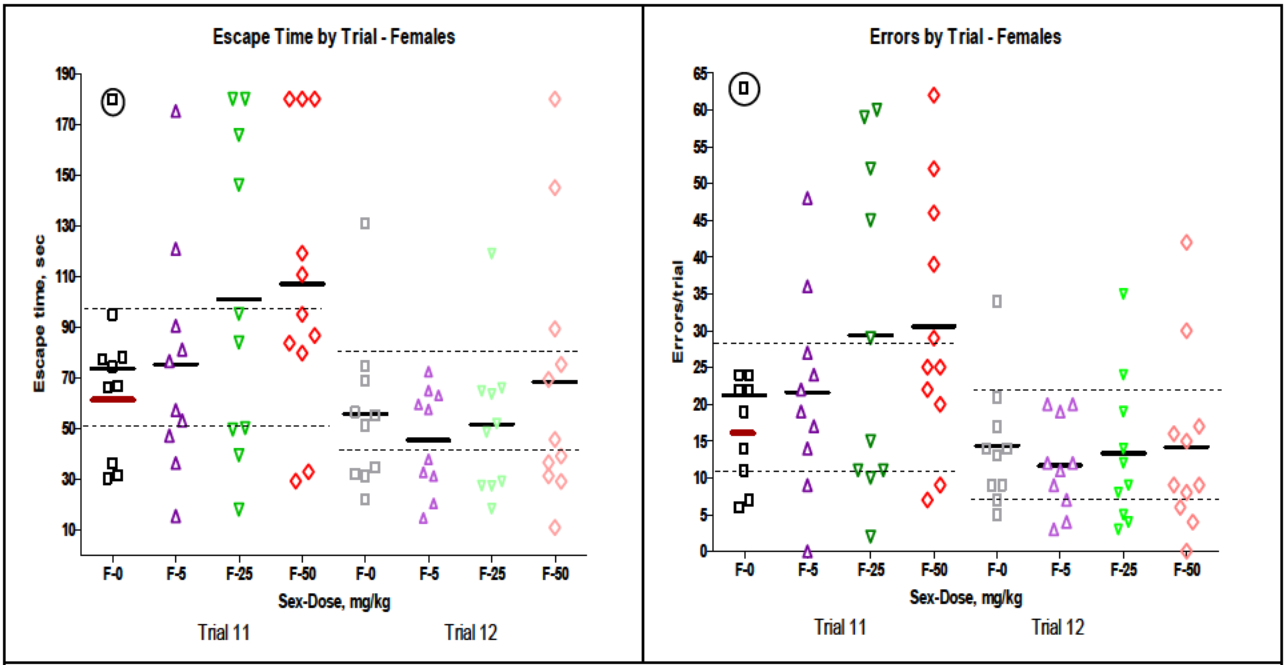
Table 8: Selected Rows Reviewer's Table - Learning and Memory - SN 02148

			Male				Female			
Phase	**Comment**		**0**	**5**	**25**	**50**	**0**	**5**	**25**	**50**
3 Memory Path A Day 27	Mean time, sec	Trial 11 SD	82.4 50.4	81.1 40.3	64.4 30.0	82.2 35.1	73.6 43.4 [61.7² 23.4]	75.3 46.0	100.7 62.4	***106.9**** 54.4
		Trial 12 SD	49.8 27.0	60.2 53.4	56.8 22.8	43.7 21.7	55.7 31.5	45.3 20.4	51.5 29.6	68.2 52.4
		Overall SD	66.1 42.7	70.9 47.2	60.6 26.2	63.0 34.6	64.6 38.0	60.3 37.9	76.1 53.8	87.6 55.8
	Historical range by trial		11: 38.3-127.5 (38.7-114.7) 12: 40.3-152.5 (8.9-110.5)				11: 50.8-97.2 (44.6-101.4) 12: 39.9-82.2 (35.6-80.8)			
	Mean errors/trial	Trial 11 SD	22.9 13.6	24.6 11.7	18.9 11.2	25.0 11.7	21.2 16.2 [16.6² 7.2]	21.6 13.5	29.4 22.6	***30.6**** 17.4

			Male				Female			
Phase	**Comment**		**0**	**5**	**25**	**50**	**0**	**5**	**25**	**50**
		Trial 12	11.6	17.6	14.8	11.7	14.3	11.7	13.3	14.2
		SD	8.9	19.0	7.6	7.1	8.4	6.3	10.2	12.2
		Overall	17.3	21.1	16.9	18.4	17.8	16.7	21.4	22.4
		SD	12.6	15.8	9.6	11.6	13.1	11.5	18.9	16.9
	Historical range by trial		11: 9.2-25.6 (1.5-27.9) 12: 9.1-27.0 (5.3-23.3)				11: 11.4-28.8 (8.8-29.2) 12: 7.3-21.8 (5.9-21.5)			

M = mean; SD = standard deviation; ² Mean and SD calculated with values for control female 45649-11 omitted, based on statistical Q test. Historical range by trial = reported maximum and minimum (Laboratory historical control mean ± 2S.D.) Blue text indicates values outside historical range.

Figure 2: Reviewer's Graphs of F1 Female Memory Trials



Thin dotted lines are the historical control minimum and maximum for each parameter Solid black line = group mean, Circled control F45649-11 could be eliminated by a statistical Q-test. Heavy dark red line is resulting mean for control females with F45649-11 excluded.

Although the F1 male groups did not display effects on memory, possible reasons exist. First, sex differences are known to exist in brain function and behavior (Mizuno and Geize 2010). For example, perinatal exposure to dexamethasone did not result in adverse clinical neurological outcomes, but did results in deficits in learning and memory functions with exposed females in all age groups more greatly affected than the exposed males (Machhor et al. 2004). Second, spatial maze test methods differ in their ability to detect deficits in learning and memory. In a study comparing four spatial maze methods, Akaike et al. (1994) found that the Biel test ranked below the Morris water maze, and radial eight-arm maze tests. Therefore, the Biel test used in Study 02148 may not have been sensitive enough to detect deficits in F1 males.

All PARs, including PAR-1, are widely expressed in the central and peripheral nervous systems throughout development (Luo et al. 2007), particularly in the late embryonic and early postnatal nervous system (Niclou et al. 1998) with greater expression in some cells of the cerebellum, the thalamus, the hippocampus and the cortex. Multiple studies indicate the direct involvement of PARs, particularly PAR-1, in brain development and function (Gorbacheva et al. 2006; Pike et al. 1996; Striggow et al. 2000; Vaughan et al. 1995; Debeir et al. 1998; Rohatgi et al. 2004).

The hippocampus is part of a system required for declarative memory in humans and spatial, as well as contextual, memory in rodents (Kandel 2009). Activation of PAR-1 either through proteolytic activity of thrombin or through a PAR-1 activating peptide potentiated hippocampal N-methyl-D-aspartate (NMDA) receptor responses in CA1 pyramidal cells of wild-type mice and rats (Gingrich et al. 2000). In addition, the potentiation of the NMDA receptor by thrombin was significantly attenuated in hippocampal neurons from PAR-1 $^{-/-}$ mice lacking PAR-1 function. Subsequently, PAR-1$^{-/-}$ animals were shown to have significant deficits in two tests of behavioral learning, passive avoidance and conditioned fear learning (Almonte et al. 2007). Although NMDA receptor function or expression was normal in PAR-1$^{-/-}$ mice (Gingrich et al. 2000; Lee et al. 2007; Almonte et al. (2013), the loss of PAR-1 function impaired the induction and ceiling for NMDA receptor-dependent long-term potentiation (LTP), resulting in deficits in hippocampus-dependent memory formation and long-term synaptic plasticity in the hippocampus (Almonte et al. 2013).

Motor activity and auditory startle response are typically ***correlated with body weight*** *and likely represent secondary effects to observed decrements in mean body weight gain and body weight was not utilized as a co-variable in the behavioral statistical analysis.*

The sponsor's statement is a generalization that is not supported by the data in this study. The reviewer did try to correlate body weight on PND 21 with the results of the acoustic startle, motor activity and memory tests. Some partial correlation was observed in the mid-dose females, but not in the high dose females. A particularly notable exception to the sponsor's statement is high dose F1 female 45678-13, who had a body weight above the maximum of the historical control range. This female had maximum escape times and maximum number of errors for both memory Trials 11 and 12, as well as an acoustic startle Vmax lower than the historical range and a Tmax above the historical range.

Sponsor's statement: The potential role of PAR-1 in reproduction and development is much less well understood than its role in platelet activation at this time.

The reviewer totally agrees with this statement.

4 Integrated Summary and Safety Evaluation

Vorapaxar (SCH 530848), an inhibitor of the protease activated receptor-1 (PAR-1), is being developed as an anti-platelet agent for the prevention of atherothrombotic events in patients with a history of myocardial infarction. The reviewer previously recommended that NDA 204886 for vorapaxar is approvable from a pharmacology and toxicology perspective because most of the toxicities identified in the non-clinical studies have adequate safety margins relative to the human exposure at the recommended human dose (RHD) or appear to be species specific. Table 9 summarizes the animal to human exposure ratios for the PPND studies. The NOAEL for decreased memory in F1 female rat offspring in the PPND study after SCH 530848 treatment of the F0 dams only has a 4-fold safety margin compared to human exposure at the RHD. The label needs to describe these potential effects for women of child-bearing age.

Table 9: Summary of Animal to Human Exposure Ratios

			Exposure at NOAEL		Safety Margin	
Study/ Species	Sex	NOAEL (mg/kg)	SCH 530848 AUC (ng*hr/L)	Metabolite M20[†] AUC (ng*hr/L)	SCH 530848[‡]	Metabolite M20[§]
Reproductive and Developmental Toxicology						
Pre/Post-natal – Rat GD 6 to weaning	F_0 -maternal	50	88300	71	67	0.3
	F_1 -prenatal	50	88300	71	67	0.3
	F_1 (perinatal)	25	41460	33	31	0.1
	F_1 (postnatal)	**50**	88300	71	67	0.3
	F_1 (behavior)	**25**	41460	33	31	0.1
	F_1 (female memory)	5	5025	4	4	0.02
	F_1 (mating/fertility)	50	88300	71	67	0.3
	F_2 prenatal fetal toxicity	25	41460	33	31	0.1

[†] Using % M20 as 0.55% for male rats, 0.08% for female rats, 11.5% for rabbits, 5.1% for male mice, 4.3% for female mice, 4.6% for male monkeys, 4.9% for female monkeys and 19.7% for human.
[‡] At the RHD of 2.5 mg, the vorapaxar total $AUC_{(0\text{-}24\ h)}$ value is 1320 ng•hr/mL (The sponsor's value for vorapaxar was obtained from Meta analysis for steady-state PK analysis (Section 5.3.5.3.4.3). [§] M20 $AUC_{(0\text{-}24\ h)}$ value is 260 ng•hr/mL

12 References

Akaike M, Ohno H, Tsutsumi S, Omosu M. 1994. Comparison of four spatial maze learning tests with methylnitrosourea-induced microcephaly rats. Teratology; 49(2): 83-89.

Almonte AG, Hamill CE, Chhatwal JP, Wingo TS, Barber JA, Lyuboslavsky PN, David Sweatt J, Ressler KJ, White DA, Traynelis SF. 2007. Learning and memory deficits in mice lacking protease activated receptor-1. Neurobiol Learn Mem.; 88(3): 295-304.

Almonte AG, Qadri LH, Sultan FA, Watson JA, Mount DJ, Rumbaugh G, Sweatt JD. 2013. Protease-activated receptor-1 modulates hippocampal memory formation and synaptic plasticity. J Neurochem.; 124(1): 109-22.

Dean RB and Dixon WJ. 1951. Simplified Statistics for Small Numbers of Observations. Anal. Chem., 23 (4): 636–638

Debeir T, Benavides J, Vigé X. 1998. Involvement of protease-activated receptor-1 in the in vitro development of mesencephalic dopaminergic neurons. Neuroscience; 82(3): 739-52.

Gingrich MB, Junge CE, Lyuboslavsky P, Traynelis SF. 2000. Potentiation of NMDA receptor function by the serine protease thrombin. J Neurosci.; 20(12): 4582-4595.

Gorbacheva LR, Storozhevykh TP, Pinelis VG, Ishiwata S, Strukova SM. 2006 Modulation of hippocampal neuron survival by thrombin and factor Xa. Biochemistry(Mosc.); 71: 1082–1089.

Kandel ER. 2009. The biology of memory: a forty-year perspective. J. Neurosci.; 29: 12748–12756.

Lee CJ, Mannaioni G, Yuan H, Woo DH, Gingrich MB, Traynelis SF. 2007. Astrocytic control of synaptic NMDA receptors. J Physiol.; 581(Pt 3): 1057-81.

Luo W, Wang Y, Reiser G. 2007 Protease-activated receptors in the brain: Receptor expression, activation, and functions in neurodegeneration and neuroprotection. Brain Research Reviews; 56: 331–345

Machhor N, Balaji T, Raju TN. 2004. Postnatal dexamethasone and long term learning and memory functions in developing rats: Effect of postnatal age and gender. Life Sci.; 74(15): 1925-35.

Mizuno K, Giese KP. 2010. Towards a molecular understanding of sex differences in memory formation. Trends Neurosci.; 33(6): 285-91.

Niclou SP, Suidan HS, Pavlik A, Vejsada R, Monard D, 1998. Changes in the expression of protease-activated receptor 1 and protease nexin-1 mRNA during rat nervous system development and after nerve lesion. Eur. J. Neurosci.; 10: 1590–1607

Pike CJ, Vaughan PJ, Cunningham DD, Cotman CW. 1996. Thrombin attenuates neuronal cell death and modulates astrocyte reactivity induced by β-amyloid in vitro. J. Neurochem.; 66: 1374–1382.

Rohatgi T, Sedehizade F, Reymann KG, Reiser G. 2004. Protease-activated receptors in neuronal development neurodegeneration, and neuroprotection: thrombin as signaling molecule in the brain. Neuroscientist; 10: 501–512.

Striggow F, Riek M, Breder J, Henrich-Noack P, Reymann KG, Reiser G, 2000. The protease thrombin is an endogenous mediator of hippocampal neuroprotection against ischemia at low concentrations but causes degeneration at high concentrations. Proc. Natl. Acad. Sci. U. S. A.; 97: 2264–2269

Vaughan PJ, Pike CJ, Cotman CW, Cunningham DD. 1995. Thrombin receptor activation protects neurons and astrocytes from cell death produced by environmental insults. J Neurosci.; 15: 5389−5401.

13 Appendix/Attachments

Appendix 1: Labeling Recommendations

8.1 Pregnancy
Sponsor's proposal:
Pregnancy Category B

Reviewer's recommendation:
Pregnancy Category B
There are no adequate and well-controlled studies of TRADEMARK use during pregnancy in humans.

Risk summary
Based on data in rats and rabbits, vorapaxar is predicted to have a relatively low probability of increasing the risk of most adverse developmental outcomes above background risk. No embryo/fetal toxicities, malformations or maternal toxicities were observed in rats exposed during gestation to 56 times the human systemic exposure at the RHD of 2.5 mg. No embryo/fetal toxicities, malformations or maternal toxicities were observed in rabbits exposed during gestation to 26 times the human systemic exposure at the RHD of 2.5 mg. The No Adverse Effect Level (NOAEL) for adverse effects on perinatal survival and body weight in off-spring exposed in utero and during lactation was 31 times the human systemic exposure at the RHD. Both male and female pups displayed effects on sensory function and neurobehavioral development at weaning, but not later in development. Although no effect was observed on learning in either sex, female, but not male pups, displayed decreased memory with a NOAEL of 4 times the human systemic exposure at the RHD. However, animal studies are not always predictive of a human response. TRADEMARK should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Animal Data
In the rat embryo/fetal developmental toxicity study, pregnant rats received daily oral doses of vorapaxar at 0, 5, 25 and 75 mg/kg from implantation to closure of the fetal hard palate. No embryo/fetal toxicities, malformations or maternal toxicities were

observed in rats exposed up to 56 times the human systemic exposure at the RHD of 2.5 mg.

In the rabbit embryo/fetal developmental toxicity study, pregnant rabbits received daily oral doses of vorapaxar at 0, 2, 10, or 20 mg/kg from implantation to closure of the fetal hard palate. The NOAEL for maternal and fetal toxicity was equal to or above the highest dose tested. However, an overall increase in the number of litters with any malformation was observed at the highest dose, where systemic exposures were 89-fold higher than the human exposure at RHD.

The effects of vorapaxar on prenatal and postnatal development was assessed in pregnant rats dosed at 0, 5, 25, or 50 mg/kg/day from implantation through the end of lactation. Rat pups exposed to vorapaxar in utero and through 21 days of lactation had decreased survival compared to the control group from birth to postnatal (PND) 4 at exposures 67 times the human exposure at the RHD , however, there was no effect on survival of pups from 4 to 21 days after birth. Body weight gain of pups was reduced from birth to postnatal day 4 and for the overall pre-weaning period at exposures 67 times the human exposure at the RHD. Both male and female pups displayed effects on sensory function (acoustic startle) and neurobehavioral (locomotor assay) development on PND 20 and 21, but not later (PND 60, 61) in development. Female, but not male, pups displayed decreased memory (PND 27) at exposures 31 times the human exposure at the RHD; however no effect was observed on learning in either sex. In utero and lactational exposure did not affect fertility or reproductive behavior of offspring at exposures up to 67 times the RHD.

8.3 Nursing Mothers
Sponsor's proposal

(b) (4)

Reviewer's recommendation:
It is unknown whether vorapaxar or its metabolites are excreted in human milk. Data in lactating female (dam) rats indicate that the level of [^{14}C]-vorapaxar in milk was 6-fold higher than the level in maternal plasma, indicating a high excretion of [^{14}C]-vorapaxar into milk (7% of the maternal dose). Exposure to vorapaxar in nursing pups was 34% of that in dams based on plasma AUC levels. No studies have been conducted to assess the impact of vorapaxar on milk production in humans, its presence in human breast milk, or its effects on the breast-fed infant. A risk to newborns and infants cannot be excluded. Because vorapaxar is predicted to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, considerable caution should be exercised when TRADEMARK is given to a nursing mother.

12.1 Mechanism of Action
Sponsor's proposal

(b) (4)

Reviewer's recommendation:
Vorapaxar is a slowly reversible inhibitor of thrombin activated PAR-1 receptors on platelets and a wide variety of cell types, including endothelial cells and neurons.. Vorapaxar inhibits thrombin-induced platelet aggregation in in vitro studies. In addition, vorapaxar inhibits thrombin receptor agonist peptide (TRAP)-induced platelet aggregation without affecting coagulation parameters or increasing bleeding time in monkeys. Vorapaxar does not inhibit platelet aggregation induced by the agonists, adenosine diphosphate (ADP), collagen and a thromboxane mimetic.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Sponsor's proposal

(b) (4)

Reviewer's recommendation:
Carcinogenicity
Carcinogenicity studies were conducted in rats and mice dosed orally with vorapaxar for two years. Male and female rats dosed at 0, 12.5, 25, or 50 mg/kg/day showed no carcinogenic potential at systemic exposures (AUC) in males and females that were 10- and 29-fold higher, respectively, than the human systemic exposure at the 2.5 mg dose. In male and female mice dosed at 0, 3, 10, and 30 mg/kg/day, vorapaxar showed no carcinogenic potential at systemic exposures (AUC) in males and females that were 28- and 34-fold higher, respectively, than the human systemic exposure.

Mutagenesis
Vorapaxar was not mutagenic in the Ames bacterial reverse mutation assay, and not clastogenic in an in vitro human peripheral blood lymphocyte assay or an in vivo mouse micronucleus assay after intraperitoneal administration.

Impairment of Fertility
Fertility studies in rats showed that vorapaxar had no effect on either male or female fertility at doses up to 50 mg/kg/day, a dose resulting in systemic exposures (AUC) in

male and female rats that are 40 and 67 times, respectively, the human systemic exposure at the 2.5 mg dose.

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

/s/

PATRICIA P HARLOW
02/19/2014

THOMAS PAPOIAN
02/19/2014
Concur.

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 204886
Supporting document/s:	1, 18, 23, 29, 38, 66
Applicant's letter date:	5/10/2013, 6/21/2013, 8/30/2013, 9/27/2013, 10/22/2013, 12/06/2013
CDER stamp date:	5/10/2013, 6/21/2013, 8/30/2013, 9/27/2013, 10/22/2013, 12/06/2013
Product:	Vorapaxar (SCH 530348)
Indication:	Reduction of atherothrombotic events in patients with a history of myocardial infarction
Applicant:	Merck (previously Schering-Plough)
Review Division:	Cardiovascular and Renal Products (DCRP)
Reviewer:	Patricia P. Harlow, Ph.D.
Supervisor/Team Leader:	Thomas Papoian, Ph.D., D.A.B.T.
Division Director:	Norman Stockbridge, M.D., Ph.D.
Project Manager:	Alison Blaus

Template Version: September 1, 2010 (Modified by DCRP: Feb. 6, 2013)

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204886 are owned by Merck or are data for which Merck has obtained a written right of reference. Any information or data necessary for approval of NDA 204886 that Merck does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204886.

TABLE OF CONTENTS

Table of Tables

Table of Figures

Table of Appendices

1 Executive Summary

1.1 Introduction (and Clinical Rationale)

Vorapaxar (SCH 530848), an inhibitor of the protease activated receptor-1 (PAR-1), is being developed as an anti-platelet agent. Under NDA 204886, vorapaxar is proposed for the prevention of atherothrombotic events in patients with a history of myocardial infarction. The dosing regimen in the Phase 3 trial was 2.5 mg of vorapaxar once a day.

1.2 Brief Discussion of Nonclinical Findings

SCH 530348 is an antagonist of a thrombin receptor now called the protease activated receptor-1 (PAR-1), which is critical in primate and human platelet aggregation and smooth muscle cell proliferation induced by thrombin. The PAR-1 receptor is one of a family of four seven-transmembrane–domain G-protein-coupled receptors that are activated by protease cleavage near the amino terminus or by exogenous agonist peptides.

SCH 530348 directly binds to human platelet membranes with a calculated K_d of 1.46 nM. Because of slow on and off rates, the binding of SCH 530348 to PAR-1 in platelet and smooth muscle cell membranes depends on assay conditions. The binding of SCH 530348 is competitive in the presence of a radiolabeled high affinity thrombin receptor agonist peptide (TRAP) ([^{3}H]-haTRAP) when both are added simultaneously, but is non-competitive when SCH 530348 is added prior to the agonist peptide. SCH 530348 inhibited the binding of haTRAP to human platelet membranes with a K_i of 8.5 nM and inhibited haTRAP-induced aggregation of washed human platelets with an IC_{50} of 15 nM. Although SCH 530848 inhibited human platelet aggregation induced by α-thrombin or various PAR-1 agonist peptides, it did not inhibit human platelet aggregation induced by ADP, thromboxane, collagen, PAR-4 agonist peptides (AYPGKF and GYPGKF) or a PAR-2 agonist peptide (SLIGRL). Therefore, SCH 530848 is specific for PAR-1 versus PAR-2 and PAR-4. The specificity of SCH 530848 for PAR-1 relative to PAR-3 is unknown.

SCH 530348 does not exhibit PAR-1 agonist activity on either platelet or human coronary arterial smooth muscle cells. SCH 530348 inhibits thrombin and haTRAP-stimulated calcium mobilization and thymidine incorporation in human coronary arterial smooth muscle cells. The major human metabolite of SCH 530848 [SCH 2046273 (M20)] also inhibited PAR-1 agonist induced calcium efflux from human coronary arterial smooth muscle cells to a similar extent as the parent SCH 530348. Although the effects of SCH 530348 are slowly reversible over time and with stringent washing, the SCH 530848 inhibition of PAR-1 signaling in platelets and smooth muscle cells is effective for many hours.

Ex vivo platelet aggregation in response to haTRAP was evaluated in whole blood collected from cynomolgus monkeys at various times after oral administration of either SCH 530348 or SCH 602539, a structurally similar analog of SCH 530848. A dose of 0.1 mg/kg SCH 530348 resulted in complete inhibition of ex vivo haTRAP-induced platelet aggregation from 2 to 5 hours after dosing and >90% inhibition of ex vivo haTRAP-induced platelet aggregation at 24 hours after dosing. Likewise, a dose of 0.1

mg/kg SCH 602539 resulted in complete inhibition of ex vivo platelet aggregation from 3 to 6 hours after dosing and >60% inhibition of ex vivo haTRAP-induced platelet aggregation at 24 hours after dosing.

SCH 602539 alone, cangrelor alone, and the combination of SCH 602539 with cangrelor were evaluated in a Folts thrombosis model in cynomolgus monkeys. In this model, platelet-dependent thrombus formation occurs after placement of a constrictor over a region of endothelial damage in the carotid artery resulting in cyclic flow reductions (CFRs). The dose of 0.1 mg/kg SCH 602539 alone reduced the frequency of CFRs by 50% and the dose of 0.1 µg/kg/min cangrelor alone reduced the frequency of CFRs by 40%. However, the combination of SCH 602539 and cangrelor reduced the frequency of CFRs by more than an additive amount, suggesting a synergistic antithrombotic effect. The similarity of the effects of SCH 530848 and SCH 602539 in inhibiting platelet aggregation in vitro and ex vivo suggests that SCH 530848 would produce results similar to that of SCH 602539 in the Folts thrombosis model in monkeys. However, SCH 530848 has not been specifically evaluated in this or any other animal model of thrombosis.

In a panel of G-protein coupled receptors, transporters, and ion channels, the selectivity of SCH 530348 binding to most receptors tested was equal to or greater than 50-fold. However, SCH 530348 at 6 µM inhibited the binding of picrotoxinin to the chloride channel by 50% to 66%. The reference compound, picrotoxinin, a convulsant with an IC_{50} of 0.93 µM primarily acts as a noncompetitive, selective $GABA_A$ receptor antagonist. The IC_{50} values for picrotoxinin and SCH 530348 differ by less than 6.5-fold.

In single dose safety pharmacology studies, SCH 530348 did not significantly affect gastrointestinal, renal, respiratory, or central nervous system function in rats or hemostasis parameters in rats and monkeys. Although SCH 530348 inhibited hERG current in mouse L cells with a nominal IC_{50} of 341 nM, it did not significantly affect action potential parameters in dog Purkinje fibers up to a maximum measured concentration of 200 nM. Since SCH 530348 is >99% bound to protein, 200 nM is 38-times the projected maximum unbound drug concentration in humans. Furthermore, oral doses up to 20 mg/kg did not produce ECG alterations or statistically significant alterations in the RR, QT, PR or QRS intervals in cardiovascular safety pharmacology studies in cynomolgus monkeys.

Bleeding liability of SCH 530848 was evaluated in cynomolgus monkeys after single or multiple doses when administered alone or in combination with aspirin and clopidogrel. Administration of 1 or 5 mg/kg SCH 530348 alone for 14 days did not increase template bleeding time compared to the bleeding time for the control group, whereas the combination of aspirin and clopidogrel prolonged bleeding time. However, administration of 1 or 5 mg/kg SCH 530348 in combination with aspirin and clopidogrel did not exacerbate the prolonged bleeding observed following administration of the combination of aspirin and clopidogrel alone.

SCH 530348 is rapidly absorbed following oral administration and slowly eliminated in monkeys and healthy humans. Monkeys and humans dosed repeatedly for 28 days showed accumulation of exposure. Systemic exposure to SCH 530348 increased as the dose of SCH 530348 increased in rats, mice, pregnant rabbits, monkeys, and humans.

Following single oral doses, vorapaxar had a mean bioavailability (F) of 33% and 86% in rats and monkeys, respectively. In most toxicokinetic studies, the maximum plasma concentration (Cmax) occurred between 1 to 4 hours following oral administration to rats and monkeys. The volume of distribution, Vss, for vorapaxar in a single dose pharmacokinetic study was 4.6 and 2.2 L/kg for rats and monkeys, respectively, indicating distribution of vorapaxar to the extracellular space and tissues in both species.

The protein binding of SCH 530348 in human plasma (99.9%) was slightly, but not significantly, higher than the protein binding of SCH 530348 to plasma from rats (99.6%), mice, rabbits and monkeys (99.8%). The protein binding of the metabolite, SCH 2046273 (99.1%), to human plasma was lower than the protein binding of SCH 530348 (99.9%) to human plasma. SCH 530348 was highly bound to human serum albumin compared to α1-acid glycoprotein at physiological concentrations.

In a whole body autoradiography study in rats, [^{14}C]-SCH 530348 was widely distributed to all tissues, except the lens of the eye. Maximal tissue concentrations occurred generally at 8 hours post dose. Subsequently, concentrations in most tissues declined so that by 48 or 72 hours post dose the concentrations were below the detection limit. This pattern of radiocarbon tissue distribution, except for the pituitary and the pigmented tissues of the eye and the skin, was similar in both sexes and in both albino and pigmented rats. Other than the gastrointestinal tract, the highest tissue concentrations were observed in the liver, spleen, adrenal gland, pituitary, thyroid gland, kidney, and brown fat. At 48 hours post-dose when most of the dose had been excreted, the highest tissue concentrations were in the pituitary, adrenal gland, and spleen. In pigmented rats the highest concentration at 48 hours post dose was in the pigmented region of the eyeball. At 168 hours post dose, the albino rats had detectable levels of radioactivity only in the pituitary, testis and epididymis. In addition to these tissues, the pigmented rats of both sexes at 168 hours post-dose also had concentrations in the pigmented region of the skin and the eye with the half-life in the eye much greater than 168 hours.

In pregnant female rats on gestation day 18, a single oral dose of [^{14}C]-SCH 530348 was distributed to both maternal and fetal tissues based on quantitative whole body autoradiography. Since the cumulative fetal blood exposure to [^{14}C]-SCH 530348 radioactivity was similar to cumulative maternal blood exposure, substantial amounts of [^{14}C]-SCH 530348 crossed the placenta.

In all species tested, SCH 530348 metabolism primarily involves oxidative carbamate cleavage and hydroxylation. One mono-hydroxy SCH 530848 metabolite (M20, SCH 2046273) has been found in human plasma at 10-31% of parent SCH 530848 levels depending upon the particular study. Although levels of SCH 2046273 are extremely low in rat plasma, the levels in mice and monkeys are adequate to allow the metabolite to be considered toxicologically qualified.

In vitro studies indicated that CYP3A4 is the major P450 enzyme metabolizing SCH 530348 to an amine metabolite M19, whereas both CYP3A4 and CYP2J2 are responsible for metabolism of SCH 530348 to the M20 metabolite, which is then further metabolized to a carboxylic acid metabolite M16 and the amine metabolite M19.

The excretion of SCH 530348 and its metabolites in all species was primarily fecal with urinary excretion accounting for <5% of the dose. Studies in bile-duct cannulated rats and monkeys indicated that biliary excretion is the primary elimination route of absorbed SCH 530348. In rats, most (>83%) of the radioactive dose was recovered in feces and urine within 72 hours after dosing.

A study in lactating rats indicated that levels of [^{14}C]-SCH 530348-derived radioactivity in milk were 6-fold higher than that in the plasma of the dams. Consequently, the nursing pups received 34% of the mother's exposure, based on plasma AUC comparisons. Over the first 24 hours following dose administration, each dam excreted 7% of the administered dose via milk. If excretion into milk is similar between rats and humans, human infants up to 1 year of age are expected to receive doses of SCH 530848 that would be expected to inhibit platelet aggregation by more than 50%.

SCH 530348 is a highly permeable (BCS Class 1 or 2) compound with apical to basolateral permeability independent of its initial concentration and higher than that of the reference compound, pindolol. The passive permeability of SCH 2046273 (M20) is also very high and is comparable to that of verapamil and metoprolol.

Studies using pooled human liver microsomes with P450 marker substrates indicated SCH 530348 did not inhibit CYP1A2, CYP2B6, CYP2E1, or CYP3A4/5 and only inhibited CYP2A6, CYP2C19, CYP2D6, or CYP2C9 at high concentrations (≥ 30 µM). However, CYP2E1 activity increased 3-fold with increasing SCH 530348 concentrations. In contrast, SCH 530348 directly inhibited CYP2C8 with an IC_{50} of 1.5 µM. Since SCH 530348 was found to be a mixed inhibitor of CYP2C8 with a K_i value of 0.86 µM, which is close to the systemic plasma C_{max} (0.94 µM) in humans after a single 40 mg loading dose, the possibility exists for drug-drug interactions of SCH 530348 with co-administered drugs that are CYP2C8 substrates. SCH 2046273 (M20) up to 1 µM also did not inhibit five human liver microsomal cytochrome P450 activities, including CYP2B6, CYP2C19, CYP2D6, and two activities of CYP3A4.

Studies with human hepatocytes indicated that the relative effectiveness of 1, 10, and 30 µM SCH 530348 to induce CYP 450 activities was less than 15%, 25%, and 40%, respectively, of the appropriate prototypical inducer. Although 10 and 30 µM SCH 530348 resulted in an increase in CYP1A2 activity of 2.7 and 3.0-fold, respectively, and an increase in CYP2B6 activity of 3.9 and 4.7-fold, respectively, the report concluded that SCH 530348 is not expected to have the potential to induce P450 liabilities at clinically therapeutic concentrations.

In the Caco-2 cell model with [^{3}H]-digoxin as a P-glycoprotein (P-gp) substrate probe, SCH 530348 was shown to be a potent P-gp inhibitor with an IC_{50} value (1.2 µM) similar to the IC_{50} value for cyclosporine A (0.8 µM). However, SCH 530348 is not a P-gp substrate. SCH 530848 and SCH 2046273 (M20) did not significantly inhibit the transporters OATP1B1, OATP1B3, OAT1, or OCT2 at the highest concentration tested (10 µM). In contrast, OAT3 and BCRP transport was inhibited by SCH 530848 with IC_{50} values of 2.2 and 2.5 µM, respectively, and by SCH 2046273 with IC_{50} values of 0.6 and 1.6 µM respectively. However, an evaluation relative to unbound concentrations concluded that vorapaxar inhibition of P-gp in the gut is the only potential clinical drug-drug interaction.

Acute toxicity studies in rats indicated the oral LD_{50} of SCH 530348 is greater than 1000 mg/kg in rats and monkeys.

Repeat dose studies in monkeys were conducted for one, three, six, and twelve months. The NOAELs were 20 mg/kg in the 1 and 6 month studies, based on a lack of findings at the highest dose. The NOAEL was 30 mg/kg in the 3 month study, based on vacuolated macrophages in the spleen and lymph nodes of males and females dosed at 60 and 90 mg/kg. The high dose females also had vacuolated macrophages in adrenal gland, bone marrow, small intestine, and thymus as well as vacuolation of liver Kupffer cells in association with Kupffer cell hyperplasia. The vacuolation in the spleen and blood was confirmed by electron microscopy as phospholipidosis. The NOAEL was 5 mg/kg in the 12 month study based on increased adrenal relative weights in both males and females dosed at 20 mg/kg.

Repeat dose studies in rats were conducted for one, three, and six months. The NOAELs were 3 mg/kg and < 50 mg/kg in the 1 and 3 month studies, respectively. The NOAELs were 3 mg/kg and 10 mg/kg in males and females, respectively in the 6 month study. In all three rat studies, phospholipidosis, confirmed by electron microscopy, was observed primarily in the epithelium of bile ducts and seminal vesicles and in macrophages in the liver, spleen, lungs, lymph nodes and small intestine.

In addition, retinal vacuolation, described as vacuoles in the inner nuclear layer of the retina consisting of distended cellular organelles and cell processes without evidence of phospholipidosis or any degenerative changes, was observed in most rat studies. Initially found in a later 1-month study in rats, retinal vacuolation was found in previously conducted rat studies upon re-examination. However, retinal vacuolation was not found in the rat carcinogenicity study, in any mouse study, or in any monkey study. Retinal vacuolation was found in rat studies after seven, but not after three doses. The finding is reversible after 4 weeks of recovery. After 6 weeks of dosing in rats, no effect was observed on retinal function in rats, although vacuolation was present histologically. After three daily doses, SCH 530848 did not induce phototoxic effects in the eyes and skin of pigmented rats after a 1 hour exposure to simulated sunlight in contrast to the positive control 8-methoxypsoralen. A greater number of older Sprague Dawley rats had retinal vacuolation than younger rats after dosing with SCH 530348. SCH 602539, a close structural analog of SCH 530348, also induced retinal vacuolation in Sprague Dawley rats; however, two structurally distinct PAR-1 inhibitors (SCH 590709 and SCH 2490130) did not, suggesting that the induction of retinal vacuolation is not related to the mechanism of action of these PAR-1 inhibitors. Retinal vacuolation was observed when the eyes were fixed under a number of conditions when the fixative was aldehyde based, but not after 24 hours refrigeration in situ or in Carnoy's fixative (acetic acid fixative). The sponsor considers retinal vacuolation to be a drug-related exaggeration of common retinal fixation artifact that is associated with SCH 530348-treatment and aldehyde-based fixation.

SCH 530348 was negative for genotoxicity in adequate assays in vitro for bacterial reversion and chromosomal aberration in human peripheral blood lymphocytes and in vivo for micronucleus formation in mice. Likewise, a batch of SCH 530848 with a higher level of impurities was negative for genotoxicity in adequate assays in vitro for bacterial reversion and chromosomal aberration in human peripheral blood lymphocytes. SCH

530348 was not mutagenic either in the presence or in the absence of solar-simulated light in Salmonella typhimurium strains TA1537 and TA102 or in Escherichia coli strain WP2 (pKM101).

In an acceptable carcinogenicity study, Sprague Dawley male and female rats received oral gavage doses of 0, 3, 10 or 30 mg/kg SCH 530348 for up to 104 weeks. Although SCH 530348 treatment had no effect on mortality, the high dose groups had 16-17% decreases in body weight gain during the study. The high dose males had increased incidences of basal cell tumor of the skin and histiocytic sarcoma: the high dose females had increased incidences of hepatocellular adenoma and uterine adenoma. The Executive CAC concluded that no neoplastic findings were related to SCH 530348 treatment under the conditions of this study, since these tumors did not have p-values that attained the significance level required for the tumor to be considered positive. At the maximum dosage of 30 mg/kg/day in males and females, the plasma concentrations at 0.5, 1 and 2 hours post dose were similar to those in the 6-month rat study. Thus, rat to human exposure ratios for the high dose male and female rats in the carcinogenicity are estimated to be 10 and 29 times, respectively, the human exposure at a dose of 2.5 mg once a day.

In an acceptable carcinogenicity study, CD-1 male and female mice received oral gavage doses of 0, 1, 5, 15 mg/kg/day SCH 530348 for up to 102 to 103 weeks. Although SCH 530348 treatment had no effect on mortality, the high dose males and females had 16% and 14% decreases, respectively, in body weight gain during the study. The incidence of bronchiolo-alveolar adenoma increased in the high dose females and the incidence of bronchiolo-alveolar carcinoma increased in the high dose males. However, the p values for each of these tumors and their combination in the trend test did not attain the significance level required for these common tumors to be considered positive. Based on dose-proportionality of Cmax and AUC values between 5 and 25 mg/kg in a pharmacokinetic study, the exposures ($AUC_{(0-24)}$) found in the three-month mouse study were used to estimate animal to human exposure comparisons. The mouse to human exposure ratios for the high dose male and female mice in the carcinogenicity study are at least 28 and 34 times, respectively, the human exposure at a dose of 2.5 mg once a day.

In an acceptable fertility and early embryo development study, male and female rats were treated with 0, 5, 25, 50 mg/kg. The NOAEL for paternal and maternal toxicity was 25 mg/kg, because body weight gain decreased in the high dose groups. No drug-related effects were observed on estrous cycling, mating or fertility in treated males or treated females. The NOAEL for fertility and embryo toxicity is 50 mg/kg.

In an acceptable embryo-fetal developmental toxicity in rats, the doses were 0, 5, 25, and 75 mg/kg. The NOAEL for maternal toxicity was 25 mg/kg based on the decreases in body weight and food consumption. The NOAEL for fetal toxicity was 25 mg/kg based on a statistically significant decrease in mean fetal weight in the high dose group. Rare malformations in the fetal heart occurred in two fetuses in two litters only at the high dose of 75 mg/kg along with an external and skeletal malformation (exencephaly) in a third litter. An increase incidence of lumbar rib and unossified sternabra also occurred in the high dose group. Although these fetal findings may be attributable to the maternal

toxicity in the high dose group, the reviewer concluded the no effect level for overall malformation is 25 mg/kg.

In an acceptable embryo-fetal developmental toxicity in rabbits, the doses were 0, 2, 10, and 20 mg/kg. The no-effect levels for maternal and embryo-fetal toxicity in rabbits were 20 mg/kg. The no-effect dose for teratogenicity was 10 mg/kg based on an increase in total malformations at 20 mg/kg.

Two pre/postnatal development (PPND) studies were conducted. In the first study, pregnant F_0 female Sprague-Dawley rats received single daily oral gavage doses of 0, 5, 25 or 50 mg/kg SCH 530348 from gestation Day 6 through postnatal day (PND) 20. Adverse effects were observed in both F_1 and F_2 pups of the high dose group. To further evaluate the effects observed in the high dose group, a cross-fostering study was conducted in two phases to assess the effects of administration of 50 mg/kg SCH 580348 to F_0 dams on the F_1 and F_2 generations.

In the first PPND study, the number of dams with a dead or missing pup during PND 0-21 was higher than in the high dose group. Prior to culling on PND 4, overall F_1 survival from birth in the high dose group was lower (84.7% per litter) than the survival in the concurrent control group (97.2% per litter) and was lower than the minimum of the historical control range. The F_1 male and female mean pup body weights in the high dose group were 5-13% lower than the mean pup body weights in the concurrent control group throughout the pre-weaning period and were either at or below the minimums of the historical control range on PND 1, PND 4, and PND 7. The F_1 male and female mean pup body weight gains in the high dose group decreased 15.8% and 22.2%, respectively, from PND 1 to PND 4 and 8.8 and 11.9%, respectively, for the overall pre-weaning period PND 1-21 compared to the gains in the control group.

Sensory function and neurobehavioral development in the F_1 pups were assessed in acoustic startle and locomotor assays. On PND 20, both the high dose F_1 males and females exhibited statistically significant increases in Tmax (the latency to maximum response amplitude or Vmax) that were greater than the maximum historical control value, indicating a slower response to the auditory startle stimulus. On PND 21, although the high dose F_1 females displayed >95% habituation, the mean overall and cumulative total and ambulatory locomotor activity counts in the high dose F_1 female group decreased compared to those in the control group, indicating a reduction in exploratory behavior. In contrast, high dose F_1 males did not display a decrease in overall total and ambulatory locomotor activity, but displayed only 50-54% habituation. The treatment-related effects on auditory response and locomotor activity observed on PND 20 and 21 did not appear to continue into the post-weaning period based on testing on PND 60 and 61.

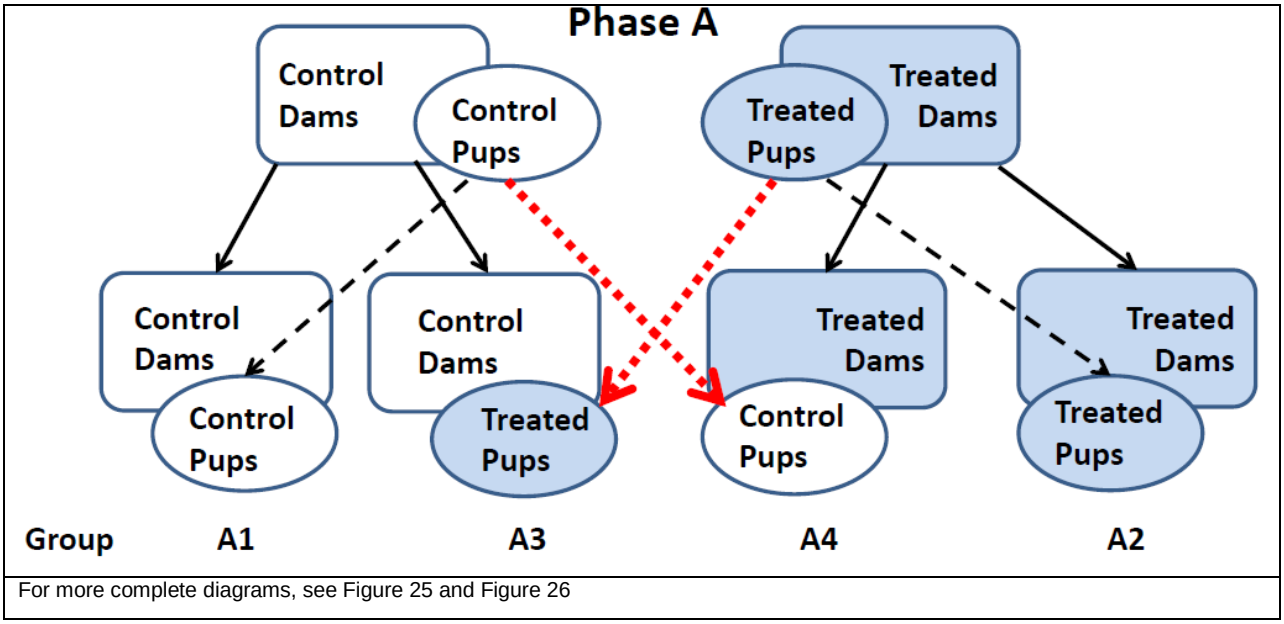
Treatment of F_0 dams with SCH 530348 did not have a clear effect on learning in F_1 pups in ten trials using a Biel water-filled T-maze. However, a potential effect on memory exists in mid and high dose F_1 female groups based on dose-dependent increases in the time to escape and in number of errors/trial in memory Trial 11 compared to the values in the control group. These mean values for the mid and high dose F_1 females are above the maximum historical control value. The difference from the control group is statistically significant in the high dose group. Furthermore, the

number of F_1 females with values above the maximum historical control value increased with dose. However, the male groups did not display these effects.

F_1 reproductive performance was not significantly different between the treated groups and the control group. However, the numbers of F_2 pups born per litter and the live litter sizes on PND 0 were slightly lower in the mid- and high dose groups than in the control group. During PND 0-7, the numbers of dead and missing F_2 pups increased and postnatal F_2 survival decreased in the mid and high dose groups compared to the control group. These effects were considered related to administration of SCH 530348 to F_0 dams. In addition, mean F_2 body weight gains in the high dose group decreased compared to those the control group and resulted in decreased mean body weights in the high dose group on PND 4 and PND 7 that were below the minimum of the historical control range.

To further evaluate the effects observed in the first PPND study, a cross-fostering study was conducted to assess the effects of administration of SCH 580348 (50 mg/kg) to F_0 dams on the F_1 and F_2 generations in two phases. In the first phase (A), F_1 pups from the control and SCH 580348 treated F_0 groups were cross-fostered after parturition to produce two additional groups of F_1 pups, one exposed pre-natally only and the other exposed post-natally only. In the second phase (B), F_2 pups from F_1 control (A1) or in pre- /postnatally-exposed F_1 animals (A2) were cross-fostered after parturition

Figure 1: Reviewer's Simplified Diagram - Cross-Fostering Phase A



For more complete diagrams, see Figure 25 and Figure 26

In the first phase (A) after cross-fostering, the percentage of live F_1 pups on PND 4 prior to culling versus either the number born or the number alive on PND 0 decreased in groups receiving either pre-/postnatal exposure (Group A2) or only postnatal exposure (Group A4) compared to the percentage in the control group. F_1 survival in Groups A2 and A4 were below the historical range. F_1 deaths/litter increased 2-fold in Groups A2 and A4 from cross-fostering to PND 4, PND 4-7 and from cross-fostering to PND 7. The

mean male and female F_1 body weights on PND 21 in Groups A2 and A4 were 13% to 14% lower than those in the control group. However, no effect of F_0 treatment was observed on estrous cycle length, or the mating, fertility and copulation indices in the F_1 animals.

At the beginning of the second phase (B), the mean number of F_2 pups born and the mean F_2 live litter size for the F_1 animals receiving in pre-/postnatal exposure (Group A2) prior to cross-fostering were 7.5% lower than the values for the concurrent control group (A1). Although these decreased values are within the historical control range, the decreases are statistically significant and consistent with the statistically significant decreases in the number of implantation sites in the F_1 females from Group A2 compared to Group A1. In addition, similar decreases in the mean number of F_2 pups born and the mean F_2 live litter size were observed for the F_1 animals from the F_0 dams treated with 25 and 50 mg/kg SCH 580348 in the previous PPND study. However, after cross-fostering no clear difference was observed in F_2 survival or F_2 pup body weights after cross-fostering. The reviewer concluded that the cross-fostering study confirmed the F_1 findings of decreased pre-weaning survival and body weight gains, but not the F_2 findings in the initial PPND study.

1.3 Recommendations

1.3.1 Approvability

NDA 204886 for vorapaxar is approvable from a pharmacology and toxicology perspective for the prevention of atherothrombotic events in patients with a history of myocardial infarction. Most of the toxicities identified in the non-clinical studies have adequate safety margins relative to human therapeutic exposures. However, the effect of SCH 530848 treatment on memory in F_1 female rat offspring has only a 4-fold safety margin based on the NOAEL dose. The label needs to warn women of child-bearing age of the potential risks for effects on their off-spring. In addition, the high levels of vorapaxar in milk of lactating rats, suggests the potential for vorapaxar exposure levels leading to inhibition of platelet aggregation and resulting bleeding in nursing neonates and infants.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

8.1 Pregnancy

Sponsor's proposal:
Pregnancy Category B

(b) (4)

(b) (4)

Reviewer's recommendation:
Pregnancy Category B
There are no adequate and well-controlled studies of TRADEMARK use during pregnancy in humans.

Risk summary
Based on data in rats and rabbits, vorapaxar is predicted to have a relatively low probability of increasing the risk of most adverse developmental outcomes above background risk. At maternally toxic exposures (285 times the steady-state human plasma exposure at the recommended therapeutic dose (RHD)) decreased fetal weights and rare heart malformations were observed in rats. At maternally nontoxic exposures (89 times the steady-state human plasma exposure at the recommended therapeutic dose) the number of litters with any malformation increased in rabbits. Adverse effects on perinatal survival and body weight were observed in off-spring exposed in utero and during lactation at exposures 67 times the RHD. At this exposure both male and female pups displayed effects on sensory function and neurobehavioral development at weaning, but not later in development. Female, but not male pups, displayed decreased memory at exposures 31 times the RHD, although no effect was observed on learning in either sex. However, animal studies are not always predictive of a human response. TRADEMARK should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Animal Data
In the rat embryo/fetal developmental toxicity study, pregnant rats received daily oral doses of vorapaxar at 0, 5, 25 and 75 mg/kg from implantation to closure of the fetal hard palate (6th to 17th day of gestation). Maternal systemic exposures were approximately 0, 7, 56, and 285 times greater than exposures in women treated at the RHD of 2.5 mg based on AUC. No embryo/fetal toxicities, malformations or maternal toxicities were observed in rats exposed up to 56 times the human systemic exposure at the RHD of 2.5 mg. At systemic exposures equal to 285 times the human systemic exposure at the RHD, reduced fetal body weight and rare heart malformations were observed in fetuses in association with maternal toxicities (decreased body weight and food consumption).

In the rabbit embryo/fetal developmental toxicity study, pregnant rabbits received daily oral doses of vorapaxar at 0, 2, 10, or 20 mg/kg from implantation to closure of the fetal hard palate (7th to 19th day of gestation). Maternal systemic exposures were 0, 1, 26, or 89 times that in women treated at the RHD of 2.5 mg based on AUC. The No Adverse Effect Level (NOAEL) for maternal and fetal toxicity was equal to or above the highest dose tested. Based on an overall increase in the number of litters with any malformation at the highest dose, the NOAEL for malformation was 10 mg/kg, where systemic exposures were 26-fold higher than the human exposure at RHD.

The effects of vorapaxar on prenatal and postnatal development was assessed in pregnant rats dosed at 0, 5, 25, or 50 mg/kg/day from implantation through the end of lactation. Maternal systemic exposures were 0, 4, 31, and 67 times the exposure in

women at the RHD based on AUC. Rat pups exposed to vorapaxar in utero and through 21 days of lactation had decreased survival from birth to 4 days after birth at exposures 67 times the RHD (84.7% survival) compared to the control group (97.2%), however, there was no effect on survival of pups from 4 to 21 days after birth. Body weight gain of pups was reduced 16% to 22% from birth to postnatal day 4 and 9% to 12% for the overall pre-weaning period PND 1 to PND 21 at exposures 67 times the RHD. At this exposure both male and female pups displayed effects on sensory function (acoustic startle) and neurobehavioral (locomotor assay) development on PND 20 and 21, but not later (PND 60, 61) in development. Female, but not male, pups displayed decreased memory (PND 27) at exposures 31 times the RHD; however no effect was observed on learning in either sex. In utero and lactational exposure did not affect fertility or reproductive behavior of offspring at exposures up to 67 times the RHD. A second study using cross-fostering confirmed the effects of in utero and lactational exposure on perinatal survival and body weight gain.

8.3 Nursing Mothers

Sponsor's proposal

(b) (4)

Reviewer's recommendation:
It is unknown whether vorapaxar or its metabolites are excreted in human milk. Data in lactating female (dam) rats indicate that the level of [^{14}C]-vorapaxar in milk was 6-fold higher than the level in maternal plasma, indicating a high excretion of [^{14}C]-vorapaxar into milk (7% of the maternal dose). Exposure to vorapaxar in nursing pups was 34% of that in dams based on plasma AUC levels. No studies have been conducted to assess the impact of vorapaxar on milk production in humans, its presence in human breast milk, or its effects on the breast-fed infant. A risk to newborns and infants cannot be excluded. Because vorapaxar is predicted to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, considerable caution should be exercised when TRADEMARK is given to a nursing mother.

12.1 Mechanism of Action

Sponsor's proposal

(b) (4)

Reviewer's recommendation:
Vorapaxar is a slowly reversible inhibitor of thrombin activated PAR-1 receptors on platelets. Vorapaxar inhibits thrombin-induced platelet aggregation in in vitro studies. In

addition, vorapaxar inhibits thrombin receptor agonist peptide (TRAP)-induced platelet aggregation without affecting coagulation parameters or increasing bleeding time in monkeys. Vorapaxar does not inhibit platelet aggregation induced by the agonists, adenosine diphosphate (ADP), collagen and a thromboxane mimetic.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Sponsor's proposal

Reviewer's recommendation:
Carcinogenicity
Carcinogenicity studies were conducted in rats and mice dosed orally with vorapaxar for two years. Male and female rats dosed at 0, 12.5, 25, or 50 mg/kg/day showed no carcinogenic potential at systemic exposures (AUC) in males and females that were 10- and 29-fold higher, respectively, than the human systemic exposure at the 2.5 mg dose. In male and female mice dosed at 0, 3, 10, and 30 mg/kg/day, vorapaxar showed no carcinogenic potential at systemic exposures (AUC) in males and females that were 28- and 34-fold higher, respectively, than the human systemic exposure.

Mutagenesis
Vorapaxar was not mutagenic in the Ames bacterial reverse mutation assay, and not clastogenic in an in vitro human peripheral blood lymphocyte assay or an in vivo mouse micronucleus assay after intraperitoneal administration.

Impairment of Fertility
Fertility studies in rats showed that vorapaxar had no effect on either male or female fertility at doses up to 50 mg/kg/day, a dose resulting in systemic exposures (AUC) in male and female rats that are 40 and 67 times, respectively, the human systemic exposure at the 2.5 mg dose.

2 Drug Information

2.1 Drug

CAS Registry Number: 705260-08-8

Generic Name: Vorapaxar

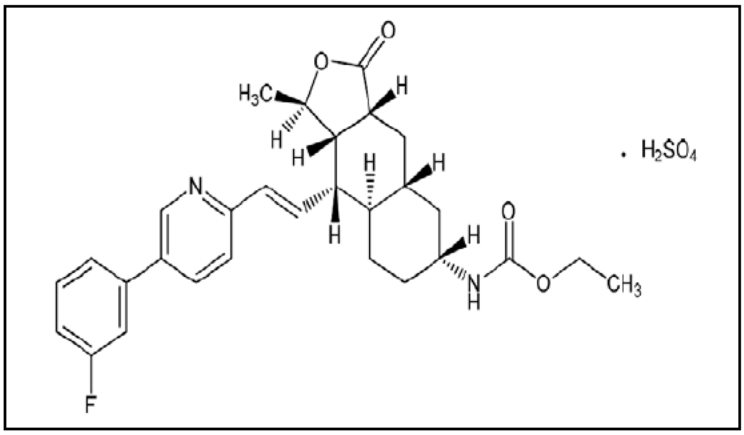
Code Names: SCH 530348 bisulfate, L-002409410, MK-5348, SCH 530348

Chemical Name:
Ethyl[(1R,3aR,4aR,6R,8aR,9S,9aS)-9-[(E)-2-[5-(3-fluorophenyl)-2-pyridinyl]ethenyl] -dodecahydro-1-methyl-3-oxonaphtho[2,3-c]furan-6-yl]carbamate bisulfate

Molecular Formula/Molecular Weight: $C_{29}H_{33}FN_2O_4 \cdot H_2SO_4$/590.7

Structure or Biochemical Description:

Figure 2: Structure of Vorapaxar



Pharmacologic Class: proteinase-activated receptor-1 (PAR-1) antagonist; an anti-platelet drug that inhibits a G protein-coupled receptor activated by thrombin .

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 71384 (Schering-Plough, Merck)
(b) (4)

2.3 Drug Formulation

Vorapaxar tablets contain vorapaxar sulfate (2.5 mg) with lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, povidone (b) (4) USP, magnesium stearate NF (b) (4) The tablets are coated with (b) (4) which contains lactose monohydrate, (b) (4) hypromellose (b) (4) titanium dioxide, triacetin/glycerol triacetate, and iron oxide yellow.

2.4 Comments on Novel Excipients

No novel excipients are used in the manufacture of vorapaxar tablets.

2.5 Comments on Impurities/Degradants of Concern

The sponsor identified three process related impurities in the final commercial process that have potential to be present in the drug substance. The exposure level in animals of each of these impurities was at least 135-fold higher than the maximum predicted exposure level in humans. One additional impurity, [redacted] (b) (4) was identified in stability studies with the drug product. This impurity has not been evaluated in toxicology studies. However, the sponsor states that this impurity was not observed above the quantification limit (<0.05%) at batch release, and it increased during storage up to [redacted] (b) (4). These four impurities are listed in Appendix 1 as specified impurities. Seven additional impurities were identified and are listed as non-specified impurities. The exposure level in animals of each of these impurities, except the [redacted] (b) (4), was at least 10-fold higher than the maximum predicted exposure level in humans. The sponsor maintains that the level of [redacted] (b) (4) in the final commercial process is less than the limit of quantification.
The synthetic process for preparation of the drug substance has been evaluated for potential formation of genotoxic impurities. All potential compounds, except the [redacted] (b) (4), were classified via in-silico evaluation and/or Ames assays as non-genotoxic. The [redacted] (b) (4) intermediate is a Category 3 potential genotoxic impurity, but the compound is unstable and will be fully hydrolyzed to a non-genotoxic intermediate in subsequent processes.

2.6 Proposed Clinical Population and Dosing Regimen

In patients with a history of myocardial infarction (MI), vorapaxar 2.5 mg daily is proposed to reduce atherothrombotic events and to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization.

2.7 Regulatory Background

IND 71384 was originally submitted to this Division (DCRP) in 12/17/04. The protocols for the rat and mouse carcinogenicity studies were evaluated by the Executive Carcinogenicity Assessment Committee on July 26, 2005 and June 28, 2005, respectively. During the development of vorapaxar, two nonclinical issues resulted in action by the Division. The first issue involved the histopathologic finding of vacuolation of the inner nuclear layer of the retina in the eyes of rats. This issue resulted in several consults to the Division of Ophthalmology Products. The second issue involved the adverse effects found in rat offspring in the pre-/postnatal development study and resulted in modifications to the Informed Consent.

3 Studies Not Reviewed

None.
A list of the studies reviewed either under IND 71384 or NDA 204886 is in Appendix 2.

4 Pharmacology

4.1 Primary Pharmacology

Background
Vorapaxar (SCH 530348) is an antagonist of a protease activated receptor (PAR) called PAR-1. First cloned from human platelets by Vu et al. (1991), this receptor was originally identified as a thrombin receptor that mediates the cellular effects of thrombin. Subsequently, additional protease activated receptors (PARs 2-4) were discovered. Currently, this family consists of four subtypes of protease-activated receptor (PAR), three of which are thrombin receptors (PAR-1, PAR-3, and PAR-4) (for review see Coughlin 2000; MacFarlane et al. 2001; Ossovskaya and Bunnett 2004). The following table (Table 1) summarizes the characteristics of the four PARs, which are present in a wide variety of cell types, including endothelial cells and neurons, and result in a wide variety of biologic activities (Adams et al. 2011).

Table 1: Comparison of Protease-Activated Receptors

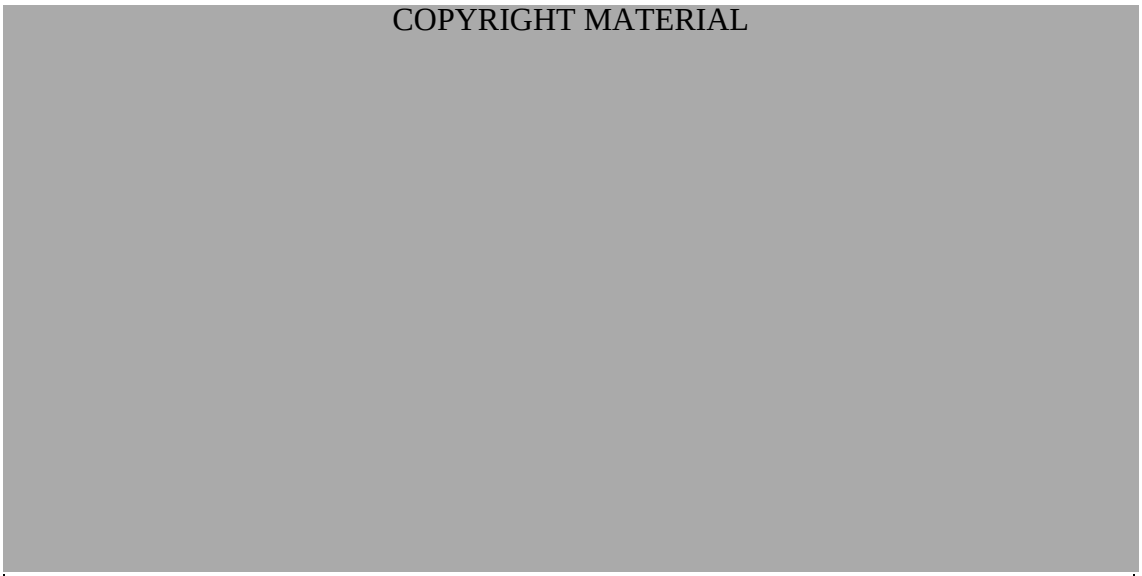
Ossovskaya and Bunnett, 2004

The PAR-1 receptor is a seven-transmembrane–domain G-protein-coupled receptor. However, in contrast to other G-protein-coupled receptors, the PAR-1 receptor has been shown to be activated by three mechanisms (Ramachandran et al. 2012) (Figure 3). First, PAR-1 can be activated by proteolytic cleavage of the amino terminus by an activating protease (Table 2) resulting in the exposure of a tethered peptide ligand that binds intramolecularly to activate the receptor and induce intracellular signal transduction, as shown in Figure 3 and Figure 4. Second, PAR-1 can be activated by exogenous agonist peptides or Thrombin Receptor Activating Peptides (TRAPs) that consist of five to fourteen amino acids corresponding to the newly generated amino-terminus of PAR-1 (Ahn et al. 1997). These TRAP peptides mimic many of the actions of thrombin, including platelet aggregation and smooth muscle cell proliferation. Third, if the PAR-1 receptor is cleaved by some proteases at a site downstream from the tethered peptide ligand sequence, the PAR-1 receptor can no longer be activated by an activating protease. Some proteases can ‘disarm’ or silence the response of the PAR-1 receptor to an activating protease (Table 2). However, recent studies have indicated that some proteases can activate PAR-1 receptor in a biased manner by selectively activating one signaling pathway in preference to another (Rajagopal et al. 2011). For instance, although MMP-1 cleaves the PAR-1 receptor at a different site than thrombin, it can induce platelet shape change similar to thrombin (Trivedi et al. 2009). However, in

endothelial cells, MMP-1 and thrombin differentially activated gene transcription through distinct PAR-1 cellular signaling pathways (Blackburn and Brinckerhoff, 2008; Austin et al. 2013). Likewise, activated protein C bound to the endothelial protein C receptor (APC-EPCR) also cleaves the PAR-1 receptor at a site distinct from thrombin and in endothelial cells results in biased signaling that is cytoprotective rather than pro-inflammatory (Mosnier et al. 2012).

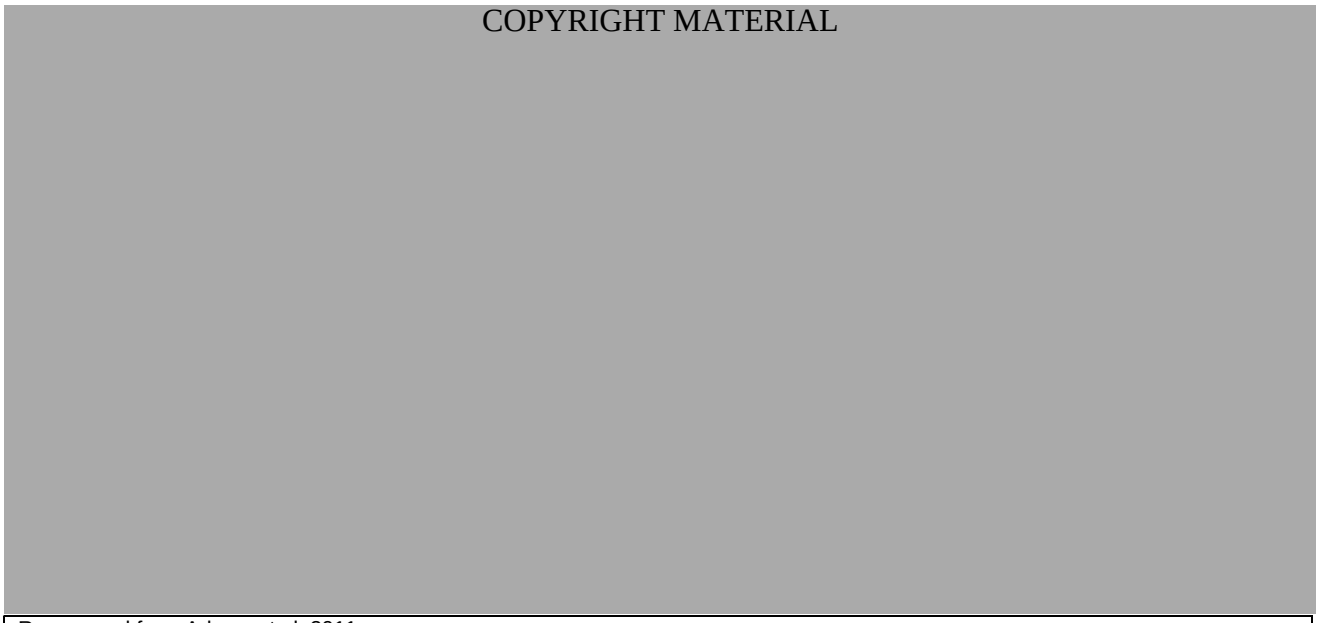
Importantly, the list (Table 2) of proteases that activate the PAR-1 receptors includes proteases that are considered pro-coagulants (thrombin, FXa) as well as proteases that are considered anti-coagulants (meizothrombin, APC-EPCR). Meizothrombin/ meizothrombin desF1 (MT/MT desF1) were shown to very rapidly induce transient calcium mobilization through PAR-1 in rat aortic smooth muscle cells comparable to that observed with alpha-thrombin (Kaufmann et al. 1998). However, meizothrombin in the presence of thrombomodulin has been shown to be at least a 6-fold better activator of protein C on the surface of endothelial cells than α-thrombin (Hackeng et al. 1996; Côté et al. 1997). Other small molecule PAR-1 antagonists, such as SCH79797 (Mosnier et al. 2012) and RWJ-58259 (Schuepbach et al. 2012) have been shown to block PAR-1 activation in endothelial cells. Since vorapaxar also binds the binding site of an agonist peptide (SFLLRN) on the PAR-1 receptor (Zhang et al. 2012; Ramachandran et al. 2012), vorapaxar could likely antagonize both the coagulant and the anticoagulant functions of PAR-1.

Figure 3: Activation of Protease-Activated Receptors



From Ramachandran et al. 2012

Table 2: Activating and Disarming Proteases for PAR Receptors

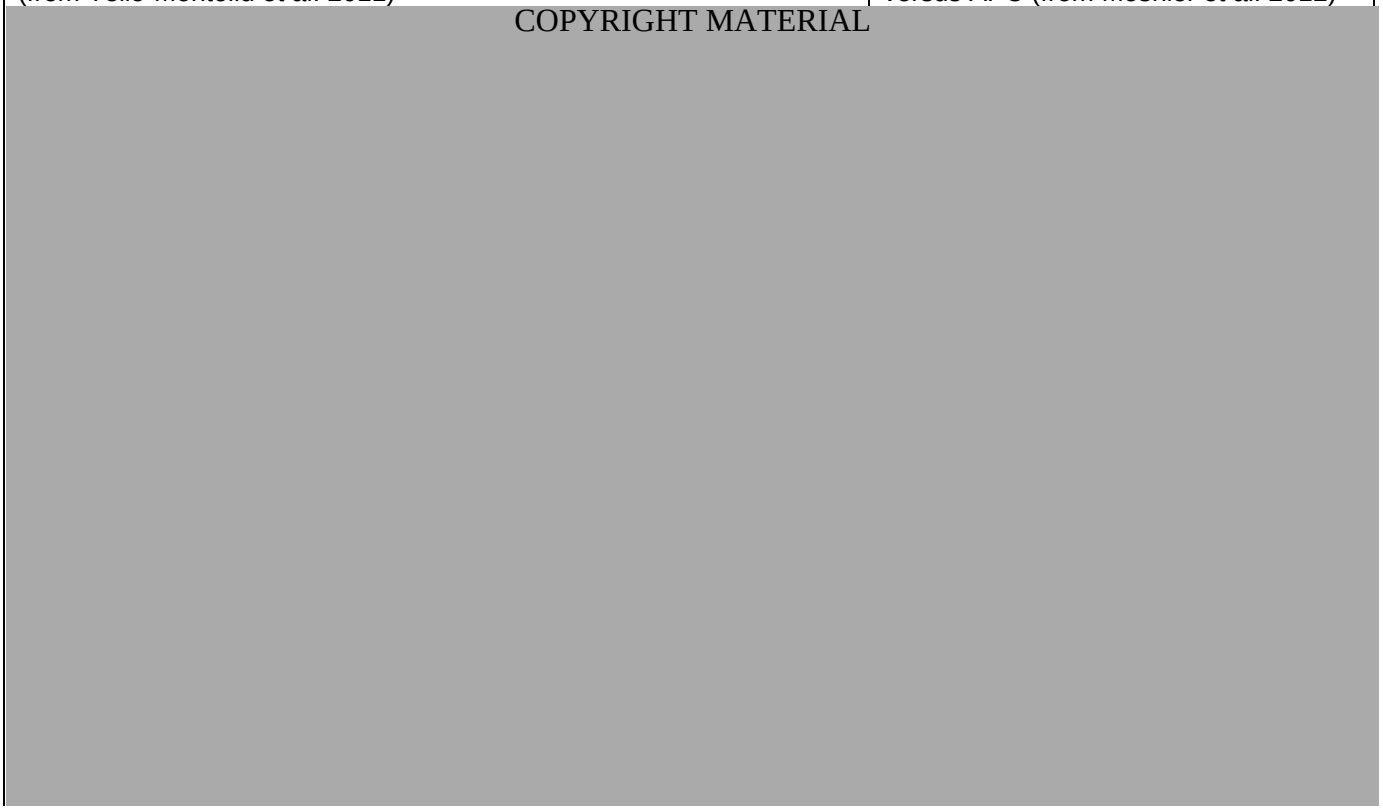


Rearranged from Adams et al. 2011

The interaction of PAR-1 with several different α-subunits, particularly $G_{q11}α$, $G_{12/13}α$ and $G_iα$, is thought to account for the pleotropic actions of the receptor (Figure 4). In platelets PAR-1 signaling is primarily through Gq (Hung et al. 1992). Mice deficient in Gqα have platelets that exhibit markedly diminished thrombin-induced aggregation and degranulation (Offermanns et al. 1997). However, in endothelial cells activation of PAR-1 by thrombin results in signaling through Rho, whereas activation of PAR-1 by APC results in signaling through β-arrestin and RAC1 (Mosnier et al. 2012).

Figure 4: PAR-1 Signaling

Pathways of platelet protease-activated receptor 1 (PAR-1) activation (from Tello-Montoliu et al. 2011)	Biased PAR-I signaling by thrombin versus APC (from Mosnier et al. 2012)



Although thrombin is a potent activator of platelets in all species, human and rodent platelets differ in the specific PAR isoforms that mediate thrombin signaling and platelet activation (Kahn et al. 1998). PAR-3 and PAR-4, but not PAR-1 is detected in platelets of mice (and presumably rats) (Sambrano et al. 2001). Although the PAR-1 agonist $TRAP_6$ (SFLLRN-NH2) induces aggregation of human, guinea pig and monkey platelets, it does not induce aggregation of rat, mouse, and dog platelets (Derian et al. 1995; Connolly et al. 1994,1996). Furthermore, platelets from PAR-1-deficient mice responded to thrombin like wild-type platelets (Connolly et al. 1996). In contrast, Kahn et al. (1999) showed that PAR-1 and PAR-4 are functionally expressed in human platelets accounting for most if not all thrombin signaling in human platelets

Both cynomolgus monkeys and humans express PAR-1 and PAR-4 on their platelets. Derian et al. (2003) showed that a specific PAR-1 antagonist, RWJ-58259 inhibited thrombosis in monkeys. In a model of electrolytic injury of the carotid artery in cynomologus monkeys, RWJ-58259 inhibited thrombus formation and extended the time to vessel occlusion from 27 ±3 minutes in vehicle treated animals to 53 ±8 min; ($p = 0.048$) after RWJ-58259 administration. After the bolus dose and at the end of the observation period, *ex vivo* platelet aggregation measurements indicated complete inhibition of aggregation in response to the PAR-1 agonist peptide, SFLLRN-NH_2 or a low concentration of thrombin (38 nM). Although guinea pigs express PAR-1, PAR-3, and PAR-4 receptors on their platelets, a similar dose of RWJ-58259 (10 mg/kg) was

only marginally effective in guinea pig models of arterial thrombosis, specifically the A-V shunt assay and the Rose Bengal intravascular photoactivation assay (Andrade-Gordon et al. 2001). Therefore, only non-human primates or humans can be used to demonstrate efficacy and anti-thrombotic activity of an antagonist specific to human PAR-1.

Drug activity related to proposed indication:
Thrombin is the most potent activator of platelets (Davey and Luscher, 1967, Martin et al. 1975). Under pathophysiological conditions, thrombin-mediated platelet activation plays an important role in arterial thrombogenesis, which triggers acute coronary syndromes and stroke. Furthermore, increased PAR-1 expression was observed in atherosclerotic plaques from human arteries (Nelken et al. 1992). Subsequently, studies using an antibody to PAR-1 (Brass et al. 1992; Takada et al. 1998), a PAR-1 knock-out mouse (Cheung et al. 1999) or a peptidomimetic PAR-1 antagonist (Andrade-Gordon et al. 2001) indicated that inhibition of PAR-1 reduced neotintimal hyperplasia following vessel injury. The pathology of intimal hyperplasia in acute coronary syndrome patients following percutaneous coronary intervention is characterized by extensive smooth muscle cell proliferation. Thus, a PAR-1 antagonist could have a potential benefit in the treatment of thrombosis and intimal hyperplasia. *In vitro* experiments using human platelets and human smooth muscle cells allowed characterization of the activity of SCH 530348 on these cell types.

Several experiments within Study D46293 were reviewed under IND 71384 in the document dated 06/01/2005. However, an amendment to D46293 that included new studies with SCH 530848 was submitted to the NDA. In addition, the effects of SCH 530848, SCH 2046273 (a metabolite of SCH 530848), and SCH 602539 (a close structural analog of SCH 530848) on PAR-1 were evaluated in three documents (PD001, D56013, and D49206, respectively) that had not been previously reviewed. These results are discussed below and integrated with brief summaries of the previously submitted results.

SCH 530348 inhibited the binding of ha(TRAP) (a high affinity PAR-1 selective agonist peptide) to human platelet membranes with a lower Ki (8.5 nM) than the K_i for SCH 602539 (26 nM) (Table 3). Likewise, the IC_{50} for SCH 530348 inhibiting aggregation of human platelets in platelet-rich plasma (PRP) induced by either TRAP or α-thrombin was lower than the IC_{50} for SCH 602539. Similarly, the antagonist dissociation constant, K_b, using Gaddum analysis (Lazareno and Birdsall 1993) was lower for SCH 530848 than for SCH 602539 in inhibiting thrombin and haTRAP-stimulated calcium mobilization in human coronary arterial smooth muscle cells and rat aortic smooth muscle cells. SCH 530348 also inhibited thrombin and Factor Xa-stimulated thymidine incorporation into human coronary smooth muscle cells with a K_i of 9.6 nM and 4.5 nM, respectively.

Table 3: Reviewer's Summary – Comparison of SCH 530848 and SCH 602539

	Compound evaluated	
Parameter	**SCH 530848**	**SCH 602539**
Documents	D46293	D49206
Inhibition of 10 nM [^{3}H]-haTRAP binding to human platelet membranes	K_i = 8.5 nM	K_i = 26 nM
Inhibition of washed human platelet aggregation induced by 300 nM haTRAP	IC_{50} = 15 nM	-
Inhibition of human platelet aggregation in PRP induced by 15 µM TRAP 10 nM α-thrombin	IC_{50} = 76 nM IC_{50} = 47 nM	IC_{50} = 187 nM IC_{50} = 83 nM
Inhibition of TK agonist-induced Ca transients in human CASMC[1] rat ASMC[2]	K_b = 0.63 nM K_b = 1.3 nM	K_b = 13.1 nM K_b = 3.9 nM
Inhibition of thrombin-induced Ca transients in human CASMC[1] rat ASMC[2]	K_b = 1.1 nM K_b = 2.9 nM	K_b = 3.9 nM -

The Thrombin Receptor Activating Peptides used above from least to most potent are: TRAP = SPLLRN (a PAR-1 agonist), TK = TFLLRNPNDK-NH2 (a PAR-1 selective agonist), haTRAP = high affinity thrombin receptor activating peptide (Ala-Phe(p-F)-Arg-Cha-HArg-Tyr-NH2). [1] Coronary aortic smooth muscle cells, [2] Aortic smooth muscle cells, K_b = antagonist dissociation constant (Lazareno and Birdsall 1993),

The activities of SCH 530848 and its major human metabolite, M20 (SCH 2046273) were compared in two studies (Table 4). Both SCH 530848 and SCH 2046273 were shown to have similar potency as antagonists of PAR-1 activity in platelets (Study PD002) and in smooth muscle cells (Study D56013).They display similar binding kinetics to platelets with similar on and off rates. Neither SCH 2046273 nor SCH 530848 was an agonist of calcium mobilization in human coronary smooth muscle cells.

Table 4: Reviewer's Summary - Comparison of SCH 530848 and SCH 2046273

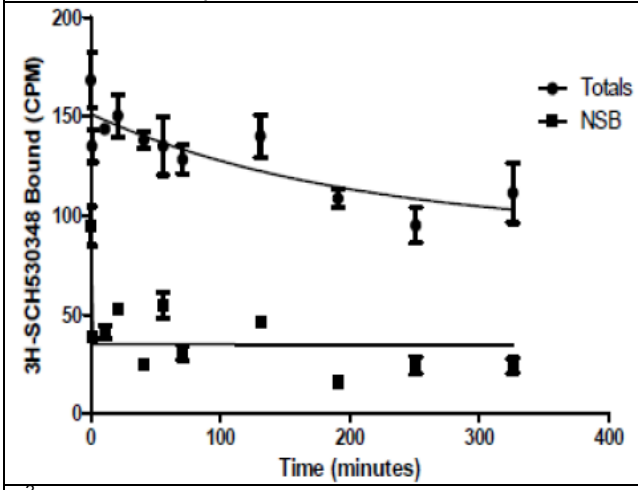
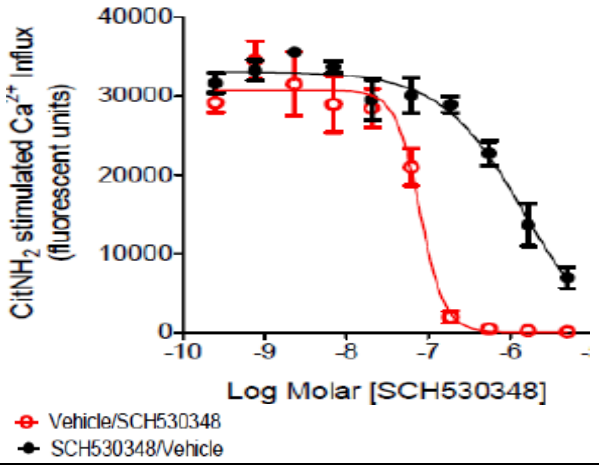
	SCH 530848 (MK-5348 or L-002409410)	**M20 metabolite (SCH 2046273 or L-003189067)**
Study PD002[†]		
Saturation binding to washed human platelets without added human plasma or extrapolated to 100% human plasma	K_d = 1.2 nM Apparent K_d = 39.1 nM	K_d = 1.6 nM Apparent K_d = 67.9 nM
Competition binding to washed human platelets without added human plasma or extrapolated to 100% human plasma	K_i = 1.0 nM Apparent K_i = 39.2 nM	K_i = 1.0 nM Apparent K_i = 91.7 nM
Association binding to washed human platelets Kd = Koff/Kon t ½ = 0.693/Koff.	K_{on} = 0.004056 $nM^{-1}min^{-1}$, K_{off} = 0.004397 min^{-1} K_d = 1.08 nM t ½ = 158 min	K_{on} = 0.003688 $nM^{-1}min^{-1}$, K_{off} = 0.008418 min^{-1} K_d = 1.14 nM t ½ = 82 min.
Dissociation from washed human platelets	K_{off} = 0.003731 min^{-1} t ½ = 186 min	K_{off} = 0.003332 min^{-1} t ½ = 208 min
Inhibition of β-arrestin association with PAR-1 induced by thrombin for 15, 90, or 180 min	IC_{50} = 12.1, 9.92 and 9.97 nM, respectively	IC_{50} = 11.2, 11.1 and 9.37 nM, respectively
Inhibition of thrombin induced calcium flux in washed human platelets after 1 and 2 hr pre-incubation	IC_{50} = 13.1 and 6.7 nM, respectively	IC_{50} = 12.1 and 5.0 nM, respectively

	SCH 530848 (MK-5348 or L-002409410)	M20 metabolite (SCH 2046273 or L-003189067)
Inhibition of TRAP peptide (SFLLRN) induced platelet aggregation in human PRP after 1 and 2 hr pre-incubation	IC_{50} = 41.01 and 105.5 nM, respectively	IC_{50} = 42.89 and 119.8 nM, respectively
Study D56013		
Inhibition of TK agonist-induced Ca efflux in human CASMC[1]	EC_{50}[§] = 4.5 nM	EC_{50}[§] = 3.4 nM
	No agonist activity at 10 µM	No agonist activity at 10 µM

[§] Report D56013 stated that SCH 530348 and SCH 2046273 produced dose dependent decreases in TK-stimulated calcium efflux with EC50 values of 4.5 and 3.4nM, respectively. These values are probably IC50 values, not EC50 values. [1] Coronary aortic smooth muscle cells, [†] Study PD002 was submitted to IND 71384 on 12/12/2013

The document PD001 demonstrated that binding of [^{3}H]-SCH 530348 to human platelet membranes is specific and saturable with a calculated K_d of 1.46 ±0.34 nM and a Bmax of 2.01±0.11 pmol/mg 1.5 nM. The K_{on} rate of 1.32 X 10^7 ±0.11 X 10^7 $M^{-1}min^{-1}$ and the K_{off} rate of 0.0056 ± 0.0016 $M^{-1}min^{-1}$ for [^{3}H]-SCH 530348 binding to human platelet membranes are slow. Scatchard analysis indicated that the binding of SCH 530348 in the presence of the agonist radiolabeled PAR-1 peptide [^{3}H]-HA-TRAP to platelet PAR-1 is competitive depending on conditions of the assay. SCH 530348 binding was competitive if human platelet membranes are exposed to SCH 530348 and [^{3}H]-HA-TRAP simultaneously. However, pretreatment of platelet membranes with SCH 530348 followed by exposure [^{3}H]-HA-TRAP resulted in non-competitive inhibition probably because of the slow off-rate of SCH 530848. Dissociation of [^{3}H]-SCH 530348 from human platelet membranes was assessed following washing in a high protein buffer and incubation for up to 5 hours (Figure 5A). Although binding of [^{3}H]-SCH 530348 was decreased by only 30% following the wash, the SCH 530348 binding to human platelet membranes was consider at least partially reversible. Functional assays using calcium influx and PAR-1/β-arrestin association also indicated that SCH 530348 can remain bound and can continue to antagonize PAR-1 receptors. Using CHO cells overexpressing the human PAR1 receptor and calcium influx as a measure of receptor activity, the dissociation of SCH 530348 from the PAR-1 receptor was evaluated following extensive washing of the cells (Figure 5B). Although the washing procedure shifted the IC_{50} for SCH 530348 to the right from 79 nM to 1467 nM, the sponsor concluded that some inhibition of PAR-1 activity by SCH 530348 was still observed. The similarity of inhibition of calcium influx in cells first treated with vehicle and then treated with 0.1 µM SCH 530848 with that in cells first treated with 1 µM SCH 530848, washed, and then treated with vehicle suggests at least 10% of the PAR-1 receptors are still inhibited after washing. These data are consistent with the slowly reversible SCH 530348 binding to platelet PAR-1 receptors. Additional studies showed that following stringent washing and incubation, particularly at increased temperatures above 37ºC, SCH 530348 can fully dissociate from PAR-1 indicating reversible binding.

Figure 5: Figures Compiled from PD001 – Reversibility of SCH 530848 Effects

A. Dissociation of [^{3}H]-SCH 530348 from human platelet membranes.	B. Effect of washing on SCH 530348 inhibition of PAR-1 mediated calcium influx.
	
[^{3}H]-SCH 530348 (10 nM) was incubated with human platelet membranes for 1 h at 37°C in the absence (totals) or presence (NSB) of 10 µM unlabeled SCH 530348. Aliquots of the binding reaction were diluted in binding buffer and incubated for the indicated time to allow dissociation of [^{3}H]-SCH 530348 from the membranes. Residual binding on the membranes was then determined.	CHO cells overexpressing human PAR-1 were pretreated with vehicle or the indicated concentration of SCH 530348 for 30 min at 37°C. Cells were then washed 3 times with growth media and incubated an additional 4 hours with washing each hour. Cells were then loaded with Calcium 4 dye. The cells initially pretreated with vehicle were treated with the indicated concentration of SCH 530348 while the cells previously treated with SCH 530348 were treated with vehicle for 30 min at 37°C. Cells were then stimulated with 92 nM PAR-1 agonist peptide [(Ala-parafluoroPhe-Arg-Cha-Cit-Try-NH2) or (Cit-NH2)] and the level of intracellular calcium was measured.

The specificity of SCH 530348 as a specific PAR-1 antagonist has been determined only *in vitro*. Previously, SCH 530348 at a concentration of 3 µM did not inhibit calcium transients induced by 1 µM to 300 µM of the PAR-2 agonist peptide, SLIGKV-NH2, in human coronary smooth muscle cells, indicating that SCH 530348 was selective for PAR-1 over PAR-2. Figure 6 shows that SCH 530348, SCH 2046273, and SCH 602539 inhibited platelet aggregation induced by the high affinity PAR-1 agonist haTRAP, but not platelet aggregation induced by ADP, thromboxane, or collagen, which bind to the $P2Y_1/P2Y_{12}$, TxA_2, and the GPVI/GPIa receptors, respectively. The effect of SCH 530848 on platelet aggregation induced by other agonists, such as platelet activating factor, epinephrine or serotonin was not evaluated. However, SCH 530348, SCH 2046273, and SCH 602539 did not inhibit platelet aggregation induced by the PAR-4 agonist peptide, GYPGKF. Recently, Zhang et al. (2012) confirmed by monitoring phosphoinositide signaling that SCH 530848 inhibited agonist peptide-induced and thrombin-induced signaling by human PAR1 (hPAR1) but not signaling by human PAR2, PAR4, or mouse PAR1 (Figure 7). However the specificity of SCH 530848 for PAR-1 over PAR-3 is unknown.

Figure 6: Sponsor's Figures - Inhibition of Agonist–Induced Platelet Aggregation

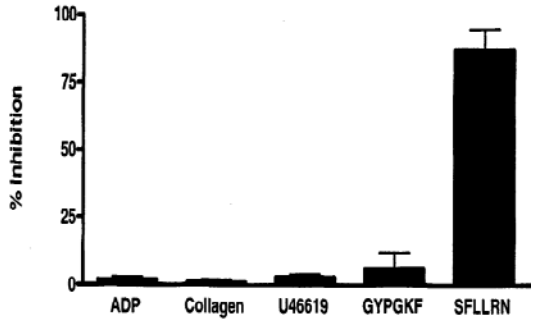
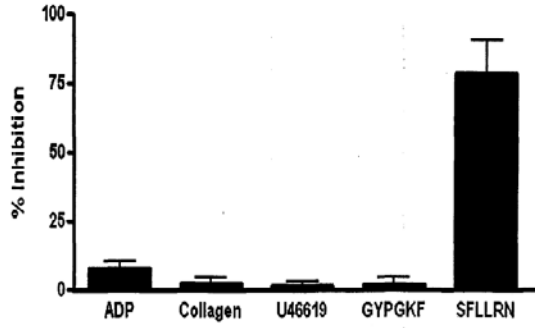
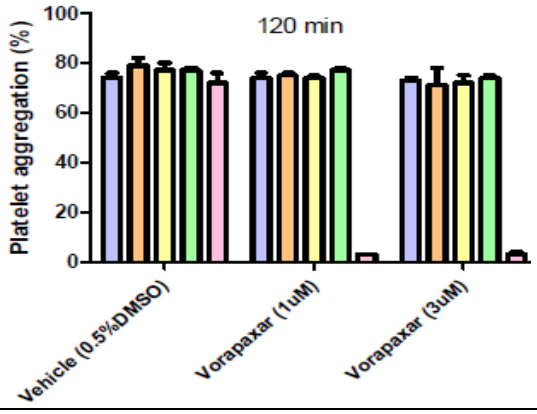
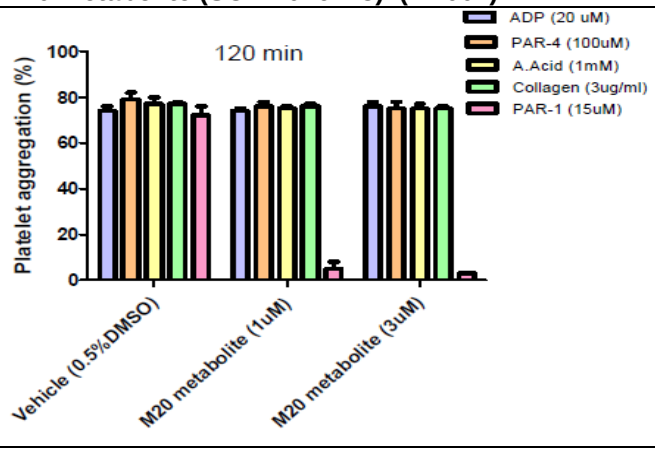
SCH 530848	SCH 602539
Amendment to D46293	**D49206**
+ 300 nM SCH 530848	+ 300 nM SCH 602539
	
Agonists: ADP (20,µM), Collagen (5 µg/ml), U46619 (10 µM, thromboxane mimetic), GYPGKF (300 µM, PAR-4 agonist peptide) and SFLLRN (15 µM, PAR-1 agonist peptide)	
SCH 530848 (L-002409410) (PD002)	**M20 metabolite (SCH 2046273) (PD002)**
	

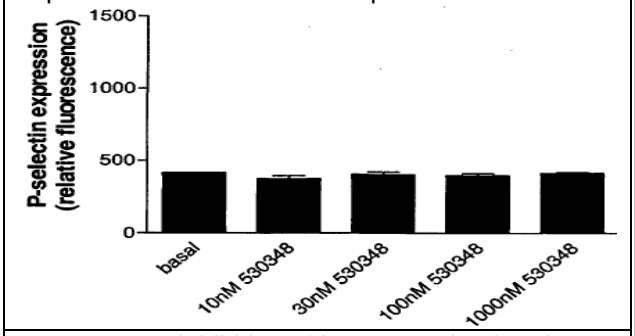
Figure 7: Specificity of SCH 530848 – From Zhang et al. 2012

Previously, the sponsor stated that SCH 530848 up to 10 µM did not induce calcium transients in human coronary smooth muscle cells. Document D56013 showed that neither SCH 530848 nor SCH 2046273 at 10 µM induced calcium efflux in human coronary smooth muscle cells (Table 3). The amendment to D46293 showed that SCH 530848 up to 1 µM did not activate human platelets as measured by expression of P-selectin. However, SCH 530848 even at 10 nM inhibited P-selectin expression induced by ha-TRAP (Figure 8A). Likewise, Zhang et al. (2012) demonstrated that 3-10 nM SCH 530848 significantly reduced SFLLRN-induced human platelet activation as measured by αIIbβIII integrin activation (Figure 8B). Binding of SCH 530848 to platelets clearly prevents activation of platelets.

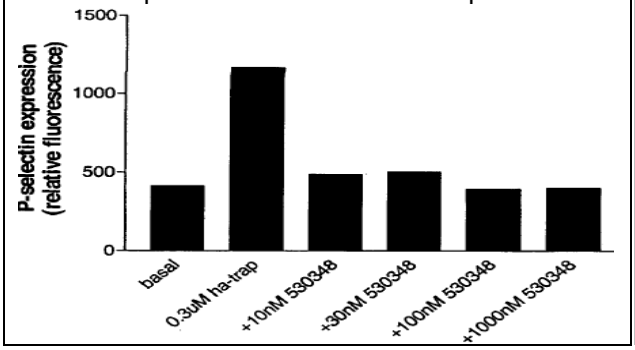
Figure 8: Reviewer's Compilation – Effect of SCH 480848 on Platelet Activation

A. Sponsor's data from Amendment to D46293

Effect of SCH 530348 on basal P-selectin expression in washed human platelets



SCH 530348 inhibition of haTRAP-stimulated P-selectin expression in washed human platelets

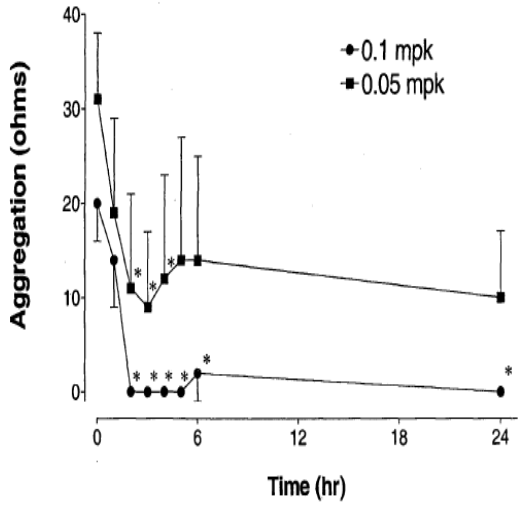
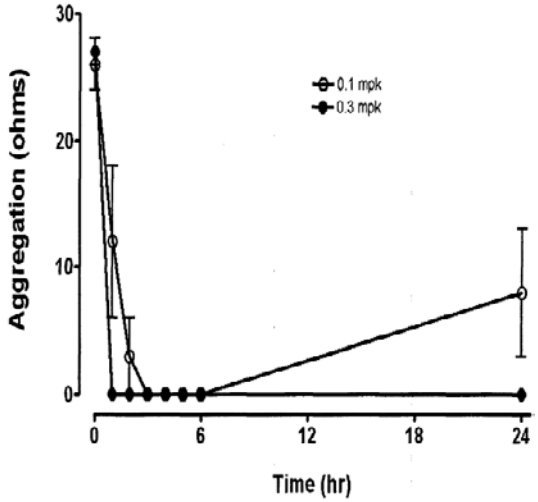


B. From Zhang et al. 2012 supplemental material

The effect of PAR-1 inhibitors on ex vivo platelet aggregation in response to 1 µM haTRAP was evaluated in whole blood collected from cynomolgus monkeys at various times after oral administration of either SCH 530348 at doses of 0.05 to 3 mg/kg or SCH 602539 at doses of 0.1 to 1 mg/kg. A dose of 0.05 mg/kg SCH 530348 resulted in about 60% inhibition of ex vivo platelet aggregation at 3 hours after dosing, whereas a dose of 0.1 mg/kg SCH 530348 resulted in complete inhibition of ex vivo haTRAP-induced platelet aggregation from 2 to 5 hours after dosing and >90% inhibition of ex vivo haTRAP-induced platelet aggregation at 24 hours after dosing (Figure 9A). Likewise, a dose of 0.1 mg/kg SCH 602539 resulted in complete inhibition of ex vivo platelet aggregation from 3 to 6 hours after dosing and >60% inhibition of ex vivo haTRAP-

induced platelet aggregation at 24 hours after dosing (Figure 9B). A separate experiment showed that ex-vivo platelet aggregation to haTRAP was inhibited at least 60% at 48 hours after a single dose of 0.1 mg/kg SCH 530348, indicating a long duration of action of SCH 530848. Oral dosing with either SCH 530848 or SCH 602539 induced similar effects on inhibition of platelet aggregation.

Figure 9: Sponsor's Figures - Effect of Oral Dosing on Ex Vivo Platelet Aggregation

Drug (Study)	A: SCH 530848 (D45293)	B: SCH 602539 (D49206)
Ex-vivo platelet aggregation in response to 1 µM haTRAP in whole blood from cynomolgus monkeys after oral dosing		

Plasma concentration	Dose, mg/kg	ng/ml at time (Hr) post dose						
		1	2	3	4	5	6	24
	0.1	5	9	9	9	7	5	1

Dose, mg/kg	Hr post dose						
	1	2	3	4	5	6	24
0.1	16	14	11	8	1	0	0
0.3	58	69	65	54	25	20	0

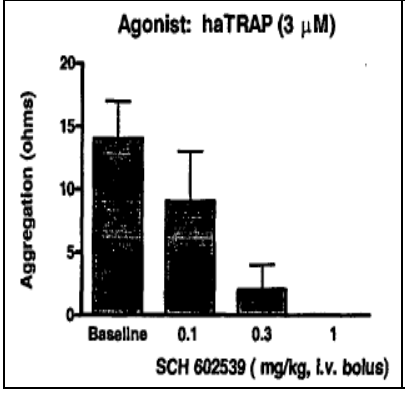
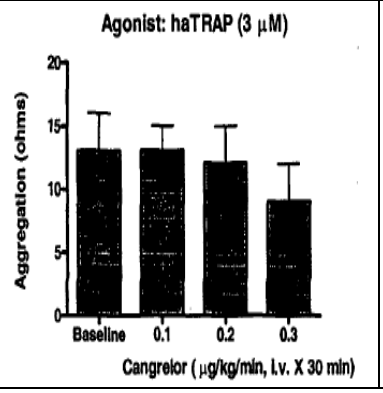
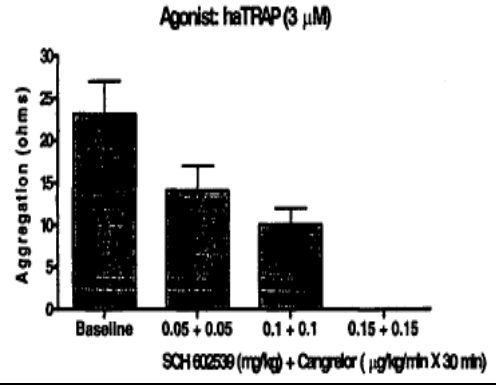
Although SCH 53048 has not been tested in an in vivo model of thrombosis, SCH 602539 alone, cangrelor alone, and SCH 602539 plus cangrelor in combination were evaluated in a Folts thrombosis model (Study D49206 and Chintala, et al. 2010). Cynomolgus monkeys were anesthetized, intubated and instrumented to maintain respiration and body temperature. The right femoral artery was cannulated for measurement of blood pressure. The right carotid artery was isolated and carotid blood flow was monitored continuously with a transonic flow probe. Mechanical damage to the endothelium was induced with a serrated hemostat and a constrictor sized to reduce mean carotid blood flow by 60% was placed around the carotid artery in the constricted region. Platelet-dependent thrombus formation occurred after placement of a constrictor over the region of endothelial damage resulting in cyclic flow reductions (CFRs). The frequency of CFRs was calculated as the number of flow reductions over a 30-minute period. After stable CFRs were achieved, vehicle was administered for a 30 min baseline period. Then vehicle or drugs were administered incrementally (every 30 min) and the effects on the frequency of CFRs were monitored in the next three, 30 min observation periods. Blood samples were collected from the femoral arterial catheter at the end of each 30 min observation period for assessment of platelet aggregation ex-

vivo. Statistically significant decreases in the frequency of CFRs were observed after treatment with the two highest doses of SCH 602539 alone and cangrelor alone (Figure 10). The dose of 0.1 mg/kg SCH 602539 reduced the frequency of CFRs by 50% and the dose of 0.1 µg/kg/min cangrelor reduced the frequency of CFRs by 40%. However, the combination of SCH 602539 and cangrelor reduced the frequency of CFRs by more than an additive amount suggesting a synergistic antithrombotic effect. The two highest doses of SCH 602539 inhibited ex vivo platelet aggregation in response to the PAR-1–selective agonist peptide ha-TRAP by more than than 70%, but did not inhibit platelet aggregation induced by ADP, the thromboxane A2 mimetic U46619, or collagen. The two highest doses of cangrelor inhibited ex vivo platelet aggregation induced by ADP, but did not inhibit platelet aggregation induced by haTRAP, the thromboxane A2 mimetic U46619, or collagen. The combination of SCH 602539 and cangrelor inhibited the aggregation induced by haTRAP and ADP in a dose-related manner with the level of inhibition similar to that for each drug alone. The similarity of the effects of SCH 530848 and SCH 602539 in inhibiting platelet aggregation in vitro and ex vivo suggests that SCH 530848 would produce results similar to that of SCH 602539 in the Folts thrombosis model in monkeys; however, SCH 530848 has not been specifically evaluated in this or any other animal model of thrombosis.

Figure 10: Sponsor's Figures - Folts Model - D49206 and Chintala et al. 2010

Folts thrombosis model in cynomolgus monkeys

Ex vivo platelet aggregation in monkeys subjected to Folts thrombosis model above

SCH 602539 alone	Cangrelor alone	SCH 602539 and Cangrelor
		

4.2 Secondary Pharmacology

The inhibitory effect of 6 µM SCH 530348 on the binding of specific radioligands was evaluated for a panel of 65 physiologically important receptors ((b) (4) study 840035). In addition, the inhibitory effect of SCH 530348 on radioligand binding was tested for a panel of 38 G-protein coupled receptors (SCH Study 47153). The assays most affected by SCH 530348 are summarized in Table 5.

The selectivity of SCH 530348 binding to most receptors tested was equal to or greater than 50-fold. However, SCH 530348 at 6 µM inhibited the binding of picrotoxinin to the chloride channel by 50% to 66%. Picrotoxinin with an IC_{50} of 0.93 µM primarily acts as a noncompetitive, selective $GABA_A$ receptor antagonist (Olsen 1982; Macdonald and Olsen 1994), since it is 40-fold less active with $GABA_C$. $GABA_A$ receptors are chloride channels that mediate postsynaptic inhibition by allowing chloride ion move into and hyperpolarize the postsynaptic neuron. By directly blocking the channel, picrotoxinin inhibits $GABA_A$-dependent chloride influx and stimulates the central nervous system. However, picrotoxinin also exhibits marked convulsive activity. The IC_{50} values for picrotoxinin and SCH 530348 differ by less than 6.5-fold.

Table 5: Reviewer's Summary - Receptor Assays Most Inhibited by SCH 530348

Receptor (species)	Reference compound	Reference IC_{50} (µM)	% inhibition by SCH 530348	Selectivity[§]
(b) (4) **study 840035 - 6 µM SCH 530348**				
P2X (rat)	α, β-MeATP	0.010	40	>600
5-HT_{2B} (human)	serotonin	0.091	43	>66
Calcium channel, L, DHP (rat)	nitrendipine	0.0012	35	>5000
Chloride channel (rat)	picrotoxininin	0.927	**58**	**<6.5**
ADO transporter (guinea pig)	NBTI	0.0002	53	~30000
5-HT transporter (human)	imipramine	0.0061	31	<984
Schering-Plough Research Institute, Report 47153				
CB2 cannabinoid (NI)	NI	NI	39% at 1.9 µM	**>100†**
Mu opioid	NI	NI	34% at 3.8 µM	**>100†**
Neurokinin NK2	NI	NI	36% at 7.2 µM	**>100†**
Adrenergic alpha 2a	NI	NI	-29% at 3.6 µM	**>100†**

NI = Not indicated, [§] Approximate IC_{50} for SCH 530348/IC_{50} for reference compound † Selectivity based on statement in report 46293

Given that the upper confidence limit for the Cmax after a 40 mg loading dose of SCH 530348 is approximately 0.6 µM, it is unlikely that SCH 530348 will significantly affect human $GABA_A$ receptors in vivo. However, the maximum SCH 530348 plasma concentrations in rat toxicology studies using doses of 30 mg/kg or higher were 3 µM or higher. Interactions of SCH 530348 with the rat $GABA_A$ receptors may have played a role in the clinical observations in these studies.

4.3 Safety Pharmacology

The safety pharmacology studies listed in Table 6 were reviewed previously under IND 71384 (DARRTS date 6/1/2005).

Table 6: Reviewer's Summary Safety Pharmacology Studies – IND 71384

Study No.	Study Title	Max. dose	GLP
D44255	Ancillary Pharmacology Studies on SCH 530348: Cardiovascular Effects in Conscious Cynomolgus Monkeys, In Vitro Effects on hERG Current and Effects on CNS, Respiratory, Renal and Gastrointestinal Function in Rats	1.5 µM, 3 mg/kg	No
SN 02127	A Single Oral (Gavage) Dose Cardiovascular Safety Study of SCH 530348 in Male Cynomolgus Monkeys	20 mg/kg	Yes
SN 02128	The Acute Central Nervous System Pharmacological Profile of SCH 530348 Following Oral Administration in Rats	100 mg/kg	Yes
SN 02129	Effect of Single Oral Dose Administration of SCH 530348 on Respiratory Parameters in Rats	100 mg/kg	Yes
SN 02203	Effect of SCH 530348 on Action Potential Parameters in Dog Isolated Cardiac Purkinje Fibres	200 nM	Yes
SN 03128	Assessment of Potential Bleeding Liability of SCH 530348 Co-Administered with Aspirin and Clopidogrel in Anesthesized Cynomolgus Monkeys	1 mg/kg	No

The findings in these safety pharmacology studies are summarized by the following statements.

1. SCH 530348 single doses of up to 100 mg/kg did not significantly affect central nervous system function or respiratory function in rats.
2. SCH 530348 single doses of up to 3 mg/kg did not significantly affect gastrointestinal, renal, or coagulation parameters in rats.
3. SCH 530348 inhibited hERG current in mouse L cells with a nominal IC_{50} of 341 nM.
4. However, SCH 530348 did not significantly affect action potential parameters in dog Purkinje fibers up to a maximum measured concentration of 200 nM. Since SCH 530348 is >99% bound to protein, the concentration of 200 nM is 38 times higher than the expected unbound plasma concentration (5.3 nM) following administration of the 40 mg loading dose in humans.
5. SCH 530348 single doses of up to 20 mg/kg did not significantly alter heart rate, blood pressures (systolic, diastolic and mean), ECG interval duration (RR, QT, PR and QRS) or ECG morphology in cynomolgus monkeys.

The previously reviewed non-GLP drug interaction study SN 03128 is briefly summarized below to allow comparison with the GLP drug interaction study SN 06077 reviewed below.

4.3.1 Assessment of potential bleeding liability of SCH 530348 co-administered with aspirin and clopidogrel (SCH 417891) in anesthetized cynomolgus monkeys

Study number: SN 03128

Four groups of cynomolgus monkeys were studied after administration of single doses were G1: control (vehicle), G2: SCH 530848 (1 mg/kg) alone, G3: aspirin (10 mg/kg) plus clopidogrel (2 mg/kg), and G4: SCH 530848 (1 mg/kg) with aspirin plus clopidogrel (Table 7).

Single doses of 1 mg/kg SCH 530848 did not increase blood loss or bleeding time significantly compared to the control group, whereas aspirin+clopidogrel increased blood loss and template bleeding time 15-fold and 7-fold, respectively, compared to the control group (Table 6). Addition of SCH 530848 to aspirin+clopidogrel did not increase blood loss or bleeding time further compared to aspirin+clopidogrel alone. The plasma concentrations of SCH 530848 were similar in groups G2 and G4.

Table 7: Reviewer's Summary - Bleeding Parameters - SN 03128

SN 03128		Blood loss	Template Bleeding time	Plasma concentration, ng/mL	
Group		mL/hr	Minutes	3.5 hr	4 hr
G1 (Vehicle)	Mean (SD)	0.13 (0.05)	3.4 (0.32)		
G2 (1 mg/kg SCH 530848 alone)	Mean (SD)	0.18 (0.03)	4.9 (0.99)	191 (39)	200 (42)
G3 (Aspirin (10 mg/kg) and clopidogrel (2.61 mg/kg)	Mean (SD)	2.0 (0.28)	23.2 (3.98)		
G4 (Aspirin (10 mg/kg) and clopidogrel (2.61 mg/kg) plus 1 mg/kg SCH 530848	Mean (SD)	2.0 (0.23)	21.9 (4.3)	181 (32)	176 (34)

4.3.2. Assessment of potential bleeding liability of SCH 530348 co-administered with aspirin and clopidogrel in anesthetized male cynomolgus monkeys

Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Study number(s): SN 06077
Date of study initiation: 05/11/2010
Drug lot/batch number: SCH 530348 Batch No.: 05-530348-X-301;
Clopidogrel Bisulfate (SCH 900859), Lot No.: AAAA0563;
Aspirin (acetylsalicylic acid)
GLP compliance: Yes
QA statement: Yes

Key Study Findings
Daily administration of 1 or 5 mg/kg SCH 530348 alone for 14 days did not increase template bleeding time. In contrast, co-administration of 10 mg/kg of aspirin and 2 mg/kg of clopidogrel prolonged bleeding time by a mean of 14 minutes (range 3-34 minutes). The report concluded that administration of 1 or 5 mg/kg SCH 530348 in combination with aspirin and clopidogrel did not exacerbate the prolonged bleeding observed following administration of a combination of aspirin and clopidogrel alone.

Purpose: This study evaluated the potential bleeding liability of SCH 530348 to cynomolgus monkeys when it was administered as repeated doses alone or in combination with aspirin and clopidogrel.

Methods:

Three groups of monkeys (8 males/group) were treated in three phases as indicated in Table 8. Phase 1 was three days in duration; Phases 2 and 3 were 14 days in duration each. The observations and measurements are summarized in Table 9. The monkeys were anesthetized during the template bleeding assay.

Table 8: Sponsor's Table Summarizing Study Design of SN 06077

Assessment of Potential Bleeding Liability of SCH 530348 Co-Administered with Aspirin and Clopidogrel in Anesthetized Male Cynomolgus Monkeys (SN 06077): **Study Design**

Group	Animal Numbers[a]	Test/Control Article	Total Daily Dose (mg/kg) (Free Base)[b]	Dose Volume (mL/kg)	Dose Conc. (mg/mL) (Salt)[c]	Duration of Dosing (Days)
Phase 1 (Days 1-3)						
G1	1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008	Control (Methylcellulose)	0	1	0	3
G2	2001, 2002, 2003, 2004, 9001, 9002, 2007, 2008	Control (Methylcellulose)	0	1	0	3
G3	3001, 3002, 3003, 3004, 9003, 9004, 3007, 3008	Aspirin	10	1	10	3
		Clopidogrel	2	1	2.6	3
Phase 2 (Days 4-17)						
G1	1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008	Control (Methylcellulose)	0	1	0	14
G2	2001, 2002, 2003, 2004, 9001, 9002, 2007, 2008	SCH 530348	1	1	1	14
G3	3001, 3002, 3003, 3004, 9003, 9004, 3007, 3008	Aspirin	10	1	10	14
		Clopidogrel	2	1	2.6	14
		SCH 530348	1	1	1	14
Phase 3 (Days 18-31)						
G1	1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008	Control (Methylcellulose)	0	1	0	14
G2	2001, 2002, 2003, 2004, 9001, 9002, 2007, 2008	SCH 530348	5	1	5	14
G3	3001, 3002, 3003, 3004, 9003, 9004, 3007, 3008	Aspirin	10	1	10	14
		Clopidogrel	2	1	2.6	14
		SCH 530348	5	1	5	14

[a] Animals remained assigned to the same group (G1, G2 or G3) throughout all three phases of the study.

[b] Dose of clopidogrel (SCH 900859) is expressed as the free base. When expressed as the bisulfate salt, this dose is equivalent to 2.610 mg/kg for Group G3.

[c] Concentration of clopidogrel (SCH 900859) is expressed as the bisulfate salt. When expressed as the free base, this concentration is equivalent to 2 mg/mL for Group G3.

Table 9: Sponsor's Table Summarizing Observations SN 06077

Assessment of Potential Bleeding Liability of SCH 530348 Co-Administered with Aspirin and Clopidogrel in Anesthetized Male Cynomolgus Monkeys (SN 06077): **Observations and Measurements**

Investigation	Performed	Investigation	Performed
Viability	At least once daily	Plasma Analysis for SCH 530348	Days 17 and 31 (1-4 hr after dosing)
Clinical Observations	At least once daily beginning Week -3 with an additional observation during Week -2/-1; at least three times daily during the dosing period; and at least once daily after the completion of dosing until return to the stock supply of animals	Hematology	Weeks -3 and -1
Body Weight[a]	On the day of randomization; and weekly beginning Week -1	Coagulation	Weeks -3 and -1; and Days 3, 17 and 31
Food Consumption (Estimated)[a]	Daily beginning Week -1	Serum Chemistry	Weeks -3 and -1
Template Bleeding Assay	Weeks -2 and -1; and Days 3, 17 and 31	Urinalysis/Urine Chemistry	Weeks -3 and -1

Note: All animals were returned to the stock supply of animals at the completion of the study.

[a] These data were not interpreted.

Results:

Mortality: No mortalities occurred.

Clinical signs: A red peri-nasal substance was observed in four of eight animals in Group G3 during Phase 1 or Phase 2.Coagulation Parameters: No significant changes occurred in either prothrombin times (PT) or activated partial thromboplastin times (APTT) for any group (Table 10).

Table 10: Reviewer's Summary of Coagulation Times - SN 06077

SN 06077			Coagulation time, sec (SD)				
			Pretest 1	Pretest 2	Phase 1	Phase 2	Phase 3
Test	Group		Week -3	Week -1	Day 3	Day 17	Day 31
PT	G1 (Control)	Mean (SD)	9.3 (0.3)	9.4 (0.2)	9.9 (0.2)	9.7 (0.2)	9.9 (0.5)
	G2 (plus 0, 1 or 5 mg/kg SCH 530848 alone)	Mean (SD)	9.5 (0.4)	9.4 (0.3)	9.8 (0.4)	9.8 (0.4)	9.9 (0.4)
	G3 (Asp. and clopid. plus 0, 1 or 5 mg/kg SCH 530848	Mean (SD)	9.3 (0.1)	9.2 (0.3)	9.6 (0.3)	9.4 (0.5)	9.6 (0.4)
APTT	G1 (Control)	Mean (SD)	20.6 (0.9)	20.7 (0.6)	20.8 (0.8)	20.5 (0.8)	21.1 (1.1)
	G2 (SCH 530848 alone)	Mean (SD)	19.5 (1.0)	19.6 (1.1)	20.0 (1.1)	19.8 (1.0)	20.4 (1.0)
	G3 (Asp. and clopid. plus 0, 1 or 5 mg/kg SCH 530848	Mean (SD)	19.2 (0.9)	19.8 (0.9)	19.8 (0.8)	19.8 (0.7)	19.9 (1.1)

Bleeding time:
Administration of 1 or 5 mg/kg SCH 530348 alone for 14 days did not increase template bleeding time compared to the control group (Table 11). In contrast, co-administration of 10 mg/kg of aspirin and 2 mg/kg of clopidogrel prolonged bleeding time by a mean of 14 minutes (Range 3-34 minutes). The report concluded that administration of 1 or 5 mg/kg SCH 530348 in combination with aspirin and clopidogrel did not exacerbate the prolonged bleeding observed following administration of aspirin and clopidogrel alone. However, some animals had increased bleeding times and others had decreased bleeding times when SCH 530848 was added to aspirin plus clopidogrel. The number of animals with increased bleeding times when 5 mg/kg SCH 530848 was added was lower than when 1 mg/kg SCH 530848 was added. Furthermore, no dose response was observed

Table 11: Reviewer's Summary of Bleeding Times - SN 06077

SN 06077		Bleeding time, min (SD)				
		Pretest 1	Pretest 2	Phase 1	Phase 2	Phase 3
				G3 Aspirin, clopidogrel plus vehicle	(Aspirin, clopidogrel plus 1 mg/kg SCH 530848	(Aspirin, clopidogrel plus 5 mg/kg SCH 530848
G1 (Control)	Mean (SD)	2.1 (0.32)	1.6 (0.18)	1.8 (0.46)	1.6 (0.52)	1.9 (0.58)
G2 (SCH 530848)	Mean (SD)	1.9 (0.5)	1.7 (0.37)	1.7 (0.37)	1.7 (0.26)	1.8 (0.27)
G3 (Aspirin, clopidogrel plus 0, 1 or 5 mg/kg SCH 530848	Mean (SD)	1.9 (0.74)	1.7 (0.26)	15.6 (11.9)	36.4 (35.4)	12.6 (11.5)
	Minimum	1.5	1.5	3.0	4.0	3.0
	Maximum	3.5	2.0	34.0	96	36.5
Number with increase in Phase 2/3 versus Phase 1					6	3
Number with decrease in Phase 2/3 versus Phase 1					2	5

Toxicokinetics:
SCH 530348 was not detected in plasma from Group G1 (control) animals on Day 17 or 31. Plasma concentrations of SCH 530348 were similar in Groups G2 and G3 on Days 17 and 31 (Table 12). As expected, plasma concentrations of SCH 530348 were higher on Day 31 (Phase 3) than on Day 17 (Phase 2), since 5 mg/kg SCH 530348 was used in Phase 3 compared to 1 mg/kg SCH 530348 used in Phase 2.

Table 12: Reviewer's Summary of Plasma Concentrations - SN 06077

SN 06077		Plasma concentration, ng/mL (SD)	
		Phase 2	Phase 3
Group		Day 17	Day 31
G1 (Control)	Mean (SD)	0	9
G2 (plus 0, 1 or 5 mg/kg SCH 530848 alone)	Mean (SD)	396.3 (82.7)	1705 (416.4)
G3 (Asp. and clopid. plus 0, 1 or 5 mg/kg SCH 530848	Mean (SD)	405.4 (122.7)	1509 (486.5)

4.3.3. Bleeding and Bleeding Reversal Studies In Cynomolgus Macaques Dosed with Vorapaxar, Aspirin, and Clopidogrel

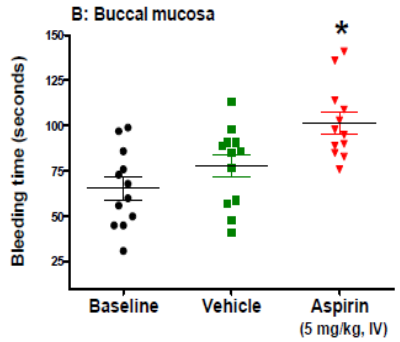
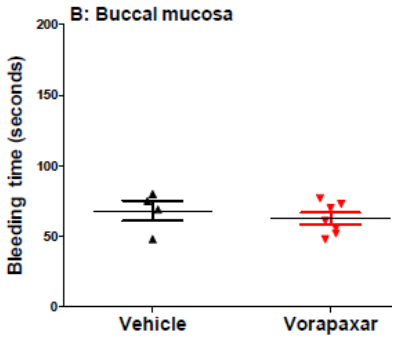
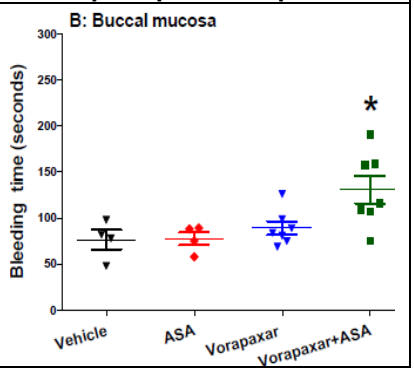
Conducting laboratory and location: Merck Research Laboratories, Kenilworth, NJ
Study number(s): PD003
Date of study initiation: Not indicated (Report date 12/03/2013
Drug lot/batch number: Vorapaxar (Merck & Co. Inc), clopidogrel (clopidogrel bisulfate: (b) (4) and aspirin (b) (4)
GLP compliance: No
QA statement: No

Key Study Findings
Treatment with vorapaxar alone did not alter bleeding times in cynomolgus monkeys. Co-treatment of vorapaxar and aspirin led to modest increases in bleeding times. Triple therapy with aspirin, clopidogrel and vorapaxar significantly increased bleeding times. The increases in bleeding times were associated with inhibition of platelet aggregation induced by the appropriate agonist. Transfusion of human platelet-rich plasma, but not platelet-poor plasma, decreased bleeding times.

Purpose:
This study evaluated the effect of vorapaxar monotherapy or combination therapy of vorapaxar, aspirin, and clopidogrel on bleeding times in cynomolgus macaques. In addition, the effect of human platelet transfusion on prolonged bleeding times was evaluated in cynomolgus macaques dosed with combination therapy of vorapaxar, aspirin, and clopidogrel.

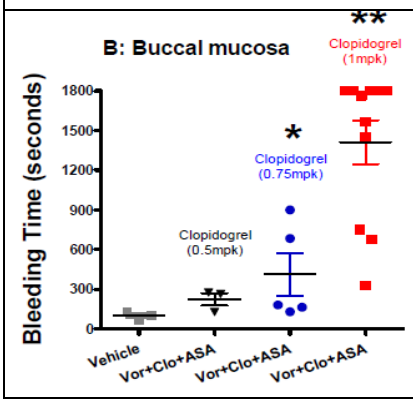
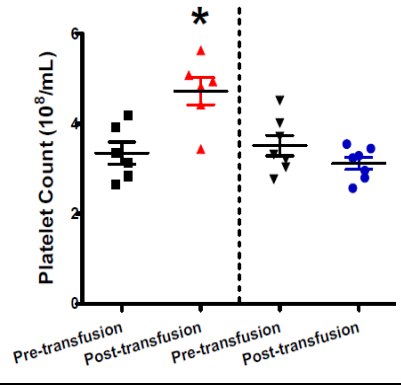
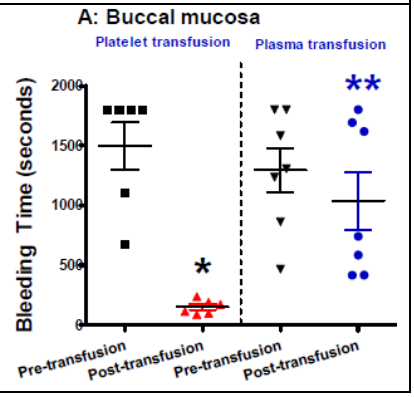
Results:
Animals treated with aspirin (5 mg/kg, IV) had a slight (<2-fold) increase in bleeding times in all three peripheral vascular beds, including buccal mucosa, tail and finger pad (Figure 11). The increase in bleeding time was associated with complete inhibition of arachidonic acid stimulated ex vivo whole blood thromboxane B2 generation and platelet aggregation. In contrast, animals treated with vorapaxar (1 mg/kg, PO) had no significant changes in bleeding times, but had complete inhibition of ex vivo whole blood platelet aggregation in response to haTRAP. Animals that received co-treatment with aspirin and vorapaxar had a slight increase in mean bleeding time. However, individual bleeding times were more variable and ranging up to 3-times greater than in the vehicle control group. When vorapaxar was administered in combination with aspirin and the P2Y12 antagonist, clopidogrel, bleeding times increased in a dose-dependent manner with the dose of clopidogrel (Figure 12). With a dose of 1 mg/kg clopidogrel in combination with vorapaxar (1 mg/kg, PO) and aspirin (5 mg/kg, IV), bleeding times increased 10-fold compared to vehicle administration.

Figure 11: Sponsor's Figures - Bleeding Times in Cynomolgus Monkeys

Aspirin alone	Vorapaxar (1 mg/kg PO) alone	Aspirin plus Vorapaxar
		

Transfusion of human platelet-rich plasma (PRP) into monkeys treated with the combination of vorapaxar, aspirin, and clopidogrel increased the number of circulating platelets and reduced bleeding times in association with increased ex vivo whole blood platelet aggregation in response to arachidonic acid (Figure 12). However, transfusion of platelet poor plasma (PPP) had no effect circulating platelet counts, bleeding times or whole blood platelet aggregation responses.

Figure 12: Sponsor's Figures – Triple Therapy and Bleeding Times

Triple combination treatment of vorapaxar (1 mg/kg, PO), aspirin (5 mg/kg, IV) and indicated doses of clopidogrel	Triple combination treatment of vorapaxar (1 mg/kg, PO), aspirin (5 mg/kg, IV) and clopidogrel (1 mg/kg, PO).		Triple combination treatment of vorapaxar (1 mg/kg, PO), aspirin (5 mg/kg, IV) and clopidogrel (1 mg/kg, PO).
	PRP	PPP	
			

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Methods of analysis

Reports were submitted validating liquid chromatographic-tandem mass spectrometric (LC-MS/MS) methods for the quantification of SCH 530348 and a metabolite, SCH

2046273, in mouse, rat, rabbit and monkey plasma. The methods involved addition of the appropriate internal standard to the sample plasma followed by extraction and analysis by LC-MS/MS. Table 13 summarizes the methods validation reports.

Table 13: Reviewer's Summary of Analytical Methods

Study number	Species	Calibration range	Accuracy (% bias)	Precision (% CV)
DM27719	Rat	8.36 to 8360 ng/mL for SCH 530348, 1.0 to 1000 ng/mL for SCH 2046273	-3.9 to 1.0 -2.8 to 2.7	4.1 to 16.2 5.3 to 14.4
DM27720	Mouse	16.7 to 16700 ng/mL for SCH 530348 2.0 to 2000 ng/mL for SCH 2046273	-6.5 to -3.8 -10.0 to -4.4	3.1 to 8.8 5.3 to 6.4
DM27722	Monkey	8.33 to 8330 ng/mL for SCH 530348 1.0 to 1000 ng/mL for SCH 2046273	-0.1 to 3.3 -6.1 to -4.5	7.7 to 9.6 4.3 to 7.6
DM27723	Rabbit	8.33 to 8330 ng/mL for SCH 530348 1.0 to 1000 ng/mL for SCH 2046273	-0.8 to 3.4 -4.5 to -1.0	2.7 to 7.3 2.4 to 11.4
SN02613	Rat	10 to 10000 ng/mL for SCH 530348	-5.3 to 1.0	3.9 to 9.5
SN02614	Monkey	10 to 10000 ng/mL for SCH 530348	-0.1 to 3.3	7.7 to 9.6
SN03136	Rabbit	10 to 10000 ng/mL for SCH 530348	2.4 to 11.4	4.2 to 11.1
SN03137	Mouse	20 to 20000 ng/mL for SCH 530348	0.3 to 9.5	3.7 to 9.1

Absorption

Following single oral doses in Study 03329, vorapaxar had a mean bioavailability (F) of 33 and 86% in rats and monkeys, respectively. In this study, the maximum concentration (Cmax) occurred at 3.3 hours and 1 hour (Tmax) following oral administration to rats and monkeys, respectively. The Tmax in subsequent toxicology studies ranged from 1 to 8 hours in mice, rats, rabbits, and monkeys. Table 14 summarizes the vorapaxar pharmacokinetic parameters after single dose administration to rats and monkeys.

Table 14: Reviewer's Compilation – Pharmacokinetic Parameters – SN 03329

	Rat (fasted)		Monkey (fasted)	
Study	SN 03329		SN 03329	
Route	IV	Oral	IV	Oral
Dose, mg/kg	10	10	1	1
Cmax, µg/mL	NA	0.33	NA	0.65
Tmax, hr.	NA	3.3	NA	1.0
$AUC_{(0-48)}$, µg*hr/mL	7.9	2.6	5.6	4.8
Cl (mL/min/kg)	21	NA	3.0	NA
Vss (L/kg)	4.6	NA	2.2	NA
MRT, hr	3.6	5.3	13	11
T½, hr	5.1	-	13	-
Absorption (%)	NA	68	NA	75
Bioavailability (%)	NA	33	NA	86
NA = not applicable				

Distribution

The volume of distribution, Vss, for vorapaxar in the single dose pharmacokinetic study (Study 03329) was 4.6 and 2.2 L/kg for rats and monkeys, respectively. Since the standard value for the plasma volume is 0.05-0.2 L/kg, distribution of vorapaxar to the extracellular space and tissues occurs in both species.

In pilot protein binding studies summarized in report SN 03358, the in vitro partitioning of ^{14}C-SCH 530848 to plasma and blood cells in heparinized human whole blood was evaluated using centrifugation. The report stated that in the concentration range of 50-500 ng/mL, ≤11.1% and <1% of ^{14}C-SCH 530848 partitioned to blood cellular components and to platelets, respectively.

The results of three separate studies that evaluated protein binding of SCH 530348 or its major human metabolite, SCH 2046273, are summarized in Table 15. In all species, the binding of SCH 530348 in plasma was constant over the evaluated SCH 530348 concentration range. The binding of SCH 530348 to human plasma was slightly, but not significantly, higher than the binding of SCH 530348 to plasma from rats, rabbits and monkeys. Given the minor differences in protein binding between species, exposure ratios in animals and humans can be based on the total concentration of SCH 530348 rather than the unbound concentration.

The binding of SCH 2046273 to human plasma was lower than the binding of SCH 530348 to human plasma. In human plasma, the percentage of unbound SCH 2046273 is 5-fold higher than the percentage of unbound SCH 530348. The percentage of unbound SCH 2046273 in monkey and mouse plasma is also higher than the percentage of unbound SCH 530348, although the unbound ratio of metabolite to parent is higher in the animal species than in the human.

Table 15: Reviewer's Summary of Protein Binding studies

Study	Compound	Species/Strain/ Material	Compund Concentration, µg/mL	Fraction bound, %	Fraction unbound, %
03359[1]	SCH 530348	Male CD1-mouse plasma	0.0353 to 9.02 µg/mL	99.7-99.8	0.2-0.3
		Male Sprague Dawley rat plasma		99.6-99.7	0.3-0.4
		Male New Zealand White rabbit plasma		99.8	0.2
		Male cynomolgus monkey plasma		99.8	0.2
		Human plasma		99.9	0.1
PK005	SCH 530348 (L-002409410)	Human plasma	0.02 to 0.04 µg/mL	99.82 to 99.84	0.16 to 0.18
	SCH 2046273 (L-003189067)		0.03 to 0.05 µg/mL	99.01 to 99.21	0.79 to 0.99
PK006	SCH 2046273 (L-003189067)	Pregnant NZW-rabbit plasma	0.54 µg/mL	99.45	0.55
		Cynomolgus monkey plasma	0.83 µg/mL	97.90	2.10
		CD1-mouse plasma	0.19 µg/mL	98.86	1.14

DM27463	SCH 530348	Human serum albumin (HSA), 4% 3% 2%	0.05, 0.5 µg/mL	 99.1, 99.2 99.0, 99.0 98.6, 98.7	 0.9, 0.8 1.0, 1.0 1.4, 1.3
		1% α1-acid glyco-protein + HSA, 4% 3% 2%		99.2, 99.3 99.2, 99.1 98.8, 99.0	0.8, 0.7 0.8, 0.9 1.2, 1.0
[1] Previously reviewed – DARRTS document date 11/16/06					

An additional study (DM27463) evaluated the binding of ^{3}H-SCH 530348 to purified human serum albumin (HSA) in the presence and absence of human α1-acid glycoprotein (AAG). The binding of ^{3}H-SCH 530348 was 99.1-99.2% to HSA at the physiological concentration of 4%. Although the binding of ^{3}H-SCH 530348 decreased when the concentration of HSA was decreased to 2%, the fraction of unbound SCH 530348 increased less than 2-fold. The addition of 0.1% AAG increased ^{3}H-SCH 530348 binding more at 2% HSA than at 4% HSA; however, the fraction of unbound SCH 530348 again increased less than 2-fold.

5.1.1 SCH 530348: tissue distribution and excretion pattern of [^{14}C]-SCH 530348-derived radiocarbon after a single oral dose to male and female, albino and pigmented rats

Study no.: SN 03342

Reviewed in DARRTS document 11/16/06

Male and female pigmented Long Evans rats and non-pigmented Sprague Dawley rats were given a single oral dose of vehicle or [^{14}C]-SCH 530348 at 3 mg/kg. At selected timepoints rats were euthanized and their carcasses were frozen and sagittal sectioned. The sections were freeze-dried prior to quantitative whole-body autoradiography using image analysis relative to [^{14}C]-calibration standards.

The major elimination route of SCH530348 was fecal in both sexes and strains of rats with less than 1% of the dose found in the urine. Most (>83%) of the radioactive dose was recovered in feces and urine within 72 hours after dosing. However, 15% of the dose was not excreted by 168 hours after dosing and presumably remained in the carcass tissue.

All tissues, except the lens of the eye, had measurable radiocarbon concentrations by 2 hours post-dose, indicating broad distribution of SCH 530848 (Table 16). Maximal tissue concentrations were generally at 8 hours post dose. Subsequently, concentrations in most tissues declined so that by 48 or 72 hours post dose the concentrations were below the detection limit. The pattern of radiocarbon tissue distribution was similar in both sexes and strains. Exceptions to this pattern were the pituitary and the pigmented tissues of the eye and the skin. Although the maximal concentration in the pituitary occurred at either 8 or 24 hours post dose, the pituitary retained up to 29% of the maximal concentration at 168 hours post dose. In contrast, the concentration in the pigmented region of the eye in pigmented rats increased to an

apparent plateau at 24 hours after dosing and was maintained to the last timepoint of 168 hours post dose.

Other than the gastrointestinal tract, the highest tissue concentrations were observed in the liver, spleen, adrenal, pituitary and thyroid glands, kidney and brown fat. At 48 hours post-dose when most of the dose had been excreted in the feces and the blood concentration was below the limit of detection, the highest tissue concentrations occurred in the pituitary, adrenal gland, and spleen of both rat strains. In pigmented rats the concentration in the pigmented region of the eyeball was equal to or greater than that in the pituitary.

At 168 hours post dose, the albino rats had detectable levels of radioactivity in the pituitary, testis and epididymis. In addition to these tissues, the pigmented rats of both sexes at 168 hours post-dose had measurable concentration in the pigmented region of the eyeball and the skin. The pigmented male rat also had detectable concentrations in the lymph node, while the pigmented female rat did not. The levels of radioactivity in the skin of pigmented rats at 168 hours post-dose had declined to 15-23% of the peak concentration in that tissue. However, the levels of radioactivity in the pigmented eyeball a 168 hours post-dose were similar to the levels at earlier timepoints.

Table 16: Tissue Distribution in Male Pigmented and Non-Pigmented Rats

		Tissue radiocarbon concentration (ng SCH 530848 equiv/g)						
Strain	**Tissue**	**0.25 hr**	**2 hr**	**8 hr**	**24 hr**	**48 hr**	**72 hr**	**168 hr**
Sprague Dawley	Blood	47.7	239	232	BQL	BQL	BQL	BQL
	Lymph Node	26.1	522	859	539[b]	134	BQL[b]	BQL
	Bladder	103[b]	394[b]	688[b]	451[b]	74.7	56.9[a]	BQL[a]
	Kidney	154	1440	1600	416	91.8	BQL[b]	BQL
	Liver	967	3110	1910	314	83.0	BQL	BQL
	Brain	BQL[b]	149	163	BQL	BQL	BQL	BQL
	Pineal Gland	BQL[a]	290[a]	492[a]	235[a]	BQL[a]	BQL[a]	BQL[a]
	Spinal Cord	BQL[a]	147[b]	164[b]	BQL[b]	BQL[b]	BQL	BQL
	Adrenal Gland	155[a]	2010[a]	3130[b]	2160[a]	314[b]	BQL[a]	BQL[b]
	Pituitary Gland	BQL[a]	846[b]	2240[b]	4010[b]	908[b]	618[b]	555[b]
	Thymus	BQL[b]	290	464	313	95.4	BQL	BQL
	Thyroid Gland	66.1[b]	1420	2130[b]	567[b]	92.0[a]	BQL[a]	BQL[b]
	Harderian Gland	BQL[a]	389[b]	647[b]	568[a]	108[a]	BQL[a]	BQL[a]
	Salivary Gland	31.1[b]	1120[b]	1380	351	116	BQL	BQL
	Brown Fat	115[b]	941[b]	1570	174	28.8	BQL	BQL
	White Fat	BQL	945	1690	139	BQL	BQL	BQL
	Epididymis	BQL	274	579	199[b]	129	156	52.5[b]
	Prostate Gland	BQL[b]	240	1140[b]	251	BQL	BQL[a]	BQL[a]
	Seminal Vesicles	BQL[b]	290	750	318[b]	146	58.6[a]	BQL
	Testis	BQL	154	214	67.0	20.4	BQL	72.5
	Myocardium	91.5	906	1170	288	22.4	BQL	BQL
	Skeletal Muscle	BQL	344	657	154	BQL	BQL	BQL
	Bone	BQL	152	105	79.4	BQL	BQL[b]	BQL
	Bone Marrow	BQL	538	925	353	153	BQL[b]	BQL
	Eyeball	BQL[a]	36.0	130[b]	197[b]	BQL[b]	BQL[a]	BQL[a]
	Eye - Lens	BQL[a]	BQL[b]	BQL[b]	BQL[a]	BQL[b]	BQL[a]	BQL[a]
	Lung	113	949	1190	354	75.3	BQL	BQL
	Pancreas	205[b]	1190	1770	583[b]	123	BQL[b]	BQL
	Spleen	177	2280[b]	2320	910	300	BQL	BQL[b]
	Skin (non-pigmented)	BQL	251	460	184	BQL	BQL	BQL
	Esophagus	96.3[b]	294[b]	415[b]	286[a]	114[b]	BQL[a]	BQL[b]
	Stomach	1420	1340	767	496	144	47.9	BQL
	Small Intestine	1900	2060	1870	393	125	BQL	BQL
	Large Intestine	70.3	511	2130	331	122	22.6	BQL

Strain	Tissue	Tissue radiocarbon concentration (ng SCH 530848 equiv/g) 0.25 hr	2 hr	8 hr	24 hr	48 hr	72 hr	168 hr
Long Evans	Blood	BQL	259	251	91.3	BQL	BQL	BQL
	Lymph Node	BQL[a]	499[a]	1490	1150	163	112[b]	280[b]
	Bladder	BQL	2040[a]	1180[a]	622[b]	207	21.5	BQL[b]
	Kidney	145[b]	1580	1930	607	55.6	BQL	BQL[b]
	Liver	791	4080	3880	596	71.1	BQL	BQL
	Brain	BQL[b]	266	174	BQL	BQL	BQL	BQL
	Pineal Gland	BQL[a]	810[a]	1070[a]	463[a]	BQL[a]	BQL[b]	BQL[a]
	Spinal Cord	BQL[b]	248[b]	163[b]	BQL[b]	BQL	BQL[b]	BQL
	Adrenal Gland	146[b]	2100[b]	4100[b]	2680[a]	182	89.0[a]	BQL[a]
	Pituitary Gland	BQL[b]	987	2930	1550[a]	952	955	424[b]
	Thymus	BQL	339	588	466	76.0	BQL	BQL
	Thyroid Gland	228[a]	2160[a]	5860	1170[a]	170[a]	25.9	BQL[a]
	Harderian Gland	BQL[b]	580[a]	1440[a]	661[b]	186[b]	BQL[b]	BQL[b]
	Salivary Gland	BQL	1120	1660	514	22.5	BQL	BQL
	Brown Fat	118	1750[b]	1760	310	BQL	BQL	BQL
	White Fat	BQL	1360	2550	254	BQL	BQL	BQL
	Epididymis	BQL	411	592[b]	215	61.2	62.2	BQL
	Prostate Gland	154	363[a]	1180	329[b]	115	32.1	BQL
	Seminal Vesicles	BQL[b]	158[a]	693	334	85.8	BQL	
	Testis	BQL	258	252	91.8	BQL	63.9	BQL
	Myocardium	64.1	1030	1570	458	BQL	BQL	BQL
	Skeletal Muscle	BQL	636	1070	325	BQL	BQL	BQL
	Bone	BQL	174	197	73.5[b]	BQL[a]	BQL	BQL[b]
	Bone Marrow	BQL	575	1270	932[b]	70.1[a]	22.7	BQL[b]
	Eyeball	BQL[b]	409[b]	858[b]	1040[b]	1040	989[b]	1040[b]
	Eye - Lens	BQL[b]	BQL[a]	BQL[b]	BQL[b]	BQL	BQL[b]	BQL[a]
	Lung	90.3	1180	2100	554	41.1	BQL	BQL
	Pancreas	108[b]	1320	2200	849	79.3	BQL	BQL
	Spleen	BQL[a]	1660	3030	1920	223[b]	BQL	BQL[b]
	Skin (non-pigmented)	BQL	425	696	181	BQL	99.7	BQL
	Skin (pigmented)	BQL	438	553	412	71.9	BQL	126
	Esophagus	76.5[b]	546[b]	438[b]	587[a]	BQL[a]	217	BQL[a]
	Stomach	2190	1660	1060	545	51.4	BQL	BQL
	Small Intestine	3970	2310	3440	714	141	BQL	BQL
	Large Intestine	1020	5000	3020	763[b]	63.4	29.4	BQL[b]

BQL: Below Quantifiable limits of 56.6 ng SCH 530348 equiv/g

5.1.2 SCH 530348: Placental Transfer of [^{14}C]-SCH 530348-Derived Radiocarbon Following a Single Oral Dose to Pregnant Rats

Study number: DM27226
Reviewed in DARRTS document 01/28/13
In pregnant female rats on gestation day 18, a single oral 5 mg/kg dose of [^{14}C]-SCH 530348 was distributed both to maternal and fetal tissues based on quantitative whole body autoradiography. The highest [^{14}C]-SCH 530348 radioactivity concentrations were generally observed at 2 hours post dose in both the dams and the fetuses (Table 17). Cumulative fetal blood and tissue exposure to [^{14}C]-SCH 530348 radioactivity was similar to cumulative maternal blood exposure. These results indicate substantial transfer of [^{14}C]-SCH 530348 radioactivity across the placenta.

Table 17: Reviewer's Summary - Placental Transfer of SCH 530848 - DM27226

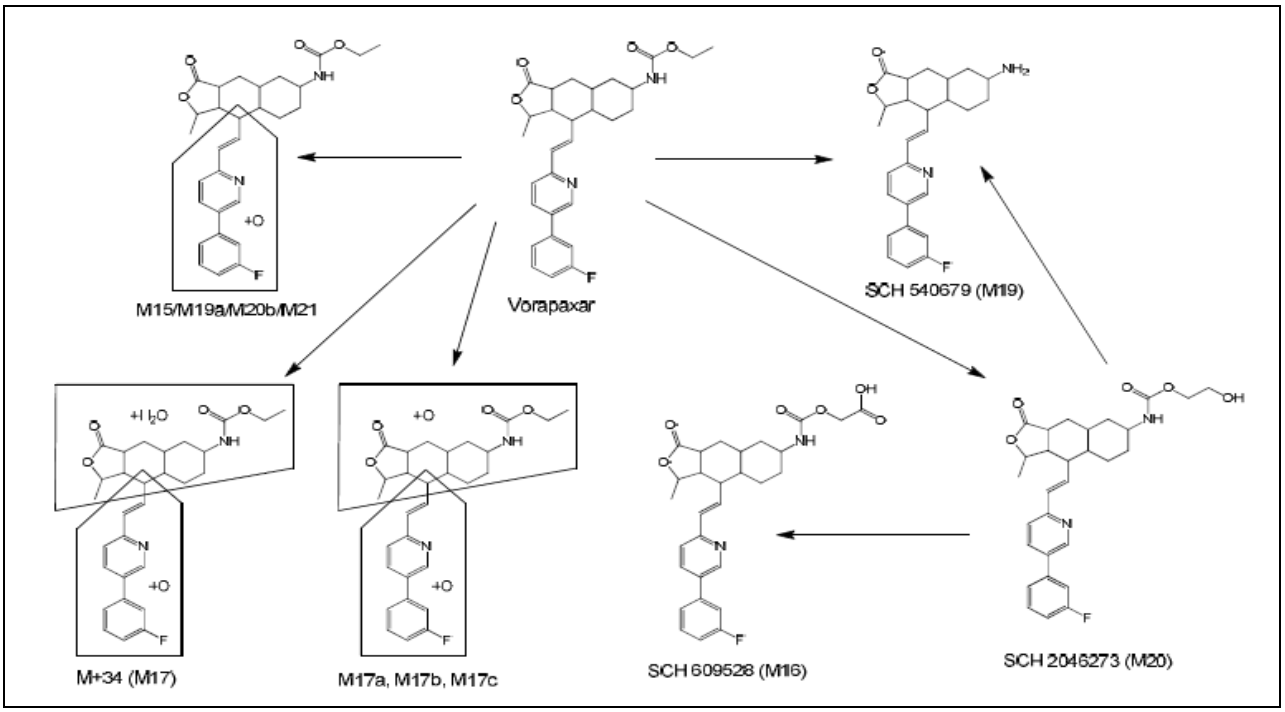
	Radioactivity (ng equivalents/gm)									
Hours post dose	**0.25**	**2**	**8**	**24**	**48**	**C_{max}**	**T_{max}**	**$AUC_{(0-tf)}$**	**tf**	**$AUC_{(0-48hr)}$**
Amniotic fluid	BQL	99.3	BQL	BQL	BQL	99.3	2	86.9	2	384
Fetal										
Blood	48.7	593	491	230	BQL	593	2	9590	24	12300
Brain	BQL	719	439	46.3	BQL	719	2	7990	24	8540
Heart	BQL	877	426	257	BQL	877	2	10100	24	13200
Kidney	BQL	744	589	258	BQL	744	2	11400	24	14500
Liver	BQL	1010	597	287	BQL	1010	2	12800	24	16200
Lung	BQL	748	479	224	BQL	748	2	9960	24	12600
Placenta	155	1790	2230	2010	394	2230	8	76500	48	76500
Maternal blood	156	874	599	199	BQL	874	2	11700	24	14100

BQL: Below quantifiable limits (137 ng SCH 530348 equiv/g).
$AUC_{(tf)}$: Area under the plasma-time concentration profile up to last measurable time point.
tf: Last time point with measurable radiocarbon concentrations.
$AUC_{(0-48\ hr)}$: Area under the plasma-time concentration profile through the 48-hr time point.

Metabolism

The sponsor's diagram (Figure 12) shows the major metabolites in the mouse, rat, monkey and human. Of these metabolites, the one of most concern was the active metabolite, M 20 (SCH 2046273, L-003189067-000X002). In clinical study P06559, steady-state levels of SCH 530848 and the metabolite M20 in humans indicated that M20 to SCH 530848 AUC ratios were similar between Day 1 (17.3%) and Day 42 (19.8%) after once-daily dosing with vorapaxar. However, M20 to SCH 530848 AUC ratios have varied from 10-31% depending upon the particular study.

Figure 13: Sponsor's Diagram of Major Metabolites in the Mouse, Rat, Monkey and Human



The plasma levels of M20 in the mouse are low, but consistently detectable; whereas the plasma levels of M20 in the rat are essentially non-existent (Table 18). However, the higher plasma levels of M20 in the monkey are comparable to those in the human.

Table 18: Reviewer's Summary of SCH 530848 and Its Metabolites in Plasma of Mice, Rats and Monkeys

	Percentage of radioactive metabolites in plasma at the indicated time post dose after an oral dose of [^{14}C]-SCH 530848 (% total chromatographic radioactivity)					
	Mouse (M)		**Rat (M, F)**		**Monkey (M, F)**	
Study	**DM27220**		**SN 04919**		**SN 03328**	
Dose	**75 mg/kg**		**3 mg/kg**		**0.5 mg/kg**	
Metabolite	**2**	**6**	**1.5**	**4**	**2.5**	**8**
SCH 530848	80.2	80.7	67.7, 74.7	67.7, 73.4	66.7, 55.3	53.5, 46.5
M5	-	-	-	-	ND, 1.9	ND, BIT
M7a	-	-	1.7, 1.0	1.5, 1.8		
M8	-	-	BIT	ND, 0.8	BIT, 1.7	ND, BIT
M16	BIT	BIT	-	-	2.1, 4.4	2.3, 3.6
M17	-	-	1.2, 2.6	1.6, 2.3	BIT	BIT
M19	17.4	15.0	15.3, 8.3	23.5, 10.6	1.5, BIT	2.2, 2.1
M19a	BIT	BIT	2.5, 3.3	4.3, 3.5	1.0, 1.3	BIT
M20	**2.4**	**2.2**	**BIT, ND**	**BIT, ND**	**26.7, 32.0**	**38.2, 43.2**
M20b	-	-	ND, BIT	ND, BIT	-	-
M21	-	-	1.2, 4.1	ND, 3.9	2.0, 2.4	3.8, 4.7
M24	-	-	2.8. BIT	1.5, BIT	-	-
Unknown	-	2.1	-	-	ND, 1.1	ND

N.D., not detected, BIT = Detection by LS-MS only, M5 = M7a = Monohydroxy-SCH 530348-gluc; M8 = Monohydroxy-SCH 530348-gluc; M16 = Carboxylic acid metabolite (SCH 609528); M17 = M+34; M19 = Amine metabolite (SCH 540679); M15, M19a, M20, M20b, M21, M24 = Monohydroxy-SCH 530348 (M20 = SCH 2046273)

Subsequent toxicokinetic studies evaluated both SCH 530848 and SCH 2046273 plasma concentrations at steady state after repeated dosing (Table 19). The SCH 2046273 plasma levels in mice, rabbits and monkeys are adequate to allow the metabolite to be considered qualified toxicologically (see Table 123).

Table 19: Reviewer's Summary – Metabolite to Parent Ratios in Various Species

				SCH 530848		SCH 2046273		Ratio
Species	**Study**	**Dose**	**Sex**	**C_{max}**	**$AUC_{(0-t)}$**	**C_{max}**	**$AUC_{(0-t)}$**	**AUC M20/ AUC P**
Rat	08378	30	M	4170	25400	23.6	161	0.0063
			F	5980	53100	4.2	14	0.0007
		75	M	9290	98200	57.5	460	0.0047
			F	11100	192000	10.8	171	0.0009
Mouse	08379	15	M	3950	36600	112	1850	0.051
			F	4190	40000	113	1730	0.043
Monkey	08381	20	M	9760	194000	417	9360	0.046
			F	10600	228000	481	10400	0.049
P = parent SCH 530848								

5.1.3 SCH 530348: Metabolism of [^{14}C]-SCH-530348 after Oral Administration of [^{14}C]-SCH-530348 Suspension to Male and Female Rats

Study number: SN 04919

Reviewed in DARRTS document dated 01/28/13

In both male and female rats, the major excretion route was fecal with urinary excretion representing less than 2% of a single oral dose of [^{14}C]-SCH 530348. The principal drug-related compounds in male and female rat plasma were the parent SCH 530348 and its amine metabolite (M19) with the percentage of the later increasing with time after dosing. SCH 530348 metabolism in rats primarily involves oxidative carbamate cleavage and hydroxylation. Although the amine metabolite (M19) was the major metabolite in male rats, mono and dihydroxy metabolites were also found in female rats.

5.1.4 SCH 530348: Biliary Excretion, Enterohepatic Circulation and Metabolism of [^{14}C]-SCH 530348-Derived Radioactivity after a Single Oral 10 mg/kg Dose to Male and Female Rats

Study number: DM27219

Reviewed in DARRTS document 01/28/13

In bile duct- and duodenal-cannulated rats, [^{14}C]-SCH 530348 radioactivity was primarily excreted into the feces (46-49%) and bile (27-31%) with only 2.2% excreted into the urine. Bile from these donor rats was administered intra-duodenally to recipient rats. The radioactive dose in recipient rats was primarily excreted into the feces (83-86%) with lower amounts in the bile (3.3-4.5%) and urine (0.13-0.14%). The adjusted biliary recovery in donor rats was 32-33% and the adjusted total absorption in recipient rats was 19-22%. The fraction of an oral dose undergoing enterohepatic circulation was

estimated to be 7.1% and 6.4% in males and females, respectively. The bile from donor rats primarily contained the amine metabolite (M19) and very little parent SCH 530348.

5.1.5 SCH 530348: Excretion and Metabolism of [^{14}C]-SCH-530348-Derived Radioactivity after a Single 75 mg/kg Oral Suspension Administration to Male Mice

Study number: DM27220

Reviewed in DARRTS document dated 01/28/13

In male mice, [^{14}C]-SCH 530348 radioactivity was excreted primarily into the feces (87%) with urinary excretion representing 2% of the dose. At 2 and 6 hours post dose, the major SCH 530348 metabolite in mouse plasma was the amine metabolite M19 (SCH 540679), which increased at the later timepoint. SCH 530348 metabolism in mice primarily involves oxidative carbamate cleavage and oxidation. Although the amine metabolite (M19) was the major metabolite in male mouse urine and feces, a carboxylic acid metabolite, M16, and two unknown metabolites were also present at lower levels in mouse feces. Parent SCH 530348 was found in mouse bile, in contrast to rat bile where very little parent was found.

5.1.6 SCH 530348: Metabolic Profiling of SCH 530348 Following Multiple Oral Doses of 20 mg/kg SCH 530348 to Non-fasted Female New Zealand White Rabbits

Conducting laboratory and location: Schering-Plough Research Institute, Kenilworth, NJ
Study number: DM 27633
Date of study initiation: June 11, 2008
Drug lot/batch number: SCH 530348; Batch No. 05-530348-X-302, purity 99.2%
GLP compliance: No
QA statement: No

Methods
Single daily oral doses of SCH 530348 were administered for 7 days at 20 mg/kg to female New Zealand White rabbits in a formulation with 0.4% (w/v) aqueous hydroxypropyl methylcellulose. Blood was collected on Day 1 at 5, 10, and 24 hr after dosing and on Day 7 - 0, 1, 3, 5, 7, 10, and 24 hr after dosing. Urine was collected on Days 1 and 7 at 0-6 hr and 6-24 hr after dosing. Plasma and urine were pooled across time points. Prior to analysis, proteins in plasma samples were precipitated with acetonitrile and urine samples subjected to solid phase extraction. Samples were analyzed by LC-MS and/or LC-MS/MS.

Results
SCH 530848 and its metabolite M20 (SCH 2046273) were the major drug-derived compounds in rabbit plasma after a single dose of SCH 530348 and at steady state on Day 7 (Table 20). The exposure of M20 at steady state was 11.5% of the exposure to SCH 530848 after accounting for the response factor of M20 to parent drug. In the toxicokinetic portion of SN 02147 (embryo-fetal development study) the $AUC_{(0\text{-}24\ hr)}$ of SCH 530848 was 117000 ng*hr/mL at steady state. Therefore, the sponsor estimated the exposure of the M20 metabolite in female rabbits was approximately 13500 ng*hr/mL. $AUC_{(0\text{-}24\ hr)}$ of the M20 metabolite at steady-state is 13500 ng*hr/mL. In urine

on Day 7, the major metabolites were M7a (38.2%), M15a (21.3%), and the carboxylic acid metabolite, SCH 609528 (18%) and M19 (14%) with SCH 530848 representing only 2% of the total peak area.

Table 20: Sponsor's Summary Metabolites in Plasma Relative to that of SCH 530348 following Oral Doses of 20 mg/kg of SCH 530348 to Female Rabbits

Metabolite Label	Name	Rt[a] (min)	m/z (Th)	Relative LC-MS Response (XIC) of SCH 530348 and Metabolites			
				Day 1			Day 7
				5 hr	10 hr	24 hr	0-24 hr
SCH 530348	Parent drug	36.8	493	100	100	100	100
M5	Dioxy-SCH 530348-glucuronide	15.1	701	ND[b]	ND	ND	BIT[c]
M7a	Monohydroxy-SCH 530348-glucuronide	17.9	685	4.15	8.11	4.94	6.13
M15a	Monohydroxy-SCH 530348-glucuronide	22.4	685	0.76	1.56	1.10	0.38
M19	Amine metabolite (SCH 540679)	30.4	421	2.25	4.61	4.11	6.00
M19a	Monohydroxy-SCH 530348	30.2	509	ND	ND	ND	BIT
M20	Monohydroxy-SCH 530348 (SCH 2046273)	30.9	509	18.9[d]	30.7	16.7	11.5

a: Retention time was obtained from LC-MS experiments. File: B8062406.
b: ND = Not detected by LC-MS/MS
c: BIT = Detected by LC-MS/MS only
d: The relative LC-MS response of M20 was multiplied by factor of 2 to adjust for a response factor of M20 to the parent drug.

5.1.7 Incubation of SCH 530348 (MK-5348) With Recombinant Human CYP2C8

Conducting laboratory and location: Merck Research Laboratories, Rahway, NJ
Study number: PK007
Date of study initiation: Not indicated (report date 09/12/2012)
Drug lot/batch number: SCH 530348 (L-002409410-002B012); Batch: Not specified
GLP compliance: No
QA statement: No

SCH 530348 at 0.1, 1 and 10 µM was incubated in vitro with recombinant CYP2C8 or with recombinant CYP3A4. The SCH 530848 metabolites (SCH 540679 (M19), SCH 2046273 (M20), or M+16 metabolites) were monitored by LC-MS/MS. None of these metabolites were detected in the incubations with recombinant CYP2C8. In the incubations with recombinant CYP34, SCH 540679 was detected at all concentrations. Trace levels of SCH 2046273 and two M+16 metabolites were detected at 1 and 10 µM.

5.1.8 SCH 530348: Identification of Human Cytochrome P450 Enzyme(s) Responsible for the Metabolism of SCH 530348

Conducting laboratory and location: Schering-Plough Research Institute, Kenilworth, NJ
Study number: SN 04025
Date of study initiation: June 7, 2007
Drug lot/batch number: SCH 530348; Batch No. 05-530348-X-302, purity 99.2% and ^{14}C-SCH 530348 (Batch No. 083591-022-24), specific activity 126.3 µCi/mg

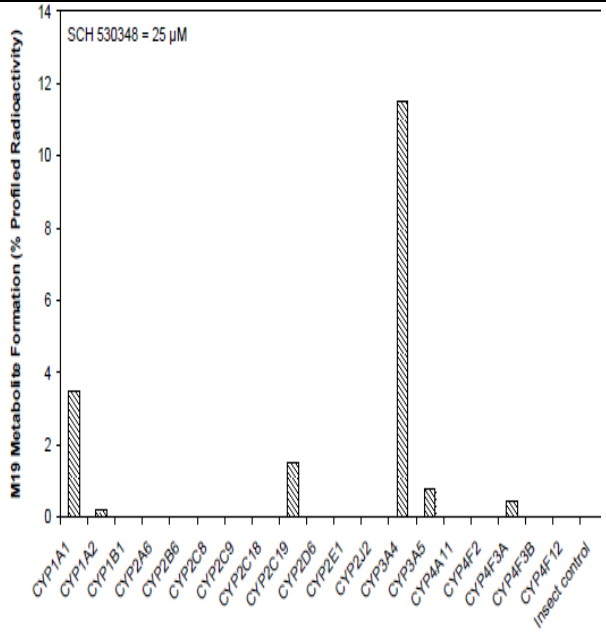
GLP compliance: No
QA statement: No

Methods
The metabolism of ^{14}C-SCH 530348 was evaluated using human liver microsomes from a single donor (H0029) with high CYP3A4 activity and 19 recombinant P450 enzymes in incubations for 30-120 min at 37°C in the presence of an NADPH generating system. Incubations of ^{14}C-SCH 530348 (25 µM) with human liver microsomes were also conducted in the presence and absence of selective inhibitors of P450. Correlation studies were performed with 10 individual human liver microsomes using a Reaction Phenotyping kit (b) (4)

Results
Human liver microsomes with high CYP3A4 activity converted 10 and 25 µM SCH 530348 to 11.5% and 7.5%, respectively, of profiled radioactivity to only one metabolite M19 (SCH 540679). The Km for formation of M19 was 23.5 µM and the Vmax was 57.9 pmol/nmol P450/min. Incubations with recombinant human CYP1A1, CYP1A2, CYP2C19, CYP3A4, CYP3A5, and CYP4F3A resulted in the formation of various amounts of M19 from SCH 530348 (Table 21). The highest formation of M19 was with CYP3A4 (11.5% profiled radioactivity) followed by CYP1A1 and CYP2C19. Even lower levels of M19 were formed with CYP3A5, CYP4F3, and CYP1A2. The formation of M19 by human liver microsomes was inhibited 89% by 2 µM ketoconazole (a selective inhibitor of CYP3A4), 34% by tranylcypromine (CYP2C19/CYP2A6 inhibitor) and 5% by ticlopidine (CYP2C19/CYP2B6 inhibitor). The IC_{50} value of ketoconazole for M19 formation was 0.73 µM. A high correlation was observed between the rate of formation of M19 determined in 10 human liver microsomal samples and midazolam 1'-hydroxylation ($r = 0.75$) or M19 formation and testosterone 6β-hydroxylation ($r = 0.92$) catalyzed by CYP3A4. No correlation was observed between M19 formation and phenacetin O-deethylation (catalyzed by CYP1A2) or M19 formation and S-mephenytoin 4'-hydroxylation (catalyzed by CYP2C19). The results of this study confirmed that CYP3A4 is the major P450 enzyme metabolizing SCH 530348 to M19.

Table 21: Compilation of Sponsor's Figure and Tables – SN 04025

Screening of [^{14}C]-SCH 530348 Metabolism to M19 by P450 SUPERSOMES



SCH 530348 = 25 µM

a: Enzyme activities are from Reaction Phenotyping Kit (n = 10)

b: p = 0.0127

c: p = 0.0001

Effect of P450-Specific Chemical Inhibitors on the Formation of M19 from [^{14}C]-SCH 530348 With Human Liver Microsomes

Inhibitors	Inhibitor of P450	Inhibitor Conc. (µM)	Percent of Inhibition (IC50)
Ketoconazole	CYP3A4/5	2	89 (0.73 ± 0[a])
Tranylcypromine	CYP2C19	100	34
Ticlopidine	CYP2C19/CYP2B6	20	5

a: ± Standard error

Correlation (r) Values Between M19 Formation Rates from SCH 530348 and P450 Enzyme Specific Activities

P450 Enzyme Specific Reaction	P450 Involved[a]	M19 (r value)
Phenacetin O-Deethylation	CYP1A2	0.22
Coumarin 7-Hydroxylation	CYP2A6	0.38
Bupropion Hydroxylation	CYP2B6	0.14
Paclitaxel 6α-Hydroxylation	CYP2C8	0.13
Diclofenac 4'-Hydroxylation	CYP2C9	0.11
S-Mephenytion 4'-Hydroxylation	CYP2C19	0.22
Dextromethorphan O-Demethylation	CYP2D6	0.68
Chlorzoxazone 6-Hydroxylation	CYP2E1	0.44
Midazolam 1'-Hydroxylation	CYP3A4/5	0.75[b]
Testosterone 6β-Hydroxylation	CYP3A4/5	0.92[c]
Lauric Acid 12-Hydroxylation	CYP4A11	0.10

5.1.9 Identification of Human Cytochrome P450 Enzyme(s) Capable of Metabolizing SCH 530348 to M20 Metabolite (SCH 2046273) and Its Downstream Metabolism

Conducting laboratory and location: Schering-Plough Research Institute, Kenilworth, NJ
Study number: DM28002
Date of study initiation: November 9, 2009
Drug lot/batch number: SCH 530348 (Batch No. IRQ-530348-07-YX-9M1); SCH 2046273 (Batch 1)
GLP compliance: NoQA statement: No

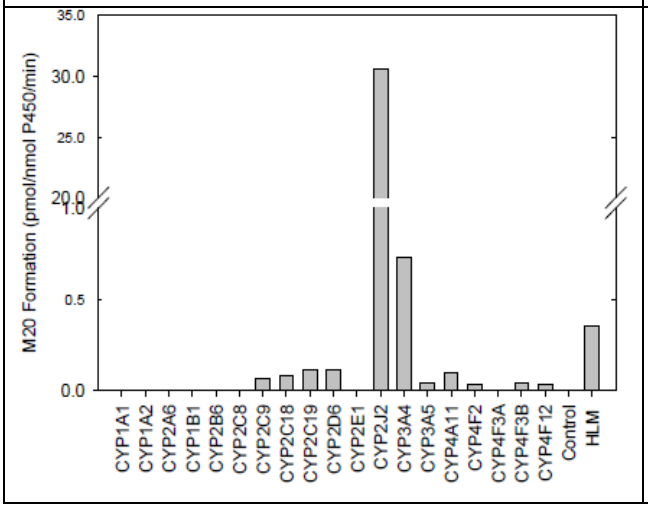
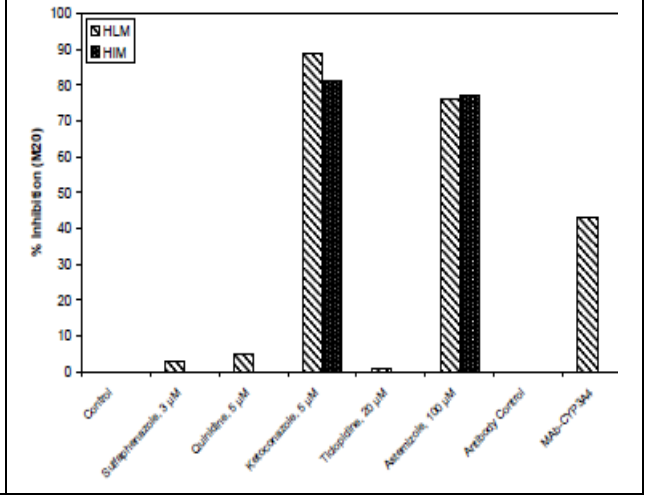
MethodsSCH 530348 (25 µM) was incubated with human liver microsomes with high CYP3A4 activity, human intestine microsomes, human lung microsomes, and 19 recombinant human P450 SUPERSOMES™ (CYP1A1, CYP1A2, CYP2A6, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, CYP3A5, CYP4A11, CYP4F2, CYP4F3A, CYP4F3B, and CYP4F12) for 120 min at 37ºC in presence of an NADPH-generating system. The same conditions were used for inhibition studies with chemical inhibitors and MAB-3A4 monoclonal antibody. Separately, M20 (SCH 2046273, 25 µM) was also incubated with human liver microsomes with high CYP3A4 activity and 19 P450 SUPERSOMES™ under the same conditions.Results

The formation of metabolite M20 was higher in incubations of SCH 530348 with human liver microsomes (21 nM) than with human intestinal microsomes (8.6 nM) or with human lung microsomes (0.97 nM). Incubations with 19 recombinant human P450 SUPERSOMES™ indicated the formation of M20 was more than 40 fold higher with CYP2J2 (30.6 pmol/nmol P450/min) than with CYP3A4 (0.73 pmol/nmol) (Figure 13). Much lower levels of M20 were detected after incubation of SCH 530348 with 2C9, 2C18, 2C19, 2D6, 3A5, 4A11, 4F2, 4F3B, and 4F12 P450 SUPERSOMES™.

In incubations with human liver microsomes, human intestine microsomes, and the SUPERSOMEs™ for CYP3A4, formation of M20 was inhibited 89%, 81% and 92%, respectively, by ketoconazole. In incubations with human liver microsomes, human intestine microsomes, and the SUPERSOMEs™ for CYP2J2, formation of M20 was inhibited 76%, 77% and 51%, respectively, by astemizole. Sulfaphenazole, quinidine, and ticlopidine did not inhibit formation of M20. The monoclonal antibody MAB-3A4 only inhibited M20 formation by 43% in incubations with human liver microsomes, suggesting the formation of M20 involves both CYP3A4 and CYP2J2.

In incubations of M20 with human liver microsomes and with recombinant P450 SUPERSOMES™, the metabolites M16 and M19 were detected with the CYP3A4 and CYP2J2 SUPERSOMES™, but not other P450 SUPERSOMES™. This study concluded that the metabolism SCH 530348 to the M20 metabolite primarily involves CYP3A4 and CYP2J2, which are also involved in the downstream metabolism of M20 to M16 and M19.

Figure 14: Sponsor's Figures – Formation of M20 - DM28002

Screening of Recombinant Human P450 SUPERSOMES With SCH 530348 (25 µM) for the Formation of M20	Inhibition of M20 Formation by P450-Selective Inhibitors and MAb-CYP3A4 in Human Liver Microsomes Expressing High CYP3A4 Activity or Human Intestinal Microsomes (HIM)
	

Excretion
The excretion of SCH 530348 and its metabolites was primarily fecal with urinary excretion accounting for <5% of the dose in animals (Table 22). Studies in bile-duct cannulated rats and monkeys indicated that biliary excretion is the primary elimination route of absorbed SCH 530348.

Table 22: Reviewer's Summary Excretion of SCH 530848 and Its Metabolites

	Percentage of dose as radioactive metabolites in urine and feces after an oral dose of [^{14}C]-SCH 530848 to intact mice, rats, monkeys, and humans									
	Mouse		**Rat, male**		**Rat, female**		**Monkey**		**Human**	
Study	**DM27220**		**SN04919**		**SN04919**		**SN03328**		**P03454**	
Metabolite	**Urine**	**Feces**	**Urine**	**Feces**	**Urine**	**Feces**	**Urine**	**Feces**	**Urine**	**Feces**
SCH 530848	0.3	36.1	0	15	0	9.2	0	5.9	0	1.6, 3.4
M20	0	0.63	ND	ND	ND	ND	0	4.4	ND	1.5
M19	2.0	56.7	0.87	83.7	0.54	50.6	0.05	9.35	2.4	40
M16	0.02	2.7	ND	ND	ND	ND	0.7	33.7	0.8	5.0
M21	BLQ	BLQ	ND	ND	0	8.3	0	6.5	0	15.1
Total	2.1	87	1.3	91.2	1.2	89.4	4.0	97.5	8.5	91.6
Based on Section 2.6.4, Table 13 and 14										

5.1.10 Mass Balance Study of [^{14}C]-SCH 530348 in Male and Female Sprague Dawley Rats Following a Single Oral or Intravenous Administration

Study number: SN 03327

Review in DARRTS document dated 12/05/12

In a mass balance study in Sprague Dawley rats, the major elimination route of SCH 530348 bisulfate was fecal regardless of route of administration. The large recovery of the radioactive dose in feces following intravenous administration indicates that biliary excretion is a major route of elimination in both male and female rats. Following intravenous administration, urinary excretion represented 3.0% and 2.6% of the dose in males and females, respectively. Most (>90%) of the radioactive dose was recovered in feces and urine within 72-96 hours after dosing.

5.1.11 Mass Balance Study of [^{14}C]-SCH 530348 in Male and Female Cynomolgus Monkeys Following a Single Oral or Intravenous Administration

Study number(s): SN03328

Review in DARRTS document dated 12/05/12

In a mass balance study in Cynomolgus monkeys, the major elimination route of SCH 530348 bisulfate was fecal regardless of route of administration. The large recovery of the radioactive dose in feces following intravenous administration indicates that biliary excretion is a major route of elimination. Following intravenous administration, urinary excretion represented 5.0% and 6.0% of the dose in males and females, respectively. Most (>90%) of the radioactive dose was recovered in feces and urine within 96-120 hours after dosing.

The excretion of drug-derived radioactivity and metabolic profiles were similar in male and female monkeys. The major circulating drug-related components in monkey plasma were SCH 530348 and a monohydroxy metabolite (M20) that had been previously detected in human plasma. At 8 hours after oral administration, the M20 metabolite represented 38% and 43% of the total chromatographic radioactivity in male and females, respectively. The biotransformation of SCH 530348 in monkeys primarily occurs by oxidation and carbamate hydrolysis.

5.1.12 SCH 530348: Transfer of Radioactivity into Milk Following a Single Oral Administration of [^{14}C]-SCH 530348 Suspension to 12-day Postpartum Rats

Study number: DM27229

Reviewed in DARRTS document dated 01/28/13

Following a single oral dose of [^{14}C]-SCH 530348 at 30 mg/kg to lactating, 12-day postpartum female (dam) rats, levels of [^{14}C]-SCH 530348-derived radioactivity in milk were 6-fold higher than that in the plasma of the dams (Table 23). Consequently, exposure in nursing pups was 34% of that in dams, based on comparison of plasma $AUC_{(0\text{-}48\ hr)}$ values. The sponsor estimated exposure to SCH 530348 and/or its metabolites in human infants via milk consumption to be approximately 6% of the orally administered dose. The reviewer calculated that over the first 24 hours following dose administration, each dam excreted 833 µg of SCH 530348-derived material or 7% of the administered dose (11.9 mg).

Table 23: Reviewer's Summary – Excretion into Milk - DM27229

		Cmax ng eq/g	**$AUC_{(0\text{-}48)}$ ng eq*hr/g**	**Tmax**
Dam	Blood	3940	48600	2
	Plasma	4920	51700	1
	Milk	29600	337000	2
	Plasma/blood	1.25	1.06	1
	Milk/blood	7.5	6.9	8
	Milk/Plasma	6.0	6.5	
Pup	Blood	423	14900	22
	Plasma	519	17700	22
	Plasma/blood	1.22	1.19	6

Drug-Drug Interactions

5.1.13 In Vitro Evaluation of SCH 530348 as an Inhibitor of Human Cytochrome P450 Enzymes

Study number(s): DM27351

Review in DARRTS document dated 1/04/2013

An in vitro evaluation was conducted using pooled human liver microsomes that were incubated in the presence or absence of SCH 530348 with P450 marker substrates. SCH 530348 did not directly inhibit CYP1A2, CYP2B6, CYP2E1, or CYP3A4/5 and only inhibited CYP2A6, CYP2C19, CYP2D6, or CYP2C9 at high concentrations (≥ 30 µM). However, an increase in CYP2E1 activity (3-fold) was observed with increasing SCH 530348 concentrations. SCH 530348 directly inhibited CYP2C8 with an IC_{50} value of 1.5 µM. Further enzymatic characterization indicated that SCH 530348 is a mixed inhibitor of CYP2C8 with a K_i value of 0.86 µM. Since this K_i value is close to the systemic plasma Cmax (0.94 µM) in humans after a single 40 mg loading dose, the possibility exists for drug-drug interactions of SCH 530348 with co-administered drugs that are CYP2C8 substrates.

5.1.14 In Vitro Evaluation of SCH 530348 as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

Conducting laboratory and location: (b) (4)
Study number: DM27413
Date of study initiation: February 28, 2007
Drug lot/batch number: SCH 530348, Batch No. 05-530348-X-302, Purity: 99.4%
GLP compliance: Not indicated
QA statement: Yes

Methods:
Three preparations of human hepatocytes from three separate human livers were treated once daily for three consecutive days with vehicle (0.1% dimethyl sulfoxide), one of three concentrations of SCH 530348 (1, 10, and 30 µM) or one of three known human CYP inducers (100 µM omeprazole, 750 µM phenobarbital or 10 µM rifampin). After treatment, cells were harvested to prepare microsomes for the analysis of phenacetin O-dealkylase (marker for CYP1A2), bupropion hydroxylase (marker for CYP2B6), amodiaquine N-dealkylase (marker for CYP2C8), diclofenac 4´-hydroxylase (marker for CYP2C9), S-mephenytoin 4´-hydroxylase (marker for CYP2C19) and testosterone 6β-hydroxylase (marker for CYP3A4/5) activity.

Results: SCH 530348 did not induce cytotoxicity based on microscopic evaluation of cell morphology during the treatment period. Hepatocytes had a cuboidal shape with intact cell membranes in a confluent monolayer with few intercellular spaces. Treatment with the prototypical inducers resulted in increases in enzyme activities in the preparations of human hepatocytes. Omeprazole resulted in a 27-fold increase in CYP1A2 activity; phenobarbital resulted in a 13-fold increase in CYP2B6 activity, and rifampin resulted in

increases in the activity of four CYP enzymes (5-fold in CYP2C8, 2.5-fold in CYP2C9, 6-fold in CYP2C19, and 8-fold in CYP3A4/5.

At 1 µM, SCH 530348 did not increase activity of the CYP enzymes measured. However, 10 and 30 µM SCH 530348 resulted in an increase in CYP1A2 activity of 2.7 and 3.0-fold, respectively and in CYP2B6 activity of 3.9 and 4.7-fold, respectively. Although 10 and 30 µM SCH 530348 also increased the activity of CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5, the increases were less than two-fold.

The report maintained that the relative effectiveness of 1, 10, and 30 µM SCH 530348 was less than 15%, 25%, and 40%, respectively, of the appropriate positive control. The report concluded that SCH 530348 is not expected to have potential P450 induction liabilities in the clinic at therapeutically relevant concentrations.

Although 750 µM phenobarbital induced the greatest increase (12.8-fold) in CYP2B6 activity, the reviewer notes that lower concentrations of 100 µM omeprazole and 10 µM rifampin induced increases of 11.5 –fold and 8.4-fold, respectively. The relative effectiveness of 30 µM SCH 530348 was 56% of 10 µM rifampin (Table 24, Figure 14). Given that the upper confidence limit for the Cmax after a 40 mg loading dose of SCH 530348 is approximately 0.6 µM, it is unlikely that SCH 530348 at therapeutically relevant concentrations will induce P450 activity.

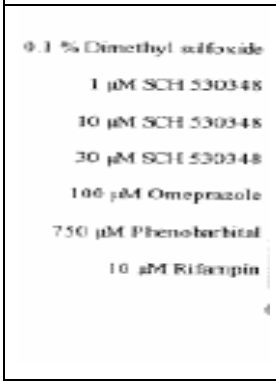
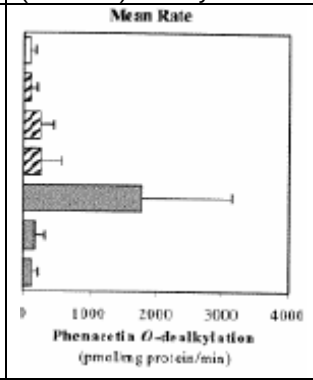
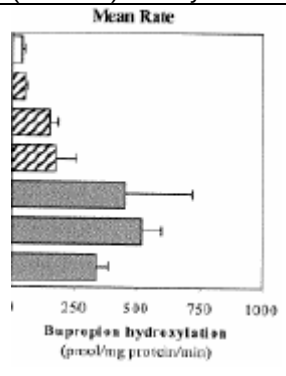
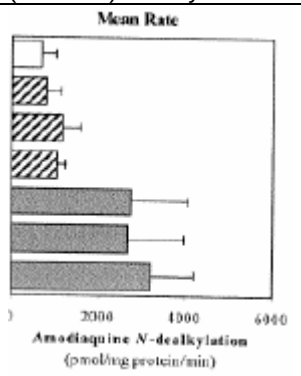
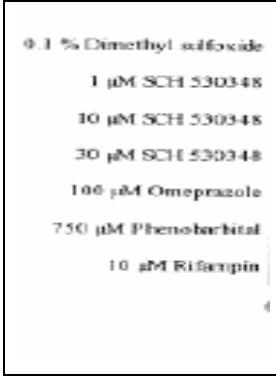
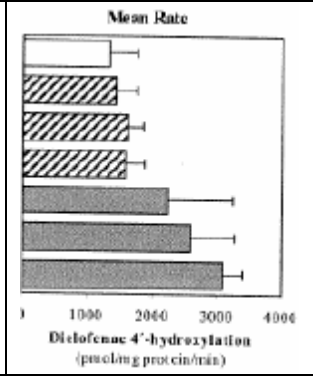
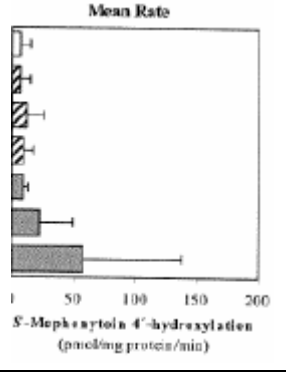
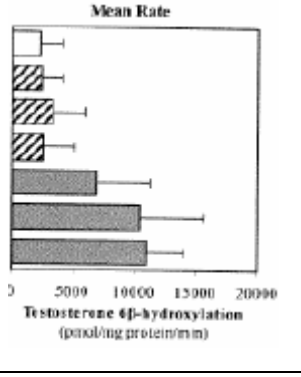
Table 24: Sponsor's Summary - CYP P450 Induction - DM27413

Treatment	Concentration	Enzyme Activity (pmol/mg Microsomal protein/min)[a]					
		Phenacetin *O*-dealkylation (CYP1A2)	Bupropion Hydroxylation (CYP2B6)	Amodiaquine *N*-dealkylation (CYP2C8)	Diclofenac 4′-hydroxylation (CYP2C9)	*S*-Mephenytoin 4′-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl Sulfoxide	0.1% (v/v)	87.4 ± 82.6	41.2 ± 9.7	683 ± 314	1340 ± 420	7.20 ± 7.80	2280 ± 1770
SCH 530348	1 µM	99.7 ± 101.5	50.6 ± 10.4	764 ± 367	1420 ± 330	7.30 ± 7.71	2360 ± 1740
SCH 530348	10 µM	237 ± 213	151 ± 36	1170 ± 410	1630 ± 230	12.3 ± 14.2	3300 ± 2690
SCH 530348	30 µM	266 ± 297	173 ± 84	1030 ± 210	1590 ± 300	9.02 ± 8.67	2490 ± 2630
Omeprazole	100 µM	1790 ± 1370	454 ± 267	2770 ± 1300	2250 ± 1000	8.87 ± 5.04	6920 ± 4340
Phenobarbital	750 µM	175 ± 43	519 ± 76	2670 ± 1290	2590 ± 680	22.5 ± 26.7	10400 ± 5200
Rifampin	10 µM	139 ± 83	336 ± 51	3200 ± 990	3090 ± 310	58.3 ± 80.1	11000 ± 2900

a: Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H749, H753 and H754) rounded to three significant figures.

Treatment	Concentration	Fold Increase[a]					
		Phenacetin *O*-dealkylation (CYP1A2)	Bupropion Hydroxylation (CYP2B6)	Amodiaquine *N*-dealkylation (CYP2C8)	Diclofenac 4′-hydroxylation (CYP2C9)	*S*-Mephenytoin 4′-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl Sulfoxide	0.1% (v/v)	1.00 ± 0.94	1.00 ± 0.24	1.00 ± 0.46	1.00 ± 0.31	1.00 ± 1.08	1.00 ± 0.78
SCH 530348	1 µM	1.08 ± 0.10	1.24 ± 0.09	1.11 ± 0.15	1.08 ± 0.10	1.04 ± 0.06	1.07 ± 0.06
SCH 530348	10 µM	2.66 ± 0.57[b]	3.91 ± 1.80	1.80 ± 0.29	1.27 ± 0.32	1.63 ± 0.22[b]	1.44 ± 0.10
SCH 530348	30 µM	2.97 ± 0.96[b]	4.66 ± 3.00	1.82 ± 1.12	1.27 ± 0.49	1.39 ± 0.23[b]	1.11 ± 0.49
Omeprazole	100 µM	27.0 ± 15.2[c]	11.5 ± 6.8[c]	4.09 ± 0.44[c]	1.68 ± 0.47	1.87 ± 1.25	3.76 ± 1.62
Phenobarbital	750 µM	2.24 ± 0.38	12.8 ± 1.8[c]	3.86 ± 0.14[c]	2.01 ± 0.52	2.86 ± 0.39	6.11 ± 3.15[c]
Rifampin	10 µM	2.16 ± 0.97	8.38 ± 1.72[c]	5.09 ± 1.44[c]	2.47 ± 0.87[c]	6.08 ± 2.80[c]	8.09 ± 6.96[c]

Figure 15: Sponsor's Figures – CYP P450 Induction - DM27413

	Phenacetin O-Dealkylase (CYP1A2) Activity	Bupropion Hydroxylase (CYP2B6) Activity	Amodiaquine N-Dealkylase (CYP2C8) Activity
			
	Diclofenac 4´-Hydroxylase (CYP2C9) Activity	S-Mephenytoin 4´-Hydroxylase (CYP2C19) Activity	Testosterone 6β-Hydroxylase (CYP3A4/5) Activity
			

5.1.15 Evaluation of L-003189067 as a Reversible Inhibitor of Five Cytochrome P450 Activities in Pooled Human Liver Microsomes

Conducting laboratory and location: (b) (4)
Study number: PK010 ((Study 120872)
Date of study initiation: Not indicated 9report date September 27, 2012)
Drug lot/batch number: L-003189067-000X002, Batch: Not indicated
GLP compliance: No
QA statement: No

The ability of L-003189067-000X002 (SCH 2046273, M20) to inhibit five human liver microsomal cytochrome P450 (CYP) activities was evaluated at 0.0003 to 1 µM. The enzyme activities included bupropion hydroxylase (CYP2B6), (S)-mephenytoin 4′-hydroxylase (CYP2C19), dextromethorphan O-demethylase (CYP2D6), midazolam 1′-hydroxylase (CYP3A4), and testosterone 6β-hydroxylase (CYP3A4). The IC_{50} values for L-003189067-000X002 were >1 µM for each of the studied enzymes (Table 25).

Table 25: Sponsor's Summary – PK010

CYP	Reaction	Absolute IC_{50} (μM)[a]	
		Control Inhibitor	L-003189067-000X002
2B6	Bupropion Hydroxylation	0.43 Ticlopidine	>1.0 (0%)[b]
2C19	*S*-Mephenytoin 4′-Hydroxylation	0.19 Benzylnirvanol	>1.0 (0%)
2D6	Dextromethorphan *O*-Demethylation	0.17 Quinidine	>1.0 (0%)
3A4	Midazolam 1′-Hydroxylation	0.023 Ketoconazole	>1.0 (0%)
3A4	Testosterone 6β-Hydroxylation	0.030 Ketoconazole	>1.0 (1.7 ± 0.88%)

[a] The absolute IC_{50} is defined as the inhibitor concentration that yields 50% of the mean control activity.
[b] The values in parentheses represent the percent inhibition (mean ± standard deviation) observed at 1 μM.

5.1.16 SCH 530348: Caco-2 Bi-directional Permeability Study

Study number(s): DM27476

Reviewed in DARRTS document dated 01/28/13

SCH 530348 was evaluated in the Caco-2 cell model to determine its permeability class and whether it is a P-glycoprotein (P-gp) substrate. SCH 530348 is highly permeable (BCS Class 1 or 2) with apical to basolateral permeability (27.9 to 34.0 10^{-6}cm/s) higher than that of the reference compound, pindolol (9.9 to 11.8 10^{-6}cm/s) and independent of its initial concentration. SCH 530348 is not a P-gp substrate.

5.1.17 Evaluation of SCH 530348 as a P-Glycoprotein (P-GP, MDR1) Inhibitor using Caco-2 Bi-Directional Permeability Assay

Study number: DM27415

Reviewed in DARRTS document dated 01/04/13

SCH 530348 was evaluated as an inhibitor of P-gp using the Caco-2 cell model and [^{3}H]-digoxin as a P-gp substrate probe. SCH 530348 inhibited digoxin efflux with an IC_{50} value of 1.2 ± 0.6 μM, while cyclosporine A inhibited digoxin efflux with an IC_{50} value of 0.8 ± 0.1 μM. SCH 530348 is a relatively potent P-gp inhibitor.

5.1.18 Passive Permeability of L-003189067 across LLC-PK1 Monolayers

Conducting laboratory and location: Merck Research Laboratories, Rahway, NJ
Study number: PK007
Date of study initiation: Not indicated (report date 01/15/2013)
Drug lot/batch number: L-003189067-000X002; Batch: Not specified
GLP compliance: No
QA statement: No

The passive permeability of L-003189067 (SCH 2046273, M20) across LLC-PK1 cell monolayers was evaluated at 1 µM in a 3-hour end-point assay from basolateral to apical (B→A) and from apical to basolateral (A → B). The passive permeability of L-003189067 (P_{app} = 25.4 x 10-6 cm/s) in LLC-PK1 cells is high with permeability comparable to that of verapamil and metoprolol and much higher than that of mannitol (Table 26).

Table 26: Sponsor's Summary SCH 2046273 Permeability – PK012

Passive Permeability of L-003189067 Across LLC-PK1 Cell Monolayers		
Compound	LLC-PK1 BA/AB Ratio	LLC-PK1 P_{app} ($CM*E^{-6}$/SEC)
1 µM Verapamil	1.4	31.9
1 µM Metoprolol	1.1	31.3
1 µM Mannitol	0.9	3.4
1 µM L-003189067	0.9	25.4

5.1.19 Interactions of MK-5348 with the Human Liver Uptake Transporters, OATP1B1 and OATP1B3, the Human Renal Uptake Transporters OAT1, OAT3, and OCT2, and the Human Efflux Transporter BCRP

Conducting laboratory and location: Merck Research Laboratories, Rahway, NJ
Study number: PK008
Date of study initiation: Not indicated (report date 08/27/2012)
Drug lot/batch number: MK-5348 (L-002409410-000X00, SCH 530848); Batch: Not specified
GLP compliance: No
QA statement: No

Methods:
The in vitro ability of MK-5348 (L-002409410-000X00, SCH 530848) to inhibit the human hepatic uptake transporters, OATP1B1 and OATP1B3, the human renal uptake transporters, OAT1, OAT3, and OCT2, and the human efflux transporter, BCRP, was evaluated using stably transfected cells as summarized in Table 27.

Results:
SCH 530848 inhibited OATP1B1, OATP1B3, OAT1, or OCT2 transport by <50% of control at the highest concentration tested (10 µM). In contrast, SCH 530848 inhibited OAT3 and BCRP transport with apparent IC_{50} values of 2.2 ± 0.5 and 2.5 ± 0.3 µM respectively (Table 27).

Table 27: Reviewer's Summary SCH 530848 Effects on Transporters - PK008

Transporter	Cell type	Transporter substrate	Positive control	Comments on MK-5348 effects	Result
OATP1B1	MDCKII	[^{3}H] pitavastatin	cyclosporin A	at 1 µM MK-5348 enhanced transport by 50%; At 10 µM, MK-5348 inhibited OATP1B1 transport ~ 31%	IC_{50} > 10 µM
OATP1B3	MDCKII	[^{3}H] BSP	cyclosporin A	At 10 µM, MK-5348 inhibited ~45% of OATP1B3 mediated BSP uptake	IC_{50} > 10 µM
OAT1	MDCKII	[^{3}H]-cidofovir	probenecid	At 5 and 10 µM, MK-5348 enhanced OAT1 transport by 50%	IC_{50} > 10 µM
OAT3	MDCKII	[^{3}H]-Estrone sulfate	probenecid	At 10 µM, MK-5348 inhibited ~93% of OAT3 mediated estrone sulfate uptake	IC_{50} = 2.2 ± 0.5 µM
OCT2	CHO-K1	[^{14}C] metformin	decynium 22	At 10 µM, MK-5348 inhibited ~19% of OCT2 mediated metformin uptake.	IC_{50} > 10 µM
BCRP	Membrane vesicles from baculovirus infected Spodoptera frugiperda (Sf9) cells containing human BCRP	[^{3}H] methotrexate	Ko143	At 10 µM, MK-5348 inhibited 74% of BCRP mediated methotrexate uptake.	IC_{50} of 2.5 ± 0.3 µM

5.1.20 Interactions Of L-003189067-000X002 with the Human Liver Uptake Transporters, OATP1B1 AND OATP1B3, the Human Renal Uptake Transporters OAT1, OAT3, AND OCT2, and the Human Efflux Transporter BCRP

Conducting laboratory and location: Merck Research Laboratories, Rahway, NJ
Study number: PK009
Date of study initiation: Not indicated (report date 08/27/2012)
Drug lot/batch number: L-003189067-000X002 (SCH 2046273, M20); Batch: Not specified
GLP compliance: No
QA statement: No

Methods:
The in vitro ability of L-003189067-000X002 (SCH 2046273, M20) to inhibit the human hepatic uptake transporters, OATP1B1 and OATP1B3, the human renal uptake transporters, OAT1, OAT3, and OCT2, and the human efflux transporter, BCRP, was evaluated using stably transfected cells as summarized in Table 28.

Results:

SCH 2046273 inhibited OATP1B1, OATP1B3, OAT1, or OCT2 transport by <50% of control at the highest concentration tested (10 µM). In contrast, SCH 2046273 inhibited OAT3 and BCRP transport with apparent IC_{50} values of 0.6 and 1.6 µM respectively.

Table 28: Reviewer's Summary SCH 2046273 Effects on Transporters - PK009

Transporter	Cell type	Transporter substrate	Positive control	Comments on SCH 2046273 effects	Result
OATP1B1	MDCKII	[^{3}H] pitavastatin	cyclosporin A	At 5 and 10 µM SCH 2046273 enhanced OATP1B1 transport by 50%;	IC_{50} > 10 µM
OATP1B3	MDCKII	[^{3}H] (sulfobromophthalein (BSP)	cyclosporin A	At 10 µM, SCH 2046273 slightly enhanced OATP1B3 mediated BSP uptake by 19%	IC_{50} > 10 µM
OAT1	MDCKII	[^{3}H]-cidofovir	probenecid	At 10 µM, SCH 2046273 slightly enhanced OAT1 mediated transport	IC_{50} > 10 µM
OAT3	MDCKII	[^{3}H]-Estrone sulfate	probenecid	At 10 µM, SCH 2046273 inhibited 98% of OAT3 mediated estrone sulfate uptake	IC_{50} = 0.6 ± 0.1 µM
OCT2	CHO-K1	[^{14}C] metformin	decynium 22	At 10 µM, SCH 2046273 inhibited ~17% of OCT2 mediated metformin uptake.	IC_{50} > 10 µM
BCRP	Membrane vesicles from baculovirus infected Spodoptera frugiperda (Sf9) cells containing human BCRP	[^{3}H] methotrex-ate	Ko143	At 10 µM, SCH 2046273 inhibited 77% of BCRP mediated methotrexate uptake.	IC_{50} = 1.6 ± 0.2 µM

5.1.21 Evaluation of Vorapaxar and SCH 2046273 as an Inhibition of Selective Gut, Liver, and Renal Transporters

Conducting laboratory and location: Merck Research Laboratories, Rahway, NJ
Study number: PK013
Date of study initiation: Not indicated (report date 02/12/2013)
Drug lot/batch number: Not applicable
GLP compliance: No
QA statement: No
Report PK013 did not contain new data, but was based on findings in studies PK008 and PK009. PK013 evaluated the potential for vorapaxar and its metabolite, SCH 2046273 to result in drug-drug interactions involving P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion-transporting polypeptides (OATP1B1, OATP 1B3). This evaluation concluded that the only potential drug-drug interactions involve vorapaxar inhibition of P-gp in the gut (Table 29).

Table 29: Reviewer's Summary – Potential for Drug-Drug Interactions – PK013

Compound	Transporter	IC_{50}	Cmax	Cmax /IC_{50}	Cmax, fu/IC_{50}	Dose/ 250 ml	Gut conc. /IC_{50}	Expected effect
Criteria for Interaction				PI>0.1	PI>0.02		PI>10	
SCH 530348	P-gp	1.2	0.16	0.13	0.0013	16.9	14.1	2.5 mg vorapaxar may inhibit P-gp in the gut
	BCRP	2.5	0.16	0.064	0.00064	16.9	6.8	No effect
	OATP1B1 & OATP1B3	>10	0.16	<0.016	<0.00016	NA	NA	No effect
	OAT1 & OCT2	>10	0.16	<0.016	<0.00016	NA	NA	No effect
	OAT3	2.2	0.16	0.072	<0.00072	NA	NA	No effect
SCH 2046273	BCRP	1.6	0.021	0.013	0.00013	NA	NA	No effect
	OATP1B1 & OATP1B3	>10	0.021	<0.0021	<0.000021	NA	NA	No effect
	OAT1 & OCT2	>10	0.021	<0.016	<0.000021	NA	NA	No effect
	OAT3	0.6	0.021	0.35	<0.00035	NA	NA	No effect
PI = Potential Interaction criteria, NA = Not applicable								

5.2 Toxicokinetics

5.2.1 Two week toxicokinetic study of SCH 530348 and SCH 2046273 (a metabolite of SCH 530348) in mice (Report Amendment 1)

Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Study number(s): SN 08379
Date of study initiation: December 18, 2008
Drug lot/batch number: SCH 530348, Batch No.: 03-530348-X-302, purity 99.2%
GLP compliance: Yes
QA statement: Yes

Key Study Findings
The toxicokinetics of SCH 530348 and its metabolite SCH 2046273 were determined in male and female mice that received single daily oral (gavage) dose of 15 mg/kg for 1, 6 or 13 days. SCH 530348 and SCH 2046273 systemic exposure was independent of sex and remained constant following repeated SCH 530348 administration. Plasma levels of the metabolite, SCH 2046273, on Days 0, 6 and 13 were 4.6%, 5.1% and 4.7%, respectively, the concentration of the parent, SCH 530348.

Purpose

The objective of this study was to determine the toxicokinetics of SCH 530348 and SCH 2046273, a metabolite of SCH 530348, following oral administration to mice for 14 days. The amendment concerned revisions to the toxicokinetic data.

Methods

Doses:	15 mg/kg/day
Frequency of dosing:	Once daily for 1, 7 or 14 days
Administration route:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Mouse (Crl:CD1[ICR])
Number/Sex/Group:	45 animals/sex
Age:	Approximately 8 weeks at start of dosing
Weight:	Males: 28.5 to 35.7 g and female: 23.6 to 30.4 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	One protocol deviation was noted in the report. The deviation did not affect the quality of the study or its interpretation.

Parameter	**Observation details and times**
Mortality	At least once daily
Clinical observations	Day -8, the day of randomization and immediately before and after dosing
Body weight	Weekly from Week -1 and the day of randomization
Toxicokinetics	Blood was collected from three animals per timepoint at 1, 2, 4, 8, and 24 hr after dosing on Days 1, 6, and 13 from the abdominal aorta under isoflurane-induced anesthesia. Animals will be sacrificed by exsanguination. Plasma samples were assayed for SCH 530348 and SCH 2046273 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of all dosing formulations were collected for concentration and homogeneity determination on the day of preparation for Week 1. The sponsor previously determined that SCH 530348 is stable in 0.4% (w/v) aqueous methylcellulose at room temperature for at least 15 days.

Mortality
No unscheduled deaths occurred during the study.

Clinical observations
No remarkable clinical observation was made during the study.

Body weight

For the 15 mice that were scheduled for the Day 14 timepoints, the mean body weight was not significantly affected by treatment with SCH 530348 (Table 30). However, two males and 5 females lost body weight between Day 0 and Day 7.

Table 30: Reviewer's Summary of Body weight

Dose, mg/kg	Day†	Males				Females			
		-7	-1	1	7	-8	-1	1	7
15	Mean, gm	30.00	31.47	31.46	31.91	24.59	25.85	25.71	25.74
	SD	1.42	1.63	1.46	1.63	0.90	0.97	0.89	0.88

Toxicokinetics

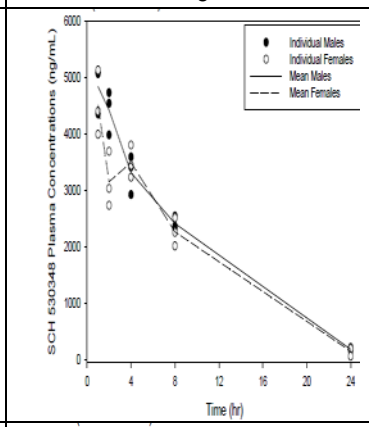
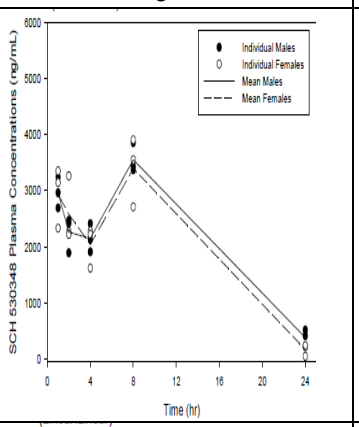
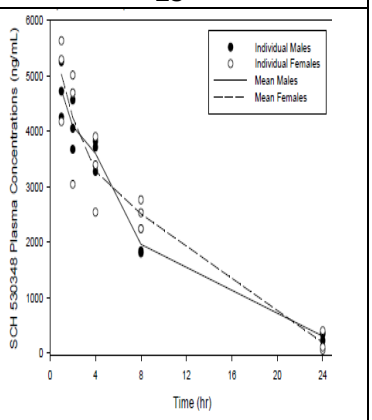
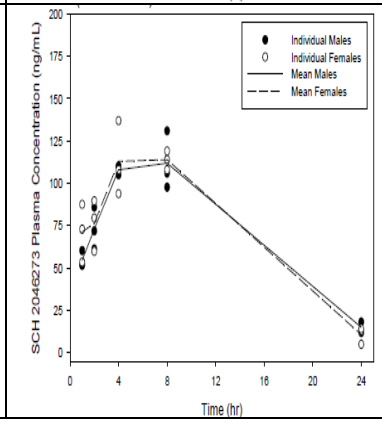
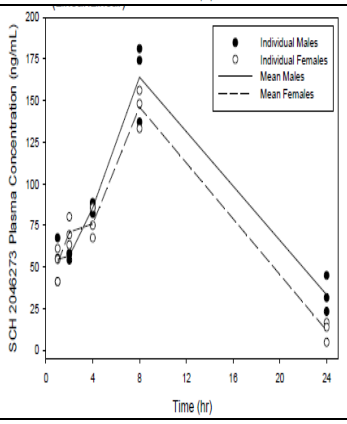
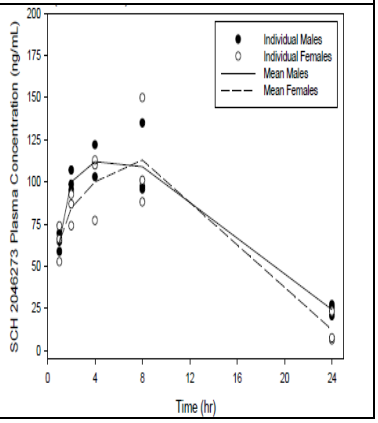
The toxicokinetic report was amended and the plasma concentrations of SCH 530348 revised downward from the original report.

Maximum SCH 530348 plasma concentrations generally occurred between 1 and 8 hr post-dose, while maximum SCH 2046273 plasma concentrations generally occurred between 4 and 8 hr post-dose (Table 31, Figure 16). Systemic exposure to SCH 530348 and SCH 2046273 was similar in females and males and did not significantly change following repeated administration at 15 mg/kg. Exposures to SCH 2046273 even after repeated administration represented 4.3% to 5.4% of the exposure to SCH 530348.

Table 31: Complied from Sponsor's Tables Summarizing Toxicokinetic Parameters for SCH 530348 and SCH 2046273

			SCH 530348				SCH 2046273				Ratio
SCH 530348 Dose (mg/kg)	Day	Sex	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(0-24 hr) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(0-24hr) (ng·hr/mL)	M to P
15	0	Female	3760	1	24	36200	114	8	24	1750	0.048
		Male	4030	1	24	39100	112	8	24	1720	0.044
	6	Female	2820	8	24	40200	146	8	24	1940	0.048
		Male	2960	8	24	43000	164	8	24	2320	0.054
	13	Female	4190	1	24	40000	113	8	24	1730	0.043
		Male	3950	1	24	36600	112	4	24	1850	0.051
M = metabolite, P = parent											

Figure 16: Sponsor's Figures - Individual and Mean SCH 530348 Plasma Concentration-Time Profiles after a Single Dose and after Repeated Dosing

Day	0	6	13
SCH 530348			
SCH 2046273			

Formulation analysis
The formulation was considered homogenous since the recoveries for individual replicates were between 98.0% and 98.7% of nominal.

5.2.2 Single-Dose Oral (Gavage) Comparative Toxicokinetic Study of SCH 530348 in Rats

Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Study number(s): SN 04317
Date of study initiation: November 30, 2004
Drug lot/batch number: SCH 530348 Batch No. 02-530348-X-004 (Batch 004) or SCH 530348 Batch No. 03-530348-X-101 (Batch 101).
GLP compliance: Yes
QA statement: Yes

Key Study Findings
The toxicokinetics of SCH 530348 and its metabolite SCH 2046273 were determined in male and female rats that received single oral (gavage) dose of 3, 20 or 50 mg/kg of

SCH 530348 Batch No. 02-530348-X-004 (Batch 004) or SCH 530348 Batch No. 03-530348-X-101 (Batch 101). The SCH 530348 systemic exposure increased with dose and was not significantly different between Batch 004 and Batch 101.

Purpose
The objective of this study was to compare the toxicokinetics of two batches of SCH 530348.

Methods

Doses:	3, 20 or 50 mg/kg
Frequency of dosing:	Single dose
Administration route:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Rat/Crl:CD®(SD)IGS BR (b) (4) ™;
Number/Sex/Group:	8 animals/sex/group
Age:	Approximately 8 weeks at start of dosing
Weight:	Males: 224.5 to 317.0 g and females: 172.0 to 223.2 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	One protocol deviation was noted in the report. The deviation did not affect the quality of the study or its interpretation.

Table 32: Sponsor's Study Design – SN 04317

Group	Test Article	Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Rats	
					Male	Female
T1	Low-Dose Batch 004	3	5	0.6	8	8
T2	Mid-Dose Batch 004	20	5	4	8	8
T3	High-Dose Batch 004	50	5	10	8	8
T4	Low-Dose Batch 101	3	5	0.6	8	8
T5	Mid-Dose Batch 101	20	5	4	8	8
T6	High-Dose Batch 101	50	5	10	8	8

Parameter	**Observation details and times**
Mortality	At least once daily
Body weight	Only on the day of randomization
Toxicokinetics	Blood was collected from three rat/sex/group per timepoint at 1, 2, 4, 8, and 24 hr after dosing from the jugular vein or from the abdominal aorta under isoflurane-induced anesthesia. Animals were sacrificed by exsanguination. Plasma samples were assayed for SCH 530348 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of the 0.6 and 10 mg/mL dosing formulations of both batches were collected for homogeneity determination on the day of preparation for Week 1. Samples of all dosing formulations of both batches were

	collected for concentration analysis. The sponsor previously determined that SCH 530348 is stable in 0.4% (w/v) aqueous methylcellulose at room temperature for at least 15 days.

Results:

Mortality
No unscheduled deaths occurred during the study.

Formulation analysis
The concentrations of SCH 530348 in all formulation samples of both batches were within 98.3% to 102% of nominal.

Toxicokinetics
Maximum SCH 530348 plasma concentrations generally occurred between 1 and 4 hr post-dose (Table 33). Systemic exposure to SCH 530348 was higher in females than in males for all doses and both batches of SCH 530348. The report concluded that systemic exposure to SCH 530348 was similar between the two batches and any difference was attributed to biological variability.

Table 33: Reviewer's Summary - Toxicokinetic Parameters – SN 04317

		Cmax (ng/ml		Tmax (hr)		AUC $_{(0\text{-}24\ hr)}$ (ng*hr/ml)	
Dose	**Sex**	**Batch 004**	**Batch 101**	**Batch 004**	**Batch 101**	**Batch 004**	**Batch 101**
3	Female	410	405	1	1	2560	2490
	Male	326	259	1	2	1620	1530
20	Female	1720	1540	2	2	13200	15600
	Male	1110	1300	2	2	8670	1200
50	Female	2670	3310	4	2	24900	31900
	Male	1890	1930	4	4	17300	19300

5.2.3 Single-Dose Oral (Gavage) Comparative Toxicokinetic Study of SCH 530348 in Mice

Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Study number(s): SN 05003
Date of study initiation: January 31, 2005
Drug lot/batch number: SCH 530348 Batch No. 02-530348-X-004 (Batch 004) or SCH 530348 Batch No. 03-530348-X-101 (Batch 101).
GLP compliance: Yes
QA statement: Yes

Key Study Findings
The toxicokinetics of SCH 530348 and its metabolite SCH 2046273 were determined in male mice that received single oral (gavage) dose of 5, 25 or 75 mg/kg of SCH 530348

Batch No. 02-530348-X-004 (Batch 004) or SCH 530348 Batch No. 03-530348-X-101 (Batch 101). The SCH 530348 systemic exposure increased with dose and was not significantly different between Batch 004 and Batch 101.

Purpose
The objective of this study was to compare the toxicokinetics of two batches of SCH 530348.

Methods

Doses:	5, 25 or 75 mg/kg (Table 34)
Frequency of dosing:	Single dose
Administration route:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Male mice/Crl:CD-1®(ICR)BR (b) (4)
Number/Sex/Group:	8 animals/sex/group
Age:	Approximately 6 weeks at start of dosing
Weight:	Males: 23.9 to 31.0 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	One protocol deviation was noted in the report. The deviation did not affect the quality of the study or its interpretation.

Table 34: Sponsor's Study Design – SN 05003

Group	Test Article	Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Male Mice
T1	Low-Dose (SCH 530348 Batch 02-530348-X-004)	5	5	1	15
T2	Mid-Dose (SCH 530348 Batch 02-530348-X-004)	25	5	5	15
T3	High-Dose (SCH 530348 Batch 02-530348-X-004)	75	5	15	15
T4	Low-Dose (SCH 530348 Batch 03-530348-X-101)	5	5	1	15
T5	Mid-Dose (SCH 530348 Batch 03-530348-X-101)	25	5	5	15
T6	High-Dose (SCH 530348 Batch 03-530348-X-101)	75	5	15	15

Parameter	Observation details and times
Mortality	At least once daily
Body weight	Only on the day of randomization

Toxicokinetics	Blood was collected from three mice/group per timepoint at 1, 2, 4, 8, and 24 hr after dosing from the abdominal aorta under isoflurane-induced anesthesia. Animals were sacrificed by exsanguination. Plasma samples were assayed for SCH 530348 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of the 1 and 15 mg/mL dosing formulations of both batches were collected for homogeneity determination on the day of preparation for Week 1. Samples of all dosing formulations of both batches were collected concentration analysis. The sponsor previously determined that SCH 530348 is stable in 0.4% (w/v) aqueous methylcellulose at room temperature for at least 15 days.

Results:

Formulation analysis
The concentrations of SCH 530348 in all formulation samples of both batches were within 96.7% to 102% of nominal.

Mortality
No unscheduled death occurred during the study.

Toxicokinetics
Maximum SCH 530348 plasma concentrations generally occurred between 1 and 2 hr post-dose (Table 35) . Systemic exposure to SCH 530348 increased with dose for both batches of SCH 530348. The report concluded that systemic exposure to SCH 530348 was similar between the two batches and any difference was attributed to biological variability.

Table 35: Reviewer's Summary - Toxicokinetic Parameters – SN 05003

SCH 530348 Batch[a,b]	Dose (mg/kg)	Cmax (ng/mL)	Tmax (hr)	tf (hr)	AUC(tf) (ng·hr/mL)	AUC(0-24 hr) (ng·hr/mL)
Batch 004	5	1020	2	8	5560	8790[c]
	25	5340	1	24	54100	54100
	75	12600	2	24	156000	156000
Batch 101	5	1320	1	8	7570	11300[d]
	25	5390	1	24	58000	58000
	75	13400	1	24	163000	163000

a: Batch 004 = SCH 530348 Batch No. 02-530348-X-004
b: Batch 101 = SCH 530348 Batch No. 03-530348-X-101
c: Percent AUC(0-24 hr) extrapolated was 36.8%
d: Percent AUC(0-24 hr) extrapolated was 32.7%

5.2.4 Toxicokinetic Study of SCH 530348 Administered Orally by Gavage in Pregnant Rats

Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Study number(s): SN 08257
Date of study initiation: August 19, 2008
Drug lot/batch number: SCH 530348 Batch No. 05-530348-X-302
GLP compliance: Yes
QA statement: Yes

Key Study Findings
The toxicokinetics of SCH 530348 were determined in pregnant female rats that received daily oral (gavage) doses of 0, 5, 25, or 75 mg/kg of SCH 530348 on gestation days 6 through 17. The body weight of high dose females decreased 39% compared to that in the control group consistent with observations in the embryo-fetal development study (SN 02145). The SCH 530348 systemic exposure increased with dose. The $AUC_{(0\text{-}24\ hr)}$ for the 5, 25 and 75 mg/kg dose groups was 8960, 73500 and 376000 ng.hr/mL, respectively.

Purpose
The objective of this study was to determine the toxicokinetics of SCH 530348 in pregnant rats.

Methods

Doses:	5, 25 or 75 mg/kg (Table 36)
Frequency of dosing:	Daily from gestation day (GD) 6 through GD 17
Administration route:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Rat/Crl:CD®(SD) ; timed-mated females
Number/Sex/Group:	8 animals/sex/group
Age:	Approximately 11-12 weeks at start of dosing
Weight:	Females: 237 to 278 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	No protocol deviation was noted in the report.

Table 36: Sponsor's Study Design – SN 08257

Group	Test/Control Articles	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Female Rats
1	Control (Methylcellulose)	0	5	0	8
2	Low-Dose (SCH 530348)	5	5	1	8
3	Mid-Dose (SCH 530348)	25	5	5	8
4	High-Dose (SCH 530348)	75	5	15	8

Parameter	**Observation details and times**
Mortality	At least once daily
Clinical observations	At least once daily on the day of randomization and on gestation Day 5 through the day of sacrifice
Body weight	Gestation Days 0, 6, 9, 12, 15 and 17
Necropsy	Only pregnancy status was evaluated on GD 17 or 18
Toxicokinetics	On GD 17, blood was collected in Groups 2-4 from four animals/group per timepoint at 1, 2, 4, 8, and 24 hr after dosing from the abdominal aorta under isoflurane-induced anesthesia. Animals were sacrificed by exsanguination. Plasma samples were assayed for SCH 530348 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of the 1 and 15 mg/mL dosing formulations were collected for homogeneity determination on the day of preparation for Week 1. Samples of all dosing formulations were collected concentration analysis. The sponsor previously determined that SCH 530348 is stable in 0.4% (w/v) aqueous methylcellulose at room temperature for at least 15 days.

Results:

Formulation analysis
The concentrations of SCH 530348 in all formulation samples were within 96.2% to 98.7% of nominal.

Mortality
No unscheduled death occurred during the study.

Clinical Observations
One high dose female had a red peri-vaginal substance on two occasions.

Body Weight
The body weight gain in the high dose group exhibited a 39% decrease in mean body weight gain over gestation Days 6 to 17 (Table 37). The decrease was greater from GD

6 to 12 than from GD 12 to 17. This decrease in body weight gain in the high dose group was consistent with observations in the embryo-fetal development study (SN 02145, see Section 9.2). Although the body weight gains in the low and mid dose groups also decreased 7.2% and 10.8%, respectively, over gestation Days 6 to 17, the sponsor did not consider these decreases toxicologically significant.

Table 37: Sponsor's Summaries of Body Weight and Body Weight Gain - SN 08257

			GROUP 1 0.4% MC 0 MG/KG	GROUP 2 SCH 530348 5 MG/KG	GROUP 3 SCH 530348 25 MG/KG	GROUP 4 SCH 530348 75 MG/KG
Body weight	DAY 0	MEAN	210	211	210	210
		S.D.	6.2	7.6	8.3	7.2
		N	7	8	8	8
	DAY 6	MEAN	259	260	257	252
		S.D.	7.1	12.4	7.8	11.5
		N	7	8	8	8
	DAY 9	MEAN	276	274	269	260
		S.D.	10.0	14.6	8.1	11.8
		N	7	8	8	8
	DAY 12	MEAN	293	293	289	267
		S.D.	12.8	16.2	9.8	21.0
		N	7	8	8	8
	DAY 15	MEAN	319	315	312	285
		S.D.	15.7	18.7	10.2	22.1
		N	7	8	8	8
	DAY 17	MEAN	342	337	332	303
		S.D.	16.1	19.8	14.9	30.4
		N	7	8	8	8
Body weight gain	DAYS 0 TO 6	MEAN	49	49	47	42
		S.D.	5.0	8.6	3.4	9.1
		N	7	8	8	8
	DAYS 6 TO 9	MEAN	16	14	12	8
		S.D.	5.0	4.3	3.4	7.1
		N	7	8	8	8
	DAYS 9 TO 12	MEAN	18	18	20	7
		S.D.	3.0	4.4	4.3	13.0
		N	7	8	8	8
	DAYS 12 TO 15	MEAN	26	22	23	18
		S.D.	6.0	6.4	4.8	9.4
		N	7	8	8	8
	DAYS 15 TO 17	MEAN	23	22	20	18
		S.D.	3.0	3.4	5.7	11.2
		N	7	8	8	8
	DAYS 6 TO 17	MEAN	83	77	74	51
		S.D.	12.8	10.8	11.7	33.9
		N	7	8	8	8

Toxicokinetics

SCH 530348 was not detected in samples from the control group. Maximum SCH 530348 plasma concentrations occurred between 1 and 2 hr post-dose (Table 38). The systemic exposure to SCH 530348 increased with increasing dose. However, the increase in exposure was greater than dose proportional with exposure ratios of 1:8:42 for the 5, 25, and 75 mg/kg doses, respectively.

.

Table 38: Sponsor's Summary - Toxicokinetic Parameters – SN 08257

Dose (mg/kg)[a]	Gestation Day	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)
5	17	1120	1	8960
25		5570	2	73500
75		22600	2	376000

a: SCH 530348

5.2.5 Toxicokinetic Study of SCH 530348 and SCH 2046273 (A Metabolite of SCH 530348) Administered Orally by Gavage in Pregnant Rabbits

Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Study number(s): SN 08380
Date of study initiation: January 7, 2009
Drug lot/batch number: SCH 530348 Batch No. 05-530348-X-302
GLP compliance: Yes
QA statement: Yes

Key Study Findings
The toxicokinetics of SCH 530348 and SCH 2046273 were determined in pregnant female rabbits that received daily oral (gavage) doses of 20 mg/kg of SCH 530348 on gestation days 7 through 19. SCH 2046273: SCH 530348 exposure ratios in individual animals ranged from 0.0937 to 0.128.

Purpose
The objective of this study was to determine the toxicokinetics of SCH 530348 in pregnant rabbits.

Methods

Doses:	20 mg/kg (Table 39)
Frequency of dosing:	Daily from gestation day (GD) 7 through GD 19
Administration route:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	New Zealand White rabbit (Hra:[NZW]SPF); timed-mated females
Number/Sex/Group:	4 animals
Age:	Approximately 5-6 months at start of dosing
Weight:	Females: 2.8 to 3.57 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	Three protocol deviations were noted in the report. However, no deviation affected the quality of the study or its interpretation.

Table 39: Sponsor's Study Design – SN 08380

Group	Test Article	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Females
1	SCH 530348	20	2	10	4

Parameter	Observation details and times
Mortality	At least once daily
Clinical observations	At least once daily on the day of randomization and GD 4; at least twice daily during dosing through the day of sacrifice
Body weight	Gestation Days 0, 7, 10, 13, 16, and 19
Food consumption	Visual estimate from GD 3 to GD 20
Necropsy	Only pregnancy status was evaluated on GD 20
Toxicokinetics	On GD 19, blood was collected from each animals at 1, 2, 4, 8, and 24 hr after dosing from the marginal ear vein, auricular artery or vena cava. Animals were sacrificed by lethal injection with Beuthanasia®-D Special. Plasma samples were assayed for SCH 530348 and SCH 2046273 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of the dosing formulation were collected for homogeneity and concentration determination on the day of preparation for Week 1. The sponsor previously determined that SCH 530348 is stable in 0.4% (w/v) aqueous methylcellulose at room temperature for at least 15 days.

Results:

Formulation analysis
The concentrations of SCH 530348 in all formulation samples were within 98.2% to 99.5% of nominal.

Mortality
One animal with very low food consumption, decreased feces, and decreased body weight was subjected to an unscheduled sacrifice on GD 15. In the absence of abnormal findings in an abbreviated necropsy, the sponsor attributed this animal's condition to scabs on the lip and not to administration of SCH 530348.

Clinical Observations
Abnormal clinical observations were limited to the animal that had an unscheduled sacrifice.

Body Weight
Of the three surviving rabbits, two animals gained body weight (0.11 and 0.17 kg) and one animal lost body weight (0.01 kg) from GD 7 to GD 19.

Toxicokinetics

Maximum SCH 530348 plasma concentrations occurred between 1 and 4 hours post-dose, while maximum SCH 2046273 plasma concentrations occurred at 4 hours post-dose (Table 40). Systemic exposure to SCH 2046273 was lower than systemic exposure to SCH 530348. SCH 2046273: SCH 530348 exposure ratios in individual animals ranged from 0.0937 to 0.128.

Table 40: Compilation from Sponsor's Tables - Toxicokinetics – SN 08380

SCH 530848				SCH 2046273			
Animal Number	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)	SCH 2046273: SCH 530348[a]
3297	3590	4	55600	331	4	6550	0.118
3299	4470	4	83000	506	4	10600	0.128
3300	4810	1	77200	381	4	7230	0.0937
Cmax (ng/mL)	Tmax[b] (hr)	AUC(0-24 hr) (ng·hr/mL)		Cmax (ng/mL)	Tmax (hr)[b]	AUC(0-24 hr) (ng·hr/mL)	SCH 2046273: SCH 530348[c]
4290 (15)	4 (1 – 4)	72000 (20)		406 (22)	4 (4 – 4)	8130 (27)	0.113 (15)

[a] N = 3
[b] median (minimum – maximum)
[c] $AUC(0\text{-}24\ hr)_{SCH\ 2046273} \div AUC(0\text{-}24\ hr)_{SCH\ 530348}$

5.2.6 A Two-Week Oral (Nasogastric) Gavage Toxicokinetic Study of SCH 530348 in Cynomolgus Monkeys

Conducting laboratory and location: (b) (4)
Study number(s): SN 08381
Date of study initiation: November 25, 2008
Drug lot/batch number: SCH 530348, Batch No.: 03-530348-X-302, purity 99.2%
GLP compliance: Yes
QA statement: Yes

Key Study Findings
The toxicokinetics of SCH 530348 and its metabolite SCH 2046273 were determined in male and female Cynomolgus monkeys that received single daily oral (gavage) dose of 20 mg/kg for 14 days. Systemic exposure to SCH 530348 and SCH 2046273 increased following repeated administration. The ratio of SCH 2046273 to SCH 530348 exposure was highest on Day 0 and was higher in males (0.12 to 0.226) than in females (0.11 to 0.14).

Purpose
The objective of this study was to determine the toxicokinetics of SCH 530348 and SCH 2046273, an active metabolite of SCH 530348, following oral administration to monkeys for 14 days. The amendment concerned revisions to the toxicokinetic data.

Methods

Doses:	20 mg/kg/day
Frequency of dosing:	Once daily for 14 days
Administration route:	Oral (nasogastric) gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Cynomolgus monkey (Mauritius origin)
Number/Sex/Group:	3 animals/sex
Age:	Approximately 2 years at start of dosing
Weight:	Males: 3.1 to 3.5 kg and female: 2.8 to 3.2 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	No protocol deviation was noted in the report.

Parameter	**Observation details and times**
Mortality	At least twice daily
Clinical observations	Once daily immediately before dosing
Body weight	On Day 0, 6 and 14
Food consumption	Qualitative estimate
Toxicokinetics	Blood was collected from three animals per timepoint at 1, 2, 4, 8, and 24 hr after dosing on Days 1, 6, and 13 from the femoral vein. Plasma samples were assayed for SCH 530348 and SCH 2046273 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of all dosing formulations were collected for concentration and homogeneity determination on the day of preparation for Week 1. The sponsor previously determined that SCH 530348 is stable in 0.4% (w/v) aqueous methylcellulose at room temperature for at least 15 days.

Results:

Formulation analysis
The formulation was considered homogenous since the recoveries for individual replicates were between 97.3% and 102% of nominal.

Mortality
No unscheduled deaths occurred during the study.

Clinical observations
No clinical observation was attributed to SCH 530848 administration.

Body weight
The mean body weights of the males and females were not statistically different from their mean body weights on Day -11 (Table 41). However, the body weight of one male 3839 was 4.5% and 3.55 lower on Days 6 and 14, respectively, of treatment than on

Day -11. Additionally, the body weights of females 3842 and 3845 were 6.7% and 4.3%, respectively, lower on Day 14 than on Day -11.

Table 41: Reviewer's Summary of Body Weight (gm)

	Males					Females				
	-11	-7	0	6	14	-11	-7	0	6	14
Mean	3318	3386	3354	3253	3299	2931	2988	3013	2925	2854
SD	226	236	225	173	205	161	265	220	224	261

Toxicokinetics

The toxicokinetic report was amended and the plasma concentrations of SCH 530348 revised downward from the original report.

Maximum SCH 530348 and SCH 2046273 plasma concentrations occurred between 1 and 8 hr post-dose. The sponsor concluded that systemic exposure to SCH 530348 and SCH 2046273 was independent of sex and discussed the combined toxicokinetic parameters (Table 42). However, accumulation of SCH 530848 exposure on Days 6 and 13 was higher in males than in females (Table 43). Systemic exposure to SCH 2046273 was lower than exposure to SCH 530348 in both males and females. However, accumulation of SCH 2046273 exposure on Days 6 and 13 was similar in males and females. The SCH 2046273 to SCH 530348 exposure ratios decreased following repeated administration and were higher in males than in females. On Day 0, the SCH 2046273:SCH 530348 exposure ratios ranged from 0.12 to 0.226 in males and 0.11 to 0.14 in females.

Table 42: Complied from Sponsor's Tables Summarizing Combined Toxicokinetic Parameters for SCH 530348 and SCH 2046273 - SN 08381

	SCH 530348					SCH 2046273				
SCH 530348 Dose (mg/kg)[a]	Day	Cmax (ng/mL)	Tmax (hr)[b]	AUC(0-24 hr) (ng·hr/mL)	R	Cmax (ng/mL)	Tmax (hr)[b]	AUC(0-24 hr) (ng·hr/mL)	R	SCH 2046273: SCH 530348[c]
20	0	3360 (28)	3 (1-8)	55500 (35)	NA[c]	439 (12)	4 (2-8)	7490 (16)	NA[d]	0.147 (32)
	6	9100 (14)	4 (4-8)	185000 (16)	3.68[d] (39)	406 (18)	8 (4-8)	9080 (16)	1.22[e] (11)	0.0490 (4)
	13	10300 (12)	6 (1-8)	211000 (16)	4.11[e] (29)	449 (23)	8 (1-8)	9860 (21)	1.33[f] (20)	0.0468 (12)

a: N = 6
b: Median (Minimum – Maximum)
c: NA = Not applicable
d: R = AUC(0-24 hr)$_{Day\ 6}$ + AUC(0-24 hr)$_{Day\ 0}$
e: R = AUC(0-24 hr)$_{Day\ 13}$ + AUC(0-24 hr)$_{Day\ 0}$

a: N = 6
b: Median (Minimum – Maximum)
c: SCH 2046273: SCH 530348 = AUC(0-24 hr)$_{SCH\ 2046273}$ + AUC(0-24 hr)$_{SCH\ 530348}$
d: NA = Not applicable
e: R = AUC(0-24 hr)$_{Day\ 6}$ + AUC(0-24 hr)$_{Day\ 0}$
f: R = AUC(0-24 hr)$_{Day\ 13}$ + AUC(0-24 hr)$_{Day\ 0}$

Table 43: Complied from Sponsor's Tables Summarizing Male and Female Toxicokinetic Parameters for SCH 530348 and SCH 2046273 - SN 08381

		SCH 530348					SCH 2046273					
Day	Sex	Cmax (ng/mL)	Tmax (hr)[b]	AUC(0-24hr) (ng·hr/mL)	R	F:M[c]	Cmax (ng/mL)	Tmax (hr)[b]	AUC(0-24 hr) (ng·hr/mL)	R	F:M[c]	SCH 2046273: SCH 530348[d]
0	Female	3620 (15)	4 (2-8)	61500 (11)	NA[d]	1.25	429 (8)	4	7220 (7)	NA[e]	0.929	0.118 (13)
	Male	3110 (42)	2 (1-4)	49400 (56)	NA	NA	449 (17)	2(2-8)	7770 (23)	NA	NA	0.175 (30)
6	Female	8500 (3)	4	174000 (4)	2.84[e] (8)	0.883	372 (4)	8	8320 (5)	1.15[f] (7)	0.845	0.0479 (4)
	Male	9710 (17)	4 (4-8)	197000 (21)	4.53[e] (38)	NA	441 (22)	8(4-8)	9850 (19)	1.28[f] (12)	NA	0.0501 (5)
13	Female	10800 (12)	8 (1-8)	228000 (13)	3.76[f] (23)	1.18	481 (30)	1(1-8)	10400 (28)	1.43[g] (23)	1.11	0.0449 (14)
	Male	9760 (11)	4 (2-8)	194000 (18)	4.46[f] (35)	NA	417 (15)	8	9360 (14)	1.23[g] (17)	NA	0.0487 (12)

a: N = 3/sex b: Median (Minimum – Maximum) c: F:M = AUC(0-24 hr)$_{Female}$ ÷ AUC(0-24 hr)$_{Male}$ d: NA = Not applicable e: R = AUC(0-24 hr)$_{Day\ 6}$ ÷ AUC(0-24 hr)$_{Day\ 0}$ f: R = AUC(0-24 hr)$_{Day\ 13}$ ÷ AUC(0-24 hr)$_{Day\ 0}$	a: N = 3/sex b: Median (Minimum – Maximum) c: F:M = AUC(0-24 hr)$_{Female}$ ÷ AUC(0-24 hr)$_{Male}$ d: SCH 2046273: SCH 530348 = AUC(0-24 hr)$_{SCH\ 2046273}$ ÷ AUC(0-24 hr)$_{SCH\ 530348}$ e: NA = Not applicable f: R = AUC(0-24 hr)$_{Day\ 6}$ ÷ AUC(0-24 hr)$_{Day\ 0}$ g: R = AUC(0-24 hr)$_{Day\ 13}$ ÷ AUC(0-24 hr)$_{Day\ 0}$

5.2.7 SCH 530348: Pharmacokinetics Of SCH 530348 Following A Single Oral Dose Of Various Capsule Or Tablet Formulations To Male Cynomolgus Monkeys

Conducting laboratory and location: (b) (4) and Merck Research Laboratories (Summit, NJ)
Study number(s): DM 28074
Date of study initiation: June 28, 2010
Drug lot/batch number: SCH 530348,
Phase III Tablets [2.48 mg SCH 530348 (bisulfate salt)/tablet (by assay); equivalent to 2.07 mg SCH 530348 free base), Lot No. 40-0756]; salt to base conversion factor = 1.2
HME with K-VA64 Tablets [2.02 mg SCH 530348 (free base)/tablet (by assay), Batch No. 68295-088]
HME with PVP 10% PEG Tablets
[1.80 mg SCH 530348 (free base)/tablet (by assay), Batch No. 68295-101]
SDD with K-VA64 Tablets [1.96 mg SCH 530348 (free base)/tablet (by assay), Batch No. 68950-022]
SDD with PVP L30 Tablets [1.95 mg SCH 530348 (free base)/tablet (by assay), Batch No. 68950-020]
SEDDS Capsules [2.04 mg SCH 530348 (free base)/capsule (by assay), Batch No. 68746-56]
GLP compliance: No
QA statement: No

Key Study Findings
The pharmacokinetics of SCH 530348 were determined in male Cynomolgus monkeys that received single dose of 2 mg/animal in six different tablet or capsule formulations. The dose-normalized mean exposures [$AUC_{(tf)}$] for the five other formulations were higher than that of the Phase III tablet and was highest for the SEDDS capsule formulation.

Purpose
The objective of this study was to determine the pharmacokinetics of SCH 530348 following a single oral dose of SCH 530348 free base, administered in six different capsule or tablet formulations to male cynomolgus monkeys.

Methods

Doses:	2.1 mg/ animal
Frequency of dosing:	Once – single dose
Administration route:	Oral
Dose volume:	Not applicable
Formulation/Vehicle:	Six different formulations (see above)
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	4 males/group
Age:	Not indicated
Weight:	Males: 4.1 to 6.5 kg
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	No protocol deviation was noted in the report.

Parameter	**Observation details and times**
Mortality	At least twice daily
Clinical observations	Pre-dose and at every timepoint
Toxicokinetics	Blood was collected from 4 monkeys/group/time point) at 0 hr (pre-dose) and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 48, and 72 hr post-dose from the cephalic or saphenous vein. Plasma samples were assayed for SCH 530348 and SCH 2046273 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)

Results:

Mortality
No unscheduled deaths occurred during the study.

Clinical observations
No clinical observation was attributed to SCH 530848 administration.

Toxicokinetics
The dose-normalized mean exposures [$AUC_{(tf)}$] for the five other formulations were higher than that of the Phase III tablet (Table 44, Figure 17). The dose-normalized mean exposure [$AUC_{(tf)}$] was the highest for the SEDDS capsule formulation. The HME with PVP 10% PEG tablet and SEDDS capsule formulations had the highest dose-normalized mean Cmax values.

Table 44: Sponsor's Summary of SCH 530848 Pharmacokinetics in DM28074

Parameter, (Units)	Group 1 Phase III Tablet	Group 2 HME With K-VA64 Tablet	Group 3 HME With PVP 10% PEG Tablet	Group 4 SDD With K-VA64 Tablet	Group 5 SDD With PVP L30 Tablet	Group 6 SEDDS Capsule
Actual Dose[a], (mg/animal)	2.07	2.02	1.80	1.96	1.95	2.04
Actual Dose, (mg/kg)	0.372	0.453	0.279	0.371	0.321	0.371
Cmax, (ng/mL)	78.6	101	77.0	70.6	79.5	100
Median Tmax, (hr)	1.75	4.00	1.75	4.00	2.00	4.00
Tmax Range, (hr)	1.5-4	2-6	1.5-2	4-4	2-4	2-4
AUC(0-24 hr), (ng·hr/mL)	783	1040	669	733	812	1110
AUC(tf), (ng·hr/mL)	1020	1720	1030	1120	1220	1570
tf, (hr)	48.0	72.0	72.0	66.0	72.0	66.0
Cmax/Dose, [(ng/mL)/(mg/kg)]	210	224	276	190	247	269
AUC(0-24 hr)/Dose, [(ng·hr/mL)/(mg/kg)]	2100	2310	2390	1970	2520	2960
AUC(tf)/Dose, [(ng·hr/mL)/(mg/kg)]	2740	3800	3670	3030	3790	4210

a: Expressed as SCH 530348 free base.

Figure 17: Sponsor's Figures – Individual and Mean Plasma Exposure and Cmax:

Individual and Mean Dose-Normalized SCH 530348 Plasma Exposure [$AUC_{(tf)}$] and Cmax Values Following a Single Oral Dose of SCH 530348 Free Base to Male Cynomolgus Monkeys

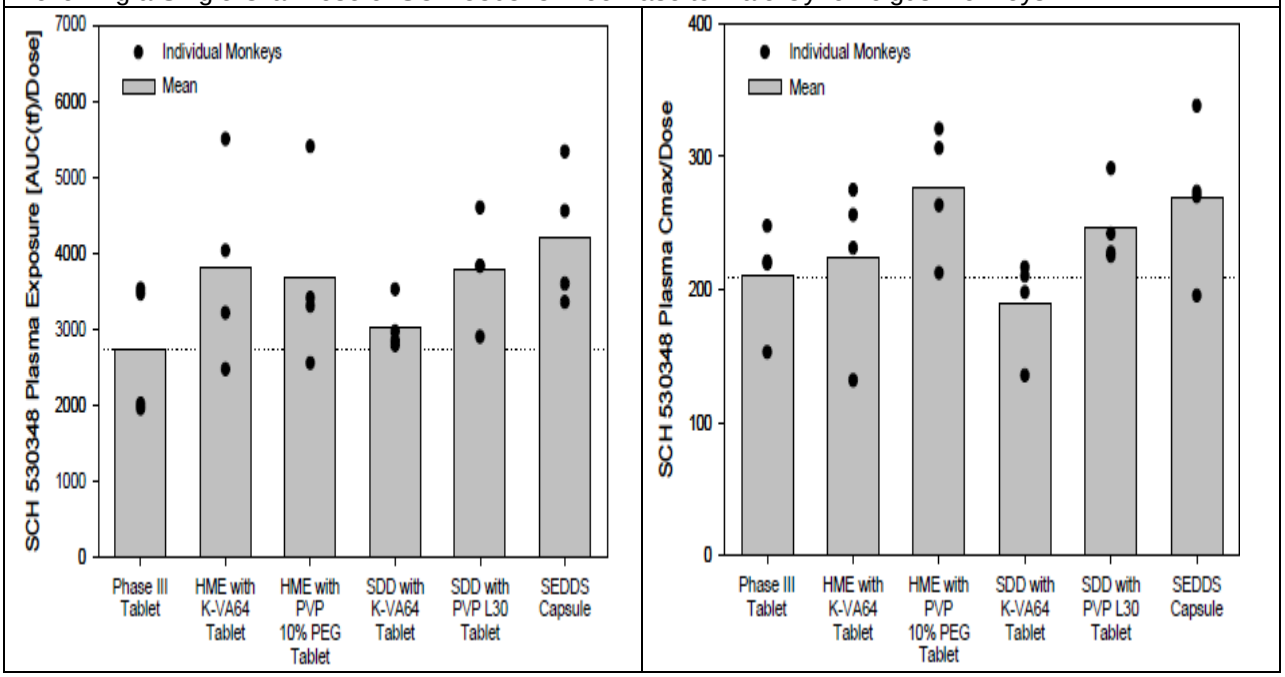


Table 45 summarizes the toxicokinetic parameters for SCH 530848 in the repeated dose toxicology studies in mice, rats, and monkeys.

Table 45: Compilation from Sponsor's Tables - SCH 530848 TK Parameters in Repeat Dose Studies

Species	Sex[a]	Dose (mg/kg)	No. of Doses	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng h/mL)	t (h)	Study Number
Mice	M, F	15	7	2890	8	41900	24	08379
	M, F	15	14	4070	1	38300	24	08379
	M, F	25	58	6620	1	68400	24	02142
	M, F	75	58	12300	1	182000	24	02142
	M, F	150	58	29700	4	525000	24	02142
Rat (ad lib feeding)	M	3	28	486	2	1870[c]	24	05265
	M	30	7, 14	4170	2	25400	24	08378
	M (six weeks)[d]	30	14	4840	2	30300	24	10119
	M (six months)[d]	30	14	4520	1	42700	24	10119
	M	50	28	4110	2	52700	24	05265
	M	50	28	5170	2	54000[c]	24	05265
	M	50	41	4060	4	44400	24	06554
	M	75	7, 14	11000	2	98200	24	08378
	F	3	28	396	1	2970[c]	24	05265
	F	30	7, 14	5980	1	53100	24	08378
	F	50	28	6360	8	93800	24	05265
	F	50	28	5860	8	82800[c]	24	05265
	F	75	7, 14	9290	4	192000	24	08378
Rat- diet restricted	M	3	29	316	1	1180	24	02125
	M	3	165	404	1	2250	24	02138
	M	10	165	769	1	5000	24	02138
	M	30	29	1960	1	10300	24	02125
	M	30	165	1580	1	13100	24	02138
	M	50	84	2050	2	18400	24	02141
	M	100	29	5430	1	41300	24	02125
	M	100	84	3820	2	33200	24	02141
	F	3	29	347	1	1790	24	02125
	F	3	165	438	1	3310	24	02138
	F	10	165	1090	1	9310	24	02138
	F	30	29	2090	1	23100	24	02125
	F	30	165	2480	1	37900	24	02138
	F	50	84	3630	2	50300	24	02141
	F	100	29	7800	4	73600	24	02125
	F	100	84	12300	4	192000	24	02141
Pregnant rat	F	5	12	1120	1	8960	24	08257
	F	25	12	5570	2	73500	24	
	F	75	12	22600	2	376000	24	

Species	Sex[a]	Dose (mg/kg)	No. of Doses	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng h/mL)	t (h)	Study Number
Monkey	M,F (8)	0.5	28	102	4 (2-4)	631	12	02126
	M,F (8)		176	82.5	4 (1-8)	1340	24	02139
	M,F (8)		179	127	2 (1-2)	1610	24	02140
	M,F (8)		362	127	2 (1-4)	1590	24	02140
	M,F (8)	5	28	901	2 (2-4)	10900	24	02126
	M,F (8)		176	1450	4 (2-8)	26800	24	02139
	M,F (8)		179	1960	2 (1-4)	34200	24	02140
	M,F (8)		362	1580	2 (1-4)	27900	24	02140
	M,F (6)	20	7	10900	4 (4-8)	222000	24	08381
	M,F (6)		14	12400	6 (1-8)	253000	24	08381
	M,F (8)		28	3460	2 (1-4)	50200	24	02126
	M,F (8)		176	8040	4 (1-8)	159000	24	02139
	M,F (8)		179	9210	3 (2-4)	167000	24	02140
	M,F (8)		362	5980	2 (2-8)	109000	24	02140
	M,F (8)	30	90	8210	1 (1-4)	117000	24	04056
	M,F (8)	60	90	11000	1 (1-4)	191000	24	04056
	M,F (5)	90	90	16400	2 (1-4)	282000	24	04056

6 General Toxicology

6.1 Single-Dose Toxicity

Single dose toxicity studies conducted in rats and monkeys were reviewed under IND 71384 in DARRTS document dated 06/01/2005. The oral LD_{50} of vorapaxar is greater than 2000 and 800 mg/kg in rats and monkeys, respectively.

6.2 Repeat-Dose Toxicity

The full reviews of most of the submitted repeat dose toxicology studies in mice, rats, and monkeys can be found in DARRTS under IND 71384. Table 46 summarizes the toxicology studies of at least 2 weeks in duration.

The principal SCH 530848 treatment-related finding was phospholipidosis in rats, mice and monkeys. Epithelial hyperplasia in the kidney, ureters, and urinary bladder of mice and retinal vacuolation in rats appear to be species specific findings.

Table 46: Reviewer's Summary of Repeated Dose Toxicology Studies

Study No	DARRTS date of review	Study Length	Doses, mg/kg	Lot	$AUC_{(0-24)}$, ng*hr/mL [Day:Dose]	Comments
Mice						
02142 (GLP)	7/12/05	3 months	0, 25, 75, and 150	03-530348-X-101	D57: 25 M: 61000 F: 75800	High dose mortality. Epithelial hyperplasia in the kidney, ureters, and urinary bladder. Vacuolation in epididymides, kidneys, testes, urinary bladder, ureters and small intestine shown to be phospholipidosis by EM. NOAEL <25 and 25 mg/kg for males and females, respectively
Rats (Crl:CD[SD])						
06527 (GLP)	08/20/09	3-, 7- and 14-days	0 or 50	05-530348-X-301		Vacuolation of the inner nuclear layer of the retina in the eyes of rats necropsied on Day 7 or Day 14, but not on Day 3. Vacuolation severity was slightly higher on Day 14 than on Day 7.
10119 (GLP)	See Section 6.2.3 below	2 weeks	0, 30	03-530348-X-101	Young: 30300; Older: 42700	Higher number of older rats had retinal vacuolation than younger rats. Greater mean number vacuoles/eye in older rats than in younger rats.
08378 (GLP)	See Section 6.2.2 below	2 weeks	30, 75	03-530348-X-302	30: M: 25400 F: 53100 75: M: 98200 F: 192000	Retinal vacuolation was not observed in eyes fixed in Carnoy's fixative or in eyes fixed in Davidson fixative after 24 hours refrigeration in situ, but was observed in the eyes fixed immediately in Davidson's fixative or in Davidson's fixative after 6 hours refrigeration in situ
02125 (GLP)	06/01/05 12/13/12	1 month	0, 3, 30, 100	02-5303348-X-004	M: 41305 F: 73550	Vacuolation in the bile duct, in macrophages in liver, spleen, lymph nodes and small intestine, and inner nuclear layer of retina. NOEL = 3 mg/kg
05265 (GLP)	12/13/12	1 month	0, 3, 50	05-530348-X-302; 03-530348-X-101	D27: 50 Batch 301: M: 52700; F: 93800	50 mg/kg with either batch resulted in retinal vacuolation, vacuolation of bile duct epithelium and foamy macrophage accumulation in mesenteric lymph nodes and ileum. Some animals had adrenal cortical hypertrophy.
06316 (GLP)	08/20/09 12/05/12	1 month	0 or 50	05-530348-X-301	No AUC. Conc 2 hr post dose = 4207 ng/mL	Vacuolation of the bile duct epithelium, common liver bile duct, and retinal inner nuclear layer of the eyes. Findings reversible after 4-week recovery

Study No	DARRTS date of review	Study Length	Doses, mg/kg	Lot	$AUC_{(0-24)}$, ng*hr/mL [Day:Dose]	Comments
06528 (GLP)	08/20/09 01/04/13	29 day	0 or 50	05-530348-X-301	No AUC. Conc 2 hr post dose = 3457 ng/mL	Retinal vacuolation observed in SCH 530348-treated rats with all three methods of fixation. Incidence of vacuolation was higher with whole body perfusion with 3% glutaraldehyde. Severity of vacuolation was lower with Davidson's solution
02141 (GLP)	06/01/05 12/13/12	3 month	0, 50, 100 and 200	02-5303348-X-004	D1: 50 M: 22500 F: 51900 D1: 200 M: 64300 F: 155000	Mortality and morbidity in mid & high dose. Phospholipidosis, confirmed by EM, in all drug treated groups in bile ducts, seminal vesicles and macrophages in liver, spleen, lungs, lymph nodes and SI. Retinal vacuolation at 50 mg/kg. NOAEL< 50 mg/kg.
02138 (GLP)	06/01/05 12/13/12	6-month	0, 3, 10, and 30	02-5303348-X-004	D164: 30 M: 13100 F: 37900	Vacuolation of bile duct epithelium and seminal vesicles. Retinal vacuolation at 30 mg/kg and two animals at 10 mg/kg. NOEL was 3 mg/kg.
Cynomolgus Monkeys						
02126 (GLP)	06/01/05	1 month	0, 0.5, 5 and 20	02-5303348-X-004	D27: 20 M: 45016 F: 55426	Several mid and high dose females had BUN values above the normal range and were increased compared to predose.
04056 (GLP)	11/21/12 12/05/12	3 month	0, 30, 60, 90 mg/kg	02-530348-X-004	D89: 30 M: 121000 F: 112000	Mid & high dose had vacuolated macrophages in the spleen, and lymph nodes. High dose females had vacuolated macrophages in adrenal gland, spleen, bone marrow, SI, & thymus and vacuolation of liver Kupffer cells with Kupffer cell hyperplasia.
02139 (GLP)	See Section 6.2.1	6 month	0, 0.5, 5, or 20	03-530348-X-101	D176: 20 M: 155250; F: 162500	No clear treatment-related findings. NOAEL = 20 mg/kg.
02140 (GLP)	11/21/12	12 months	0, 0.5, 5, 20	03-530348-X-101	D362: 20 M: 106000 F: 112000 D362: 5 M: 27900, F: 27800	Adrenal weights relative to body weight increased in high dose males and females. NOAEL = 5 mg/kg

Table 47 compares the results in the chronic rat and monkey toxicology studies.

Table 47: Reviewer's Comparison of Rat and Monkey Chronic Toxicology Studies

Species	Rat (Sprague Dawley)			Cynomolgus monkeys		
Study length	6 months			12 months		
Study code	SN 02138			SN 02140		
Administration	Oral gavage			Oral gavage		
Doses (mg/kg)	0, 3, 10, and 30 mg/kg			0, 0.5, 5, 20 mg/kg		
SCH 530348 lot	02-5303348-X-004			03-530348-X-101		
Number/sex/group	Main study: 15 TK: 15, except for control			4		
Mortality	None treatment-related			None		
Adverse clinical signs	None attributed to SCH 530348, but convulsions in 1 control M, 1 M at 10 mg/kg 3 F at 30 mg/kg with a total 5 incidences			No treatment-related change		
Body weight gain	Body weight gain decreased 8.5 and 7.8% in high dose males and females			Decreased body weight gain in a few high dose animals		
Food consumption	No treatment-related effect			Incidence of low/no food consumption greater for mid- and high doses groups		
Ophthalmoscopy:	No effect attributed to treatment, but retinal degeneration in 2 mid and 2 high dose males			No treatment-related change		
ECG	Not evaluated			No treatment-related change		
PK/TK AUC (ng.hr/mL) at study end	Dose	Male	Female	Dose	Male	Female
	3	2250	3310	0.5	1540	1650
	10	5000	9310	5	27900	27800
	30	13100	37900	20	106000	112000
Hematology and coagulation	No treatment-related effects			Sampling did not include an early timepoint. Decreased reticulocyte counts in high dose		
Blood chemistry	Elevations in glucose above normal range in 3 high dose animals. Elevations in ALT/AST in 3 high dose females			Sampling did not include an early timepoint. Increased bilirubin values found for one high dose male		
Urinalysis	No treatment-related effects			No treatment-related change		
Macroscopic pathology	No treatment-related effects			No treatment-related change		
Relative organ weights	Increased kidney absolute and relative weight at 30 mg/kg			Adrenal weights relative to body weight were increased in the high dose males and the mid and high dose females.		
Microscopic pathology	Epithelial vacuolation in seminal vesicles of high dose males. Vacuolation of bile duct epithelium in mid and high dose males and mid dose females. Retinal vacuolation in high dose males and females			No treatment-related change		
Reviewer's NOAEL	M: 3 mg/kg; F: 10 mg/kg			5 mg/kg		
HED for NOAEL (fold human dose[1])	0.49 mg/kg (11.7)			1.62 (39)		
Base for reviewer's NOAEL	Decrease body weight gain, increased kidney weight in high dose and vacuolation in mid and high dose males			Decrease body weight gain and increased adrenal relative weights in both high dose males and females		
Sponsor's NOAEL	10 mg/kg			20 mg/kg		
[1] Human dose of 2.5 mg/day is 0.042 mg/kg for a 60 kg human						

Based on the NOAELs in the chronic toxicology studies, safety margins were calculated below based on total and unbound exposures (Table 24). The 21 to 25-fold safety margin from the chronic monkey study is higher than the 1.7 to 8.3 safety margin in the chronic rat study.

Table 48: Reviewer's Summary of Safety Margins based on Chronic Toxicology Studies

			Exposure at NOAEL		Safety Margin	
Study/ Species	Sex	NOAEL (mg/kg)	Total AUC (ng*hr/mL)	Unbound AUC (ng*hr/mL)	Based on Total AUC	Based on Unbound AUC
6 month - rat	M	3	2250	7.9	1.7	3.5
	F	10	9310	18.6	7.0	8.3
12-month - monkey	M	5	27900	55.8	21	24.9
	F	5	27800	55.6	21	24.9
At the RHD of 2.5 mg, the mean total human $AUC_{(0\text{-}24\ h)}$ value is 1320 ng•hr/mL (The sponsor's value for vorapaxar was obtained from Meta analysis for steady-state PK analysis (Section 5.3.5.3.4.3)), Unbound AUC is 2.24 ng*hr/mL Unbound fractions in humans, rats, and monkeys are 0.35%, 0.2% and 0.17%, respectively.						

The following five toxicology studies had not been previously reviewed.

6.2.1 Six-Month Oral (Gavage) Toxcity and Toxicokinetic Study of SCH 530348 in Cynomolgus Monkeys

Conducting laboratory and location: (b) (4)
Study number(s): SN 02139 ((b) (4))
Date of study initiation: October 20, 2003
Drug lot/batch number: SCH 530348, Batch No.: 03-530348-X-101, purity 99.2%
GLP compliance: Yes
QA statement: Yes

Key Study Findings
SCH 530348 was administered to cynomolgus monkeys as single daily oral gavage doses of 0.5, 5, or 20 mg/kg/day for six months. No clear treatment-related findings were observed. Although systemic exposure to SCH 530348 was independent of sex, accumulation of SCH 530348 was greater at the higher doses and in females (3.1-fold) compared to males (2.3-fold). The exposure ratios in male and female monkeys at the high dose are estimated to be 118 and 123 times, respectively, the human exposure ($AUC_{(0\text{-}24)}$ of 1320 ng*hr/mL) at the recommended dose of 2.5 mg once a day.

Purpose
This study evaluated the toxicity and toxicokinetics of SCH 530348 administered daily to cynomolgus monkeys for 6 months.

Methods

Doses:	0, 0.5, 5 or 20 mg/kg/day as indicated in Table 49.
Frequency of dosing:	Once daily for 182 days
Administration route:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Cynomolgus monkey (Macaca fascicularis)
Number/Sex/Group:	4 animals/sex/main group
Age:	Approximately 2-5 years at start of dosing
Weight:	Males: 2.5 to 3.5 kg, females: 2.3 to 3.0 g
Satellite groups:	None
Unique study design:	Immunophenotyping was conducted
Deviation from study protocol:	Twenty protocol deviations were noted in the report. Of these deviations, ten involved not feeding particular animals or animals having access to more than one food well.

Table 49: Sponsor's Summary of Study Design

Six-Month Oral Gavage Toxicity and Toxicokinetic Study of SCH 530348 in Cynomolgus Monkeys (SN 02139): **Study Design**

Group	No. of Animals		Dose Level[b] (mg/kg/day)	Dose Concentration[b] (mg/mL)
	Male	Female		
1 (Control)[a]	4	4	0	0
2 (Low)	4	4	0.5	0.1
3 (Mid)	4	4	5	1
4 (High)	4	4	20	4

a: Group 1 animals received 0.4% (w/v} aqueous methylcellulose only.

b: The dose volume was 5 mL/kg.

Parameter	Observation details and times
Mortality	At least twice daily
Clinical observations	Observations with animal removed from the cage were performed at least once daily beginning week -1. Cageside clinical observations were performed daily at 1 to 3 hours postdose beginning Day 1 of dosing.
Physical examinations	All animals were examined physically twice prior to initiation of dosing and once during Weeks 5 and 25 of dosing. Examinations included measurement of vital signs (heart rate, respiration rate, rectal body temperature, and blood pressure).
Body weight	Weekly from Day -20 through Day 183 and at necropsy.
Food consumption	Beginning Week -1, food consumption was assessed qualitatively once daily.

Ophthalmoscopy	Examinations using an indirect ophthalmoscope and a slitlamp were conducted on all animals pretest in Week -2 and all surviving animals during week 26 of dosing.
Electrocardiographic Examinations	Twice pretest and once during Weeks 5 and 25 at 1 to 4 hours postdose. Evaluation included P, QRS, and T waveform morphology, measurements of PR, QRS, and QT interval duration and HR or RR interval. QTc interval duration was calculated according to the method of Fridericia(3).
Hematology	Blood was collected for hematology three times pretest and once during Weeks 12, 21, and 24. Parameters included red blood cell (erythrocyte) count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, mean platelet volume, white blood cell (leukocyte) count, differential blood cell count (percent and absolute), reticulocyte count, and blood cell morphology.
Coagulation	Blood was collected for coagulation three times pretest and once during Weeks 12, 21, and 24. Initially only prothrombin time and activated partial thromboplastin time were evaluated at Weeks 21 and 24, additional parameters of antithrombin III, D-dimer, and fibrinogen were evaluated
Clinical chemistry	Blood was collected for clinical chemistry twice pretest and once during Weeks 12, 21, and 24. Clinical chemistry parameters included glucose, urea nitrogen, creatinine, total protein, albumin, globulin, albumin/globulin ratio, cholesterol, total bilirubin, triglycerides, alanine aminotransferase, alkaline phosphatase, gamma glutamyltransferase, aspartate aminotransferase, calcium, inorganic phosphorus, sodium, potassium, and chloride
Urinalysis	Urine was collected twice pretest and once during Weeks 12 and 24. Urinalysis parameters included appearance/color, pH, protein, glucose, volume, ketones, bilirubin, blood, urobilinogen, and osmolality
Immunophenotyping	Blood was collected twice pretest and once during Week 12. Samples were assayed for expression of CD3+, CD3+/CD4+, CD3+/CD8+, and CD3-/CD20+ by fluorescence-activated cell sorting (FACS).
Gross pathology	At the end of treatment, the animals were euthanized using sodium pentobarbital, weighed, exsanguinated, and necropsied. The tissues and organs collected and processed from all main animals are summarized in Table 50. The tissues were fixed in 10% neutral buffered formalin, except for the eyes, which were fixed using Davidson's fixative.
Organ weights	The following organs were weighed: adrenal glands, brain, epididymides, heart, kidneys, liver with gallbladder (drained), lungs, ovaries, pituitary gland, prostate gland, spleen, testes,

	thymus, thyroid gland/parathyroid gland(s), and uterus with cervix
Histopathology	Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections was performed on protocol-designated tissues indicated in Table 50 from all control and high dose animals and unscheduled deaths.
Toxicokinetics	Blood was collected from all animals on Day 1 and during Week 26 at 1, 2, 4, 8, and 24 hours postdose. Plasma samples were assayed for SCH 530348 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of all dosing formulations, including the control, were collected for concentration determination on the day of preparation for Weeks 1, 13, and 26. Samples for homogeneity were collected from the low and high dose group formulations during Week 1 only. The sponsor previously determined that SCH 530348 is stable in 0.4% (w/v) aqueous methylcellulose at room temperature for at least 15 days.

Table 50: Sponsor's Summary of Tissues Collected

Tissues Collected	
adrenal glands	parathyroid glands
animal identification[a]	peripheral nerve - sciatic
aorta - thoracic	pituitary gland
bone - (femur, rib[a], and sternum)	prostate gland
bone marrow section - (rib[a] and sternum)	salivary glands - mandibular
brain	seminal vesicles
epididymides	skeletal muscle - biceps femoris
esophagus	skin
eyes[b]	small intestine - (duodenum, jejunum, and ileum)
femur - (articular surface of the distal end)	spinal cord - thoracolumbar
gallbladder	spleen
heart	stomach
kidneys	testes
lacrimal glands	thymus
large intestine - (cecum and colon)	thyroid gland
lesions (gross findings)[c]	tongue[a]
liver	trachea
lungs	urinary bladder
lymph nodes - mandibular and mesenteric	uterus with cervix
mammary gland	vagina
ovaries	
pancreas	

a: Collected but not processed.
b: Collected in Davidson's fixative.
c: Collected as deemed necessary by the pathologist present at necropsy.

Results

Mortality
No mortality was related to SCH 530348 administration. However, the euthanasia of one control female in Week 8 was attributed to an oral gavage accident.

Clinical observations
No clinical observation was clearly related to SCH 530348 administration.

Physical examinations
No physical examination finding was related to SCH 530348 administration. All body temperature, respiration rate and blood pressure values were considered to be within normal limits.

Body weight
Mean body weight was not affected by SCH 530348 administration (Table 51) .

Table 51: Compilation from Sponsor's Tables - Body Weight (kg)

		Males				Female			
Day	Dose, mg/kg	0	0.5	5	20	0	0.5	5	20
-20	Mean	2.9	2.8	2.9	3.1	2.6	2.8	2.6	2.7
	SD	0.16	0.05	0.28	0.46	0.05	0.14	0.17	0.15
	N	4	4	4	4	4	4	4	4
1	Mean	2.8	2.7	2.7	3.0	2.5	2.7	2.5	2.7
	SD	0.18	0.13	0.32	0.41	0.08	0.17	0.18	0.24
	N	4	4	4	4	4	4	4	4
29	Mean	2.9	2.8	2.8	3.1	2.6	2.7	2.6	2.7
	SD	0.14	0.10	0.29	0.46	0.00	0.19	0.17	0.21
	N	4	4	4	4	4	4	4	4
57	Mean	2.9	2.8	2.8	3.2	2.6	2.8	2.6	2.7
	SD	0.10	0.13	0.29	0.48	0.06	0.10	0.22	0.21
	N	4	4	4	4	3	4	4	4
120	Mean	2.9	2.8	2.9	3.3	2.6	2.8	2.6	2.7
	SD	0.21	0.10	0.28	0.60	0.06	0.06	0.22	0.15
	N	4	4	4	4	3	4	4	4
182	Mean	3.1	3.0	3.1	3.6	2.7	2.9	2.8	2.7
	SD	0.14	0.17	0.33	0.62	0.06	0.14	0.17	0.29
	N	4	4	4	4	3	4	4	4

Food consumption
No effect on food consumption was clearly related to SCH 530348 administration.

Ophthalmoscopy
No animal had visible ophthalmic lesions either pre-dose or at Week 26 of dosing.

Electrocardiographic Examinations
The consulting veterinary cardiologist determined that all animals were in sinus rhythm. The heart rates, waveform magnitude (mV), and timing of electrical events (PR, QRS,

and QT intervals) were considered to be within normal limits. No test article-related effects on electrocardiographic evaluations or heart rate measurements were noted.

Clinical Pathology (Hematology, Coagulation, Clinical chemistry, and Urinalysis)
The clinical pathology report concluded that SCH 530348 treatment had no clear effect on clinical pathology results. The report maintained that any differences between control and treated groups were small in magnitude, not consistent between sexes and sampling timepoints, and not clearly test article-related. Given the high variably among individual animals, it is difficult to identify any treatment related differences in clinical pathology parameters.

However, the reviewer noted that the maximum pre-dose value for bilirubin was 0.9 and 0.5 mg/dL in males and females, respectively (Table 52). At week 12, one high dose male 835 had a bilirubin value of 1.0 mg/dL, a value slightly above the pre-dose maximum of 0.9 mg/dL for males. However, at week 12, three high dose females had bilirubin values above the pre-dose maximum of 0.5 mg/dL for females. Subsequently in weeks 21 and 24, the bilirubin values declined in both the high dose males and female groups. The high dose female (859) with the highest bilirubin value (1.0 mg/dL) not only had minimal mononuclear cell infiltration in the liver, but minimal hepatocellular necrosis as well. This female also had the highest values for D-dimer (1.62 and 1.45 µg/mL) at Weeks 21 and 24, respectively, compared to a maximum value in the control group of 0.8 µg/mL

Table 52: Compilation from Sponsor's Tables - Bilirubin

Mg/kg	Group		T BILI MG/DL Week -3	T BILI MG/DL Week -1	T BILI MG/DL Week 12	T BILI MG/DL Week 21	T BILI MG/DL Week 24
0	1M	Mean	0.4	0.5	0.5	0.2	0.2
		SD	0.13	0.31	0.19	0.05	0.13
		N	4	4	4	4	4
0.5	2M	Mean	0.3	0.3	0.3	0.2	0.2
		SD	0.06	0.12	0.05	0.05	0.05
		N	4	4	4	4	4
5	3M	Mean	0.3	0.4	0.5	0.3	0.2
		SD	0.10	0.14	0.17	0.06	0.05
		N	4	4	4	4	4
20	4M	Mean	0.2	0.3	0.6	0.3	0.3
		SD	0.05	0.10	0.30	0.10	0.06
		N	4	4	4	4	4
	4M	I00835	0.3	0.4	1.0	0.3	0.3
	4M	I00836	0.2	0.3	0.5	0.4	0.2
	4M	I00841	0.2	0.2	0.7	0.4	0.3
	4M	I00842	0.2	0.2	0.3	0.2	0.2
	Maximum individual pre-dose value = 0.9						

	Group		T BILI MG/DL Week -3	T BILI MG/DL Week -1	T BILI MG/DL Week 12	T BILI MG/DL Week 21	T BILI MG/DL Week 24
0	1F	Mean	0.4	0.4	0.3	0.2	0.2
		SD	0.05	0.06	0.06	0.06	0.10
		N	4	4	3	3	3
0.5	2F	Mean	0.3	0.3	0.5	0.2	0.2
		SD	0.13	0.15	0.17	0.05	0.05
		N	4	4	4	4	4
5	3F	Mean	0.3	0.4	0.5	0.2	0.2
		SD	0.10	0.06	0.08	0.00	0.00
		N	4	4	4	4	4
20	4F	Mean	0.4	0.3	0.7	0.3	0.4
		SD	0.06	0.05	0.22	0.05	0.14
		N	4	4	4	4	4
	4F	I00849	0.3	0.2	0.6	0.3	0.4
	4F	I00850	0.4	0.3	0.5	0.4	0.6
	4F	I00859	0.4	0.3	1.0	0.3	0.3
	4F	I00860	0.3	0.3	0.8	0.3	0.3
	Maximum individual pre-dose value = 0.5						

Immunophenotyping
Evaluation of lymphocyte subsets indicated no test article-related effects.

Gross pathology
No macroscopic findings were noted in any treated animal. Two control females had macroscopic lesions. One had a red focus in the stomach; the other had adhesions in the esophagus and pancreas as well as a red areas in the epicardiam. The later female was euthanized in Week 8.

Organ weights
The pathologist concluded that no organ weight changes were related to SCH 530348 administration. However, he did note that compared to the concurrent control group the mid- and high-dose male groups had higher mean absolute and relative weights for the testes, prostate and epididymides as well as lower mean absolute and relative weights for the thymus. He attributed both organ weight changes to differences in sexual maturity. All four of the control group males were sexually immature histologically. In contrast, one high dose male was almost fully mature and another high dose male was partially mature. Examination of individual testes weights relative to histologic appearance for the high dose animals indicated a correlation of testes weight and maturity (Table 53). One mid-dose male and two high dose males had testes weights greater than 2 standard deviations above the mean of the control group and were the individuals responsible for the higher reproductive organ weights of these groups. These same males had thymus weights greater than 2 standard deviations below the mean for the control group and were the individuals responsible for the lower thymus for their respective groups. The pathologist concluded that these lower thymus weights were attributable to physiologic involution associated with maturity. Therefore, the

differences in thymus, testes, prostate and epididymides in the treated males were attributed to maturity and not to treatment with SCH 530348.

Table 53: Reviewer's Summary of Selected Organ weights

		Males				Females			
Dose, mg/kg		0	0.5	5	20	0	0.5	5	20
Thymus	Mean	6.809	6.422	5.492	5.382	3.129	4.060	4.901	3.420
(gm)	SD	1.117	2.035	1.480	3.690	1.141	1.922	0.823	1.495
% TBW	Mean	0.236	0.239	0.196	0.177	0.123	0.149	0.191	0.134
	SD	0.029	0.082	0.064	0.152	0.043	0.066	0.033	0.047
Testis	Mean	1.358	1.030	1.853	4.619				
(gm)	SD	0.527	0.422	2.000	4.608				
% TBW	Mean	0.047	0.038	0.060	0.124				
	SD	0.017	0.014	0.057	0.112				

% TBW = total body weight

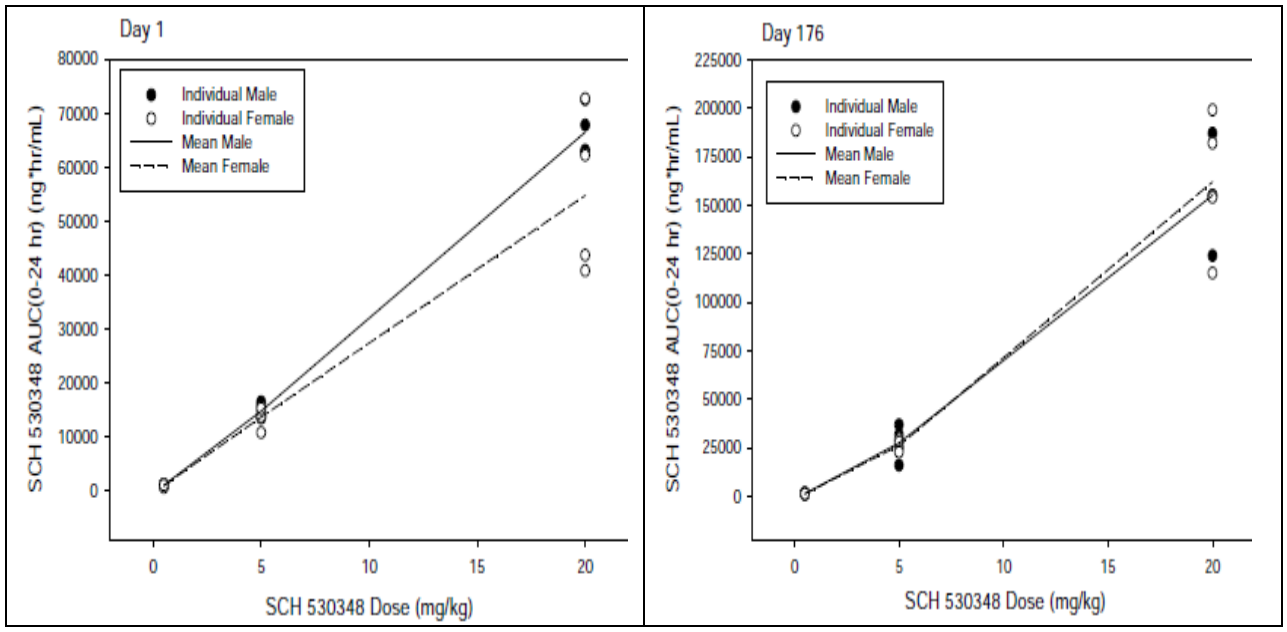
Histopathology
The pathologist concluded that all histopathologic findings were findings common in laboratory monkeys and were unrelated to administration of SCH 530348. The reviewer noted the presence of vacuolated macrophages in the lymph nodes of a high dose male and a high dose female, but not in control animals. Likewise, a higher incidence of mononuclear cell infiltration was observed in some tissues of the high dose males and females. For instance, mononuclear cell infiltration was observed in the livers of all four high dose females compared to only one control female and in the lungs of three high dose males compared to no control males.

Toxicokinetics
Maximum SCH 530348 plasma concentrations generally occurred at 4 hr post-dose. Systemic exposure to SCH 530348 was not affected by sex (Table 54, Figure 18). Systemic exposure was dose-related and approximately dose proportional on Day 1. However, on Day 176 systemic exposure was more than dose proportional. Accumulation of SCH 530348 in plasma was 1.3-1.4, 1.8-1.9, and 2.3-3.1 following daily administration of 0.5, 5, or 20 mg/kg, respectively, for 176 days.

Table 54: Reviewer's Summary of TK Parameters

	Study Day		Males, Dose, mg/kg			Females, Dose, mg/kg		
			0.5	5	20	0.5	5	20
Cmax, ng/mL	1	Mean	87.8	890	3995	72.0	895	2870
		SD	20.7	62	71	27.0	176	836
	176	Mean	89.7	1423	7550	75.3	1475	8539
		SD	13.6	441	1217	26.5	197	1660
$AUC_{(0\text{-}24\ hr)}$, ng*hr/mL	1	Mean	1064	14850	66525	986	13675	54850
		SD	119	1529	4608	249	2016	15214
	176	Mean	1370	27525	155250	1306	26100	162500
		SD	189	8944	25721	347	3014	36702

Figure 18: Sponsor's Graphs of $AUC_{(0\text{-}24\ hr)}$ versus Dose



Formulation analysis
The formulations were considered homogenous since the recoveries for individual replicates were between 95.3% and 98.4% of nominal. All SCH 530348 formulations throughout the study were within 93.9% to 99.3% of nominal. No SCH 530348 was detected in the control formulations.

6.2.2 Two week toxicokinetic study of SCH 530348 and SCH 2046273 (a metabolite of SCH 530348) in rats (Report Amendment 1)

Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Study number(s): SN 08378
Date of study initiation: December 19, 2008
Drug lot/batch number: SCH 530348, Batch No.: 03-530348-X-302, purity 99.2%
GLP compliance: Yes
QA statement: Yes

Key Study Findings
Male and female Sprague Dawley rats received oral gavage doses of 30 or 75 mg/kg SCH 530348 for 14 days. Analysis of plasma concentrations of SCH 530348 and its active metabolite, SCH 2046273, indicated exposure to SCH 530348 and SCH 2046273 increased with increasing dose. Systemic exposure to SCH 530348 was higher in

females than in males at both doses. In contrast, systemic exposure to SCH 2046273 was higher in males than in females. Although exposure to SCH 530348 did not change following repeated administration at 30 mg/kg, exposure to SCH 530348 increased following repeated administration at 75 mg/kg. However, exposure to SCH 2046273 increased following repeated administration at both doses. Exposures to SCH 2046273 even after repeated administration represented less than 1% of the exposure to SCH 530348 at both doses.

Histopathological examination of the eyes treated with different fixation procedures indicated vacuolation of the inner nuclear layer of the retina was not observed in eyes fixed in Carnoy's fixative or in eyes fixed in Davidson fixative after 24 hours refrigeration in situ. However, vacuolation was observed in the eyes fixed immediately in Davidson's fixative and in eyes fixed in Davidson's fixative after 6 hours refrigeration in situ.

The pathologist concluded that vacuolation in the inner nuclear layer of the retina in the eyes of SCH 530348-treated rats represented postmortem morphological alterations associated with aldehyde-based fixation and not an in vivo alteration in the morphology of the inner nuclear layer.

Purpose

The two objectives of this study were to 1) determine the toxicokinetics of SCH 530348 and SCH 2046273, a metabolite of SCH 530348, following oral administration to rats for 14 days and 2) to collect the eyes and evaluate the effect of fixation method on the incidence of vacuoles in the retina. The amendment concerned revisions to the toxicokinetic data.

Methods

Doses:	30 or 75 mg/kg/day as indicated in .
Frequency of dosing:	Once daily for 14 days
Administration route:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Rat (Crl:CD[SD]), Sprague Dawley
Number/Sex/Group:	15 animals/sex/group
Age:	Approximately 8 weeks at start of dosing
Weight:	Males: 252.2 to 296.9 g (males) and females: 197.3 to 238.5 g
Satellite groups:	None
Unique study design:	Comparison of fixatives for the eye.
Deviation from study protocol:	Two protocol deviations were noted in the report. Neither deviation affected the quality of the study or its interpretation.

Table 55: Sponsor's Summary of Study Design

Two Week Toxicokinetic Study of SCH 530348 and SCH 2046273 (a Metabolite of SCH 530348) in Rats (SN 08378): **Study Design**

Group	Test Article	No. of Rats/Sex	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Duration of Dosing (Days)
T1	Low-Dose (SCH 530348)	15	30	5	6	14
T2	High-Dose (SCH 530348)	15	75	5	15	14

Parameter	**Observation details and times**
Mortality	At least once daily
Clinical observations	Day -8, the day of randomization and immediately before and after dosing
Body weight	Weekly from Week -1 and the day of randomization
Gross pathology	At the end of treatment, the animals were euthanized using carbon dioxide, and necropsied. Only the eyes were collected. The eyes were fixed in one of the following procedures: 1) Immediately in Davidson's fixative 2) Eyes refrigerated in situ (in the skull) for 6 hr (low-dose group) or 24 hr (high-dose group), then placed into Davidson's fixative 3) Eyes collected in Carnoy's fixative (absolute alcohol/ glacial acetic acid).
Histopathology	Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections of the eye was performed on all animals.
Toxicokinetics	Blood was collected from three animals per timepoint at 1, 2, 4, 8, and 24 hr after dosing on Day 1 and Day 7 from the jugular vein, and on Day 14 from the vena cava. Plasma samples were assayed for SCH 530348 using liquid chromatography with tandem mass spectrometry (LC-MS/MS) □
Formulation analysis	Samples of all dosing formulations were collected for concentration and homogeneity determination on the day of preparation for Week 1. The sponsor previously determined that SCH 530348 is stable in 0.4% (w/v) aqueous methylcellulose at room temperature for at least 15 days.

Mortality
The pathologist concluded that no mortality was related to SCH 530348 administration. However, one high dose female was found dead immediately following blood collection. The death was attributed to trauma from the bleeding procedure.

Clinical observations
Although no clinical observation was clearly related to SCH 530348 administration, one high dose male refluxed a portion of the dose on Day 6.

Body weight
The high dose groups gained less body weight from Day 1 to Day 7 than from Day -8 to Day -1 (Table 56.

Table 56: Reviewer's Summary of Body Weight

Dose, mg/kg	Day[†]	Males -8	Males -1	Males 1	Males 7	Females -8	Females -1	Females 1	Females 7
30	Mean, gm	206.2	269.3	275.6	314.5	183	213.3	215.5	226.7
	SEM	2.7	3.1	3.1	3.5	2.5	2.9	3.4	3.6
			D-8 to D-1		D1 to D7		D-8 to D-1		D1 to D7
	Gain, gm		63.1		38.9		30.3		11.2
75	Mean	207	270.6	276.4	308.7	185.3	213.1	215	224.1
	SEM	2.5	3	3.1	3.8	2.5	2.9	2.5	3.5
			D-8 to D-1		D1 to D7		D-8 to D-1		D1 to D7
	Gain, gm		63.6		32.3		27.8		9.1
BW gain high vs low dose			100.8%		83.0%		91.7%		81.3%

[†] Data for Day 14 was not provided in the report.

Histopathology
The pathologist appeared to base scoring of vacuolation on the following criteria. If an eye had 3 or fewer vacuoles, it was scored as a 0. If the mean number of vacuoles per eye was between 4 and 21, the vacuolation was scored as minimal. If the mean number of vacuoles was greater than 21, the vacuolation was scored as mild (Table 57, Table 58).

Based on these criteria, vacuolation of the inner nuclear layer of the retina was not observed in eyes fixed in Carnoy's fixative or in eyes fixed in Davidson fixative after 24 hours refrigeration in situ. However, vacuolation was observed in the eyes fixed immediately in Davidson's fixative and in eyes fixed in Davidson's fixative after 6 hours refrigeration in situ.

The pathologist concluded that vacuolation in the inner nuclear layer of the retina in the eyes of SCH 530348-treated rats represented postmortem morphological alterations associated with aldehyde-based fixation and not an in vivo alteration in the morphology of the inner nuclear layer.

Table 57: Reviewer's Compilation from Sponsor's Tables - Vacuoles/Eye

Fixative	Males				Females		
	Dose Group (mg/kg)	Animal No./Sex	Number of Vacuoles		Animal No./Sex	Number of Vacuoles	
			Eye No. 1	Eye No. 2		Eye No. 1	Eye No. 2
Davidson's immediate	30	1001M	14	11	1501F	16	17
		1002M	29	20	1502F	17	5
		1003M	5	2	1503F	35	47
		1004M	33	25	1504F	14	29
		1005M	19	17	1505F	32	43
	75	2001M	47	57	2501F	54	35
		2002M	34	24	2502F	44	16
		2003M	24	18	2503F	7	15
		2004M	3	8	2504F	34	19
		2005M	0	6	2505F[a]	-	-
Davidson's post 6 hr refrigerated	6-Hour Refrigeration In Situ[a]				6-Hour Refrigeration In Situ[a]		
	30	1006M	17	12	1506F	8	4
		1007M	11	9	1507F	5	6
		1008M	0	0	1508F	3	3
		1009M	23	14	1509F	3	14
		1010M	16	28	1510F	5	4
Davidson's post 24 hr refrigerated	24-Hour Refrigeration In Situ[b]				24-Hour Refrigeration In Situ[b]		
	75	2006M	0	2	2506F	0	1
		2007M	0	0	2507F	0	2
		2008M	0	2	2508F	2	1
		2009M	3	1	2509F	2	1
		2010M	3	0	2510F	1	0
Carnoy's fixative	30	1011M	0	0	1511F	0	0
		1012M	0	0	1512F	1	0
		1013M	0	3	1513F	3	3
		1014M	1	0	1514F	1	0
		1015M	0	0	1515F	0	1
	75	2011M	0	0	2511F	0	0
		2012M	0	0	2512F	2	1
		2013M	0	0	2513F	0	3
		2014M	0	0	2514F	0	0
		2015M	2	0	2515F	0	1

Table 58: Reviewer's Summary - Eye Vacuolation with Different Fixatives

Fixative	Dose		Males	Females
Davidson's immediate	30	Vacuolation, inner nuclear layer, unilateral, minimal	1/5	0/5
		Vacuolation, inner nuclear layer. minimal	2/5	2/5
		mild	2/5	3/5
	75	Vacuolation, inner nuclear layer, unilateral, minimal	2/5	0/4
		Vacuolation, inner nuclear layer. minimal	1/5	1/4
		mild	2/5	3/4
Davidson's post 6 hr refrigerated	30	Vacuolation, inner nuclear layer, unilateral, minimal	0/5	1/5
		Vacuolation, inner nuclear layer. minimal	3/5	3/5
		mild	1/5	0/5

Fixative	Dose		Males	Females
Davidson's post 24 hr refrigerated	75	Vacuolation, inner nuclear layer, unilateral, minimal	0/5	0/5
		Vacuolation, inner nuclear layer. minimal	0/5	0/5
Carnoy's fixative	30	Vacuolation, inner nuclear layer, unilateral, minimal	0/5	0/5
		Vacuolation, inner nuclear layer. minimal	0/5	0/5
	75	Vacuolation, inner nuclear layer, unilateral, minimal	0/5	0/5
		Vacuolation, inner nuclear layer. minimal	0/5	0/5

Toxicokinetics
The toxicokinetic report was amended and the plasma concentrations of SCH 530348 revised downward from the original report.

The toxicokinetic report stated that no differences were observed when SCH 530348 plasma concentrations were compared on Day 6 and Day 13. Therefore, the Day 6 and Day 13 data were combined under multiple-dose data. The reviewer examined the Day 6 and Day 13 data and agrees that the overall data on Day 6 and Day 13 are generally similar. However, the reviewer notes that individual data were highly variable, particularly in females (Figure 19, Table 59).

Maximum SCH 530348 and SCH 2046273 plasma concentrations generally occurred between 1 and 4 hr post-dose. Systemic exposure to SCH 530348 and SCH 2046273 increased with increasing dose. Systemic exposure to SCH 530348 was higher in females than in males at both doses. In contrast, systemic exposure to SCH 2046273 was higher in males than in females.

Systemic exposure to SCH 530348 did not significantly change following repeated administration at 30 mg/kg; however, systemic exposure to SCH 530348 increased 1.8 fold in females and 1.35 in males following repeated administration at 75 mg/kg.

Systemic exposure to SCH 2046273 increased following repeated administration at both doses. However, accumulation of SCH 2046273 was greater at 75 mg/kg than at 30 mg/kg in both males (1.66 versus 1.2) and females (2.7 versus 1.5).

Exposures to SCH 2046273 even after repeated administration represented less than 1% of the exposure to SCH 530348 at both doses. In males, the AUC ratios of SCH 2046273 to SCH 530348 were 0.005 and 0.004 after the single doses of 30 and 75 mg/kg, respectively. These AUC ratios increased slightly to 0.006 and 0.005 following repeated administration at 30 and 75 mg/kg, respectively.

Figure 19: Sponsor's Figures - Individual and Mean SCH 530348 Plasma Concentration-Time Profiles after a Single Dose and after Repeated Dosing

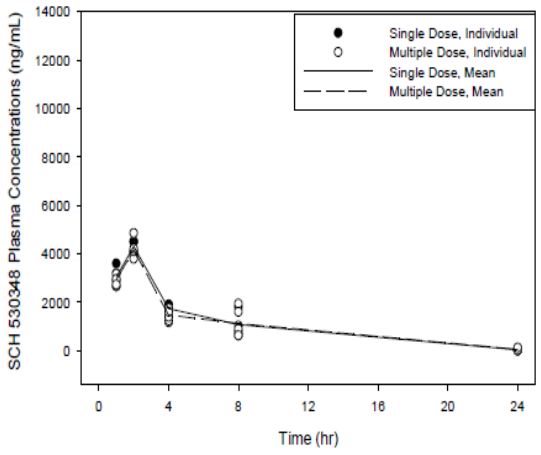
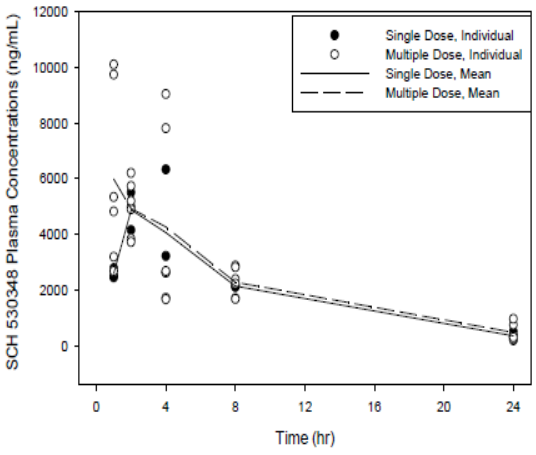
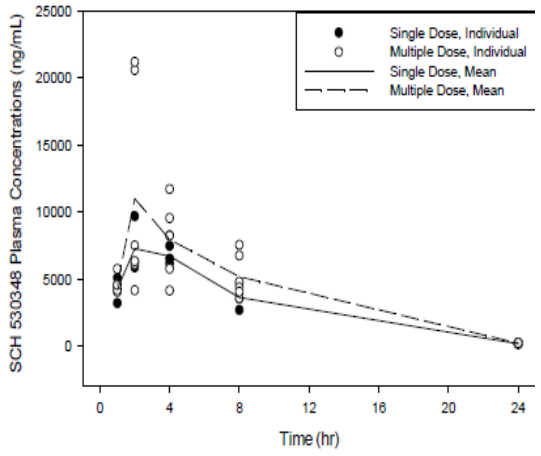
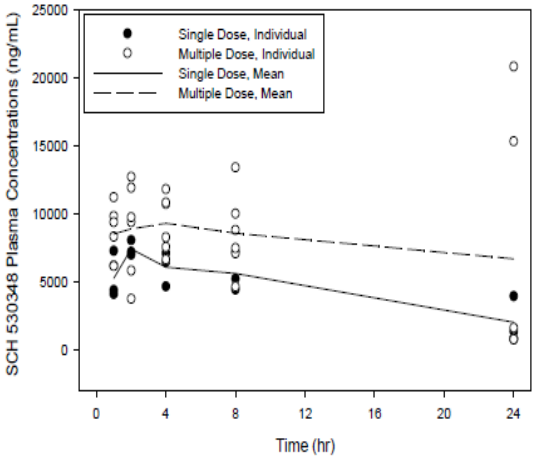
Dose	Males	Females
30 mg/kg		
75 mg/kg		

Table 59: Complied from Sponsor's Tables Summarizing Toxicokinetic Parameters for SCH 530348 and SCH 2046273

			SCH 530348				SCH 2046273			
	Sex	SCH 530348 Dose (mg/kg)	Cmax (ng/mL)	Tmax (hr)	AUC(0-8hr) (ng·hr/mL)	AUC(0-24hr) (ng·hr/mL)	Cmax (ng/mL)	Tmax (hr)	AUC(0-8hr) (ng·hr/mL)	AUC(0-24hr) (ng·hr/mL)
Single dose	Female	30	4880	2	26400	46400	3.05	2	13.9	NR[e]
		75	7410	2	45800	107000	5.94	2	29.7	63.0
	Male	30	4310	2	17000	26000	17.2	2	83.6	NR
		75	7260	2	42500	72800	34.9	2	165	276
Multiple dose	Female	30	5980	1	31000	53100	4.22	2	21.1	NR
		75	9290	4	70200	192000	10.8	2	71.6	171
	Male	30	4170	2	15900	25400	23.6	2	99.9	161
		75	11000	2	55300	98200	57.5	2	264	460

[e] NR = Not reported. AUC(0-24 hr) not reported when AUC extrapolated > 25%

Formulation analysis
Both formulations were considered homogenous since the recoveries for individual replicates were between 98.0% and 100% of nominal. The low and high dose formulations were 98.5% and 100%, respectively, of nominal.

6.2.3 Two-Week Oral (Gavage) Investigative Study Of SCH 530348 In Young And Older Male Rats

Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Summit, NJ
Study number(s): SN 10119
Date of study initiation: August 2, 2010
Drug lot/batch number: SCH 530348, Batch No.: 03-530348-X-101, purity 99.2%
GLP compliance: Yes
QA statement: Yes

Key Study Findings
Male Sprague Dawley rats that were six-week-old and six-month-old were treated with 0 or 30 mg/kg SCH 530348 for 14 days. The sponsor concluded systemic exposure to SCH 530348 was equivalent for the younger and older rats. However, administration of SCH 530348 to older rats had a greater effect on body weight gain than administration to younger rats. Additionally, a higher number of older rats (13/15) had vacuolation in the eyes than younger rats (6/15). The mean number vacuoles/eye was greater in older rats (12.1 ±9.1) than in younger rats (6.2 ±8.6). Although the mean number of vacuoles/eye is not statistically different between the older and younger rats, the distribution profile clearly shows a 4-fold increase in the number of rats with >20 vacuoles per eye in the older rats compared to the younger rats. Exposure to SCH 530348 higher in older rats (42700 ng*hr/mL) than in younger rats (30300 ng*hr/mL)

Purpose:
The study objectives were to evaluate the effect of age on the toxicokinetics of SCH 530348 administered to rats for two weeks and on the incidence of retinal vacuolation.

Methods

Doses:	0, 30 mg/kg (Table 60)
Frequency of dosing:	Once daily for 14 days
Administration route:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Rat (Crl:CD[SD])
Number/Sex/Group:	30 males/group
Age:	Young rats: 6 weeks at start of dosing Older rats: 6-7 months old

Weight:	Young males: 148.8 to 198.3 g Older males: 458.0 to 742.6 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	One protocol deviation was noted in the report. The deviation did not affect the quality of the study or its interpretation.

Table 60: Sponsor's Summary of Study Design

Group	Group Name	No. of Male Rats	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Duration of Dosing (Days)
G1	6-Week-Old Rats: Vehicle Control (Methylcellulose)	15	0	5	0	14
G2	6-Week-Old Rats: SCH 530348	15	30	5	6	14
G3	6-Month-Old Rats: Vehicle Control (Methylcellulose)	15	0	5	0	14
G4	6-Month-Old Rats: SCH 530348	15	30	5	6	14

Parameter	**Observation details and times**
Mortality	At least once daily
Clinical observations	Day -7, the day of randomization and once daily
Body weight	Weekly from Week -1, the day of randomization, and day prior to necropsy
Gross pathology	At the end of treatment, the animals were euthanized using carbon dioxide, and necropsied. Only the eyes were collected. The eyes were fixed in 3% glutaraldehyde.
Histopathology	Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections of the eye was performed on all animals.
Toxicokinetics	Blood was collected from three animals per timepoint at 1, 2, 4, 8, and 24 hr after dosing on Day 14 from the vena cava. Plasma samples were assayed for SCH 530348 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of all dosing formulations were collected for concentration and homogeneity determination on the day of preparation for Week 1. The sponsor previously determined that SCH 530348 is stable in 0.4% (w/v) aqueous methylcellulose at room temperature for at least 15 days.

Mortality
No unscheduled mortality occurred in the study.

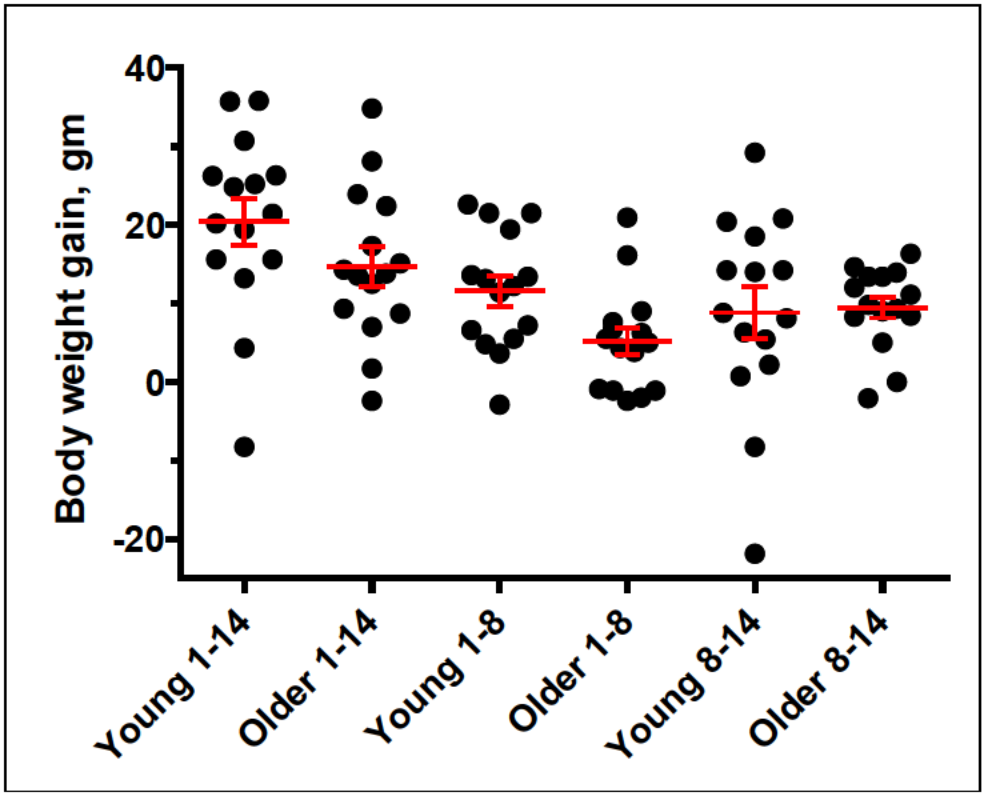
Clinical observations
No clinical observation was clearly related to SCH 530348 administration.

Body weight
The sponsor concluded that any changes in body weight in both the younger and older rats were not related to SCH 530348 administration. No significant change in body weight was observed in the younger rats. However, the mean body weight gain in the older rats treated with SCH 530348 was 28% lower than the gain in the corresponding control group for the whole dosing period (Table 61). This decrease was attributed to the 55% decrease in mean body weight gain in the treated rats from Day 1 to Day 8 compared to the gain in the control group. The sponsor maintains that this effect was transient because from Day 8 to Day 14 the older treated rats gained more weight than did the rats in the control group. However, examination of the individual data indicates that the apparent greater gain in the older treated rats is attributable to the decrease in body weight for control older male 3002 (Figure 20). Between Day 8 and 14, this animal lost body weight compared not only to Day 1 and day 8, but also compared to Day -7 as well. If this animal is excluded, the body weight gain for the older treated rats is 13% and 35% less between Days 8-14 and Days 1-14, respectively, than the mean body weight gain for the remaining control older rats. Although the reduction in body weight gain is less than during the first week of treatment, a reduction still occurred. Administration of 30 mg/kg of SCH 530348 to older rats had a greater effect on body weight gain than administration to younger rats.

Table 61: Reviewer's Summary of Body Weight and Body Weight Gain

Dose,		Young males					Older males				
mg/kg	Day	-7	-1	1	8	14	-8	-1	1	8	14
0	Mean, gm	115.8	165.8	169.9	222.1	268.4	598.2	612.3	609.8	621.4	630.2
	SD	11.9	14.6	14.8	20.6	27.5	71.6	76.0	76.0	74.1	76.6
	Interval			-7 - 1	1 - 8	8 -14			-7 - 1	1 - 8	8 -14
	Gain, gm			54.1	52.1	46.3			11.6	11.6	8.8
	Overall gain, 1-14					98.4					20.4
						(14.0)					(11.6)
30	Mean, gm	118.2	166.1	171.1	221.0	267.3	598.8	615.1	612.5	617.6	627.1
	SD	10.6	14.0	15.5	21.8	26.5	74.7	76.1	76.7	76.0	77.5
	Interval			-7 – 1	1 - 8	8 -14			-7 – 1	1 - 8	8 -14
	Gain, gm			52.9	49.9	46.3			13.7	5.2	9.5
	Overall gain, 1-14					96.3					14.7
	(SD)					(15.0)					(9.7)
	% difference in gain					-2.1%					-28%

Figure 20: Reviewer's Plots of Individual Body Weight Gains



Histopathology

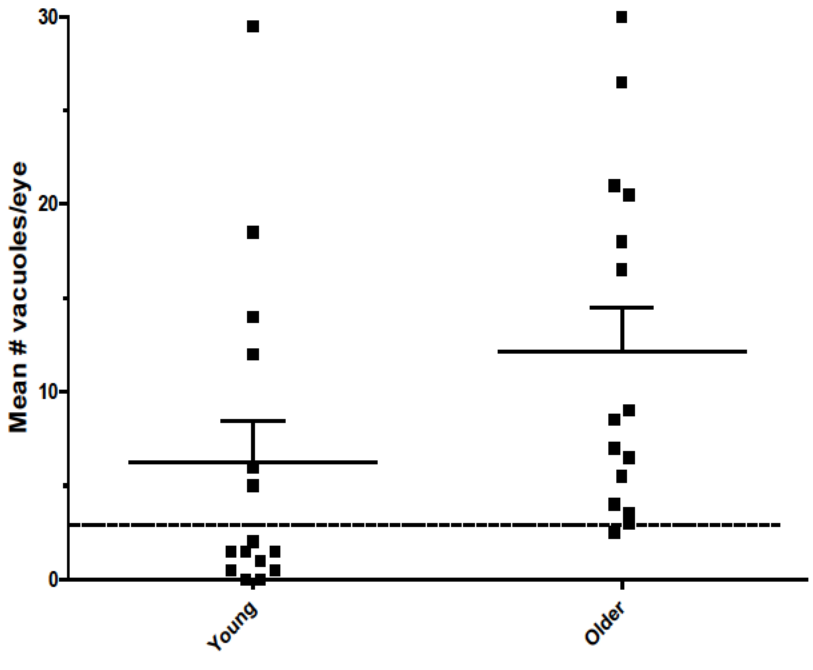
Vacuolation of the inner nuclear layer of the retina was observed in both the younger and older male rats that had received 30 mg/kg SCH 530348 for 2 weeks. The pathologist appeared to define the minimal category as greater than 3 vacuoles per eye to 25 vacuoles per eye and the mild category as greater than 25 vacuoles per eye. More of the older rats (13/15) were affected than younger rats (6/15) (Table 62). The pathologist concluded that the severity of vacuolation was minimal for most of the affected rats and was not associated with degradation or necrosis. Because this finding did not occur in control animals of either age, it is considered a drug-related amplification of a retinal fixation/processing artifact that is related to the administration of SCH 530348.

However, the reviewer notes that the severity categories used by the pathologist minimize the findings in the older rats. The mean number vacuoles/eye was greater in older rats (12.1 ±9.1) than in younger rats (6.2 ±8.6). Although the mean number of vacuoles/eye is not statistically different between the older and younger rats, the distribution (Figure 21) clearly shows a 4-fold increase in the number of rats with >20 vacuoles per eye in the older rats compared to the younger rats. Therefore, the severity of the vacuolation is greater in older rats.

Table 62: Sponsor's Table – Eye Vacuolation

Age at Dosing Initiation:	6 Weeks		6 Months	
Dose (mg/kg):	0	30	0	30
Number of Animals:	15	15	15	15
Finding/Severity	Incidence			
- vacuolation inner nuclear layer retina				
total	**0**	**6***	**0**	**13***
minimal	0	5*	0	11*
mild	0	1*	0	2*

Figure 21: Reviewer's Plots of Vacuoles/Eye for Individual Rats



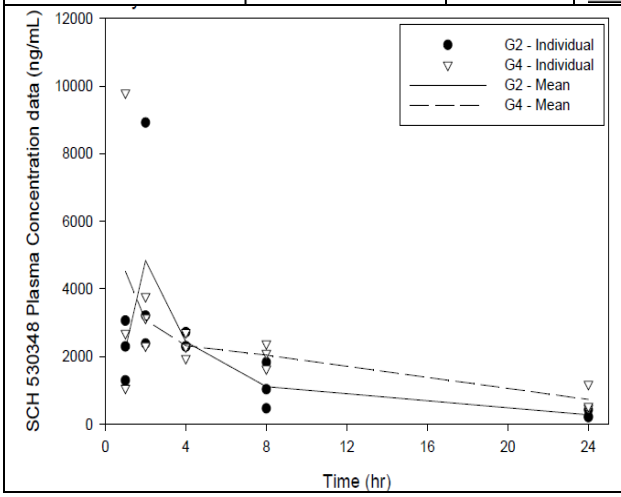
Dotted line indicates the value of 3 vacuoles/eye separating background from a minimal finding.

Toxicokinetics

No SCH 530348 was detected in plasma from control animals of either age. Maximum SCH 530348 plasma concentrations occurred at 1 to 2 hr post-dose in both age groups. Although Cmax values were similar in both age groups, the $AUC_{(0\text{-}24\ hr)}$ value was higher in the older rats than in the younger rats (Table 63). However, the sponsor's plot of individual and mean plasma concentrations suggested no major difference in exposure between young and older male rats. The sponsor concluded systemic exposure to SCH 530348 was equivalent for the six-week-old and six-month-old male rats dosed for 14 days with 30 mg/kg SCH 530348.

Table 63: Compilation from Sponsor's Tables and Figure - Toxicokinetics

SCH 530348 Dose (mg/kg)	Group	Age	Cmax (ng/mL)	Tmax (hr)	AUC(0-24 hr) (ng·hr/mL)
30	G2	6 wk	4840	2	30300
	G4	6 mo	4520	1	42700



	Age	
Time, hr	**6 wks**	**6 mo**
1	2220[b] (40)	4520 (103)
2	4840 (74)	3080 (24)
4	2440 (10)	2320 (16)
8	1110 (62)	2040 (18)
24	281 (44)	730 (53)

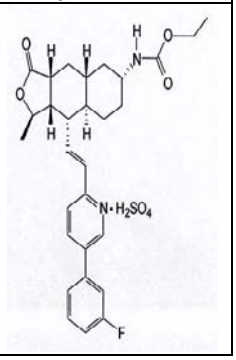
N = 3/timepoint/group
[b] SCH 530348 plasma concentration units are ng/mL.

Formulation analysis
The formulation was considered homogenous since the recoveries for individual replicates were between 95.7% and 103% of nominal. No SCH 530348 was detected in the control formulation.

6.2.4 Investigative Two-Week Oral (Gavage) Study Of SCH 590709, SCH 2490130 And SCH 602539 In Male Rats

Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Study number(s): SN 10805
Date of study initiation: May 20, 2010
GLP compliance: No
QA statement: No
Drug lot/batch number: See Figure 22.

Figure 22: Structures of PAR-1 Inhibitors Evaluated in SN 10805

SCH 590709	SCH 2490130 -	SCH 602539 -	SCH 530348
Structurally distinct from SCH 530348	Competitor compound (b) (4)	Structural analog of SCH 530348	
Batch 88416-100	Batch ELS014-112-19	Batch 21	Not tested in this study
(b) (4)			

Key Study Findings

Sprague Dawley male rats were treated with vehicle or one of three PAR-1 antagonists by daily oral (gavage) doses for two weeks. These compounds included SCH 602539 (60 mg/kg, a close structural analog of SCH 530348) and two structurally distinct compounds: SCH 590709 (20 or 200 mg/kg) and SCH 2490130 (100 or 1000/500 mg/kg). All drug treated groups had a reduction in mean body weight compared to the control group at study termination. Body weight gain decreased by 10.2%, 31.8%, and 49.6% with 60 mg/kg SCH 602539, 200 mg/kg SCH 590709, and 100 mg/kg SCH 2490130, respectively, relative to the control group on Day 14. No significant vacuolation or phospholipidosis in the liver was observed in rats treated with SCH 602539 or SCH 590709. However, vacuolation of the inner nuclear layer of the retina was observed in all male rats that had received 60 mg/kg SCH 602539. In contrast, vacuolation of the eyes was not detected in the groups treated with either of the two structurally distinct PAR-1 inhibitors, SCH 590709 or SCH 2490130. Although the sponsor suggests that retinal vacuolation induced by SCH 602539 or SCH 530348 is not related to the mechanism of action of these PAR-1 inhibitors, the reviewer notes that exposures to SCH 590709 and SCH 2490130 were lower than the exposure to SCH 602539.

Purpose:

The study objective was to evaluate whether other PAR-1 inhibitors also induce retinal vacuolation. SCH 602539, a close structural analog of SCH 530348, was compared to two structurally distinct PAR-1 inhibitors, SCH 590709 and SCH 2490130 (b) (4) .

Methods

Doses:	As indicated in Table 64
Frequency of dosing:	Once daily for 14 days
Administration route:	Oral gavage
Dose volume:	5 or 10 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Rat (Crl:CD[SD]), Sprague Dawley
Number/Sex/Group:	10 male rats/group
Age:	6 weeks at start of dosing
Weight:	162.4 to 199.7 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	No protocol deviation was noted in the report. However, Group 6 was euthanized on Day 6, because of toxicity.

Table 64: Sponsor's Summary of Study Design

INVESTIGATIVE TWO-WEEK ORAL (GAVAGE) RETINAL VACUOLATION STUDY OF SCH 590709, SCH 2490130 AND SCH 602539 IN MALE RATS

Group	Test/Control Article	Total Daily Dose (mg/kg)[a]	Dose Volume (mL/kg)	Dose Conc. (mg/mL)[b]	Number of Male Rats[c]
G1	Control (Methylcellulose – 0.4% [w/v])	0	5	0	10
G2	SCH 602539	60	5	13.2	10
G3	SCH 590709	20	5	4	10
G4	SCH 590709	200	5	40	10
G5	SCH 2490130	100	5	23.1	10
G6	SCH 2490130	1000	10	115	10

a: Doses are expressed as the free form. When expressed as the hydrochloride salt, the dose for the G2 group (SCH 602539) is equivalent to 66.2 mg/kg. When expressed as the hydrobromide salt, the dose for the G5 and G6 groups (SCH 2490130) are equivalent to 115 and 1153 mg/kg, respectively.

b: Concentrations are expressed as the hydrochloride salt for group G2 and the hydrobromide salt for groups G5 and G6. When expressed as the free form, the concentrations are equivalent to 30, 4, 40 and 200 mg/mL for the for the G2, G3, G4, and G5 groups respectively.

c: Repeat-dose toxicokinetic analysis will be performed on the last three rats in groups G2-G6 on Day 14.

Because of excessive toxicity in Group 6, the dose was reduced to 500 mg/kg on Day 4. Group 6 was subsequently terminated on Day 6

Parameter	Observation details and times
Mortality	At least once daily
Clinical observations	The day of randomization and once daily prior to dosing
Body weight	The day of randomization and on Days 1, 8, and 14.

Gross pathology	At the end of treatment, the animals were subjected to isoflurane anesthesia and exsanguinated. Only the eyes and liver were collected. The eyes from all groups were fixed in 3% glutaraldehyde. The livers from groups G1, G2, G3 and G4 were fixed in 10% neutral formalin.
Histopathology	Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections of the eyes was performed on all animals. Only the livers from groups G1, G2, G3 and G4 were examined microscopically.
Toxicokinetics	Blood was collected from the last three animals per group pre-dose and at 1, 2, 4, 7, and 24 hr after dosing on Day 14. Plasma samples were assayed for the indicated compounds using liquid chromatography with tandem mass spectrometry (LC-MS/MS) □

Mortality and clinical observations
The mortality and clinical observations are summarized in Table 65. The death and clinical observations in Group 6 resulted in reduction of the dose from 1000 mg/kg to 500 mg/kg. The continuation of clinical signs and the deaths on Days 5 and 6 resulted in termination of all Group 6 animals on Day 6.

Table 65: Reviewer's Summary - Mortality and Clinical Observations – SN 10805

Group	Test article	Dose, mg/kg	Mortality	Clinical observations
1	Vehicle	0	None unscheduled	None remarkable
2	SCH 602539	60	2004 euthanized D 7	Excessive salivation, Gasping in 2004, necropsy showed perforation of esophagus
3	SCH 590709	20	None unscheduled	None remarkable
4	SCH 590709	200	None unscheduled	Chromorhinorrhea in two animals
5	SCH 2490130	100	5002 found dead D 13	5002 – dehydrated, cool to touch on D 12. This rat lost 6.3% of body weight between Day 1 and Day 8
6	SCH 2490130	1000 /500	6007 found dead D 4 6008 euthanized D 5 6002 found dead D 6 Remaining G6 rats euthanized D 6	Chromorhinorrhea &/or chromodacryorrhea in all rats, dehydration, hunched appearance; cool to touch; scant, loose and/or soft stool; fecal-stained fur; tremors weakness; gasping; abdominal distention

Body weight
All drug treated groups had some reduction in mean body weight compared to the control group at study termination (Table 66). All group 6 animals terminated on Day 6 lost 25% of their body weight from Day 1. Body weight gain was reduced by 10.2%, 3.5%, 31.8%, and 49.6% in Groups 2, 3, 4, and 5, respectively, relative to the control group 1 from Day 1 to 14. Although the 10.2% decrease in body weight gain for Day 1 to 14 induced by SCH 602539 was not statistically significant, the 12.5% decrease in body weight gain for Day 1 to Day 8 was statistically significant.

Table 66: Reviewer's Summary – Body Weight and Body Weight Gain – SN 10805

Group	Test article	Dose, mg/kg	Day	Body weight, gm -1	1	8	14	BW gain, gm D 1 to 8	D 8 to 14	D 1 to 14
1	Vehicle	0	Mean, gm	181.5	190.1	255.0	310.4	65.0	55.4	120.4
			SD	9.8	10.6	16.9	21.6	9.5	6.7	15.9
2	SCH 602539	60	Mean, gm	181.1	189.7	246.6	297.8	56.9*	51.2	108.1
			SD	10.0	11.0	13.3	15.7	6.1	5.2	9.5
3	SCH 590709	20	Mean, gm	181.1	189.5	250.3	305.7	60.8	55.4	116.2
			SD	9.8	10.4	12.9	17.8	6.0	7.0	9.5
4	SCH 590709	200	Mean, gm	181.5	190.4	226.8	272.4	36.4*	45.6	82.0*
			SD	9.1	8.8	28.1	35.6	21.5	17.8	29.6
5	SCH 2490130	100	Mean, gm	180.7	188.4	212.1	249.3	23.6*	33.1*	60.6*
			SD	10.1	10.9	20.7	36.9	16.9	26.2	35.8
6	SCH 2490130	1000/ 500	Mean, gm	180.4	189.6	144.2*		-47.5*		
			SD	9.1	8.4	5.0		5.0		

* On Day 6, day of group termination * p<0.05

Histopathology

No significant vacuolation or phospholipidosis in the liver was observed in rats treated with SCH 602539 or SCH 590709 (Table 67). However, vacuolation of the inner nuclear layer of the retina was observed in all male rats that had received 60 mg/kg SCH 602539, a structural analog of SCH 530348 for 2 weeks. The pathology report did not indicate the number of vacuoles per eye, but simply categorized severity as grade 1 (minimal). In contrast, vacuolation of the eyes was not detected in the groups treated with either of the two structurally distinct PAR-1 inhibitors, SCH 590709 or SCH 2490130. The sponsor suggests that retinal vacuolation induced by SCH 602539 or SCH 530348 is not related to the mechanism of action of these PAR-1 inhibitors. However, this conclusion must be tempered by the fact that exposures to SCH 590709 and SCH 2490130 were lower than the exposure to SCH 602539 (Table 68).

Table 67: Sponsor's Summary of Histopathology - SN 10805

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0), Incl. Deaths

Sex		Males					
Dose Group		G1	G2	G3	G4	G5	G6
No. Animals per Dose Group		10	10	10	10	10	10
EYES	No.Examined	10	10	10	10	10	10
	NAD	10	1	10	10	10	10
- Vacuolation		-	9	-	-	-	-
LIVER	No.Examined	10	10	10	10	-	-
	NAD	5	6	5	6	-	-
- Vacuolation:Periportal		1	-	-	2	-	-
	Grade 1	1	-	-	2	-	-
- Necrosis:Focal		-	1	1	-	-	-
	Grade 1	-	1	1	-	-	-
- Mononuclear infiltration		4	3	5	3	-	-
	Grade 1	4	3	5	3	-	-

NAD = Nothing abnormal discovered
Group G1, Control (Methylcellulose), males: (0 mg/kg)
Group G2, SCH 602539, males: (60 mg/kg)
Group G3, SCH 590709, males: (20 mg/kg)
Group G4, SCH 590709, males: (200 mg/kg)
Group G5, SCH 2490130, males: (100 mg/kg)
Group G6, SCH 2490130, males: (500 mg/kg)

Toxicokinetics
On a molar basis, molar exposure to SCH 602539 was 17-, 2.4-, and 14-fold higher than the exposure following 20 mg/kg SCH 590709, 200 mg/kg SCH 590709, and 100 mg/kg SCH 2490130, respectively (Table 68). Exposure in rats treated at 1000/500 mg/kg SCH 2490130 was not evaluated because of the unscheduled termination of Group 6. Assuming a linear dose proportionality, an exposure to SCH 2490130 of 149 µM*hr to 297 µM*hr might have been expected for Group 6. However, molar exposure to SCH 602539 was 1.4 to 2.8-fold higher than the expected exposure to SCH 2490130 for Group 6.

Table 68: Reviewer's Summary of Toxicokinetic Parameters - SN 10805

Group	Test article	Dose, mg/kg	$AUC_{(0\text{-}24\ hr)}$, µg*hr/mL	$AUC_{(0\text{-}24\ hr)}$, µM*hr	Tmax, hr	Cmax, µg/mL
1	Vehicle	0	-	-	-	-
2	SCH 602539	60	201	423	1	16.9
3	SCH 590709	20	10	24.9	2	1.47
4	SCH 590709	200	69.6	173	7	4.8
5	SCH 2490130	100	15.7	29.7	7	0.70
6	SCH 2490130	1000/ 500	NE*	NE*	NE*	NE*
NE = not evaluated, * Day 6 group termination						

6.2.5 Fourteen-day exploratory oral toxicity study of L-003959712 in male Wistar rats with an interim necropsy

Conducting laboratory and location: Merck Research Laboratories, Summit, NJ
Study number(s): TT 11-1513
Date of study initiation: March 3, 2011
Drug lot/batch number: L-003959712, Batch No.: L-003959712-00W020 (L-003959712 is another name for SCH 602539).
GLP compliance: No
QA statement: No

Key Study Findings
L-003959712, also called SCH 602539, is a close structural analog of SCH 530348. In a previous study (SN 10805), SCH 602539 at 60 mg/kg induced retinal vacuolation in the eyes of male Sprague Dawley rats. In the current study, 60 mg/kg L-003959712 administered to Wistar rats for 7 or 14 days did not induce eye vacuolation. Body weight gain in Wistar rats was not significantly affected by administration of 60 mg/kg L-003959712 for 14 days. In contrast, a 10.2% decrease in body weight gain for Day 1 to 14 was induced by SCH 602539 in Sprague Dawley rats. At 2 hours post dose, the plasma concentration of L-003959712 in Wistar rats was about 17 µg/mL. This concentration was similar to concentrations of SCH 602539 (16.9 and 15.7 µg/mL) at 1 and 2 hours, respectively, post dose in Sprague Dawley rats (SN 10805).

Purpose
The study objective was to evaluate retinal vacuolation following administration of L-003959712 to male Wistar rats for 7 or 14 days

Methods

Doses:	0, 60 mg/kg (Table 69)
Frequency of dosing:	Once daily for 14 days
Administration route:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Rat (Crl:WI[HAN]), Wistar
Number/Sex/Group:	20 male rats/group
Age:	6 weeks at start of dosing
Weight:	116.2 to 153.9 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	Protocol deviations were not listed in the report.

Table 69: Sponsor's Summary of Study Design - SN TT 11-1513

Fourteen Day Exploratory Oral Toxicity Study of L-003959712 in Male Wistar Rats with an Interim Necropsy

Group	Group Name	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Number of Male Rats[a]
G1	Vehicle Control (Methylcellulose)	0	5	0	20
G2	Test Article (L-003959712)	60	5	12	20

[a] The first 10 animals per group (by numerical order) will be euthanized for interim necropsy on Day 8

Parameter	Observation details and times
Mortality	At least twice daily
Clinical observations	On Day -4, the day of randomization and once daily prior to dosing
Body weight	On Day -4, the day of randomization, and on Day 1, Day 7, and Day 14.
Gross pathology	On Days 8 and 15, 10 animals/group were subjected to isoflurane anesthesia and exsanguinated. Only the eyes were collected. The eyes from all groups were fixed in 3% glutaraldehyde.
Histopathology	Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections of the eyes was performed on all animals.

Toxicokinetics	Blood was collected from the first three animals per group at 2 hr after dosing on Day 7 and Day 14. Plasma samples were assayed for the indicated compounds using liquid chromatography with tandem mass spectrometry (LC-MS/MS)

Mortality and clinical observations
No mortality or notable clinical observations were observed, except that reflux was observed in one L-003959712-treated animal on Day 12.

Body weight
The body weights and body weight gains were not significantly different between the control and drug treated groups, although the mean body weight gain was lower by 2.6% in the L-003959712-treated group on Day 14 (Table 70). In contrast, the mean body weight gain in Sprague Dawley rats treated with 60 mg/kg SCH 602539 was 10.2% lower on Day 14 (SN 10805).

Table 70: Reviewer's Summary – Body Weight and Body Weight Gain – SN TT 11-1513

Group	Test article	Dose, mg/kg	Day	Body weight, gm -4	-1	1	7	14	BW gain, gm D 1 to 7	D 7 to 14	D 1 to 14
1	Vehicle	0	Mean, gm	134.1	157.4	161.8	199.7	238.7	37.8	40.1	78.4
			SD	8.3	9.4	9.0	11.5	13.0	3.5	3.6	5.6
2	SCH 602539	60	Mean, gm	134.2	156.8	159.6	195.0	232.1	35.4	41.3	76.4
			SD	9.2	11.5	11.8	13.7	20.3	4.1	6.8	9.8

Histopathology
No vacuolation was observed in the eyes of Wistar rats treated with 60 mg/kg L-003959712 (Table 71). However, a dose of 60 mg/kg SCH 602539 induced vacuolation in Sprague Dawley rats in another study (SN 10805). The sponsor suggests that the retinal vacuolation was limited to Sprague-Dawley rats, indicating the vacuolation is rat strain specific.

Table 71: Sponsor's Summary of Histopathology - SN TT 11-1513

Day 8

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: INTERIM SACRIFICE GROUP (K1)

Sex		Males		
Dose Group No. Animals per Dose Group		G1 10	G2 10	
EYES	No.Examined	10	10	
	NAD	10	10	

NAD = Nothing abnormal discovered
Group G1, Vehicle Control, males: L-003959712 (0 mg/kg)
Group G2, L-003959712, males: L-003959712 (60 mg/kg)

Day 15

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0)

Sex		Males		
Dose Group No. Animals per Dose Group		G1 10	G2 10	
EYES	No.Examined	10	10	
	NAD	10	10	

NAD = Nothing abnormal discovered
Group G1, Vehicle Control, males: L-003959712 (0 mg/kg)
Group G2, L-003959712, males: L-003959712 (60 mg/kg)

Toxicokinetics

The sponsor did not determine exposure (AUC), but only evaluated SCH 602539 plasma concentrations at one time point. At 2 hours post dose, the plasma concentration of L-003959712 in Wistar rats was about 17 µg/mL (Table 72. This concentration was similar to the plasma concentrations of SCH 602539 (16.9 and 15.4 µg/mL) at 1 and 2 hours, respectively, post dose in Sprague Dawley rats (SN 10805).

Table 72: Reviewer's Summary of Plasma Concentrations - SN TT 11-1513

Group	Test article	Dose, mg/kg	Necropsy Day	C2hr, µM	C2hr, µg/mL
1	Vehicle	0	8	0	0
			15	0	0
2	SCH 602539	60	8	35.3 (3.49)	16.8
			15	36.8 (1.21)	17.5

7 Genetic Toxicology

7.1 Chromosome Aberration Study of SCH 530348 with Impurities in Human Peripheral Blood Lymphocytes

Conducting laboratory and location: (b) (4)
Study number(s): SN 06042 (b) (4)
Date of study initiation: May 18, 2006
Drug lot/batch number: SCH 530348 with impurities, Batch: 05-530348-X-302
GLP compliance: Yes
QA statement: Yes

Key Study Findings
SCH 530348 with impurities did not induce increases in chromosome aberrations in human peripheral whole blood chromosome aberration assay. The maximum dose levels evaluated for chromosome aberrations in absence of metabolic activation were 278 µg/mL for a 4-hour treatment and 100 µg/mL for a 19-hour treatment. The maximum dose levels evaluated for chromosome aberrations with metabolic activation were 555 µg/mL for the initial 4-hour treatment, and 500 µg/mL in the confirmatory 4-hour treatment. SCH 530348 with impurities did not induce an increase in chromosome aberrations in cultured whole blood human lymphocytes in the presence or absence of metabolic activation in valid assays.

Purpose
This in vitro assay was designed to evaluate the ability of a lot of SCH 530348 with impurities to induce excess structural chromosome aberrations in cultured human lymphocytes in the presence and absence of a metabolic activation system.

Methods

Cell line: Human venous whole blood cultures
Concentrations in definitive study:
Nonactivation:
4 h exposure: 4.34, 8.67, 17.3, 34.7, 69.3, 139, 278, and 555 µg/mL
24 h exposure: 7.5, 15, 30, 45, 60, 80, 100, 125, 188, and 250 µg/mL
Activation: 4 h exposure:
Trial 1: 4.34, 8.67, 17.3, 34.7, 69.3, 139, 278, and 555 µg/mL
Trial 2: 30, 60, 80, 100, 125, 188, 250, and 500 µg/mL
Basis of concentration selection of high dose:
Dose selection was based on the concentration dependent precipitation and/or cytotoxicity (50% inhibition of mitotic index) after exposure to test article
Negative control: vehicle controls contained 1% DMSO
Positive control: Nonactivation - Mitomycin C
4 hour treatment used 0.75, 1, and 1.5 µg/mL
19 hour treatment used 0.2, 0.3, and 0.4 µg/mL
Activation - Cyclophosphamide (20, 25, and 40 µg/mL)
Formulation/Vehicle: DMSO
Incubation & sampling times:
Heparinized whole blood from healthy volunteers was added to RPMI 1640 media supplemented with 20% heat-inactivated fetal bovine serum, 2% phytohemagglutinin-M (PHA-M), mitogen phytohaemagglutinin (PHA), and incubated for 48 hrs. Dilutions of SCH 530348 with impurities were added to duplicate cultures in the presence or absence of a metabolic activation system. In Trial 1 the cultures were treated for 4 hrs with and without metabolic activation (Table 73). The lymphocytes were then washed and resuspended in fresh growth medium. Twenty-four hours after initiation of treatment, the cells were harvested. In Trial 2, cells were exposed to test article for 19 hrs without metabolic activation. Two hours prior to harvest, colcemid was added to arrest dividing cells in metaphase. Cells were harvested by centrifugation and resuspended in hypotonic KCl solution (0.075 M). The cells were fixed with a fixative of methanol:glacial acetic acid (3:1, v/v). After fixation in ethanol/glacial acetic acid, the cells were dropped onto slides, and stained with 5% Giemsa stain.

Table 73: Sponsor's Summary of Treatment Schedule – Study SN 06042

Test Condition	Test Article Addition	Test Article Exposure Time	Wash Completed	Colcemid® Added	Harvest Started
INITIAL ASSAY (Trial 1)					
-S9	0	4 ± 0.5	5 ± 0.5	20 ± 0.5	22 ± 1
+S9	0	4 ± 0.5	5 ± 0.5	20 ± 0.5	22 ± 1
CONFIRMATORY ASSAY (Trial 2)					
-S9	0	19 ± 0.5	20 ± 0.5	20 ± 0.5	22 ± 1
+S9	0	4 ± 0.5	5 ± 0.5	20 ± 0.5	22 ± 1

Cytotoxicity and mitotic index were determined from 1000 cells per culture. For the chromosome aberrations, 100 cells were analyzed from each duplicate culture from negative controls, vehicle controls, and at least three dose levels of the test article. The percentages of polyploidy and endoreduplication were derived from at least 100 cells from each duplicate culture.

Osmolality of SCH 530348 with impurities at 555 µg/mL in RPMI 1640 culture media (441 mOsm/kg) was similar to that for 10 µL/mL of DMSO in RPMI 1640 culture media (455 mOsm/kg water). The pH was 7.5 for the culture medium alone and for the culture medium containing SCH 530348 with impurities at concentrations of 139 µg/mL to 1110 µg/mL. Analysis of the formulations of the doses evaluated for clastogenicity indicated the concentrations were 86.3% to 104% of nominal for Trial 1 and 95.3% to 108% of nominal for Trial 2.

Results

Exposure to SCH 530348 with impurities for 4 hours in the absence of metabolic activation in Trial 1 did not induce an increase in mean percentage of aberrant cells (0.0-0.5%) when tested up to 278 µg/mL, the highest concentration limited by precipitation. The percentages of aberrant cells at 278 µg/mL (0-0.5%, 0-1.5%) were within the historical negative (0-1.5%, 0-4.5%) and vehicle control (0-2.5%, 0-5.5%) ranges whether gaps were excluded or included.

Continuous exposure to SCH 530348 with impurities for 19 hours in Trial 2 did not induce an increase in mean percentage of aberrant cells when tested up to 100 µg/mL, the highest concentration limited by precipitation and >50% decreases in mitotic index. All values for SCH 530348 with impurities when gaps were included (0-0.5%) or excluded (0%) were within the historical negative (0-2.0%, 0-4.5%) and vehicle control ranges (0-2.5%, 0-5.0%). The structural aberrations found in the SCH 530348 treated cultures were gaps and simple breaks. The mitomycin positive control induced the expected increase in aberrant cells in both trials.

Exposure to SCH 530348 with impurities for 4 hours in the presence of metabolic activation did not induce an increase in mean aberrant cells mean percentage of aberrant cells when tested up to 555 µg/mL in Trial 1 and 500 µg/mL in Trial 2. The maximum concentrations were limited by precipitation. All values for SCH 530348 when gaps were included (0-3.0%) or excluded (0-1.0%) were within the historical negative (0-4.5, 0-3.0%) and vehicle (0-5.0%, 0-3.0%) control ranges. The structural aberrations found in the SCH 530348 treated cultures were gaps and simple breaks. The cyclophosphamide positive control induced the expected increase in aberrant cells in both trials.

SCH 530348 with impurities did not induce chromosome aberrations either in the presence or absence of metabolic activation

Table 74: Reviewer's Compilation from Sponsor's Tables – Study SN 06042

Without Metabolic Activation (Trial 1) – 4-Hour Treatment and 22-Hour Harvest

				# Cells Scored for Aberrations	% Mitotic Index Reduction*	PP & ER # of pp Cells	PP & ER # of er Cells	Chromosome aberrations Totals* -g	Chromosome aberrations Totals* +g
Controls									
Negative:	RPMI 1640		A	100		1	0	0	0
			B	100		0	0	0	0
			Total	200				0	0
			Average	%	--	0.5	0.0	0.0	0.0
Vehicle:	DMSO	10 µL/mL	A	100		1	0	0	0
			B	100		0	0	0	0
			Total	200				0	0
			Average	%	0	0.5	0.0	0.0	0.0
Positive:	MMC	1 µg/mL	A	50		0	0	21	21
			B	50		0	0	15	16
			Total	100				36	37
			Average	%	52	0.0	0.0	36.0	37.0
Test Article		34.7 µg/mL	A	100		0	0	0	2
			B	100		0	0	0	1
			Total	200				0	3
			Average	%	0	0.0	0.0	0.0	1.5
		69.3 µg/mL	A	100		0	0	0	0
			B	100		0	0	0	0
			Total	200				0	0
			Average	%	0	0.0	0.0	0.0	0.0
		139 µg/mL	A	100		0	0	0	0
			B	100		0	0	0	0
			Total	200				0	0
			Average	%	1	0.0	0.0	0.0	0.0
		278 µg/mL	A	100		0	0	1	2
			B	100		0	0	0	0
			Total	200				1	2
			Average	%	27	0.0	0.0	0.5	1.0

A precipitate was observed after dosing at ≥139 µg/mL, at wash at ≥278 µg/mL, and at harvest at 555 µg/mL. The mean % mitotic index was 10% and 9.3% for the negative and vehicle controls, respectively.

Without Metabolic Activation (Trial 2) 19-Hour Treatment, ~ 22-Hour Harvest

				# Cells Scored for Aberrations	% Mitotic Index Reduction*	PP & ER # of pp Cells	PP & ER # of er Cells	Chromosome aberrations Totals* -g	Chromosome aberrations Totals* +g
Controls									
Negative:	RPMI 1640		A	100		1	0	0	1
			B	100		0	0	0	0
			Total	200				0	1
			Average	%	--	0.5	0.0	0.0	0.5
Vehicle:	DMSO	10 µL/mL	A	100		0	0	0	0
			B	100		0	0	0	0
			Total	200				0	0
			Average	%	0	0.0	0.0	0.0	0.0
Positive:	MMC	0.3 µg/mL	A	50		0	0	20	25
			B	50		0	0	16	23
			Total	100				36	48
			Average	%	67	0.0	0.0	36.0	48.0
Test Article		30 µg/mL	A	100		0	0	0	1
			B	100		0	0	0	0
			Total	200				0	1
			Average	%	5	0.0	0.0	0.0	0.5
		45 µg/mL	A	100		0	0	0	1
			B	100		0	0	0	1
			Total	200				0	2
			Average	%	22	0.0	0.0	0.0	1.0
		60 µg/mL	A	100		0	0	0	1
			B	100		0	0	0	1
			Total	200				0	2
			Average	%	38	0.0	0.0	0.0	1.0
		100 µg/mL	A	100		1	0	0	1
			B	100		0	0	0	3
			Total	200				0	4
			Average	%	52	0.5	0.0	0.0	2.0

A precipitate was observed after dosing and at wash at ≥80 µg/mL. The mean % mitotic index was 10.5% and 9.8% for the negative and vehicle controls, respectively

With Metabolic Activation (Trial 1) 4-Hour Treatment, 22-Hour Harvest

				# Cells Scored for Aberrations	% Mitotic Index Reduction*	PP & ER # of pp Cells	PP & ER # of er Cells	aberrations Totals* -g	aberrations Totals* +g
Controls									
Negative:	RPMI 1640		A	100		0	0	0	0
			B	100		0	0	1	1
			Total	200				1	1
			Average	%	--	0.0	0.0	0.5	0.5
Vehicle:	DMSO	10 µL/mL	A	100		0	0	0	1
			B	100		0	0	1	1
			Total	200				1	2
			Average	%	0	0.0	0.0	0.5	1.0
Positive:	CP	25 µg/mL	A	50		0	0	24	26
			B	50		0	0	23	25
			Total	100				47	51
			Average	%	40	0.0	0.0	47.0	51.0
Test Article		34.7 µg/mL	A	100		0	0	0	0
			B	100		0	0	0	1
			Total	200				0	1
			Average	%	0	0.0	0.0	0.0	0.5
		69.3 µg/mL	A	100		0	0	0	2
			B	100		0	0	0	0
			Total	200				0	2
			Average	%	17	0.0	0.0	0.0	1.0
		139 µg/mL	A	100		0	0	0	0
			B	100		0	0	0	0
			Total	200				0	0
			Average	%	19	0.0	0.0	0.0	0.0
		555 µg/mL	A	100		0	0	0	0
			B	100		0	0	0	0
			Total	200				0	0
			Average	%	35	0.0	0.0	0.0	0.0

A precipitate was observed after dosing and at wash at ≥139 µg/mL and at harvest at 555 µg/mL. The mean % mitotic index was 13.3% and 9.6% for the negative and vehicle controls, respectively

With Metabolic Activation (Trial 2) 4-Hour Treatment, 22-Hour Harvest

				# Cells Scored for Aberrations	% Mitotic Index Reduction*	PP & ER # of pp Cells	PP & ER # of er Cells	aberrations Totals* -g	aberrations Totals* +g
Controls									
Negative:	RPMI 1640		A	100		0	0	0	0
			B	100		0	0	0	1
			Total	200				0	1
			Average	%	--	0.0	0.0	0.0	0.5
Vehicle:	DMSO	10 µL/mL	A	100		1	0	2	3
			B	100		0	0	0	3
			Total	200				2	6
			Average	%	0	0.5	0.0	1.0	3.0
Positive:	CP	25 µg/mL	A	50		0	0	17	19
			B	75		0	0	23	25
			Total	125				40	44
			Average	%	72	0.0	0.0	32.0	35.2
Test Article		60 µg/mL	A	100		0	0	1	4
			B	100		0	0	0	4
			Total	200				1	8
			Average	%	16	0.0	0.0	0.5	4.0
		100 µg/mL	A	100		0	0	0	1
			B	100		1	0	0	1
			Total	200				0	2
			Average	%	11	0.5	0.0	0.0	1.0
		250 µg/mL	A	100		0	0	0	0
			B	100		0	0	0	0
			Total	200				0	0
			Average	%	36	0.0	0.0	0.0	0.0
		500 µg/mL	A	100		0	0	1	2
			B	100		2	0	1	2
			Total	200				2	4
			Average	%	49	1.0	0.0	1.0	2.0

A precipitate was observed after dosing at ≥80 µg/mL, at wash at ≥100 µg/mL, and at harvest at 500 µg/mL. The mean % mitotic index was 11.7% and 12.2% for the negative and vehicle controls, respectively

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

7.2 Other Genetic Toxicity Studies

Most of the genotoxicity studies were reviewed with the original submission to IND 71384, although two studies, SN 06068 and SN 06043, were reviewed more recently. The findings of these studies are briefly summarized below and in Table 75.

Exploratory bacterial mutagenicity study of SCH 530348

Study no.: SN 02038 (S-41656)

Review in DARRTS document dated 06/01/05

In one valid assay, SCH 530348 at a maximum dose of 500 µg/plate, limited by precipitation, did not induce excess reverse mutations in six recommended bacterial strains (S. typhimurium TA97a, TA98, TA100, TA102, TA1537 and E. coli WP2 uvrA) in the absence and presence of metabolic activation.

Bacterial Mutagenicity Study of SCH 530348

Study no.: SN 02130

Review in DARRTS document dated 06/01/05

In two valid assays, SCH 530348 at a maximum dose of 1250 µg/plate, limited by precipitation, did not induce excess reverse mutations in five recommended bacterial strains (S. typhimurium TA98, TA100, TA1535, TA1537 or E. coli WP2 uvrA) in the absence and presence of metabolic activation.

Chromosome Aberration Study of SCH 530348 in Human Peripheral Blood Lymphocytes

Study no.: SN 02131

Review in DARRTS document dated 06/01/05

In a valid study, SCH 530348 did not induce excess chromosomal damage in human peripheral lymphocytes following treatment in vitro with doses resulting in precipitation at the highest dose in the presence and absence of S9 metabolic activation.

Mouse Bone Marrow Erythrocyte Micronucleus Study of SCH 530348

Study no.: SN 02149

Review in DARRTS document dated 06/01/05

In one valid assay, SCH 530348 did not increase excess micronucleus formation in rats after 2 days of treatment with a maximum tolerated dose of 250 mg/kg/day. Transient bone marrow toxicity was observed in the high dose males.

Salmonella - Escherichia reverse mutation assay of SCH 530348 in the Presence of solar simulated light

Study number: SN 06068

Review in DARRTS dated: 12/05/12

In two trials, SCH 530348, was not mutagenic either in the presence or in the absence of solar-simulated light in Salmonella typhimurium strains TA1537 and TA102 or in Escherichia coli strain WP2 (pKM101). However, the positive control article, 8-methoxypsoralen (8-mop), increased revertants in the presence, but not in the absence, of solar-simulated light in the TA102 and WP2(pKM101) strains.

Bacterial Mutagenicity Study for SCH 530348 with Impurities

Study number: SN 06043

Review in DARRTS document dated 01/04/13

A batch of SCH 530348 (05-530348-X-302), containing higher levels of impurities, was not mutagenic either in the presence or in the absence of metabolic activation in Salmonella typhimurium strains TA1535, TA97a, TA98, TA100, TA102 or in Escherichia coli strain WP2uvrA in acceptable assays in which the positive control articles induced appropriate increases in revertants.

Table 75: Reviewer's Summary of Genotoxicity Studies with SCH 530348

	In vitro		***In vivo***
Study title	Bacterial Mutagenicity Study of SCH 530348	Chromosome Aberration Study of SCH 530348 in Human Peripheral Blood Lymphocytes	Mouse Bone Marrow Erythrocyte Micronucleus Study of SCH 530348
Study code	**SN 02130**	**SN 02131**	**SN 02149**
Location in N000	Vol 1.22, Tab Ref 10	Vol 1.22, Tab Ref 11	Vol 1.22, Tab Ref 12
Conducting laboratory and location	Schering-Plough Research Institute, Lafayette, NJ	(b) (4)	
Study initiation	2/4/03	1/30/03	12/024/04
GLP/QA	Yes	Yes	Yes
Drug lot/purity	SCH 530348, batch 02-530348-X-004, purity 99.0%	SCH 530348, batch 02-530348-X-004, purity 99.0%	SCH 530348, batch 02-530348-X-004, purity 99.0%
Formulation or vehicle	DMSO	DMSO	0.4% aqueous methylcellulose
Metabolic activation	Yes, induced rat liver S9	Yes, induced rat liver S9	Not applicable – in vivo
Maximum dose	Assay 1, 5000 µg/plate Assay 2: 2500 µg/plate	Assay 1, 1200 µg/mL ±S9 Assay 2: 600 µg/mL ±S9	Two doses of 250 mg/kg/day , based on range finding study
Appropriate replication	Triplicate plates for each dose in two assays	Duplicate cultures for each dose in two assays	6/sex/group.

	In vitro		*In vivo*
Study title	Bacterial Mutagenicity Study of SCH 530348	Chromosome Aberration Study of SCH 530348 in Human Peripheral Blood Lymphocytes	Mouse Bone Marrow Erythrocyte Micronucleus Study of SCH 530348
Study code	**SN 02130**	**SN 02131**	**SN 02149**
Toxicity or exposure	Precipate in both assays +/- S9 at 2500 µg/plate	Precipate in both assays +/- S9 for two highest doses in each assay	No toxicokinetics. Clinical signs (tremors, hypoactivity, irregular respiration and mortality) in 1 mid-dose and two high dose males
Appropriate controls	Yes, with and without S9	Yes, with and without S9	Yes, cyclophosphamide
Study Comments	Five recommended strains.	Without S9; 4 hr exposure in one assay & 19 hr exposure in the other assay. With S9, 4 hr exposure in two assays.	IP administration, while clinical administration is oral. Two timepoints (24 and 48 hr after last dose)
Study result	**Negative**	**Negative**	**Negative**
Study evaluation	Both assays acceptable	Both assays acceptable	Acceptable

8 Carcinogenicity

8.1 104-Week Carcinogenicity Study of SCH 530348 in Rats

Study number: 02143
Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Date of study initiation: 9/2/2005 (Dosing initiated 9/14/2005)
Drug lot/batch number: SCH 530348 (free base):

Batch	Manufacture date (Process)	Purity	Dates of administration
03-530348-X-101	8/4/2003 (S2)	99.2%	9/14/2005 to 4/25/2006
05-530348-X-301	6/7/2005 (C1)	98.5%	4/26/2006 to 9/20/2007

GLP compliance: Yes
QA statement: Yes
CAC Dose Concurrence: Yes. On July 26, 2005, the Executive CAC concurred with the doses of 0, 3, 10, 30 mg/kg/day in a rat carcinogenicity study with the qualification that the free base of SCH 530348 and diet restriction are used as conducted in the 13 and 26 week toxicology studies (Appendix 2).

Key Study Findings

Introduction

Sprague Dawley rats received oral gavage doses of vorapaxar for up to 104 weeks at dosages of 0, 3, 10, and 30 mg/kg/day. Based on similarity of plasma concentrations at 0.5-2 hours post-dose in the carcinogenicity study to plasma concentrations in the 6-

month toxicology study (SN02138), the mean $AUC_{(0-24h)}$ values were estimated to be 2.2, 5.0, and 13.1 µg*hr/mL in males and 3.3, 9.3, and 37.9 µg*hr/mL in females at 3, 10 and 30 mg/kg/day, respectively. Thus, exposure ratios in the high dose male and female rats in the carcinogenicity study are estimated to be 10 and 29 times, respectively, the human exposure at the recommended dose of 2.5 mg once a day.

Summary of Non-neoplastic Findings

The non-neoplastic findings exhibiting a dose relationship included pododermatitis, focal/multi-focal adrenal cortical hyperplasia, vacuolation in the adrenal cortex, pancreatic islet cells, and the pituitary, endocardial hyperplasia in the heart, hemorrhage in the eye and urinary bladder, and atrophy of the testes and ovaries. Across all tissues, total hemorrhages were slightly increased in the treated groups compared to the control groups; however, no dose response was observed in either males or females.

Adequacy of Carcinogenicity Study

The Executive CAC concurred with the doses of 0, 3, 10, and 30 mg/kg/d, where the high dose represents approximately one third of the lethal dose at 100 mg/kg. The study length was acceptable since the rats were treated for at least 104 weeks. No treatment-related effect on mortality was observed. At study end, the high dose males and females had a 10% decrease in mean body weight and a 16-17% decrease in mean body weight gain compared to concurrent controls.

The Executive CAC acceptance of the protocol stipulated that the free base of vorapaxar and diet restriction be used in the cancer bioassay as was used in the 13-week preliminary studies. The sponsor adhered to both stipulations.

Appropriateness of Test Model

The Sprague Dawley rat strain is an appropriate model because this strain is known to be responsive to known carcinogens and historical control data are available. The proposed metabolic pathway of vorapaxar in rat and man is generally similar producing monohydroxylated and amine metabolites. The major human metabolite M20 (monohydroxy-SCH 530348, SCH 2046273) is present at 15% to 24% that of the parent SCH 530348 in human plasma. In contrast, SCH 2046273 is present at low levels in rat plasma (0.3-0.6% in males and 0.03-0.09% in females) compared to the levels in humans. However, the levels of this metabolite are higher in mice (4.3-5.4%).

Summary of Tumor Findings

The high dose males had increased incidences of basal cell tumor of the skin and histiocytic sarcoma; however, the p values for these tumors did not attain the significance level required for the tumors to be considered positive.

The high dose females had increased incidences of hepatocellular adenoma and uterine adenoma. The incidence of uterine adenoma did not have a p-value that attained the significance level required for the tumor to be considered positive. In contrast, the incidence of hepatocellular adenoma in the high dose females was 4-fold above the maximum of the sponsor's historical control range. If hepatocellular adenoma in female rats is considered a rare tumor, then the p values for both the trend test and the pairwise test for this tumor attain the criteria ($p_t<0.025$ and $p_p<0.05$) required for a

rare tumor to be considered positive, but not if hepatocellular adenoma in female rats is considered a common tumor.

Evaluation of Tumor Findings

Although the FDA nonclinical and statistical reviewers concurred with the sponsor that no significant evidence of tumor findings related to SCH 530348 treatment was observed in male Sprague Dawley rats, the FDA nonclinical and statistical reviewers disagreed with the sponsor concerning the evaluation of hepatocellular adenoma in female rats. The sponsor's detailed historical control data indicated the mean incidence of hepatocellular adenoma in female rats is 0.42%. Therefore, hepatocellular adenoma in female rats should be considered a rare tumor for the conducting laboratory. The p values for both the trend test and the pairwise test for hepatocellular adenoma in female rats attained the criteria (p_t<0.025 and p_p<0.05) required for a rare tumor to be considered positive. Therefore, hepatocellular adenoma in female rats was considered a positive finding by the nonclinical and statistical reviewers. However, on October 15, 2013, the Executive CAC concluded that hepatocellular adenoma in female rats is a common tumor, because the incidence of hepatocellular adenoma in the concurrent control group was 1%, the lower threshold for being considered a common tumor (≥1%). The p values for both the trend test and the pairwise test for hepatocellular adenoma in female rats did not attain the criteria (p_t<0.005 and p_p<0.01) required for a common tumor to be considered positive. Therefore, the Executive CAC concluded that there were no drug-related neoplasms in male or female rats in an adequate carcinogenicity study.

Purpose

The carcinogenic potential of SCH 530348 was evaluated in male and female rats following administration of daily oral doses of 3, 10 or 30 mg/kg for at least 104 weeks.

Methods

Doses:	0, 3, 10 or 30 mg/kg/day as indicated in Table 76.
Frequency of dosing:	Once daily for at least 104 weeks
Administration route:	Oral gavage
Dose volume:	5 mL
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Rat (Crl:CD®[SD] (b) (4))
Number/Sex/Group:	50 animals/sex/main group
Age:	Approximately 6 weeks at start of dosing
Weight:	Males: 164 to 216 g, females: 120 to 165 g
Satellite groups:	9 animals/sex/group for toxicokinetics
Unique study design:	1. Two control groups were used. 2. Beginning on Day -7, males were offered 21 g of food daily and females were offered 17 g of food daily.

Deviation from study protocol: Twenty protocol deviations were noted in the report. Of these deviations, ten involved not feeding particular animals or animals having access to more than one food well.

Table 76: Sponsor's Summary of 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 for Toxicity Portion (Weeks)
		Toxicity Portion	Satellite Portion[a]				
C1	Control (Methylcellulose)	50	9	0	5	0	105 or 106
C2	Control (Methylcellulose)	50	0	0	5	0	105 or 106
T1	Low-Dose (SCH 530348)	50	9	3	5	0.6	105 or 106
T2	Mid-Dose (SCH 530348)	50	9	10	5	2	105 or 106
T3	High-Dose (SCH 530348)	50	9	30	5	6	105 or 106

a: These animals were designated for analysis of SCH 530348 plasma concentrations only.

Parameter	**Observation details and times**
Mortality	At least once daily
Clinical observations	At least once on Day -7, the day of randomization and the day of sacrifice; and at least once weekly beginning on the first day of dosing.
Body weight	Day of randomization; weekly from Week -1 through 24; every two weeks from Week 25 through 36; every four weeks thereafter; prior to the first day of necropsy; and at necropsy.
Food consumption	Weekly from Week -1 through 24; every two weeks from Week 25 through 36; every four weeks thereafter; and prior to the first day of necropsy.
Ophthalmoscopy	Examinations using focal illumination and indirect ophthalmoscopy were conducted on all main animals pretest and all surviving main animals during weeks 53 and 103 of dosing.
Hematology	Blood smears were prepared at necropsy, but were not evaluated.
Gross pathology	At the end of treatment, the animals were euthanized using isoflurane followed exsanguination, and subjected to necropsy. The tissues and organs collected and processed from all main animals are summarized in Table 77. The tissues were fixed in 10% neutral buffered formalin, except for the eyes and Harderian glands, which were fixed using 3% glutaraldehyde.

Histopathology	Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections was performed on protocol-designated tissues indicated in Table 77 from all main study animals and unscheduled deaths.
Toxicokinetics	Blood was collected from 3 toxicokinetic animals/timepoint at 0.5, 1, and 2 hours postdose during weeks 4 and 24. Plasma samples were assayed for SCH 530348 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of all dosing formulations, including the control, were collected for concentration determination on the day of preparation for Weeks 1, 12, 24, 36, 48, 60, 72, 84 and 100. Samples for homogeneity were collected from Groups T1 and T3 during Week 1 only.

Table 77: Sponsor's Summary of Tissues Collected

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

a: Collected in 10% neutral buffered formalin unless otherwise indicated
b: Bone marrow smears will be prepared for all toxicity portion rats except those found dead during the morning viability check. Bone marrow smears will be evaluated at the discretion of the Pathologist. Evaluated bone marrow smears will be documented in the raw data and acknowledged by the Study Director.
c: Collected in 3% glutaraldehyde
d: Collected but not processed
e: Examined histopathologically when present in routine section

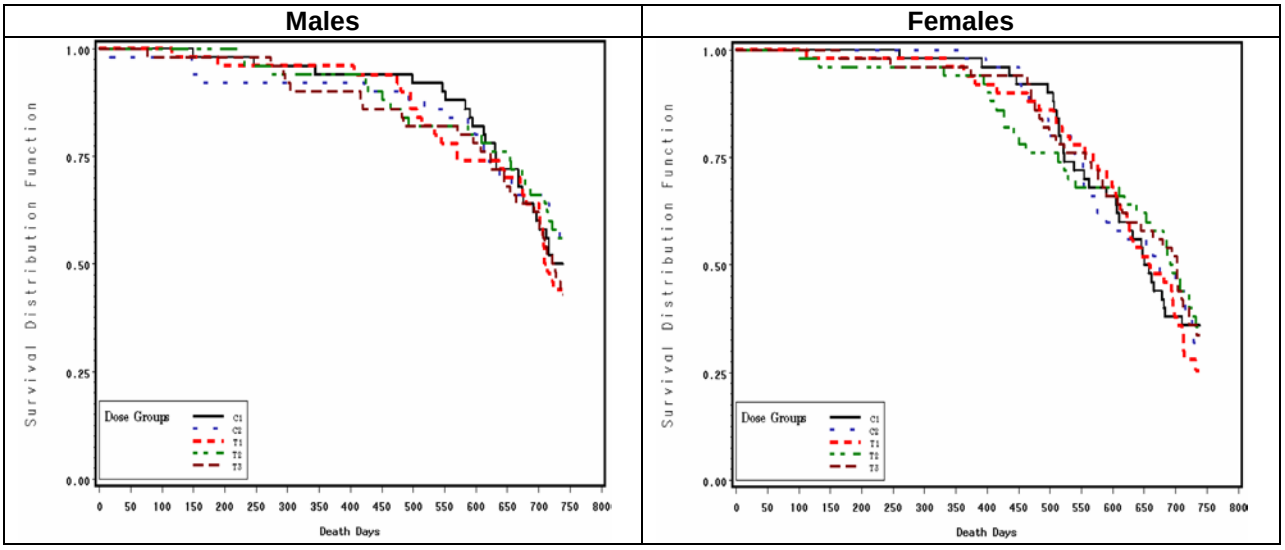
Results

Mortality
Treatment with SCH 530348 did not affect survival or mortality of males or females (Table 78, Figure 23). The pathologist concluded that no cause of death was consistently related to treatment with SCH 530348.

Table 78: Reviewer's Summary of Survival and Mortality

Main animals	Males					Females				
Dose, mg/kg	0	0	3	10	30	0	0	3	10	30
Group	1	2	3	4	5	1	2	3	4	5
Total number/group	50	50	50	50	50	50	50	50	50	50
Number surviving to terminal sacrifice	25	28	22	28	22	18	16	13	18	17
% survival	50	56	44	56	44	36	32	26	36	34
Intercurrent deaths	25	22	28	22	28	32	34	37	32	33
% mortality	50	44	56	44	56	64	68	74	64	66

Figure 23: Sponsor's Kaplan-Meier Survival Graphs



Clinical signs

The pathologist noted necropsy findings related to cage sores. A summary of the group incidences of cage sores as a clinical sign was not provided. The incidences of cage scores in Table 79 are the result of a search of the report Table 5 for the word “cage sores.” The incidences of cage sores were slightly higher in SCH 530348 treated groups relative to concurrent controls.

In performing the above search, the reviewer noted a high incidence of convulsions, particularly in the treated groups. Therefore, an additional search was conducted for the word “convulsion.” Although many of the convulsions occurred during handling, some animals had convulsions in their cages and some had convulsions post-dosing. The number of animals with any convulsion, with convulsion in cage or with convulsion post-dose increased in the SCH 530348 treated groups, particularly the high dose group, relative to concurrent controls. The study director attributed the convulsions to the repeated stress of frequent handling (b) (4) He concluded that the higher incidence of convulsions the mid- and high-dose groups was secondary to the additional stress of SCH 530348 administration and not a SCH 530348-related effect.

Incidence of convulsions reported by [redacted] (b) (4) was 2.3% and 0.7% in female and male Wistar rats. In eleven carcinogenicity studies, Satomoto et al. (2012) reported similar average spontaneous rates of 2.9% and 1.9% in male and female Sprague Dawley rats, respectively.. The maximum incidences were 10% in males and 4.5% in females. Thus, the control incidences in the current carcinogenicity study of 17% and 7% in males and females, respectively, are higher than those reported in the literature. Furthermore, the incidences in the high dose group of 40-42% for any convulsion are higher than the maximum reported by Satomoto et al. (2012).

Additionally, the reviewer notes that 6 µM SCH 530348 inhibited the binding of picrotoxinin to the chloride channel by 58%. Picrotoxinin is a noncompetitive selective antagonist of the $GABA_A$ receptor (Olsen 1982; Macdonald and Olsen 1994), which is a chloride channel that mediates postsynaptic inhibition by allowing chloride ion movement into the postsynaptic neuron resulting in hyperpolarization. Picrotoxinin inhibits $GABA_A$-dependent chloride influx, stimulates the central nervous system, and induces marked convulsive activity. The IC_{50} values for picrotoxinin (0.93 µM) and SCH 530348 differ by less than 6.5-fold. The measured plasma concentrations in the current study were 2.3-3.4 µM in males and 3.3-4.1 µM in females (see Table 89). Therefore, the possibility should not be excluded that the convulsions, particularly post-dose and in the cage, in the high dose animals were facilitated by the interactions of SCH 530348 with the chloride channel.

Table 79: Reviewer's Summary of Clinical Observations

	Males					Females				
Dose, mg/kg	**0**	**0**	**3**	**10**	**30**	**0**	**0**	**3**	**10**	**30**
Number/group	50	50	50	50	50	50	50	50	50	50
# with cage scores	13	19	20	16	26	27	27	23	36	32
# with any convulsion	9	8	12	13	21	4	3	6	11	20
# with convulsions in cage	6	2	6	9	10	2	0	4	4	9
# with convulsions, post-dose	8	7	8	12	16	4	3	4	10	14
Based on Table 5, Clinical Signs: Summary Report										

Body weights

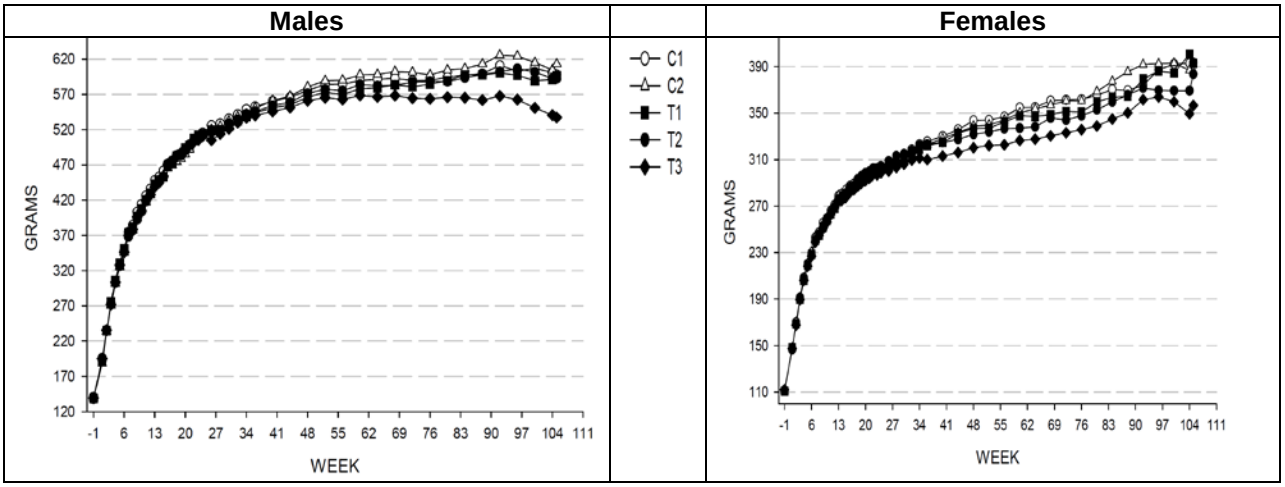
At week 104 of treatment, the high dose males had a 10% decrease in mean body weight and a 16% decrease in mean body weight gain compared to concurrent controls (Table 80). The high dose females had a 10% decrease in mean body weight and a 17% decrease in mean body weight gain compared to concurrent controls. The mid-dose females had a 9% decrease mean body weight gain compared to concurrent controls. These effects on body weight, visualized in the sponsor's body weight graphs (Figure 24), were not accompanied by decreases in food consumption.

Table 80: Reviewer's Summary of Body Weights and Body Weight Gains

Dose/ Group/ Week		Mean body weight[1], gm						Mean body weight gain[2], gm					
		0	0	0	3	10	30	0	0	0	3	10	30
		1	2	Mean 1+2	3	4	5 (% 1+2)	1	2	Mean 1+2	3	4	5 (% 1+2)
Males	1/2[3]	193.1	188.5	190.8	191.8	195.9	195.0 (102)	41.9	45.2	43.56	43.0	39.5	40.6 (93.2)
	13	448.0	441.1	444.6	442.9	441.2	439.1 (98.8)	254.8	252.7	253.8	251.1	245.2	244.1 (96.2)
	26	525.9	520.3	523.1	519.7	516.4	505.0 (96.5)	333.0	332.0	332.5	328.1	320.4	310.1 (93.3)
	40	560.4	561.3	560.8	550.9	554.3	545.9 (97.3	367.5	373.1	370.3	359.2	358.3	350.8 (94.7)
	52	584.2	589.3	586.8	573.0	577.1	565.2 (96.3)	391.2	401.0	396.1	381.3	381.1	370.6 (93.6)
	64	591.5	598.4	595.0	579.5	582.3	566.4 (95.2)	398.5	409.9	404.2	387.8	385.9	371.8 (92.0)
	76	589.9	597.7	593.8	584.9	588.4	566.1 (95.3)	397.1	409.7	403.4	398.0	391.7	369.9 (**91.7**)
	92	611.1	625.8	618.4	600.6	602.1	567.7 **(91.8)**	417.5	439.1	428.3	408.1	405.3	373.6 (**87.2**)
	104	600.9	604.5	602.7	591.3 (98.1)	592.6 (98.3)	540.7 (**89.7**)	406.9	417.4	412.2	399.5 (96.9)	396.3 (96.1)	346.0 (**84.0**)
Females	1/2[3]	193.1	148.0	147.3	148.4	147.5	147.5 (100)	23.3	22.0	22.65	20.3	20.8	20.2 (89.2)
	13	278.7	279.2	279.0	273.9	275.7	274.2 (98.3)	132.1	131.2	131.6	125.5	128.3	126.7 (96.2)
	24	304.8	305.4	305.1	303.1	308.8	300.2 (98.4)	158.2	157.4	157.8	154.8	161.1	152.7 (96.8)
	40	330.1	328.1	329.1	324.7	324.7	313.1 (95.1)	183.4	180.2	181.8	176.4	177.1	162.6(89.4)
	52	344.1	339.9	342.0	337.1	333.9	322.1 (94.2)	197.5	191.9	194.7	188.7	186.2	174.9 (89.8)
	64	355.1	353.7	354.4	347.2	338.2	327.7 (92.5)	208.3	205.8	207.0	198.0	190.0	180.6 (87.2)
	76	361.8	360.6	361.2	351.0	347.7	335.8 (93.0)	215.0	212.5	213.8	201.6	200.1	185.7 (86.9)
	92	374.0	391.9	383.0	379.4	371.6	361.6 (94.4)	228.8	243.8	236.3	237.8	221.6	217.6 (92.1)
	104	393.0	387.0	390	400.6	369.3 (94.6)	349.5 **(89.6)**	247.5	237.9	242.7	253.7	220.9 (91.0)	202.2 **(83.3)**

[1] Data from Table 9, Mean Body Weight Values; [2] Data from Table 10, Mean body Weight Gain Values; (% 1+2) = % mean of 1+2, [3] Week 1 for body weight, Week 2 for body weight gain.

Figure 24: Sponsor's Body Weight Graphs



Food consumption
The males and females in all groups consumed almost all of the 21 gm and 17 gm, respectively, offered daily (Table 81). When food consumption is calculated on a gm/kg/day basis, the high dose males and females had 13% and 14%, respectively, increases in food consumption compared to the concurrent controls.

Table 81: Reviewer's Summary of Food Consumption

Dose/ Group/ Week		Mean food consumed gm/animal/day[1]					Mean food consumed gm/kg/day[1]				
		0	0	3	10	30	0	0	3	10	30
		1	2	3	4	5	1	2	3	4	5
Males	1	21.2	21.4	21.1	21.0	20.7	109.8	113.7	110.4	106.9	106.2
	13	21.0	21.0	20.9	20.9	20.9	46.8	47.6	47.3	47.5	47.6
	26	20.9	21.0	20.9	20.9	20.9	39.9	40.4	40.2	40.5	40.8
	40	20.9	20.9	20.9	20.8	20.8	37.3	37.2	37.7	37.4	38.0
	52	20.9	21.0	20.9	20.9	20.9	35.7	35.7	36.3	35.9	37.1
	64	20.9	21.0	20.9	20.8	20.9	35.3	35.2	35.8	35.2	37.0
	76	20.9	20.8	20.9	20.9	20.9	35.4	34.8	35.9	35.2	37.0
	92	20.9	21.0	20.8	20.9	21.0	34.3	33.3	34.8	34.4	37.1
	104	20.4	20.9	21.0	20.9	20.9	33.6	34.5	35.8	35.2	38.4
Females	1	16.3	16.7	16.5	16.5	16.6	111.7	113.2	111.7	112.2	113.1
	13	16.6	16.5	16.5	16.7	16.6	59.7	59.4	60.3	60.8	60.8
	24	16.5	16.6	16.7	16.6	16.4	54.6	54.2	55.5	53.7	54.5
	40	16.5	16.8	16.9	16.8	16.9	50.1	51.4	52.3	51.8	53.8
	52	16.8	16.9	16.9	16.9	16.9	49.0	49.1	50.5	50.6	52.2
	64	16.9	16.7	16.9	16.9	16.9	47.5	47.5	49.2	50.5	52.0
	76	16.8	16.8	16.9	16.9	16.9	47.1	46.5	48.8	48.4	51.0
	92	16.2	16.9	16.7	16.9	17.0	44.0	43.8	44.2	46.2	47.0
	104	16.9	17.0	17.0	16.4	16.9	43.6	43.8	42.8	45.1	49.9

[1] Data from Table 14, Mean food Consumption Values

Ophthalmology
The veterinary ophthalmologist concluded that no SCH 530348-related findings were noted during the Week 53 and Week 103 ophthalmoscopic examinations.

Gross Pathology

Although the pathologist concluded that no necropsy finding was SCH 530348-related, he did note the slightly higher incidence of cage sores in some SCH 530348 dose groups compared to the concurrent control groups (Table 82). However, cage sores were not considered to be related to SCH 530348 treatment, because the incidences were within historical incidences and are common in rats housed in wire-bottom cages.

Table 82: Sponsor's Summary of Macroscopic Lesions

	Males					Females				
Dose (mg/kg):	0	0	3	10	30	0	0	3	10	30
Organ/Finding	Incidence[a]									
Skin	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- cage sore(s), hindlimb, unilateral	1	0	1	1	2	3	3	1	1	1
- cage sore(s), hindlimb	4	7	13	4	10	5	1	3	7	11
- cage sore(s), hindpaw, unilateral	0	0	0	0	0	0	0	0	0	1
- cage sore(s), hindpaw	2	0	0	1	1	0	0	1	1	0
- cage sore(s), unilateral	2	2	0	5	1	0	6	4	4	2
- cage sore(s)	2	7	5	6	9	7	4	5	13	5
Total[c]	**11**	**16**	**19**	**17**	**23**	**15**	**14**	**14**	**26**	**20**

Histopathology

Neoplastic findings:
The incidences of the tumors in the rat carcinogenicity study that were noted either by the sponsor or the FDA statistician are summarized in Table 83 below. The sponsor's summary of all tumors is presented in Table 84 and Appendix 4. The sponsor's statistical evaluations and historical control ranges are summarized in Appendix 5 and Appendix 6, respectively. The reader is also referred to the FDA statistical review by Dr. Atiar Rahman.

The sponsor's pathologist concluded that no tumor occurrence was related to SCH 530348 treatment and that the incidences of most tumors were similar across all groups. However, the incidences of a few tumors were specifically noted. These included hepatocellular adenoma and uterine adenoma in the high-dose females and basal cell tumors in skin in the high-dose males. The pathologist did not consider the higher incidences of these tumors to be related to SCH 530348 treatment, because the incidences were within the published historical control incidence range for these tumors. The reviewer notes that the pathologist made comparisons to the (b) (4) (b) (4) and the Registry of Industrial Toxicology Animal (RITA, 2008) databases and not the historical control data for the sponsor's laboratory. The sponsor's statistician stated that all evaluated tumors, except malignant fibrous histiocytoma in skin, were considered to be common tumors.

The incidence of hepatocellular adenoma increased in the high dose females (Table 83). The sponsor calculated a p value in the trend test of 0.015 for this tumor, which was considered a common tumor. The sponsor concluded that hepatocellular adenoma in female rats was not a positive finding, because a p value of 0.015 in the trend test did not attain the significance level of $p_t < 0.005$ required for a common tumor to be considered positive.

In contrast, the FDA statistician calculated a p-value of 0.0085 in the trend test and a p value of 0.046 in the pair-wise test for hepatocellular adenoma in female rats. Since the overall incidence of heptaocellular adenoma in the concurrent control female rats was 1%, the FDA statistician concluded that this was a rare tumor based on CDER guidance (2001) that defines a rare tumor as one with a background rate of 1% or less. Because the p-value of 0.0085 in the trend test and a p value of 0.046 in the pair-wise test are below the critical p values of 0.025 and 0.05, respectively according to current CDER guidance (2001), the increased incidence of hepatocellular adenoma in female rats is considered a positive finding. Furthermore, although the incidence of hepatocellular adenoma (8%) in the high dose females is within the control range reported by (b) (4) (0-13%), this incidence is 4-fold above the maximum of the laboratory's historical control range (0-2%). In addition, the laboratory's control range of 0-2% suggests that the mean incidence for hepatocellular adenoma in female rats is less than 1%, based on published ranges and mean incidences (van Ravenzwaay and Tennekes 2002).

The literature indicates that some authors (Tennekes et al. 2004) consider hepatocellular adenoma to be a common tumor, whereas other authors (Keenan et al. 1996) consider hepatocellular adenoma to be a rare tumor. The mean incidence of hepatocellular adenoma was shown to vary up to 20-fold depending upon rat strain (van Ravenzwaay and Tennekes 2002) with the mean incidence generally lower in females than in males. Furthermore, in Sprague Dawley female rats, the mean incidence of hepatocellular adenoma was 0.36-0.48% for two contract research organizations, whereas the mean incidence was 1.1-2.9% for four contract research organizations (van Ravenzwaay and Tennekes 2002). Therefore, the determination of whether hepatocellular adenoma in female rats is considered a rare or common tumor is also highly dependent upon the background incidence in the particular laboratory conducting the study.

The sponsor provided detailed historical control data for hepatocellular tumors upon request. Although the incidence range for hepatocellular adenoma in female rats was 0 to 2%, the mean incidence was 0.42% (Table 85, Appendix 7). Therefore, for the laboratory conducting the study, hepatocellular adenoma in female rats should be considered a rare tumor. The p values for both the trend test and the pairwise test for hepatocellular adenoma in female rats attained the criteria (p_t<0.025 and p_p<0.05) required for a rare tumor. Therefore, hepatocellular adenoma in female rats was considered a positive finding by the nonclinical and statistical reviewers.

The incidence of the rare tumor, basal cell tumor increased in the high dose males (p_t = 0.054). However, the incidence was within the historical control range and the p value in the trend test did not attain the significance level of $p_t < 0.025$ required for a rare tumor to be considered positive.

The incidence of the rare tumor, uterine adenoma, increased in the high dose females. Although the incidence was above the historical control range, neither the p value for the trend test (p_t = 0.043) nor the pairwise test (p_p = 0.115) attained the significance levels ($p_t < 0.025$, $p_p < 0.05$) required for a rare tumor to be considered positive.

The FDA statistical reviewer noted increased incidences of histiocytic sarcoma in some tissues (p_t = 0.038), including large intestine, lungs, prostate, seminal vesicle, stomach

and thymus, of the high dose males. When the incidence of histiocytic sarcoma was combined over all body sites, the combined incidences increased in the mid and high dose males, but the p values for this tumor in the trend and pairwise test did not attain the significance levels required for a common tumor to be considered positive. Furthermore, the incidences in both the mid and high dose groups were within the sponsor's historical control range.

The FDA statistical reviewer also noted increased incidences of parathyroid adenoma in the mid-dose males and pars distalis pituitary adenoma in the mid-dose females. The p values for neither the trend test nor the pairwise test for parathyroid adenoma reached the significance levels required for a common tumor to be considered positive and the incidence was within the sponsor's historical control range. Although the p-value (p_p = 0.008) for the pair-wise test for pars distalis pituitary adenoma in the mid-dose females attained the significance level for this common tumor to be considered positive, the p values for the trend test and the pairwise test for the high dose did not. Furthermore, the incidences even in the mid-dose females were within the historical control range.

On October 15, 2013, the Executive CAC concluded that hepatocellular adenoma in female rats is a common tumor (Appendix 8). The p values for both the trend test and the pairwise test for hepatocellular adenoma in female rats did not attain the criteria (p_t<0.005 and p_p<0.01) required for a common tumor to be considered positive. Therefore, the Executive CAC concluded that there were no drug-related neoplasms in male or female rats in an adequate carcinogenicity study.

Table 83: Reviewer's Summary of Notable Neoplastic Findings

Rat Carcinogenicity Study		SCH 530348 Dose (mg/kg/day)							
Neoplastic findings		Male				Female			
All animals		0	3	10	30	0	3	10	30
Organ/Tissue Finding #/group		100	50	50	50	100	50	50	50
Liver (Mean rate 2, 1.6%)	# E	100	50	50	50	100	50	50	**50**
Hepatocellular adenoma (B)	#	0	1	3	1	1	0	1	4
[M: 0-8% (0-8%);	%	0	2	6	2	1	0	2	**8**
F: 0-2% (0-13%)]									
Peto-Pike trend test, p-value					0.085				**0.015**
Skin (Mean rate 0.5%)	# E	100	50	50	**50**	100	50	50	50
Basal cell tumor (B)	#	0	1	1	**2**	0	0	0	0
[M: 0-4% (0-4%);	%	0	2	2	**4**	0	0	0	0
F: 0-0% (0-1.7%)]									
Peto-Pike trend test, p-value					**0.054**				-
Uterus (Mean rate 0.13%)	# E					100	50	50	**50**
Adenoma (B)	#					0	0	0	**2**
[F: 0-2% (0-1.9%)]	%					0	0	0	**4**
Peto-Pike trend test, p-value									**0.043**
Primary Site Undetermined	# E	100	50	50	**50**	100	50	50	50
Histiocytic sarcoma (M)	#	1	1	3	**2**	1	1	1	1
[M: 2-12% (0-6%);	%	1	2	6	**4**	1	2	2	2
F: 0-6% (0-3%)]									
Peto-Pike trend test, p-value					**0.090**				na

One-Sided Exact Fisher Test, p ≤ 0.05, † Values for individual control groups
[Historical control ranges based on carcinogenicity studies conducted between 1999 and 2008 at Schering-Plough Research Institute, Lafayette, NJ (historical control ranges from (b) (4); 2004)]

Table 84: Sponsor's Table Summarizing Neoplastic Findings

Incidental Neoplastic Findings According to Tissue or Organ of Origin										
Sex:	Males					Females				
Dose (mg/kg):	0	0	3	10	30	0	0	3	10	30
Organ/Finding	Incidence[a]									

APPEARS THIS WAY ON ORIGINAL

Incidental Neoplastic Findings According to Tissue or Organ of Origin										
Sex:	Males					Females				
Dose (mg/kg):	0	0	3	10	30	0	0	3	10	30
Organ/Finding	Incidence[a]									

APPEARS THIS WAY ON ORIGINAL

Incidental Neoplastic Findings According to Tissue or Organ of Origin										
Sex:	Males					Females				
Dose (mg/kg):	0	0	3	10	30	0	0	3	10	30
Organ/Finding	Incidence[a]									
Thyroid Gland	(49)	(48)	(49)	(48)	(50)	(50)	(49)	(50)	(50)	(50)
- follicular cell carcinoma [M]							1	1		
- follicular cell adenoma [B]		1	3		1					1
- C-cell carcinoma [M]						1			1	
- C-cell adenoma [B]	8	6	6	2	3	3	3	3	7	2
Urinary Bladder	(50)	(50)	(47)	(50)	(49)	(50)	(50)	(50)	(50)	(50)
- transitional cell papilloma [B]				1						
Uterus						(50)	(50)	(50)	(50)	(50)
- endometrial stromal polyp [B]						2	3	3	4	4
- granular cell tumor [B]								1		
- endometrial stromal sarcoma [M]						1	3		3	2
- leiomyosarcoma [M]									1	
- hemangioma [B]							1			
- adenoma [B]										2
Vagina						(50)	(50)	(50)	(50)	(50)
- polyp [B]								1		
Primary Site Undetermined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- histiocytic sarcoma [M]		1	1	3	2		1	1	1	1
- lymphoma [M]									1	1
- large granular-cell lymphoma [M]			1							
- squamous cell carcinoma [M]		1								
- fibrosarcoma [M]								1		
- adenocarcinoma [M]								1		
- mesothelioma [M]					1					
- lipoma [B]				1						

[B] = Benign tumor; [M] = Malignant tumor

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

b: ( ) = Number examined microscopically.

Table 85: Reviewer's Summary - Historical Control Data for Lafayette, NJ – Hepatocellular Tumors in Female Rats

				Hepatocellular adenoma		Hepatocellular carcinoma	
Study Number	**Date**	**Feeding regimen**	**# animals**	**# with tumor**	**% with tumor**	**# with tumor**	**% with tumor**
SN 01304	2008	DR†	100	0	0	0	0
SN 00261	2005	DR	100	2	2	0	0
SN 00121	2005	DR	100	0	0	0	0
SN 96459	2000	DR	100	0	0	0	0
SN 95088	1999	DR	100	0	0	0	0
SN 00065	2002	Ad lib	50	0	0	0	0
		DR	200	1	0.5	0	0
SN 99328	2001	Ad lib	50	0	0	0	0
		DR	150	1	0.67	0	0
Summary							
		DR	850	4	0.47	0	0
		Ad lib	100	0	0	0	0
		All studies	950	4	0.42	0	0

† DR = Diet restricted

Non-neoplastic findings
The pathologist concluded that no SCH 530348-related non-neoplastic changes occurred in this study.

Although the high-dose males had a higher incidence of pododermatitis that correlated with macroscopic observations related to cage sores, the pathologist concluded the increased incidence was not related to SCH 530348 administration because the incidences were within the historical control incidence in similar studies at this facility. However, the reviewer notes that the severity of pododermatitis was increased in the high dose males (Table 86).

The pathologist also noted the higher incidence of adrenal gland diffuse cortical hyperplasia in the mid- and high-dose groups. However, the finding was considered incidental because of the low incidence and the lack of a SCH 530348 dose related increase in adrenal gland tumors. However, the reviewer also noted an increased incidence of focal/multi-focal adrenal cortical hyperplasia, particularly in the males.

The reviewer also noted an increased incidence of vacuolation of the adrenal cortex in the mid and high dose males along with vacuolation in pancreatic islet cells and the pituitary. However vacuolation in the liver was not increased in SCH 530348 treated groups. Additionally, vacuolation was not found in the eyes (Table 87).

An increased incidence of atrophy of the testes and ovaries was observed in the high dose males and female, respectively. Endocardial hyperplasia in the heart was observed in the mid and high dose groups, but not the control groups.

The reviewer also noted increased incidences of hemorrhage in the eye and urinary bladder in the high dose males (Table 88). Across all tissues, hemorrhage was slightly increased in the treated groups compared to the control groups; however, no dose response was observed in either males or females.

Table 86: Reviewer's Summary of Notable Non-Neoplastic Findings

Rat Carcinogenicity Study		SCH 530348 Dose (mg/kg/day)							
Non-neoplastic findings		Male				Female			
All animals		0	3	10	30	0	3	10	30
Organ/Tissue Finding #/group		100	50	50	50	100	50	50	50
Adrenal gland, vacuolation, cortex	E	100	50	50	50	100	50	50	50
	#	34	18	22	27	5	6	4	6
	%	**34**	**36**	**44**	**54**	**5**	**12**	**8**	**12**
Minimal	#	16	9	12	6	2	2	1	3
Mild	#	16	8	8	21	3	4	2	2
moderate	#	2	1	2	0	0	0	1	2
Adrenal gland, hyperplasia	E	99	50	50	50	100	50	50	50
Total	#	16	6	15	19	22	12	11	14
	%	**16**	**12**	**30**	**38**	**22**	**24**	**22**	**28**
Cortex, Focal/multifocal	#	12	6	14	14	22	10	10	13
	%	**12**	**12**	**28**	**28**	**22**	**20**	**20**	**26**
Cortex, Diffuse	#	0	0	1	3	0	0	1	1
	%	**0**	**0**	**2**	**6**	**0**	**0**	**2**	**2**
Cortex	#	4	0	0	2	0	2	0	0
	%	**8**	**0**	**0**	**4**	**0**	**4**	**0**	**0**
Heart, hyperplasia endocardial	E	100	50	50	50	100	50	50	50
	#	0	0	2	1	0	0	1	1
	%	**0**	**0**	**4**	**2**	**0**	**0**	**2**	**2**
Ovary, atrophy	E	-	-	-	-	100	50	49	50
	#	-	-	-	-	48	28	31	37
	%	-	-	-	-	**48**	**56**	**62**	**74**
Liver, heptocellular vacuolation	E	100	50	50	50	100	50	50	50
	#	11	5	5	6	26	8	7	6
	%	**11**	**10**	**10**	**12**	**26**	**16**	**14**	**12**
Pancreas, islet cell vacuolation	E	100	50	50	50	100	50	50	50
	#	0	0	0	1	0	0	0	0
	%	**0**	**0**	**0**	**2**	**0**	**0**	**0**	**0**
Pituitary gland, vacuolation	E	100	50	50	50	100	50	50	50
	#	0	0	0	1	0	0	0	0
	%	**0**	**0**	**0**	**2**	**0**	**0**	**0**	**0**
Skin, pododermititis	E	100	50	50	50	100	50	50	50
	#	21	15	16	21	19	11	18	13
	%	**21**	**30**	**32**	**42**	**19**	**22**	**36**	**26**
Minimal	#	0	0	0	0	2	0	3	2
Mild	#	2	2	5	1	9	6	6	6
Moderate	#	12	8	6	9	7	2	6	4
Severe	#	7	5	5	11	1	3	3	1
Testes, atrophy, tubular	E	100	50	50	49	-	-	-	-
	#	7	2	4	6	-	-	-	-
	%	**7**	**4**	**8**	**12**	-	-	-	-

E = number evaluated, # = number of animals with finding, % = percentage of animals with finding

Table 87: Sponsor's Table – Histopathology in the Eye

		Incidence of Findings									
		Males					Females				
FINDINGS	TREATMENT	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3
EYES		(47)	(49)	(45)	(47)	(49)	(48)	(46)	(44)	(47)	(47)
Not Remarkable		46	42	44	43	40	48	43	44	46	46
Fold(s).											
minimal		1									
Ulcer, cornea.											
severe			1								
Mineralization.											
moderate					1						
Keratitis.											
severe						2					
Inflammation, acute.											
severe						1					
Inflammation, cornea.											
minimal						1					
mild				1		1					
Hemorrhage(s).											
moderate					2	1					
Cataract(s).											
minimal					1						
mild								1			
moderate			3			1					
severe			1			1					
Atrophy, retina.											
mild					1	2		2			1
moderate			2		2					1	

Table 88: Reviewer's Summary of Hemorrhage across All Tissues

Rat Carcinogenicity Study		SCH 530348 Dose (mg/kg/day)							
		Male				Female			
Hemorrhage in Various Tissues		0	3	10	30	0	3	10	30
Organ/Tissue Finding #/group		100	50	50	50	100	50	50	50
Adrenal gland,									
hemorrhage, focal/multi-focal	minimal	0	1	1	0	0	0	0	2
	mild	0	1	0	0	2	2	2	1
	moderate	0	1	0	0	0	0	0	1
hemorrhage, diffuse	mild	0	0	0	0	1	1	1	0
	moderate	0	0	0	0	1	0	1	0
Bone marrow, hemorrhage,	mild	1	2	0	0	0	0	0	2
Brain, hemorrhage,	minimal	0	0	0	0	2	0	0	0
	mild	0	0	0	0	0	0	1	0
	moderate	0	0	0	0	1	0	1	0
Esophagus, hemorrhage, focal/multi-focal,	minimal	0	0	2	1	0	0	1	0
	mild	1	1	0	0	0	0	0	1
Eye, hemorrhage		0	0	2	1	0	0	0	0
Kidney, hemorrhage,	mild	0	2	0	0	0	0	0	0
Liver, hemorrhage, focal/multi-focal,	minimal	0	0	0	0	1	0	0	0
	mild	0	0	0	1	1	0	0	0
	moderate	0	1	0	0	0	0	0	1
Lungs, hemorrhage, focal/multi-focal,	minimal	0	1	2	0	0	0	0	0
	mild	0	0	1	1	0	2	1	1
	moderate	0	0	0	1	0	1	0	0
Mandibular lymph node, hemorrhage,	minimal	0	0	1	0	0	0	0	0
Ovaries, hemorrhage, focal/multi-focal,	minimal	0	0	0	0	1	0	1	0
Prostate, hemorrhage,	mild	0	0	0	1	0	0	0	0
	moderate	0	0	1	1	0	0	0	0

Rat Carcinogenicity Study		SCH 530348 Dose (mg/kg/day)							
		Male				Female			
Hemorrhage in Various Tissues		0	3	10	30	0	3	10	30
Organ/Tissue Finding #/group		100	50	50	50	100	50	50	50
Salivary glands, focal/multi-focal,	mild	1	0	0	0	0	0	0	0
Seminal vesicles, hemorrhages,	mild	0	0	0	2	0	0	0	0
	moderate	0	0	1	0	0	0	0	0
Small intestine, hemorrhages,	moderate	0	0	1	0	0	0	0	0
Spleen, hemorrhages, focal/multi-focal,	mild	0	0	0	0	0	1	0	0
Stomach, hemorrhages focal/multi-focal,	minimal	0	0	0	0	0	0	1	0
Testes, hemorrhages,	mild	1	0	0	0	0	0	0	0
Thymus, hemorrhages focal/multi-focal,	minimal	2	3	0	2	0	0	2	0
	mild	1	3	1	0	1	1	0	2
Urinary bladder, hemorrhages,	minimal	0	0	0	1	0	0	0	0
	mild	0	0	1	0	0	0	0	0
	moderate	0	0	0	1	0	0	0	0
	severe	0	0	0	1	0	0	0	0
Uterus, hemorrhages,	minimal	0	0	0	0	1	0	0	0
	mild	0	0	0	0	0	1	0	0
Vagina, hemorrhages,	mild	0	0	0	0	0	1	0	0
Larynx, hemorrhage, focal/multi-focal,	mild	0	0	0	1	1	0	0	0
Pharnyx, hemorrhage, focal/multi-focal,	mild	0	1	0	0	0	0	1	0
Ureter, hemorrhages,	mild	0	0	1	0	0	0	0	0
Uterus, hemorrhages,	minimal	0	0	0	0	1	0	0	0
	mild	0	0	0	0	0	1	0	0
All incidences of hemorrhage across all tissues	#	7	17	15	15	14	11	13	11
	%	7	34	30	30	14	22	16	22

Toxicokinetics

The sponsor only evaluated plasma concentrations of SCH 530348 at three timepoints following dose administration on Days 27 and 167 (Table 89). At least one of the measured concentrations was similar to or greater than the Cmax found in study SN02138, a six month toxicity and toxicokinetic study of SCH 530348 in rats. Therefore, the exposures ($AUC_{(0-24)}$) found in the six-month study can be used in estimating animal:human exposure comparisons. Based on a steady state ($AUC_{(0-24)}$ of 1320 ng*hr/mL following repeated administration of 2.5 mg doses to humans, the animal to human exposure ratios for the high dose of 30 mg/kg are at least 10 and 29 for male and female rats, respectively.

Table 89: Reviewer's Summary of Toxicokinetic Data

Study	Study Day	Hour post dose	Plasma concentration SCH 530348, ng/mL (SD) Males Dose, mg/kg 3	10	30	Females Dose, mg/kg 3	10	30
SN2143	27	0.5	61.5 (12.9)	650.0 (329.1)	782.0 (108.5)	209.0 (48.7)	708.3 (324.2)	2040.0 (194.7)
		1	379.0 (35.6)	1280.0 (166.4)	1990.0 (455.7)	341.3 (91.1)	922.0 (212.7)	1936.7 (223.0)
		2	255.7 (48.2)	675.7 (146.6)	1682.0 (687.8)	374.3 (117.4)	928.7 (109.3)	2336.7 (431.3)
	167	0.5	248.3 (29.5)	371.7 (149.5)	897.0 (538.5)	774.7 (190.0)	1280.0 (323.6)	2430.0 (919.9)
		1	167.0 (17.3)	1000.7 (409.3)	1362.3 (631.0)	224.3 (57.2)	1230.0 (112.7)	2363.3 (600.1)
		2	165.0 (24.0)	619.0 (259.0)	1029.7 (151.1)	279.0 (126.7)	1137.0 (272.8)	2423.3 (859.8)
SN02138	164	Cmax	404	769	1580	438	1090	2480
		Tmax	1	1	1	1	1	1
		$AUC_{(0-24)}$	2250	5000	13100	3310	9310	37900

Cmax = ng/mL; $AUC_{(0-24)}$ = ng*hr/mL)

Formulation analysis:
The formulations were considered homogenous since the recoveries for individual replicates were between 96.2% and 100% of nominal. All SCH 530348 formulations throughout the study were within 97.2% to 106% of nominal. Analysis of samples stored at room temperature indicated that SCH 530348 was stable in 0.4% (w/v) aqueous methylcellulose at a wide range of concentrations for at least 15 days. No SCH 530348 was detected in the control formulations.

8.2 104-Week Carcinogenicity Study of SCH 530348 in Mice

Study number: 02144
Conducting laboratory and location: Schering-Plough Research Institute (SPRI), Lafayette, NJ
Date of study initiation: 10/26/2005 (Dosing initiated 10/27/2005)
Drug lot/batch number: SCH 530348 (free base):

Batch	Manufacture date (Process)	Purity	Dates of administration
03-530348-X-101	8/4/2003 (S2)	99.2%	11/03/2005 to 8/02/2006
05-530348-X-301	6/7/2005 (C1)	98.5%	8/03/2006 to 10/23/2007

GLP compliance: Yes
QA statement: Yes
CAC Dose Concurrence: Yes. On July 28, 2005, the Executive CAC concurred with the doses of 0, 1, 5, 15 mg/kg/day in a mouse carcinogenicity study based on a mouse to human AUC ratio of at least 25-fold the final human AUC (Appendix 9).

Key Study Findings

Introduction
CD-1 male and female mice received oral gavage doses of 0, 1, 5, and 15 mg/kg/day SCH 530348 for up to 102 or 103 weeks. Based on dose-proportionality of Cmax and AUC values between 5 and 25 mg/kg in a single dose pharmacokinetics study (SN05003), the exposures ($AUC_{(0-24)}$) found in the three-month mouse study (Study SN02142) were used to estimate animal to human exposure comparisons. The exposure ratios in male and female mice at the high dose in the carcinogenicity study are estimated to be 28 and 34 times, respectively, the human exposure ($AUC_{(0-24)}$ of 1320 ng*hr/mL) at the recommended dosage of 2.5 mg once a day.

Summary of Non-neoplastic Findings
No significant non-neoplastic findings were observed.

Adequacy of Carcinogenicity Study
The Executive CAC concurred with the doses of 0, 1, 5, and 15 mg/kg/d as long as the mouse to human AUC ratio was at least 25-times the final human AUC. The study length was acceptable since the mice were treated for at least 102 weeks. Although SCH 530348 treatment had no statistically significant effect on mortality, the high dose males and females had decreases in body weight gain of 16% and 14%, respectively, during the study.

Appropriateness of Test Model
The CD-1 mouse strain is an appropriate model because this strain is known to be responsive to known carcinogens and historical control data are available. The proposed metabolic pathway of vorapaxar in mice and man is generally similar producing monohydroxylated and amine metabolites. The major human metabolite M20 (monohydroxy-SCH 530348, SCH 2046273) is present at 15% to 24% that of the parent SCH 530348 in human plasma, whereas SCH 2046273 is present at levels of 4.3-5.4% that of SCH 530348 in mouse plasma.

Summary of Tumor Findings
The incidence of bronchiolo-alveolar adenoma increased in the high dose females and the incidence of bronchiolo-alveolar carcinoma increased in the high dose males. However, the p values for each of these tumors and their combination in the trend test did not attain the significance level of $p_t < 0.005$ required for these common tumors to be considered positive.

Evaluation of Tumor Findings
The FDA nonclinical and statistical reviewers concurred with the sponsor that no significant evidence of tumor findings related to SCH 530348 treatment was observed in male and female CD-1 mice.

On October 15, 2013, the Executive CAC concluded that there were no drug-related neoplasms in male or female mice in an adequate carcinogenicity study.

Purpose

The carcinogenic potential of SCH 530348 was evaluated in male and female mice following administration of daily oral doses of 0, 1, 5, 15 mg/kg/day for at least 104 weeks.

Methods

Doses:	0, 1, 5, 15 mg/kg/day as indicated in Table 90 .
Frequency of dosing:	Once daily for at least 102 or 103 weeks
Administration route:	Oral gavage
Dose volume:	5 mL
Formulation/Vehicle:	0.4% (w/v) aqueous methylcellulose
Species/Strain:	Mouse (Crl:CD1®[ICR] (b) (4)
Number/Sex/Group:	50 animals/sex/main group
Age:	Approximately 6 weeks at start of dosing
Weight:	Males: 24.4 to 34.6 g, females: 17.0 to 25.6 g
Satellite groups:	18 animals/sex/group for toxicokinetics
Unique study design:	Two control groups were used.
Deviation from study protocol:	Twenty-one protocol deviations were noted in the report. Of these deviations, the most notable are the following: 1. Dosing of mid dose males 2012M-2033M with the 15 mg/kg formulation instead of the 5 mg/kg formulation. 2. Four instances of eyes being placed into 10% neutral buffered formalin instead of 3% glutaraldehyde. 3. Escape of animals on six instances, one of which resulted in total loss of the animal.

Table 90: Sponsor's Summary of Study Design

104-Week Carcinogenicity Study of SCH 530348 in Mice (SN 02144): **Study Design**

Group	Test/Control Article	No. of Mice/Sex: Toxicity Portion	No. of Mice/Sex: Satellite Portion[a]	Total Daily Dose (mg/kg)	Dose Volume (mL/kg)	Dose Conc. (mg/mL)	Duration of Dosing for Toxicity Portion (Weeks)
C1	Control (Methylcellulose)	50	18	0	5	0	102 or 103[b]
C2	Control (Methylcellulose)	50	0	0	5	0	102 or 103[b]
T1	Low-Dose (SCH 530348)	50	18	1	5	0.2	102 or 103[b]
T2	Mid-Dose (SCH 530348)	50	18	5	5	1	102 or 103[b]
T3	High-Dose (SCH 530348)	50	18	15	5	3	102 or 103[b]

a: These animals were designated for analysis of SCH 530348 plasma concentrations only.
b: Based on mortality percentages (considered incidental), all surviving females were sacrificed during Week 102 or 103 and all surviving males were sacrificed during Week 103.

Parameter	Observation details and times
Mortality	At least once daily
Clinical observations	At least once on Day -7, the day of randomization and the day of sacrifice; and at least once weekly beginning on the first day of dosing.

Body weight	Day of randomization; weekly from Week -1 through 24; every two weeks from Week 25 through 36; every four weeks thereafter; prior to the first day of necropsy; and at necropsy.
Food consumption	Weekly from Week -1 through 24; every two weeks from Week 25 through 36; every four weeks thereafter.
Ophthalmos-copy	Examinations using focal illumination and indirect ophthalmoscopy were conducted on all main animals pretest and all surviving main animals during weeks 51 and 102 of dosing.
Hematology	Blood smears were prepared at necropsy, but were not evaluated.
Gross pathology	At the end of treatment, the animals were euthanized using isoflurane followed exsanguination, and subjected to necropsy. The tissues and organs collected and processed from all main animals are summarized in Table 91 . The tissues were fixed in 10% neutral buffered formalin, except for the eyes and Harderian glands, which were fixed using 3% glutaraldehyde.
Histopathology	Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections was performed on protocol-designated tissues indicated in Table 91 from all main study animals and unscheduled deaths.
Toxicokinetics	Blood was collected from 3 toxicokinetic animals/timepoint at 0.5, 1, and 2 hours postdose during weeks 4 and 24. Plasma samples were assayed for SCH 530348 using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
Formulation analysis	Samples of all dosing formulations, including the control, were collected for confirmation of content on the day of preparation for Weeks 1, 12, 24, 36, 48, 60, 72, 84 and 100. Samples for confirmation of homogeneity were collected from Groups T1 and T3 during Week 1 only.

Table 91: Sponsor's Summary of Tissues Collected

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

a: Collected in 10% neutral buffered formalin unless otherwise indicated
b: Bone marrow smears will be prepared for all toxicity portion mice except those found dead during the morning viability check. Bone marrow smears will be evaluated at the discretion of the Pathologist. Evaluated bone marrow smears will be documented in the raw data and acknowledged by the Study Director.
c: Collected in 3% glutaraldehyde
d: Collected but not processed
e: Examined histopathologically when present in routine section
f: As deemed necessary by the pathologist

Results

Mortality

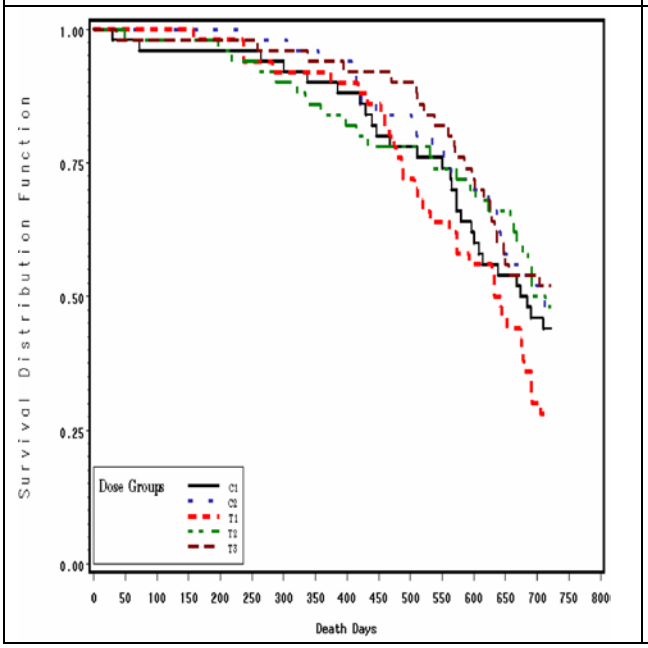
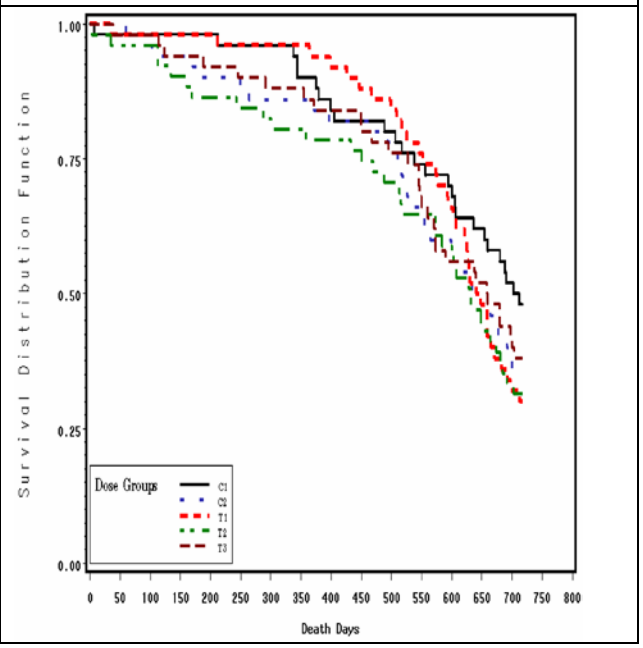
Treatment with SCH 530348 did not significantly affect survival or mortality of males or females (Table 92, Figure 25). The pathologist concluded that no cause of death was consistently related to treatment with SCH 530348.

Table 92: Reviewer's Summary of Survival and Mortality

Main animals	**Males**					**Females**				
Dose, mg/kg	**0**	**0**	**1**	**5**	**15**	**0**	**0**	**1**	**5**	**15**
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Total number/group	50	50	50	50	50	51[a]	50	50	51[a]	50
Number surviving to terminal sacrifice	22	23	14	24	26	24	18	15	16	19
% survival	44	46	28	48	52	48	36	30	32	38
Intercurrent deaths	28	27	36	26	24	26[b]	32	35	35	31
% mortality	56	54	72	52	48	52	64	70	70	62

a: N = 51 animals due to replacement, b: An additional female was missing from its cage and never located.

Figure 25: Sponsor's Kaplan-Meier Survival Graphs

Males	Females
	

Clinical signs
The sponsor concluded that no clinical sign was related to treatment. Unlike the rat carcinogenicity study, the incidence of convulsions was low with 4% of control males, 1% of control females, 2% of high dose male and 2% of high dose females having convulsions.

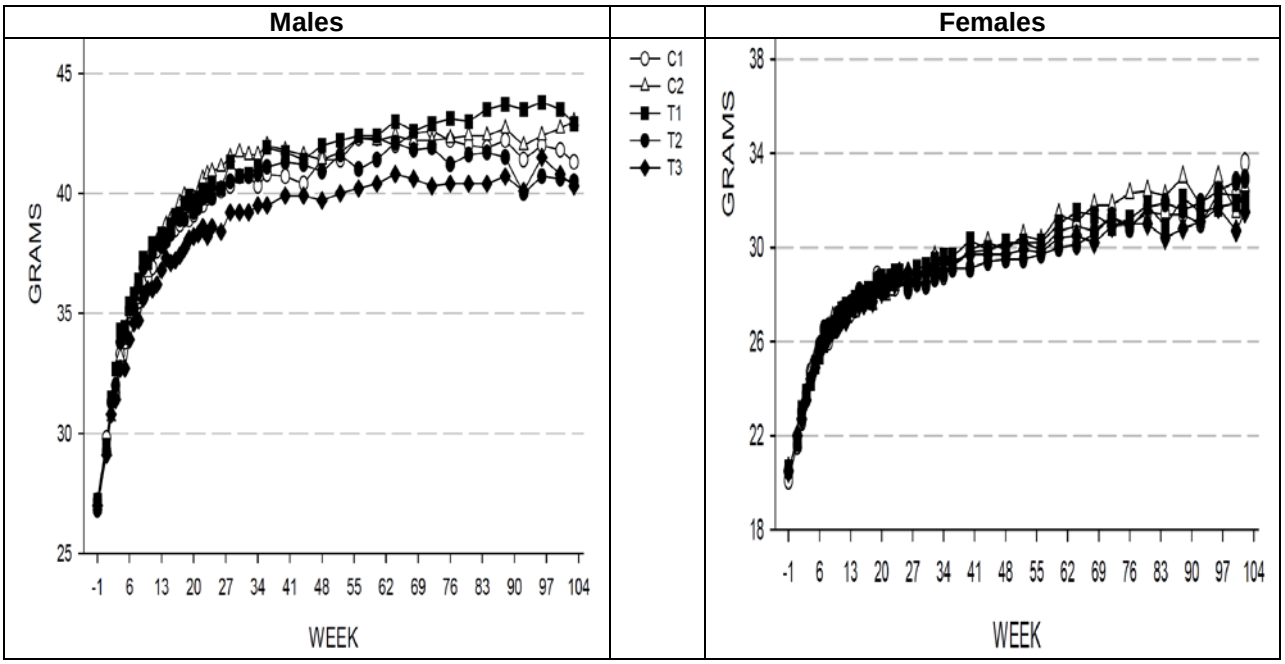
Body weights
At week 103 of treatment, the high dose males had a 4.4% decrease in mean body weight and a 15.7% decrease in mean body weight gain compared to concurrent controls (Table 93). The high dose females had a 4.8% decrease in mean body weight and a 14% decrease in mean body weight gain compared to concurrent controls. The mid-dose males had an 8.7% decrease mean body weight gain compared to concurrent controls. These effects on body weight, visualized in the sponsor's body weight graphs (Figure 26), were not accompanied by decreases in food consumption.

Table 93: Reviewer's Summary of Body Weights and Body Weight Gains

Dose/ Group/ Week		Mean body weight[1], gm						Mean body weight gain[2], gm					
		0 1	0 2	0 Mean 1+2	1 3	5 4	15 5 (% 1+2)	0 1	0 2	0 Mean 1+2	1 3	5 4	15 5 (% 1+2)
Males	1/4[3]	29.8	29.4	29.6	29.5	29.3	29.1	3.4	3.8	3.6	4.7	4.5	3.6
	13	38.2	38.0	38.1	38.3	37.8	36.8	8.4	8.6	8.5	8.8	8.5	7.5
	26	40.1	41.1	40.6	40.2	40.2	38.2	10.3	11.7	11	10.6	10.9	9.2
	40	40.7	41.8	41.3	41.7	41.3	39.9	10.8	12.4	11.6	12.1	12.0	10.7
	52	41.4	41.7	41.6	42.2	41.5	40.0	11.6	12.3	12.0	12.6	12.2	10.8
	64	42.0	42.4	42.2	42.6	41.8	40.3	12.3	13.1	12.7	13.3	12.7	11.6
	76	42.2	42.3	42.3	43.1	41.2	40.4	12.5	13.0	12.8	13.3	11.9	11.2
	92	41.4	42.0	41.7	43.5	40.0	40.1	11.8	12.7	12.3	13.5	10.8	10.8
	100	41.8	42.7	42.3	43.5	40.6 (96.1)	40.8 **(96.6)**	12.0	13.5	12.8	13.5	11.7 (91.8)	11.1 **(87.1)**
	103	41.3	43.0	42.2	42.9	40.5 (96.1)	40.3 **(95.6)**	11.4	14.0	12.7	13.0	11.6 (91.3)	10.7 **(84.3)**
Females	1	21.6	21.7	21.7	21.7	21.9	22.0	3.0	3.0	3.0	2.7	2.4	2.4
	13	27.2	27.3	27.3	27.5	27.6	26.9	5.5	5.7	5.6	6.1	5.7	5.5
	24	28.3	28.4	28.4	28.7	28.2	28.9	6.7	6.9	6.8	7.0	6.4	6.9
	40	29.8	29.9	29.9	30.3	29.1	29.7	8.1	8.3	8.2	8.6	7.3	7.7
	52	30.2	30.5	30.4	30.2	29.5	29.9	8.5	9.0	8.8	8.5	7.6	8.0
	64	30.9	31.1	31.0	31.5	30.1	30.4	9.1	9.4	9.3	9.8	8.2	8.6
	76	30.9	32.3	31.6	31.2	30.8	31.0	9.1	10.6	9.8	9.6	8.9	9.2
	92	31.0	31.8	31.4	31.5	31.9	31.1	9.3	10.2	9.8	10.0	10.1	9.5
	100	32.2	31.5	31.9	31.9	32.9	30.7 **(96.4)**	10.6	10.0	10.3	10.4	10.9	9.1 **(88.4)**
	102	33.6	32.6	33.1	32.0	32.9	31.5 **(95.2)**	11.9	10.9	11.4	10.4	11.1	9.8 **(86.0)**

[1] Data from Table 9, Mean Body Weight Values; [2] Data from Table 10, Mean body Weight Gain Values; (% 1+2) = % mean of 1+2, [3] Week 1 for body weight; Week 4 for body weight gain

Figure 26: Sponsor's Body Weight Graphs



Food consumption
Treatment with SCH 530348 did not reduce the amount of food consumed (Table 94). When food consumption is calculated on a gm/kg/day basis, the high dose males and females had 10% and 9%, respectively, increases in food consumption at week 100 compared to the concurrent controls.

Table 94: Reviewer's Summary of Food Consumption

		Mean food consumed gm/animal/day[1]									
		Males					Females				
Dose/ Group/		0 1	0 2	1 3	5 4	15 5	0 1	0 2	1 3	5 4	15 5
Week	1	5.3	5.4	5.3	5.3	5.3	1	4.7	4.7	4.8	4.8
	13	5.1	5.2	5.2	5.1	5.0	13	4.8	4.9	5.0	4.8
	26	4.9	4.9	5.0	4.9	4.8	24	4.5	4.7	4.8	4.7
	40	4.9	4.8	4.7	4.8	4.7	40	4.5	4.7	4.8	4.6
	52	4.9	4.9	4.9	4.7	4.7	52	4.4	4.7	4.8	4.5
	64	4.5	4.6	4.7	4.6	4.6	64	4.2	4.4	4.5	4.2
	76	4.9	4.9	4.8	4.7	4.7	76	4.3	4.5	4.6	4.5
	92	4.4	4.6	4.9	5.4	4.9	92	4.1	4.1	4.3	4.6
	100	4.3	4.6	4.6	4.4	4.7	100	4.1	4.1	4.2	4.3

[1] Data from Table 13, Mean food Consumption Values

Ophthalmology
The veterinary ophthalmologist concluded that no SCH 530348-related findings were noted during the Week 51 and Week 102 ophthalmoscopic examinations.

Gross Pathology
The pathologist concluded that no necropsy finding was SCH 530348-related.

Histopathology

Neoplastic findings:
The pathologist concluded that no neoplastic finding was related to SCH 530348 treatment and that the incidences of most tumors were similar across all groups. The sponsor's summary of all tumors is presented in Appendix 10. The sponsor's statistical evaluations and historical control ranges are summarized in Appendix 11 and Appendix 12, respectively. The reader is also referred to the FDA statistical review by Dr. Atiar Rahman.

The incidence of bronchiolo-alveolar adenoma increased in the high dose females and the incidence of bronchiolo-alveolar carcinoma increased in the high dose males (Table 95). However, the p values for each of these tumors and their combination in the trend test did not attain the significance level of $p_t < 0.005$ required for these common tumors to be considered positive. Furthermore, the incidences were within either the laboratory's historical control range or the control range reported by (b) (4) The sponsor's summary of neoplastic findings is in Table 96. The Executive CAC concurred that there were no drug-related neoplasms in male or female mice in an adequate carcinogenicity study (Appendix 8).

Table 95: Reviewer's Summary of Notable Neoplasms

Mouse Carcinogenicity Study Neoplastic findings		SCH 530348 Dose (mg/kg/day)							
		Male				Female			
	All animals	0	1	5	15	0	1	5	15
Organ/Tissue Finding	#/group	100	50	50	50	100	50	50	50
Lungs	# E	100	50	50	50	100	50	51	**50**
Bronchiolo-alveolar	#	19	16	12	9	13	6	7	10
adenoma (B)	%	19	32	24	18	13	12	13.7	**20**
[M: 10-30% (8-38%); F: 10-30% (0-16%)]									
Peto-Pike trend test, p-value					0.540				0.116
Bronchiolo-alveolar carcinoma (M)	#	2	1	1	4	4	1	4	0
[M: 6-18% (1.4-20%); F: 4-10% (0-20%)]	%	2	2	2	8	4	2	7.8	0
Peto-Pike trend test, p-value					0.084				0.694
Bronchiolo-alveolar	#	21	17	13	13	17	7	11	10
adenoma plus carcinoma	%	21	34	26	26	17	14	22	20
[M: 16-48% (10-50%); F: 14-40% (0-36%)]									
Peto-Pike trend test, p-value					0.237				0.204

One-Sided Exact Fisher Test, $p \leq 0.05$, † Values for individual control groups
[Historical control ranges based on carcinogenicity studies conducted between 1999 and 2005 at Schering-Plough Research Institute, Lafayette, NJ (historical control ranges from [redacted](b) (4); 2010)]

Table 96: Sponsor's Table Summarizing Neoplastic Findings

Incidental Neoplastic Findings According to Tissue or Organ of Origin

Sex:	Males					Females				
Dose (mg/kg):	0	0	1	5	15	0	0	1	5	15
Organ/Finding	Incidence[a]									
Adrenal Glands	(48)[b]	(50)	(49)	(49)	(49)	(50)	(50)	(50)	(50)	(50)
- subcapsular cell adenoma [B]	2					1	2		1	1
- subcapsular cell carcinoma [M]						1				
- pheochromocytoma [B]								1		
Bone	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
- fibrosarcoma [M]							2			
- osteosarcoma [M]						1				
Brain	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(51)	(50)
- oligodendroglioma [M]		1								
Gallbladder	(41)	(43)	(35)	(44)	(44)	(43)	(42)	(38)	(39)	(43)
- papillary adenoma [B]					1					
Harderian Glands	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(49)	(51)	(50)
- adenoma [B]	8	3	7	3	5	2	2		1	
Kidneys	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
- renal tubule adenoma [B]	1									
Liver	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
- hepatocellular carcinoma [M]		2	1		2					
- hepatocellular adenoma [B]	5	6	7	7	3					1
- hemangiosarcoma [M]			1							
- hemangioma [B]	2		2		1	2	2			1

Incidental Neoplastic Findings According to Tissue or Organ of Origin										
Sex:	Males					Females				
Dose (mg/kg):	0	0	1	5	15	0	0	1	5	15

APPEARS THIS WAY ON ORIGINAL

Incidental Neoplastic Findings According to Tissue or Organ of Origin

Sex:	Males					Females				
Dose (mg/kg):	0	0	1	5	15	0	0	1	5	15
Uterus						(50)	(50)	(50)	(51)	(50)
- endometrial stromal polyp [B]						1	1	1		
- granular cell tumor [M]							1			
- leiomyosarcoma [M]						2		1	2	1
- leiomyoma [B]						5	2	3	4	3
- hemangioma [B]						1	1	1	1	1
- fibroma [B]									1	
- carcinoma [M]									1	
- adenocarcinoma [M]							1			
Vagina						(50)	(49)	(50)	(50)	(49)
- fibrosarcoma [M]							1			
Primary Site Undetermined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
- lymphoma [M]	6	7	8	6	4	13	11	17	14	13
- histiocytic sarcoma [M]		1								1
- mast cell tumor [M]				1						

[B] = Benign tumor; [M] = Malignant tumor
a: Incidence = Number affected. The absence of a numeral indicates that the specified finding was not present in that group.
b: ( ) = Number examined microscopically.

Non-neoplastic findings
The pathologist concluded that no SCH 530348-related non-neoplastic changes were observed. Vacuolation was not found in the eyes (Table 97).

The incidence of hemorrhage was comparable in the control and SCH 530348 treated groups across all tissues. The lungs had the highest incidence of hemorrhage. Table 98 shows that hemorrhage in the lung was comparable across groups.

The incidence of hyperplasia was comparable in the control and SCH 530348 treated groups (Table 99). Mucosal hyperplasia in the urinary bladder and ureters, previously reported in the 3-month mouse study, was observed at a similar incidence in control and treated groups in the carcinogenicity study.

Table 97: Sponsor's Table – Histopathology in the Eye

		Incidence of Findings									
		Males					Females				
FINDINGS	TREATMENT	0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3	0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3
EYES		(47)	(48)	(45)	(46)	(47)	(48)	(45)	(43)	(43)	(47)
Not Remarkable		33	42	40	38	37	38	38	31	37	37
Cellular infiltration, cornea, unilateral.											
minimal		1		1						1	
mild			1								
Rupture, cornea.											
minimal								1			
Uveitis, acute, unilateral.											
minimal						2					1
mild			1			1					
moderate									1		
Retinitis, chronic, focal.											
minimal						1					
Mineralization, iris, focal.											
minimal		4	1		2	2	2				
Mineralization, cornea, unilateral.											
minimal		2	2		2	1	1	1	1		3
mild		1				1					
LYMPHOMA [M], metastatic site.		3	3	3	4	1	5	2	8	5	5
LEIOMYOSARCOMA [M], metastatic site.										1	
Keratitis, acute, ulcerative.											
mild						1					
moderate		1						1			
Keratitis, acute.											
minimal		1									
Keratitis, mononuclear cell, unilateral.											
minimal						2					1
mild		1									
Hypertrophy, cornea.											
mild		1									
Hyperplasia, corneal stroma.											
mild				1							
Cataract(s), unilateral.											
minimal							2	2			
mild						1					
Cataract(s).											
mild									1		
Blepharitis, acute, ulcerative.											
mild											1
moderate									1		

Table 98: Sponsor's Table – Hemorrhage in the Lungs

		Incidence of Findings									
		Males					Females				
FINDINGS	TREATMENT	0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3	0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3
LUNGS		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
Hemorrhage(s), focal/multifocal.											
minimal		2			1	2	1	1		1	1
mild							1		1	1	
severe						1					
Hemorrhage(s), multifocal, periarteriolar.											
minimal				1							
mild										1	
moderate				1							

Table 99: Sponsor's Table of Selected Hyperplastic Changes

	Males					Females				
Dose (mg/kg):	0	0	1	5	15	0	0	1	5	15
Organ/Finding/Severity	Incidence[a]									
Ureters	(47)	(47)	(45)	(47)	(49)	(48)	(46)	(48)	(47)	(48)
- hyperplasia, mucosal[c]										
minimal			1		2	1				1
mild	3			1		1	1			
moderate	1									

a: Incidence = Number affected. The absence of a numeral indicates that the specified finding was not present in that group.
b: ( ) = Number examined microscopically.
c: Unilateral and bilateral combined.

APPEARS THIS WAY ON ORIGINAL

Toxicokinetics

The sponsor only evaluated plasma concentrations of SCH 530348 at three timepoints following dose administration on Days 27 and 167 (Table 100). The measured

concentrations for the high dose were comparable to concentrations (3534, 4404 ng/ml) that one would expect for a 15 mg/kg dose based on the Cmax values for the dose of 25 mg/kg found in study SN02142 and the doses of 5 and 25 mg/kg in Study SN05003. Since the Cmax and AUC values in Study SN05003 were approximately dose-proportional, the exposures ($AUC_{(0-24)}$) for the 25 mg/kg dose found in Study SN02142 can be multiplied by a factor of 0.6 to estimate animal to human exposure comparisons. Based on a steady state $AUC_{(0-24)}$ of 1320 ng*hr/mL following repeated administration of 2.5 mg doses to humans, the animal to human exposure ratios for the high dose of 15 mg/kg are at least 28- and 34-fold for male and female mice, respectively.

Table 100: Reviewer's Summary of Toxicokinetic Data

Study	Study Day	Hour post dose		Plasma concentration SCH 530348, ng/mL Males Dose, mg/kg 1	5	15	Females Dose, mg/kg 1	5	15
SN2144	27	0.5	Mean	229.0	1173.7	3390.0	222.3	1233.3	5246.7
			SD	54.1	296.8	1654.6	77.7	225.0	1353.0
		1	Mean	172.3	791.5	3383.3	203.5	1270.0	4473.3
			SD	13.5	147.8	466.1	4.9	254.6	480.9
		2	Mean	146.2	862.3	2366.0	187.3	1360.0	4006.7
			SD	42.6	372.0	1467.9	12.0	70.0	237.6
	167	0.5	Mean	281.3	2010.0	3920.0	401.3	1337.0	3783.3
			SD	94.3	329.1	2049.1	109.8	378.2	2806.3
		1	Mean	215.0	1280.0	5080.0	335.0	1486.7	4226.7
			SD	121.9	111.4	445.3	84.8	398.0	1685.6
		2	Mean	163.3	1090.0	3880.0	242.0	1226.7	4286.7
			SD	28.0	365.1	173.2	22.6	153.1	828.5
SN02142		**Dose**		**25**	**75**	**150**	**25**	**75**	**150**
	57	Cmax		5890	10800	32100	7340	14000	30300
		Tmax		1	4	1	1	1	1
		$AUC_{(0-24)}$		61000	171000	571000	75800	196000	490000
SN05003		**Dose**		**5**	**25**	**75**			
	1	Cmax		1170	5365	13000			
		Tmax		1.5	1	1.5			
		$AUC_{(0-24)}$		10045	56050	159500			

Cmax = ng/mL; $AUC_{(0-24)}$ = ng*hr/mL)

Formulation analysis:
The formulations were considered homogenous since the recoveries for individual replicates were between 99.0% and 104% of nominal. All SCH 530348 formulations throughout the study were within 96.5% to 115% of nominal. Analysis of samples stored at room temperature indicated that SCH 530348 was stable in 0.4% (w/v) aqueous methylcellulose at a wide range of concentrations for at least 15 days. No SCH 530348 was detected in the control formulations.

9 Reproductive and Developmental Toxicology

Study reports for the reproductive and developmental studies using oral gavage administration (Fertility and Early Embryo Development [FEED] in rats, Embryo-Fetal Development [EFD] in rats and rabbits, and Pre-/Postnatal Development [PPND] in rats) were previously reviewed under IND 71384 (Table 101). The full reviews of these studies, summarized in Table 102, can be found in DARRTS.

Table 101: Overview of Reproductive and Developmental Studies

Study number	Study	SCH-530848 Lot number	GLP	IND 71384 review date in DARRTS
SN 02134	Pilot Fertility and Early Embryonic Developmental Toxicity Study of SCH 530348 Administered Orally by Gavage in Rats	02-530348-X-004	No	6/7/2005
SN 02145	Fertility and Early Embryonic Developmental Toxicity Study of SCH 530348 Administered Orally by Gavage in Rats	02-530348-X-004	Yes	6/7/2005
SN 02135	Pilot embryo-fetal developmental toxicity study of SCH 530348 administered orally by gavage in rats	02-530348-X-004	No	6/7/2005
SN 02146	Embryo-Fetal Developmental Toxicity Study of SCH 530348 Administered Orally by Gavage in Rats	02-530348-X-004	Yes	6/7/2005
SN 02136	Dose Range-Finding and Pilot Embryo-Fetal Developmental Toxicity Study of SCH 530348 Administered Orally by Gavage in Rabbits	02-530348-X-004	No	6/7/2005
SN 02147	Embryo-fetal developmental toxicity and toxicokinetic study of SCH 530348 administered orally by gavage in pregnant rabbits	02-530348-X-004	Yes	6/7/2005
SN 02148	A Prenatal and Postnatal Developmental Toxicity and Maternal Function Study of SCH 530348 Administered Orally by Gavage in Rats	05-530348-X-301	Yes	5/7/2013
SN 07358	Cross Fostering Study of SCH 530348 Administered Orally by Gavage in Rats	05-530348-X-301	Yes	5/7/2013

Table 102: Reviewer's Summary of Previously Reviewed FEED and EFD Studies

Study	FEED - Rat	FEED - Rat	EFD - Rat	EFD - Rat	EFD - Rabbit	EFD - Rabbit
Species	Rat	Rat	Rat	Rat	Rabbit	Rabbit
Study code	SN 02134	SN 02145	SN 02135	SN 02146	SN 02136	SN 02147
Conducting lab and location	Schering-Plough Research Institute, Lafayette, NJ	Schering-Plough Research Institute, Lafayette, NJ	Schering-Plough Research Institute, Lafayette, NJ	Schering-Plough Research Institute, Lafayette, NJ	Schering-Plough Research Institute, Lafayette, NJ	(b) (4)
Study initiation	1/22/2003	4/11/2003	1/7/2003	4/11/2003	12/20/2003	8/25/2003
GLP/QA	No	Yes	No	Yes	No	Yes
Vehicle	0.4% (w/v) aqueous methylcellulose	0.4% (w/v) aqueous methylcellulose	0.4% (w/v) aqueous methylcellulose	0.4% (w/v) aqueous methylcellulose	0.4% (w/v) aqueous methylcellulose	0.4% (w/v) aqueous methylcellulose
Strain	Sprague Dawley	Sprague Dawley	Sprague Dawley	Sprague Dawley	New Zealand white	New Zealand white

Study	FEED - Rat	FEED - Rat	EFD - Rat	EFD - Rat	EFD - Rabbit	EFD - Rabbit
Number/group	8/sex/group)	25/sex/group	6/sex/group	25 female/group	4 female/group	20 female/group
Doses, mg/kg	0, 50, 75, 100	0, 5, 25, 50	0, 50, 100, 200	0, 5, 25, 75	0, 25, 75, 150	0, 2, 10, 20
Route	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage	Oral gavage
Treatment duration for males (M) and females (F)	M: daily from 18-22 d prior to mating for a total of 35-38 d. F: daily for 15 d prior to mating through GD 7	M: daily from 28 d prior to mating for a total of 49 d. F: daily for 14 d prior to mating through GD 7	F: daily from GD 6 through GD17	F: GD 6 through GD 17	F: GD 7 to 19	F: GD 7 to 19
Cesarean section day	Gestation day (GD) 14	GD 14	GD 21	GD 21	F: GD 29	F: GD 29
Study acceptability	Litter numbers/ group not acceptable. High dose adequate, because decreased body weight gain and food consumption resulted in group termination	Litter numbers /group acceptable. High dose acceptable - BW gain decrease 21% in males and 15% in females in high dose group	Litter number/group not acceptable. Doses acceptable - BW gain decrease 64% and 19% in mid and high dose on GD 9. High and mid dose terminated on GD 11 and 15, respectively	Litter number/group acceptable. High dose was acceptable based on the decreases in BW gain (15%) on GD 17 and food consumption (12%) in high dose group.	Litter number/group not acceptable. High dose was acceptable based on the decreases in BW gain and food consumption at 75 and 150 mg/kg resulted in termination on GD 10.	Litter number/group acceptable. High dose was acceptable based on the decreases in BW gain at 25 mg/kg in dose finding study
Comments: Parental	Decreased body weight gain and food consumption resulted in termination of high dose group. Slight decrease in food consumption in males at 75 mg/kg	No mortality. Food consumption decreased in high dose males. Although the time to mating increased 30% in the high dose group, values within concurrent and historical ranges. The absolute and relative testes weight increased 6% in high dose group.	Mid and high dose groups not evaluated, no remarkable C-section findings at 50 mg/kg	No mortality. No remarkable necropsy or unusual placental findings. Mean post-implantation loss increased in the mid (0.8) and high dose (1.2) groups compared to control group (0.3), but values within historical range.	53% decrease in BW gain at 25 mg/kg during dosing GD 7 to 19.	1 abortion in mid dose. Mortality of 2 low and mid dose females not drug-related. No clear effect on BW or food consumption. No remarkable necropsy or unusual placental findings
Comments: Embryo/fetal/ offspring	No drug-related effects	No drug-related effects	No adverse drug-related effects. No malformations or variations in the control or 50 mg/kg dose groups. Fetal body weight was 5% higher in low dose group.	Significant decrease in mean fetal weight in the high dose group was considered SCH 530348-related	No adverse drug-related effects. No malformations reported.	Although the number of litters and the number of fetuses with any malformation increased with dose, most (domed head) occurred in one litter.

Study	FEED - Rat	FEED - Rat	EFD - Rat	EFD - Rat	EFD - Rabbit	EFD - Rabbit
Comments: Other findings:	No drug-related effects on estrous cycling, mating or fertility in treated M or F.	No drug-related effects on estrous cycling, mating or fertility in treated M or F.	No maternal toxicity, fetal toxicity or fetal malformations was observed at 50 mg/kg	Rare malformations in the ventricular chamber in hearts of 2 high dose fetuses and higher incidence of skeletal findings in the high dose could be due to maternal toxicity		litter and no malformations at 25 mg/kg
Parental NOAEL, mg/kg	M: 50 F: 75	M: 25 F: 25	50	25	<25	20
Offspring NOAEL, mg/kg	Embryo toxicity: & fertility: 75	Embryo toxicity & fertility: 50	Fetal toxicity & malformation: 50	Fetal toxicity & malformation: 25	Fetal toxicity & malformation: 25	Fetal toxicity: 20; malformation: 10
HED	Parental: M: 8.1 F: 12.2 Embryo: 12.2	Parental: 4 Embryo: 8.1	Parental: 8.1 Fetal: 8.1	Parental: 4 Fetal: 4	Parental: <8.3 Fetal: 8.3	Parental: 6.6 Embryo: 3.3
Animal/human based on BSA	Parental: M: 192 F: 290 Embryo: 290	Parental: 95 Embryo: 192	Parental: 192 Fetal: 192	Parental: 95 Fetal: 95	Parental: <198 Fetal: 198	Parental: 157 Embryo: 79
AUC ng*hr/mL at	50: 52700 75: 192000	25: M – 23460 25: F – 41460 50: M – 52700 50: F - 88300	50: 224750	25: F – 73500	20: F – >117000	20: F 117000 10: F- 34600
Ratio exposure at NOAEL to human exposure	Parental: 50: 40 75: 145 Embryo: 75: 145	25: M – 19 25: F – 31 50: M – 40 50: F - 67	50: 170	25: F – 56	25: F – >89	20: 89 10: 26
Human daily dose = 2.5 mg/day = 0.042 mg/kg/day; Human exposure 1320 ng/hr/ml						

In the following sections, the reviewer briefly summarizes for each previously reviewed GLP reproductive and developmental study those parameters that affect the determination of the reviewer's NOAELs above.

9.1 Fertility and Early Embryonic Development

In an acceptable fertility and early embryo development study, male and female rats were treated with 0, 5, 25, 50 mg/kg/d. The NOAEL for paternal and maternal toxicity was 25 mg/kg, because body weight gain decreased in the high dose groups (Table 103). No drug-related effects were observed on estrous cycling, mating or fertility in treated males or treated females. The NOAEL for fertility and embryo toxicity is 50 mg/kg.

Table 103: Reviewer's Summary Rat FEED – SN 02145

Rat FEED	Dose (mg/kg/d)				
SN 02145	**0**	**5**	**25**	**50**	**Historical***
Body weight gain: M, D 1-49	184	165	172	147	
F, GD 0-7	39	39	36	33	
Males evaluated	25	25	25	25	
Males mated	25	25	24	23	
Days in cohabitation	3.0	2.5	3.3	3.9	2.9 (1.7-5.8)
Females pregnant	25	24	20	22	
Fertility index	100	96	83	96	94.6 (47.2-100)
Corpora lutea /litter	16.5	16.8	16.3	16.5	16.4 (14.1-18.0)
Implantations/litter	15.7	16.2	15.6	16.0	15.6 (11.4-17.0)
Females with viable fetus	25	24	20	22	
Females with no live fetus	0	0	0	0	
Viable fetuses/litter	15.0	15.3	14.8	15.0	14.5 (10.1-15.9)
Preimplantation loss/litter	0.8	0.6	0.8	0.5	
Postimplantation loss/litter	0.8	0.9	0.8	1.0	
Total resorptions/litter	0.8	0.9	0.8	1.0	

* Historical studies used necropsy on GD 13, not GD 14. Data from (b) (4) Historical control Data, (b) (4)

Table 104 below compares the exposures of rats at the NOAEL dose and at the dose at which toxicity was observed in the FEED study with exposures in patients receiving the recommended daily dose of 2.5 mg.

Table 104: Comparison of Rat FEED Exposures to Human Exposures

		Comparisons to human exposure[1]			
Rat FEED	**NOAEL, mg/kg**	**Based on NOAEL dose**		**Based on toxic dose**	
SN 02145		**AUC**	**Fold**	**AUC**	**Fold**
Parental M	25	M: 23460	18	M: 52700	40
F	25	F: 41460	31	F: 88300	67
Embryo toxicity	50	88300	67	> 88300	>67
Fertility M	50	52700	40	> 52700	>40
F	50	88300	67	> 88300	>67

Exposures for rats estimated from studies 05265 and 08378
[1] At the RHD of 2.5 mg, the mean total human $AUC_{(0\text{-}24\ h)}$ value is 1320 ng•hr/mL (The sponsor's value for vorapaxar was obtained from Meta analysis for steady-state PK analysis (Section 5.3.5.3.4.3))

9.2 Embryonic Fetal Development

Rat

In an acceptable rat embryo-fetal development study (Study 02146), female rats were dosed with 0, 5, 25 and 75 mg/kg from day 6 through day 17 of gestation. The NOAEL for maternal toxicity was 25 mg/kg based on the decreases in body weight and food consumption (Table 105). Although number of early resorptions and the percentage of dams with early resorptions increased in the mid- and high dose groups, the values were not statistically significant and were less than the maximum in the MARTA historical database. However, the statistically significant decrease of 0.3 gm in mean fetal weight in the high dose group was considered treatment related. Rare malformations in the fetal heart occurred in two fetuses in two litters only at the high dose of 75 mg/kg (a dosage not tested in the pilot study). These malformations occurred in two separate litters along with an external and skeletal malformation (exencephaly) in

a third litter. An increased incidence of lumbar rib and unossified sternabra also occurred in the high dose group. Although these findings may be attributable to the maternal toxicity in the high dose group, the reviewer concluded the no effect level for overall malformation can be considered to be 25 mg/kg.

Table 105: Reviewer's Summary Rat EFD – Study 02146

Rat EFD – Study 02146	Dose , mg/kg/d			
	0	**5**	**25**	**75**
Dam Body weight gain: F, GD 0-20	179	191	188	164
Females mated	25	25	25	25
Females pregnant	20	22	22	22
Females evaluated	20	22	22	22
Females with normal placenta	20	22	22[1]	22
Females with viable fetuses	20	22	22	22
Corpora lutea/litter	12.5	12.1	13.8	13.6
Implantation sites/litter	11.2	11.5	12.0	12.2
Pre-implantation loss, #/litter	1.3	0.7	0.9	1.5
Postimplantation loss, #/litter	0.3	0.2	0.8	1.2
Early resorption/litter	0.3	0.2	0.8	1.2 (0.8)[2]
Late resorption/litter	0	0	0	0
Total resorption/litter	0.3	0.2	0.8	1.2
Total number early resorptions	7	4	17	27 (16)[2]
Dead fetuses/litter	0	0	0	0
Live fetuses/litter	10.9	11.3	12.1	11.0
% males	52.7	48.3	52.2	45.6
Fetal weight, gm	5.8	5.9	5.8	**5.5***
# fetuses with external malformation	0	0	0	1
# fetuses with external variation	0	0	0	0
# fetuses with visceral malformation	0	0	0	**2**
# fetuses with visceral variation	11	6	6	9
# fetuses with skeletal malformation	0	0	1	1
# fetuses with skeletal variation	87	84	94	94
# litters with any malformation	0	0	1	3

, [1] One female had a fused placentae at 2:11 fetal sites, [2] Omits Female 85 with 11 resorptions * Statistically significant, p<0.05,

Table 106 below compares the exposures of rats at the NOAEL dose and at the dose at which toxicity was observed in the EFD study with exposures in patients receiving 2.5 mg of vorapaxar once a day. The exposures in rats are based on a separate GLP toxicokinetic study (SN 08257) in which pregnant Sprague Dawley female rats received 0, 5, 25, or 75 mg/kg from GD 6 through 17.

Table 106: Comparison of Rat EFD Exposures to Human Exposures

Rat EFD		Comparisons to human exposure[1]				
Study 02146	NOAEL mg/kg	Based on NOAEL dose		Toxic dose, mg/kg	Based on toxic dose	
		AUC[2]	Fold		AUC[2]	Fold
Maternal	25	73500	56	75	376000	285
Fetal toxicity	25	73500	56	75	376000	285
Malformation	25	73500	56	75	376000	285

[1]At the RHD of 2.5 mg, the mean total human $AUC_{(0\text{-}24\ h)}$ value is 1320 ng•hr/mL (The sponsor's value for vorapaxar was obtained from Meta analysis for steady-state PK analysis (Section 5.3.5.3.4.3)). [2] AUC (ng*hr/mL) values from SN 08257 in pregnant Sprague Dawley rats

Rabbit

In an acceptable embryo-fetal development study in rabbits, pregnant rabbits received daily gavage doses of 2, 10 or 20 mg/kg SCH 530348 on gestation Days 7 through 19. The no effect level for maternal and embryo-fetal developmental toxicity in rabbits was 20 mg/kg (Table 107). Although the number of live fetuses per liter decreased in the high dose group, pre-implantation loss also decreased in this group. The sponsor maintained that the fetal external malformations were not test article related, because of the finding of domed head occurred in six fetuses of one high dose female. However, three other high dose females also had fetuses with malformations. Since the overall number of litters with any malformed fetus and the total number of fetuses with any malformation increased at 20 mg/kg in the absence of maternal toxicity, the reviewer's no effect level for malformation is 10 mg/kg.

Table 107: Reviewer's Summary Rabbit EFD – Study 02147

Rabbit EFD	**Dose, mg/kg**			
Study 02147	**0**	**2**	**10**	**20**
Body weight gain kg, GD 7-20	0.25 kg	0.25	0.28	0.28
Females mated	20	20	20	20
Female deaths	0	1	1	0
Females with implantations	17	19	18	17
Females aborted	0	0	1	0
Females evaluated	17	18	16	17
Females with total resorption	0	0	0	0
Females with any resorption	6	6	3	6
Females with live fetuses (%)	17 (100)	18 (100)	16 (100)	17 (100)
Females with normal placenta	17	18	16	17
Corpora lutea/litter (range)	8.8	9.1	9.0	9.5
Implantations/litter (range)	8.6	9.0	8.6	8.2
Pre-implantation loss, #/litter	1.8	1.5	5.0	13.7
Early resorption/litter	0.2	0.2	0.1	0.4
Late resorption/litter	0.2	0.4	0.2	0.2
Total resorption, #/litter	0.4	0.7	0.2	0.6
Dead fetuses/litter	0	0	0.1	0
Live fetuses/litter	8.2	8.2	8.3	**7.6**
% males	58.6	50.9	45.7	62.1
Fetal weight, gm	45.3	43.0	43.7	44.2
# fetuses (litters) with any malformation	1 (1)	2 (2)	2 (2)	**9* (4)**
# fetuses (litters) with any variation	53 (14)	76 (16)	62 (14)	52 (11)
# fetuses (litters) with any external malformation	1 (1)	0 (0)	0 (0)	**8* (3)**
# fetuses (litters) with any external variation	0 (0)	0 (0)	0 (0)	0 (0)
# fetuses (litters) with any visceral malformation	1 (1)	0 (0)	0 (0)	**8* (3)**
# fetuses (litters) with any visceral variation	4 (2)	2 (2)	1 (1)	2 (2)
# fetuses(litters) with any skeletal malformation	0 (0)	2 (2)	2 (2)	**8* (3)**
# fetuses (litters) with any skeletal variation	51 (15)	76 (18)	61 (15)	53 (14)
P<0.01				

Table 108 below compares the exposures of patients and exposures of rabbits at the NOAEL dose and the dose at which toxicity was observed in the EFD study. The rabbit exposures were determined in the same study.

Table 108: Comparison of Exposures in the Rabbit Oral EFD Study to Human Exposures

Rabbit EFD		Comparisons to human exposure[1]			
Study 02147	NOAEL mg/kg	Based on NOAEL dose		Based on toxic dose	
		AUC	Fold	AUC	Fold
Maternal	20	117000	89	>117000	>89
Fetal toxicity	20	117000	89	>117000	>89
Malformation	10	34600	26	117000	89

[1] At the RHD of 2.5 mg, the mean total human $AUC_{(0\text{-}24\ h)}$ value is 1320 ng•hr/mL (The sponsor's value for vorapaxar was obtained from Meta analysis for steady-state PK analysis (Section 5.3.5.3.4.3))

9.3 Prenatal and Postnatal Development

Two pre/postnatal development (PPND) studies were conducted. The first was a standard pre/postnatal development study in which pregnant F0 female Sprague-Dawley rats received single daily oral gavage doses of 0, 5, 25 or 50 mg/kg SCH 530348 from gestation Day 6 through postnatal day (PND) 20. Adverse effects were observed in both F1 and F2 pups of the high dose group. To further evaluate the effects observed in the high dose group in the first PPND study, a cross-fostering study was conducted in two phases to assess the effects of administration of 50 mg/kg SCH 580348 to F0 dams on the F1 and F2 generations. In the first phase (A), F1 pups from the control and SCH 580348 treated F0 groups were cross-fostered with dams from the other group after parturition to produce two additional groups of F1 pups, one exposed prenatally only and the other exposed postnatally only. In the second phase (B), F2 pups from F1 control or from F1 females that received both prenatal and postnatal exposure were cross-fostered after parturition with dams from the other group (see Figure 27 and Figure 28).

Prenatal/Postnatal Development Standard Study

For a complete discussion of this study, the reader is referred to the review dated 05/07/2013 in DARRTS under IND 71384.

In the initial prenatal/postnatal development study (Study 02148), no drug related mortality of F0 dams occurred. No adverse effect in F0 dams was observed on body weight, body weight gain, food consumption, and maternal performance, including length of gestation, duration of parturition, number of implantations, number of live pups or dead F1 pups at birth, sex ratio (% males/females), live birth index, pregnancy rate, gestation index, placentae, or maternal behavior. Although the number of F1 pups born per litter was similar in all dose groups, the number of F0 dams with a dead or missing F1 pup during the pre-weaning period (PND 0-21) was higher in the high dose group (Table 109). The immediate post-natal period PND 1-7 showed the greatest increase in the number of F0 dams with a dead or missing F1 pup in the high dose group.

Table 109: Reviewer's Summary Rat PPND – F0 Parameters – Study 02148

Rat PPND	Dose (mg/kg)				
Study 02148	**0**	**5**	**25**	**50**	**Historical [1]**
Number of dams	25	25	25	25	
Number pregnant (%)	23 (92%)	24 (96%)	25 (100%)	25 (100%)	
Number not pregnant	2	1	0	0	
Number with Total Litter loss	1	0	0	0	
Number with Viable pups (%)	22 (95.7)[1] [23 (100)][2]	24 (100)	25 (100)	25 (100)	
Gestation length (SD)	21.6 (0.5)	21.6 (0.5)	21.8 (0.5)	21.4 (0.5)	21.5, 22.3
Implantation sites/litter at weaning (SD)	16.0 (1.2)	15.4 (2.2)	15.8 (1.9)	15.6 (1.4)	13.46, 16.94
F_1 born/litter (SD)	15.1 (1.2)	15.0 (2.2)	15.2 (2.2)	14.9 (1.9)	12.48, 16.12
Unaccounted sites	0.9 (0.9)	0.4 (0.6)	0.6 (0.8)	0.7 (1.0)	0.0, 1.38
Live litter size (PND 0)	15.0 (1.3)	15.0 (2.1)	14.9 (2.3)	14.7 (2.0)	12.22, 15.98
# F_0 Dams with dead or missing pup on PND 0	2	1	6	4	
PND 1-3	6	4	6	15	
PND 4-7	1	4	4	6	
PND 8-21	1[†]	1	1	2	
Total # F_0 Dams with dead or missing pup, PND 0-21	11	8	14	17	
# F_0 Dams dying or euthanized, PND 0-4	0	0	0	0	
# F_0 Dams dying or euthanized, post PND 4	1[†]	0	0	0	
# F_0 Dams rearing F_1 pups to PND 4	23	24	25	25	
# F_0 Dams rearing F_1 pups to PND 21	22	24	25	25	

† All pups from F45693 were found dead or missing between PND 8 and 15 [1] Laboratory historical control mean ± 2S.D.

Although the numbers of F1 pups born/litter were similar across all groups, the number of F1 pups found dead or missing (presumed cannibalized) was 3-fold higher in the high dose group compared to the control group (Table 110). However, survival in the high dose group was lower than the minimum of the historical control range for PND 1-4, but not for PND 0-1. Prior to culling on PND 4, overall survival from birth in the high dose group (84.7% per litter) was lower than the survival in the concurrent control group (97.2% per litter), and was lower than the minimum of the historical control range. In addition, survival in the mid dose group was slightly lower than the concurrent control for PND 1-4 and for birth to PND 4, although the values were neither statistically significant nor lower than the minimum of the historical control range. The lower postnatal F1 survival in the high dose group prior to culling on PND 4 was considered related to SCH 530348 treatment of the F0 dams.

The F1 pup deaths in the high dose group primarily occurred between PND 1 and PND 3 and involved 15 dams (Table 4). In contrast, the pup deaths in the high dose group between PND 4 and PND 7 involved primarily three dams. The sponsor's calculations of survival included F45693 in the control group. When F45693 is included in pup mortality calculations, F1 pup mortality/litter for the control group is increasd compared to the mortality in the low dose group. When F45693 is excluded in pup mortality calculations,

F1 pup mortality/litter for the control group is similar to that in the low dose group. In contrast, the F1 pup mortality/litter both overall and particularly for PND1-3 in the high dose group is more than 5-fold higher than the mortality/litter in the control and low dose groups.

Table 110: Reviewer's Compilation of F1 Pre-Weaning Survival - SN 02148

Rat PPND	Dose (mg/kg)				
Study 02148	**0**	**5**	**25**	**50**	**Historical[a]**
Number of litters	22[1] (23[2])	24	25	25	
F_1 born/litter (SD)	15.1 (1.2)	15.0 (2.2)	15.2 (2.2)	14.9 (1.9)	12.48, 16.12
Live litter size (PND 0)	15.0 (1.3)	15.0 (2.1)	14.9 (2.3)	14.7 (2.0)	12.22, 15.98
F_1 sex (% males/litter)	51.1 (10.5)	45.7 (9.9)	54.7 (12.4)	47.9 (10.5)	44.52, 55.64
Total # F_1 dead or missing (#/litter)	20 (0.87) [12 (0.54)][1]	13 (0.54)	21 (0.84)	70 (2.8)	
Post-natal F_1 pup survival (% per litter)[2] [3]					
PND 0	99.1	99.7	98.1	98.6	94.94, 100
PND 0-1	99.5	98.6	99.3	**96.0***	97.32, 100
PND 1-4 (pre-cull)	98.5	98.9	97.4	89.1	95.94, 100
PND 4-7 (post-cull)	98.9	99.0	99.0	94.5	95.38, 100
PND 7 -14	96.2	99.5	99.4	97.5	96.38, 100
PND 14-21	95.7	100	100	100	97.28, 100
Birth to PND 4 (pre-cull)	97.2	97.1	94.8	84.7	91.64, 100
PND 4 (post) – PND 21	94.9	98.4	98.5	93.0	92.18, 100
Number of F_1 pups dead or missing [#/litter]					
PND 0	3 [0.13]	1 [0.04]	7 [0.28]	5 [0.2]	
PND 1-3	7 [0.30]	7 [0.29]	9 [0.36]	41 [1.64]	
PND 4-7	2 [0.09]	4 [0.17]	4 [0.16]	22[‡] [0.88]	
PND 8-21	8[†] (0[1]) [0.35]	1 [0.04]	1 [0.04]	2 [0.08]	
PND 0-7	12 [0.52]	12 [0.5]	20 [0.8]	68 [2.72]	

* p<0.05, [1] Excludes F45693 [2] Includes F45693 [3] Sponsor's calculations [†] All pups were from F45693, [‡] Pups were primarily from F 45669 (9), F45668 (4), and F45703 (6), [a] Laboratory historical control mean ± 2S.D. Blue text indicates values outside historical range.

The F1 male and female mean pup body weights in the high dose group were 5-13% lower than the mean pup body weights in the concurrent control group throughout the pre-weaning period and were either at or below the minimums of the historical control range on PND 1, PND 4, and PND 7 (Table 111). The F1 male and female mean pup body weight gains in the high dose group decreased 15.8% and 22.2%, respectively, from PND 1 to PND 4 and 8.8 and 11.9%, respectively, for the overall pre-weaning period PND 1-21 compared to the gains in the control group. The number of litters with F1 pups that lost body weight from PND 1 to PND 4 increased with dose.

The F_1 male and female mean pup body weight gains from PND 1 to PND 4 decreased 15.8% and 22.2%, respectively in the high dose group compared to the gains in the control group. For the overall pre-weaning period PND 1 to PND 21, the F_1 male and female mean pup body weight gains decreased 8.8 and 11.9%, respectively, compared to the control group. The difference in overall body weight gain was statistically significant for the females.

No malformed pups were observed in any group. The number of dead pups with the finding “milk not present” in the stomach increased in the two highest dose groups. SCH 530348 treatment of F_0 females did not affect attainment of balanopreputial separation in F_1 males, attainment of vaginal patency in F_1 females or the estrous cycle duration in F_1 females.

Table 111: Reviewer's Compilation of F1 Pre-Weaning Body Weight - SN 02148

Rat PPND		Dose (mg/kg)				
Study 02148		**0**	**5**	**25**	**50**	**Historical[a]**
F_1 pup body weight [1], gm, Mean (SD)						
PND 1	males	6.8 (0.7)	6.8 (0.6)	6.9 (0.6)	6.4 (0.8)	6.60, 7.60
	female	6.3 (0.7)	6.4 (0.5)	6.5 (0.6)	6.0 (0.7)	6.20, 7.20
PND 4 pre-cull	males	8.7 (1.1)	9.0 (0.9)	8.8 (1.1)	8.0 (1.5)	8.84, 11.16
	females	8.1 (1.0)	8.5 (0.9)	8.3 (1.1)	7.5 (1.4)	8.38, 10.62
PND 4 post-cull	males	8.7 (1.0)	9.0 (0.9)	8.9 (1.1)	8.0 (1.5)	
	females	8.1 (1.0)	8.5 (0.9)	8.3 (1.0)	7.5 (1.4)	
PND 7	males	13.5 (2.6)	14.3 (1.8)	13.6 (2.2)	11.9 (2.9)	12.86, 17.74
	females	12.6 (2.3)	13.5 (1.4)	12.8 (2.0)	10.9 (2.9)	12.16, 16.84
PND 10	males	20.2 (2.9)	20.9 (2.3)	20.1 (3.1)	17.5 (4.2)	
	females	18.6 (3.7)	19.7 (1.7)	19.0 (3.0)	16.2 (4.4)	
PND 14	males	29.9 (3.2)	30.1 (2.8)	29.7 (3.4)	26.6 (5.9)	23.0, 37.8
	females	27.8 (5.6)	28.8 (2.2)	28.2 (3.1)	24.9 (6.0)	22.28, 36.12
PND 21	males	46.8 (5.3)	47.0 (4.7)	46.8 (6.0)	43.0 (8.2)	37.14, 57.86
	females	44.9 (4.9)	44.9 (3.7)	44.1 (5.1)	40.0 (9.3)	36.08, 55.12
F_1 Mean BW gain PND 1-4, gm (SD)	males	1.9 (0.6)	2.2 (0.7)	1.9 (0.9)	1.6 (1.0)	
	females	1.8 (0.5)	2.1 (0.6)	1.8 (0.8)	1.4 (1.0)	
F_1 Mean BW gain PND 1-21, gm (SD)	males	40.0 (4.9)	40.2 (4.6)	39.9 (5.8)	36.5 (7.8)	
	females	38.5 (4.5)	38.5 (3.5)	37.6 (4.8)	**33.9 (8.9)***	
# litters with F_1 BW decrease PND 1-4		1[†]	2	3	4	

$p<0.05$, [1] Includes control F45693 [†] All pups were from control F45693, [a] Laboratory historical control mean ± 2S.D.
Blue text indicates values outside historical range. **Bold** text indicates statistically significant values

Sensory function and neurobehavioral development in the F_1 pups were assessed in acoustic startle and locomotor assays. Both the high dose F1 males and females exhibited statistically significant increases of 23.5% and 18.2%, respectively, in Tmax, indicating a slower response to the auditory startle stimulus (Table 112). Furthermore, the mean Tmax values for the high dose F1 males and females were greater than the maximum historical control values.

Table 112: Reviewer's Summary - Acoustic Startle Responses – PND 20 - SN 02148

	F_1 Males				F_1 Females			
Dose, mg/kg	**0**	**5**	**25**	**50**	**0**	**5**	**25**	**50**
V_{max}	135	150.5	154.9 *(140.8[1])*	**88.4****	121.6	159.9	144.7	111.1
SD	43.3	52.4	48.2	29.6	51.3	71.6	54.4	27.5
T_{max}	25.5	26.4	25.3	**31.5***	25.8	24.1	26.7	**30.5****
SD	2.8	4.1	3.0	7.1	4.2	2.4	3.4	4.0
V_{ave}	30.9	33.2	35.4 *(32.6[1])*	**21.5***	27.2	34	33.6	26.2
SD	11.2	11.2	10.1	5.4	11.9	14.6	12.8	6.8
Historical mean ±2SD on PND 20	**V_{max}** M: 88.4, 213.6 F: 79.6, 212.4		**T_{max}** M: 22.4, 27.6 F: 21.4, 26.4		**V_{ave}** M: 16.8, 45.2 F: 12.6, 45.4			

`V_{max} and V_{ave} in millivolt; T_{max} in millisecond; SD = standard deviation; Statistical test shown for Treatment F-test, * p<0.05; ** p<0.01;
[1] Value after elimination of outlier animal value by Q test. Italic text – values calculated by reviewer based on individual animal data, Blue text indicates values outside historical range.

Because of the findings on PND 20, the sponsor increased the size of each group evaluated on PND 60 by including F_1 animals that had not been evaluated on PND 20. The treatment-related effects on auditory response observed on PND 20 in F1 treated groups did not appear to continue into the post-weaning period on PND 60 in either the previously tested or the previously untested animals.

In the locomotor assays on PND 21, the mean overall total and ambulatory locomotor activity counts in the high dose F1 female group decreased 26% and 30%, respectively, compared to the counts in the control group (Table 113). The resulting 27% and 32% decreases in cumulative total and ambulatory, respectively, locomotor activity counts in the high dose group compared to the control group indicate a reduction in exploratory behavior. However, the high dose F1 females did display >95% habituation. In contrast, the high dose F1 males displayed only 50-54% habituation as a result of increased activity during the later time intervals, although they did not display a decrease in overall total and ambulatory locomotor activity. The mean activity values, except for the high dose F1 females in the 31-45 minute interval, were within the historical control range. The treatment-related effects on locomotor activity observed on PND 21 did not appear to continue into the post-weaning period (PND 61).

Table 113: Reviewer's Summary - Locomotor Activity - SN 02148

			Male					Female				
Day	**Type**	**Interval min or Cum.**	**Hist.[a]**	**0**	**5**	**25**	**50**	**Hist.[a]**	**0**	**5**	**25**	**50**
21	Total	0-15 M	192-661	376	382	343	337	185-722	412	409	354	315
		16-30 M	22-271	155	130	103	163	12-316	143	179	104	137
		31-45 M	9-220	139	105	122	177	19-241	60	160	71	**17**
		46-60 M	8-205	142	143	77	170	11-227	46	69	82	14
		0-60 M		203	190	161	212		165	204	153	121
		Cum.	267-1309	811	760	645	847	279-1506	660	816	611	483

		Interval	Male					Female				
Day	Type	min or Cum.	Hist.[a]	0	5	25	50	Hist.[a]	0	5	25	50
21	Amb.	0-15 M	76-257	137	126	120	133	67-273	147	137	106	108
		16-30 M	1-94	46	30	37	60	0-95	39	50	21	32
		31-45 M	0-89	43	25	38	68	1-73	13	37	12	3
		46-60 M	0-63	46	47	23	61	0-69	10	17	18	0
		0-60 M		68	57	55	80		52	60	39	36
		Cum.	78-453	272	227	218	322	84-510	209	241	156	143
61	Total	0-15 M	692-1296	1031	948	985	1059	797-1198	965	989	977	943
		16-30 M	322-639	475	431	564	**585***	246-629	423	510	493	435
		31-45 M	147-473	354	278	352	324	131-418	244	229	299	296
		46-60 M	76-371	252	118	227	166	92-374	121	221	262	215
		0-60 M		528	444	532	534		438	487	508	472
		Cum.	1452-2527	2112	1776	2128	2134	1403-2342	1753	1950	2032	1888
	Amb.	0-15 M	182-482	394	336	357	379	259-519	420	421	421	400
		16-30 M	80-227	155	134	188	190	76-247	158	195	187	161
		31-45 M	33-163	115	77	109	96	37-149	86	78	104	112
		46-60 M	21-123	71	34	74	49	26-134	38	75	93	71
		0-60 M		184	145	182	178		176	192	201	186
		Cum.	373-920	735	581	728	713	460-969	703	769	804	744

Cum. = cumulative; Hist.[a] = historical control reported minimum and maximum; M = mean; Amb. = ambulatory; Blue text indicates values outside historical range.

Learning and memory were assessed beginning on PND 22 using a Biel water-filled T maze. Table 114 summarizes the learning and memory trials. The values that are outside the laboratory's historical control range are in blue text and values that are statistically significant in bold text. The sponsor's analysis indicated no statistically significant effects overall for any phase of the study. However, the reviewer noted statistically significant increases in escape time and errors/trial for Trial 1 in all F_1 female treated groups compared to the control group. The F_1 female low, mid, and high dose groups displayed > 2-fold increases for escape time and for errors/trial compared to the control group. The mean control F_1 female values for time to escape and errors/trial for Trial 1 were below the minimum of the historical control values, whereas the mean values for the treated F_1 female groups were close to the maximum of the historical control values. However, no statistically significant effect was observed in F_1 females in the later learning trials (2-10) or in F_1 males. Moreover, the increases in Trial 1 did not exhibit a dose-dependency and the number of F_1 females with values above the maximum historical control value decreased with dose.

Although the reviewer agrees that treatment of F_0 dams with SCH 530348 did not have a clear effect on learning in F_1 off-spring, the reviewer notes a potential effect on memory in F_1 females. The mid and high dose F_1 female groups in Trial 11 had dose-dependent increases of 37% and 45%, respectively, in the time to escape and increases of 39% and 44%, respectively, in number of errors/trial relative to the control

means. In addition, the high dose F_1 female group in Trial 12 had a 22% increase in the time to escape relative to the control group (Table 114). However, most animals in each group displayed a decrease in the time to escape in Trial 12 compared to Trial 11, indicating some learning ability.

The differences in mean values from the control values for Trials 11 and 12 were not statistically significant as calculated by the sponsor. However, the reviewer noted highly aberrant values for control female 45649-11, whose values could be rejected based on a statistical Q-test (Dean and Dixon, 1951). When the values for this female are omitted, the difference between mean values for the high dose and control F_1 females for Trial 11 is statistically significant. Furthermore, the mean values in Trial 11 for the high dose F_1 females are above the maximum historical control values for time to escape and for number of errors/trial. Additionally, the number of F_1 females with values above the maximum historical control value increased with dose (1, 2, 4, 5 at 0, 5, 25, 50 mg/kg). However, the F_1 male groups did not display these effects.

Since the sponsor did not evaluate learning and memory later in the post-weaning period, it is unclear whether memory in the mid- and high dose females improves with developmental age. To assess whether the effect on F_1 memory was related to body weight as a measure of overall development, an analysis of escape times and errors relative to body weight was conducted by the reviewer. Although some correlation exists in the mid-dose group, no clear correlation exists in the high dose group. For example, high dose F_1 female 45678-13, who had a body weight above the maximum of the historical control range, had maximum escape times and maximum number of errors for both Trials 11 and 12. The decreased memory in the high dose F_1 females does not appear to be related solely to developmental stage.

Table 114: Reviewer's Summary of Learning and Memory Trials - SN 02148

			Male				Female			
Phase	**Comment**		**0**	**5**	**25**	**50**	**0**	**5**	**25**	**50**
1 Swimming Day 22	Mean time, sec	Mean (SD)	11.48 (4.28)	14.13 (6.16)	13.82 (4.90)	*18.23* (20.36)	11.78 4.05	11.14 4.60	13.10 4.26	11.72 (6.20)
		[Mean[1]] [(SD[1])]				[10.90] [(3.19)]				[11.92] [(6.46)]
	Historical range		M: 9.0-17.1 (5.8-16.6)				F: 7.5-19.4 (6.1-17.3)			
2 Learning Path A Days 22, 23	Mean time, sec	Trial 1	80.5	67.8	73.8	53.6	46.6	***105.9****	***98.6****	***90.4****
		Trial 2	63.0	33.5	54.8	60.6	59.7	79.0	63.7	69.8
		Trial 3	41.7	49.6	47.5	42.3	63.4	65.9	47.3	39.0
		Trial 4	28.0	38.1	40.1	40.7	40.1	56.2	55.2	49.5
		Overall	53.3	47.2	54.1	49.3	52.5	76.8	66.2	62.2
	Historical range by trial		1: 58.6-103.2; 2: 52.6-115.6; 3: 31.9-104.9; 4: 25.1-72.5				1: 55.5-110.5; 2: 48.2-114.6; 3: 43.4-95.2; 4: 29.3-65.0			
	Errors/trial	Trial 1	14	13	12.6	9.3	8.2	***21.7****	***18****	***17.5****
	Errors/trial	Overall	10	10	10	9	11	17	13	12
	Historical range by trial		1: 9.9-20.2; 2: 9.3-21.6; 3: 5.4-18.9; 4: 3.6-14.3				1: 9.5-20.7; 2: 6.7-19.1; 3: 6.7-19.7; 4: 5.8-14.2			

			Male				Female			
Phase	**Comment**		**0**	**5**	**25**	**50**	**0**	**5**	**25**	**50**
2 Learning Path B Days 24, 25, 26	Mean time, sec	Trial 5	159.0	139.6	154.2	164.3	137.5	163.5	139.2	134.6
		Trial 6	158.8	109.5	136.5	97.5	136.9	145.1	121.4	151.9
		Trial 7	122.3	78.0	105.8	130.8	120.8	105.2	105.1	117.9
		Trial 8	125.2	75.9	83.0	89.2	98.4	63.5	90.1	114.9
		Trial 9	82.6	52.9	73.8	60.8	113.9	83.6	79.9	97.7
		Trial 10	81.0	31.8	56.5	67.8	67.6	57.3	54.4	84.1
		Overall	121.5	81.3	101.6	101.7	112.5	103.0	98.4	116.8
	Historical range by trial		5: 113.3-158.5; 6: 86.7-152.5; 7: 87.3-148.5; 8: 56.6-117.5; 9: 37.5-113.6; 10: 40.6-96.1				5: 115.7-168.6; 6: 82.5-147.5; 7: 63.6-133.6; 8: 46.6-106.9; 9: 51.9-125.0; 10: 33.6-82.2			
	Errors/trial	Trial 5	35	30	36	36	28	36	33	29
	Errors/trial	Overall	26	17	21	21	25	22	21	24
	Historical range by trial		5: 16.1-33.3; 6: 15.3-31.0; 7: 13.5-34.0; 8: 8.6-28.2; 9: 9.1-19.4; 10: 6.5-15.5				5: 13.7-34.3; 6: 15.8-26.0; 7: 6.0-26.8; 8: 8.4-21.4; 9: 8.1-25.6; 10: 5.2-15.2			
3 Memory Path A Day 27	Mean time, sec	Trial 11	82.4	81.1	64.4	82.2	73.6	75.3	100.7	***106.9****
		SD	50.4	40.3	30.0	35.1	43.4 [61.7² 23.4]	46.0	62.4	54.4
		Trial 12	49.8	60.2	56.8	43.7	55.7	45.3	51.5	68.2
		SD	27.0	53.4	22.8	21.7	31.5	20.4	29.6	52.4
		Overall	66.1	70.9	60.6	63.0	64.6	60.3	76.1	87.6
		SD	42.7	47.2	26.2	34.6	38.0	37.9	53.8	55.8
	Historical range by trial		11: 38.3-127.5; 12: 40.3-152.5				11: 50.8-97.2; 12: 39.9-82.2			
	Mean errors/trial	Trial 11	22.9	24.6	18.9	25.0	21.2	21.6	29.4	***30.6****
		SD	13.6	11.7	11.2	11.7	16.2 [16.6² 7.2]	13.5	22.6	17.4
		Trial 12	11.6	17.6	14.8	11.7	14.3	11.7	13.3	14.2
		SD	8.9	19.0	7.6	7.1	8.4	6.3	10.2	12.2
		Overall	17.3	21.1	16.9	18.4	17.8	16.7	21.4	22.4
		SD	12.6	15.8	9.6	11.6	13.1	11.5	18.9	16.9
	Historical range by trial		11: 9.2-25.6; 12: 9.1-27.0				11: 11.4-28.8; 12: 7.3-21.8			

M = mean; SD = standard deviation; Ambul. = ambulatory; [1] Mean and SD calculated with values for high dose males (668-06 and 697-05) or high dose female (668-14) omitted. These animals were euthanized prior to start of Phase 2. [2] Mean and SD calculated with values for control female 45649-11 omitted, based on statistical Q test. Historical range by trial = reported maximum and minimum, Blue text indicates values outside historical range.

F_1 reproductive performance was not significantly different between the treated groups and the control group, based on the mean numbers of days between pairing and coitus, the mean lengths of estrous cycles, the percentage of pregnant F_1 females, and the percentage of F_1 males that sired a litter. However, the numbers of F_2 pups born/litter and the live litter sizes on PND 0 were slightly lower in the mid- and high dose F_1 groups compared to the values for the concurrent control group. Subsequent to PND 0, the numbers of F_2 pups found dead or missing increased 3-10 fold in the mid and high dose F_1 groups compared to the numbers for the control group during PND 1-3 and PND 4-7 (Table 115). The total number of F_2 pups found dead or missing increased 6-fold on a per litter basis in the mid and high dose F_1 groups compared to the concurrent control group. Based on the sponsor's calculations, F_2 postnatal survival decreased in the high dose F_1 group from birth to PND 0 (92.9% per litter) and PND 1-7 (81.7% per litter) compared to the survival in the control group (99.7% and 97.6% per litter,

respectively). The difference in F_2 survival was statistically significant for PND 1-7, but was not statistically significant for birth to PND 0. In addition, F_2 postnatal survival decreased in the mid-dose group from PND 1-4 (92.9% per litter) and PND 1-7 (87.2% per litter) compared to the survival in the control group (99.6% and 97.9% per litter, respectively). Overall F_2 survival from birth to PND 7 decreased in the mid and high dose groups (85.6% and 81.7% per litter, respectively) compared to survival in the concurrent control group (97.6% per litter), but was not indicated as statistically significant. The decreased F_2 postnatal survival in the mid and high dose groups compared to survival in the control group correspond to increased numbers of dead and missing F_2 pups in these groups. The report concluded the decreased F_2 survival was considered related to administration of SCH 530348 to F_0 dams. In addition, F2 mean body weight gains in the high dose group during PND 1-4 and PND 4-7 were 27-30% and 16-17% lower, respectively, than those the control group. Since the lower F_2 body weights were associated with decreased postnatal survival in the high dose group, the report considered the decreases related to administration of SCH 530348 to F_0 dams

Table 115: Reviewer's Compilation of F2 Survival and Body Weight - SN 02148

Dose (mg/kg)		**0**	**5**	**25**	**50**	**Historical[a]**
Number of litters with viable F_2 pups on PND 7		20	22	24	19	
Number F_2 born/litter (SD)		14.3 (2.8)	14.8 (1.6)	13.0 (3.3)	13.5 (4.3)	12.48, 16.12
Live litter size on PND 0 (SD)		14.2 (2.8)	14.5 (2.0)	12.7 (3.4)	13.2 (4.4)	12.22, 15.98
Live litter size on PND 7[1]		13.9 (2.8)	13.9 (1.8)	10.8 (4.0)	11.4 (4.1)	
F_2 sex (% males/litter)		44.6 (13.8)	49.3 (10.3)	46.3 (17.4)	47.1 (11.2)	44.52, 55.64
Post-natal F2 pup survival (% per litter)						
PND 0 relative to # born		99.7	98.0	97.8	92.9	94.94, 100
PND 0 to PND 1		99.0	98.3	97.8	98.1	**97.32**, 100
PND 1 to PND 4		99.6	98.5	92.9	95.1	**95.94**, 100
PND 4 to PND 7		99.2	98.7	94.3	94.0	95.38, 100
PND 1 to PND 7		97.9	95.5	87.2	***88.0****	
Birth to PND 4						91.64, 100
Birth to PND 7		97.6	93.6	85.6	81.7	
Number of F_2 pups dead or missing on						
PND 0		1	6	7	7	
PND 1-3		4	9	25	13	
PND 4-7		2	6	21	21	
Total F_2 dead or missing PND 0-7 (# pups/litter)		7 (0.35)	21 (0.95)	53 (2.2)	41 (2.2)	
F_2 pup weight, gm, Mean (SD)						
PND 1	male	6.6 (0.7)	6.5 (0.5)	6.9 (0.9)	6.7 (0.8)	6.60, 7.60
	female	6.1 (0.6)	6.2 (0.5)	6.7 (1.1)	6.3 (0.7)	6.20, 7.20
PND 4	male	8.9 (1.4)	8.9 (1.2)	8.9 (2.0)	8.4 (1.8)	8.84, 11.16
	female	8.4 (1.2)	8.4 (1.0)	8.7 (2.3)	7.9 (0.4)	8.38, 10.62
PND 7	male	12.9 (2.3)	12.6 (1.8)	12.7 (3.2)	11.7 (3.2)	12.86, 17.74
	female	12.1 (1.9)	11.9 (1.6)	12.6 (3.4)	11.0 (3.2)	12.16, 16.84
F_2 BW gain PND 1-4, gm Mean (SD)	male	2.4 (0.9)	2.4 (0.8)	2.0 (1.3)	1.7 (1.2)	
	female	2.2 (0.8)	2.2 (0.7)	2.0 (1.4)	1.6 (1.2)	
F_2 BW gain PND 1-7, gm Mean (SD)	male	6.4	6.1	5.6	5.0	
	female	5.9	5.7	5.7	4.7	

* $p<0.05$, [1] Value includes mid and high dose dams with complete litter loss, [a] Laboratory historical control mean ± 2S.D. Blue text indicates values outside historical range.

Although there were findings on F1 perinatal survival and behavior, the comparisons of animal exposure at the NOAEL dose to the human exposure at the RHD indicated acceptable safety margins above 30-fold (Table 116. However, the effect on F1 female memory has less than a 4-fold safety margin at the NOAEL dose.

Table 116: Comparison of Rat Exposures in the PPND Study to Human Exposure

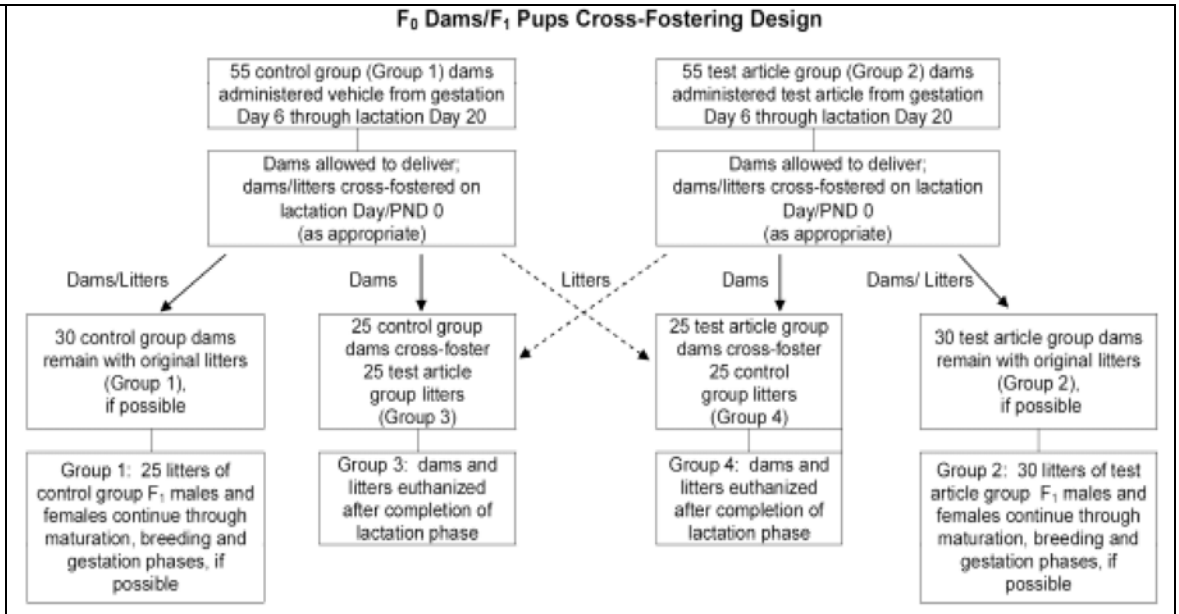
Rat PPND		**Comparisons to human exposure**			
Study 02148	**NOAEL mg/kg**	**Based on NOAEL dose**		**Based on toxic dose**	
		AUC	**Fold**	**AUC**	**Fold**
F0 maternal toxicity	50	88300	67	88300	67
F1 prenatal toxicity	50	88300	67	88300	67
F1 perinatal toxicity (PND 0-7)	25	41460	31	88300	67
F1 postnatal development	50	88300	67	88300	67
F1 behavior (acoustic startle, exploration)	25	41460	31	88300	67
F1 female memory	5	5025	3.8	41460	31
F1 mating/fertility	50	88300	67	88300	67
F2 prenatal fetal toxicity	25	41460	31	88300	67
Exposures for rats estimated from studies 05265 and 08378. At the RHD of 2.5 mg, the mean total human $AUC_{(0\text{-}24\ h)}$ value is 1320 ng•hr/mL (The sponsor's value for vorapaxar was obtained from Meta analysis for steady-state PK analysis (Section 5.3.5.3.4.3))					

Prenatal/Postnatal Development Cross-Fostering Study

To better evaluate the effects observed in the first PPND study, a cross-fostering study was conducted to assess the effects of administration of SCH 580348 (50 mg/kg) to F0 dams on the F1 and F2 generations in two phases. In the first phase (A), F1 pups from the control and SCH 580348 treated F0 groups were cross-fostered after parturition to produce two additional groups of F1 pups, one exposed pre-natally only and the other exposed post-natally only. In the second phase (B), F2 pups from F1 control or in pre-/postnatally-exposed F1 animals were cross-fostered after parturition. Phases A and B are diagrammed in Figure 27 and Figure 28, respectively. For a complete discussion of this study, the reader is referred to the review dated 05/07/2013 in DARRTS under IND 71384.

Figure 27: Reviewer's Modification of Sponsor's Diagram of Phase A Cross-Fostering of F_1 Pups - SN 07358

Phase A

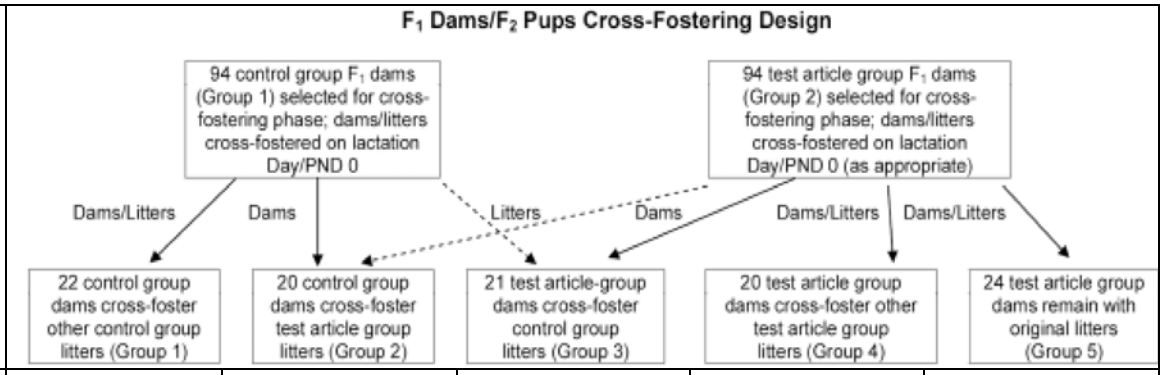


Group	A1	A3	A4	A2
Dam	F_0-0	F_0-0	F_0-50	F_0-50
Pup	F_1-0	F_1-50	F_1-0	F_1-50
CF	No CF	CF	CF	No CF
Code	A1: F_0-0/F_1-0	A3: F_0-0XF_1-50	A4: F_0-50XF_1-0	A2: F_0-50/F_1-50

X indicates cross-fostering, / indicates that pups remained with the original dam and no cross-fostering occurred

Figure 28: Reviewer's Modification of Sponsor's Diagram of Phase B Cross-Fostering of F2 Pups - SN 07358

Phase B



Group	B1	B2	B3	B4	B5
Dam	F_1-0	F_1-0	F_1-50	F_1-50	F_1-50
Pup	F_2-0	F_2-50	F_2-0	F_2-50	F_2-50
CF	CF	CF	CF	CF	No CF
Code	B1: F_1-0XF_2-0	B2: F_1-0XF_2-50	B3: F_1-50XF_2-0	B4: F_1-50XF_2-50	B5: F_1-50/F_2-50

X indicates cross-fostering, / indicates that pups remained with the original dam and no cross-fostering occurred

In the first phase (A) after cross-fostering, the reviewer agrees with the sponsor that survival was similar across the four groups for the post-cull period PND 4 to PND 21, but disagrees concerning pre-cull survival of F1 pups receiving either pre-/postnatal exposure (Group A2) or only postnatal exposure (Group A4) compared to the survival in the control group. Both sponsor's and reviewer's methods of calculation result in Group A2 having the lowest percentage of live pups on PND 4 pre-cull versus the number on PND 0 at cross-fostering (Table 117, Table 118). The percentages of live pups in Groups A3 and A4 on PND 4 pre-cull versus the number on PND 0 at cross-fostering also decreased and are in-between the percentages for Groups A2 and A1. However, these differences are not statistically significant and historical data was not provided to impart context.

The sponsor did provide historical control values for the percentage of F1 pups alive on PND 4 pre-cull versus the number born from standard PPND studies. In addition to percentages based on total pup numbers, the reviewer also calculated percentage of F1 pups alive on PND 4 pre-cull versus the number born for Groups A1 and A2 using the sponsor's method. The values using either method are almost identical. Group A2 (84.4%) had a lower percentage of F1 pups alive on PND 4 pre-cull versus the number born compared to the percentage in the control group (89.0%). This percentage in Group A2 was lower than the minimum (86.6%) reported in the historical data range.

Table 117: Summary of F1 Survival Pre-Cross-Fostering - Study SN 07358

	S	**R**	**S**	**R**	**S**	**R**	**S**	**R**
Dose, mg/kg	**0**		**50**					
# litters	**51**		**52**					
Pre-cross-fostering (CF) relative to number born								
Number F_1 born		832		850				
Number alive PND 0 pre-CF		790		800				
% alive PND 0 pre-CF [minimum]	**95.3 [29.3]**	95.1	**94.3 [8.3]**	94.1				
# deaths birth to CF		42		50				
% deaths birth to CF		5.0		5.8				

S = sponsor's value from Report Table 29 in bold text, R = reviewer's analysis based on Report Table 31 (Individual litter viability), Values in red text are below the historical control range, † Excluded litters that lost all pups in the indicated group beginning PND 1, ‡ In blue text, reviewer used sponsor's calculation method, but excluded dams that lost all pups by PND 1,
Historical control (HC) ranges
[1] Birth to PND 4 (pre-cull), mean ± 2S.D.= 91.64, 100; mean ± 3S.D = 89.5, 100; minimum, maximum = 86.6, 98.7
[2] PND 4 post-cull to PND 21, mean ± 2S.D.= 92.18, 100; mean ± 3S.D = 89.4, 100; minimum, maximum = 86.7, 100
[3] PND 4 pre-cull to PND 1, mean ± 2S.D.= 95.9, 100; mean ± 3S.D = 94.55, 100; minimum, maximum = 94.1, 100

Table 118: Summary of F1 Survival Post-Cross-Fostering Study SN 07358

Group	**A1**		**A2**		**A3**		**A4**	
Dam/pup	**F_0-0/F_1-0**		**F_0-50/F_1-50**		**F_0-0XF_1-50**		**F_0-50XF_1-0**	
F_1 Exposure period	**None**		**Pre & post-natal**		**Pre-natal**		**Post-natal**	
Number of litters on PND 0	**26**		**27**		**25**		**25**	
Post-cross-fostering (CF)								
# F_1 pups born		423		445		405		409
# Alive PND 0 at CF		396 (391†)		412 (411†)		391		393 (377†)
# alive PND 4 pre-cull		377		376		361		351
% alive at CF vs. # born/ # litters	**94.0/26**	93.6	**92.1/27**	92.6	**100/25**	96.5	**100/25**	96.0
% alive PND 1 vs. PND 0/ # litters	**94.4/26**		**94.7/27**		**98.7/25**		**92.6/25**	
% alive PND 4 pre-cull vs. PND 1/ # litters [HC = 94.1, 100]³	**97.5/25**		**93.0/26**		**93.3/25**		**96.3/24**	
% alive PND 4 pre-cull vs. PND 0 at CF/ # litters	**92.1/26** (96.0/25‡)	95.2 (96.4†)	**88.4/27** (91.7/26‡)	91.2 (91.5†)	**92.2/25** (92.2/25)	92.3 92.3	**89.8/25** (93.5/24‡)	89.3 (93.0†)
% alive PND 4 pre-cull vs. # born/ # litters [HC = 86.6, 100]¹	89.0/26	89.1	84.4/27	84.4		89.1		85.8
# culled		179		176		169		162
# alive PND 4 post-cull		198		200		194		189
# alive PND 21		187		189		185		181
% alive PND 21 vs. PND 4 post-cull/# litters [HC = 86.7, 100]²	**93.5/25**	94.5	**94.5**	94.5	**96.3/25**	95.4	**95.8/24**	95.8

S = sponsor's value from Report Table 29 in bold text, R = reviewer's analysis based on Report Table 31 (Individual litter viability), Values in red text are below the historical control range, † Excluded litters that lost all pups in the indicated group beginning PND 1, ‡ In blue text, reviewer used sponsor's calculation method, but excluded dams that lost all pups by PND 1,
Historical control (HC) ranges
¹ Birth to PND 4 (pre-cull), mean ± 2S.D.= 91.64, 100; mean ± 3S.D = 89.5, 100; minimum, maximum = 86.6, 98.7
² PND 4 post-cull to PND 21, mean ± 2S.D.= 92.18, 100; mean ± 3S.D = 89.4, 100; minimum, maximum = 86.7, 100
³ PND 4 pre-cull to PND 1, mean ± 2S.D.= 95.9, 100; mean ± 3S.D = 94.55, 100; minimum, maximum = 94.1, 100

The reviewer's analysis of F1 pup mortality focused on deaths after cross-fostering, because notations of deaths prior to cross-fostering were not consistent for the groups that were cross-fostered. Sponsor's numbers indicated an increase of 1.6 fold for number of dead or missing pups/litter from birth to PND 21 in Group A2 compared to Group A1 (Table 119). However, evaluation of F1 pup deaths after cross-fostering indicates that F1 deaths/litter increased at least 2.4 fold in Group A2 and 2-fold in Group A4 from cross-fostering to PND 4 and cross-fostering to PND 7. Although Group A3 did not have increased deaths/litter from cross-fostering to PND 4, F1 deaths increased 4-fold in this group from PND 4 to 7 so that F1 deaths from cross-fostering to PND 7 also increased 2-fold in Group A3. Overall, F1 deaths/litter increased at least 2-fold in Groups A2 and A4 from cross-fostering to PND 4, PND 4-7 and from cross-fostering to PND 7.

Table 119: Summary of F1 Mortality in Cross-fostering Study SN 07358

Group	A1: F_0-0/F_1-0	A2: F_0-50/F_1-50	A3: F_0-0XF_1-50	A4: F_0-50XF_1-0
F_1 Exposure to SCH	**none**	**Pre & post-natal**	**Pre-natal**	**Post-natal**
Number of litters	26	27	25	25
Sponsor's numbers – birth to PND 21				
F_1 found dead	38	61	10	14
F_1 found missing	11	22	27	36
Total F_1 dead or missing [#/litter]	49 [1.88]	83 [3.07]	37 [1.48]	50 [2.0]
Reviewer's analysis based on report Table 31 (Individual litter viability)				
# pup deaths including all litters, [#/litter]				
CF to PND 3	17 [0.65]	32 [1.19]	13 [0.52]	39 [1.56)
PND 4-7	5 [0.19]	12 [0.46]	20 [0.8]	9 [0.38]
PND 8-21	7 [0.27]	3 [0.11]	4 [0.16[	2 [0.08]
PND 4-21	12 [0.46]	15 [0.56]	24 [0.96]	11 [0.44]
CF to PND 7	22 [0.85]	44 [1.63]	33 [1.32]	48 [1.92]
CF to PND 21	29 [1.12]	47 [1.74]	37 [1.48]	34 [1.36]
# pup deaths excluding females who had no pups alive on PND 1, [#/litter]				
Female (# pups) excluded	F759 (5)	F831 (1)	-	F750 (16)
Number of litters	25	26	25	24
CF to PND 3	12 [0.48]	31 [1.19]	13 [0.52]	23 [0.96]
PND 4-7	5 [0.2]	12 [0.46]	20 [0.8]	9 [0.38]
PND 8-21	7 [0.28]	3 [0.12]	4 [0.16]	2 [0.08]
PND 4-21	12 [0.48]	15 [0.57]	24 [0.96]	11 [0.46]
CF to PND 7	17 [0.68]	43 [1.65]	33 [1.32]	32 [1.33]
CF to PND 21	24 [0.96]	47 [1.80]	37 [1.48]	34 [1.41]

After cross-fostering on PND 1, the mean F1 body weights in groups A2, A3, and A4 were below the minimum of the historical control range. Furthermore, the 6-7% decreases in mean male and female F1 body weights were statistically significant in group A2 and A3 that were exposed to SCH 530348 prenatally. The mean F1 body weights in group A2 continued to be below the historical range through PND 7 in both sexes.

The mean male and female F1 body weights on PND 21 in Groups A2 and A4 were 13 to 14% lower than those in the control group. F1 body weight gains were lowest, except for PND 14-17, for F1 pups in Group A2 receiving both pre- and postnatal exposure to SCH 530348. Beginning PND 4-7, F1 body weight gains were next lowest, except for PND 14-17, for F1 pups in Group A4 receiving only postnatal exposure to SCH 530348. For the pre-weaning period PND 1-21, the overall F1 body weight gain decreased 14-15% in Groups A2 and A4 compared to the control group. Consequently, the mean male and female F1 body weights on PND 21 in Groups A2 and A4 were 13 to 14% lower than those in control Group A1. The mean male and female F1 body weights on PND 21 in Group A3 were also 7-8% lower than those in control Group A1. However, the mean F1 body weights in all groups were within the historical control range on PND 21.

Table 120: Reviewer's Summary F_1 Bodyweights - SN 07358

Group	A1: F_0-0/F_1-0		A2: F_0-50/F_1-50		A3: F_0-0XF_1-50		A4: F_0-50XF_1-0		Historical (Mean ± 2 S.D.)
F1 Exposure to SCH	None		Pre & post-natal		Pre-natal		Post-natal		
Sex	M	F	M	F	M	F	M	F	
Mean F_1 body weight, gm									
PND 0 pre-CF	6.1	5.8	6.0	5.6	NA	NA	NA	NA	
PND 0 post-CF	6.3	5.9	6.0	5.5	6.0	5.6	6.0	5.7	
PND 1 (% decrease)	6.6	6.2	**6.1*** (7.6)	**5.8*** (6.5)	**6.2*** (6.0)	**5.8*** (6.5)	6.4 (3.0)	6.0 (3.2)	6.60/7.60 6.20/7.20
PND 4 pre-cull (% decrease)	8.9	8.4	7.9 (11.2)	7.4 (11.9)	8.4 (5.6)	7.9 (6.0)	8.6 (3.4)	8.1 (3.6)	8.84/11.16 8.38/10.62
PND 7 (% decrease)	14.0	13.4	11.9 (15.0)	11.2 (16.4)	13.4 (4.3)	12.4 (7.5)	13.0 (7.1)	12.2 (9.0)	12.86/17.74 12.16/16.84
PND 14 (% decrease)	28.9	27.8	23.9 (17.3)	22.4 (19.4)	26.7 (7.6)	25.5 (8.3)	23.9 (17.3)	22.4 (19.4)	23.62/37.38 22.9/35.9
PND 21 (% decrease)	44.8	43.1	38.9 (13.2)	37.1 (13.9)	41.5 (7.4)	39.8 (7.7)	39.1 (12.7)	37.0 (14.2)	37.96/57.84 36.78/55.02
Mean F_1 body weight gain, gm									
PND 0 - 1	0.4	0.3	0.2	0.2	0.2	0.1	0.3	0.3	
PND 1 - 4	2.2	2.2	1.8	1.6	2.2	2.1	2.2	2.1	
PND 4 - 7	5.2	4.9	4.0	3.8	4.9	4.5	4.4	4.1	
PND 7 - 10	5.9	5.7	4.8	4.6	5.4	5.2	4.9	4.4	
PND 10 - 14	8.6	8.4	7.0	6.2	7.9	8.0	6.0	5.8	
PND 14- 17	6.2	6.4	6.4	6.4	7.1	6.9	6.6	6.4	
PND 17-21	9.7	8.9	8.6	8.4	7.8	7.4	8.6	8.1	
PND 1 – 21 (% decrease)	38.2	36.8	**32.8*** (14.1)	**31.3*** (14.9)	35.3 (7.6)	34.0 (7.6)	**32.7*** (14.4)	31.0 (15.8)	

† Sponsor's calculations excluded litters that lost all pups in the indicated group beginning PND 1, ¹ Excludes F766 who lost all pups by PND 1. Blue text indicates values outside historical range.

During the post-weaning period, Group A2 mean F1 male and female body weights were 12-15% lower than those for the control group during the first three weeks after weaning. Mean body weight gains in the Group A2 F1 males and females were also 10% lower through PND 42. Subsequently, the differences in body weight gains decreased in both males and females. No effect of F0 treatment was observed on estrous cycle length, or the mating, fertility and copulation indices in the F1 animals.

At the beginning of the second phase (B), the mean number of F2 pups born and the mean F2 live litter size for the F1 animals receiving pre-/postnatal exposure (Group A2) prior to cross-fostering were 7.5% lower than the values for the concurrent control group (A1). Although these decreased values are within the historical control range, the decreases are statistically significant and consistent with the statistically significant decreases in the number of implantation sites in the F1 females from Group A2 compared to Group A1. In addition, similar decreases in the mean number of F2 pups born and the mean F2 live litter size were observed for the F1 animals from the F0 dams treated with 25 and 50 mg/kg SCH 580348 in the previous PPND study.

The survival and mortality of the F_2 pups to PND 7 after cross-fostering were not significantly different among the five groups (Table 121). Although the F_2 survival was

slightly lower for Group B5 (F_1-50/F_2-50) compared to the survival for Group B1 (F_1-0XF_2-0), the F_2 survival for Group B4 (F_1-50XF_2-50) was higher than the survival for Group B1. In addition, no clear difference was observed in F2 pup body weights after cross-fostering.

Table 121: Reviewer's Summary of F_2 Mortality and Survival – SN 07358

Group	B1	B2	B3	B4	B5
Dam/Pup	F_1-0XF_2-0	F_1-0XF_2-50	F_1-50XF_2-0	F_1-50XF_2-50	F_1-50/F_2-50
Number of litters	22	20	21	20	24
F_2 surviving to PND 7	306	245	304	272	289
F_2 surviving to PND 7/litter	13.9	12.3	14.5	13.6	12.0
F_2 found dead or missing after CF	16	7	9	6	21
F_2 dead or missing/litter	0.72	0.35	0.42	0.3	0.88
Total number of F_2 pups CF	322	252	313	278	310
% mortality by PND 7	5.0	2.8	2.9	2.2	6.8
% survival to PND 7	95	97.2	97.1	97.8	93.2
Based on Report Table 101: Summary of Clinical Observations with Disposition, CF = cross-fostered					

10 Special Toxicology Studies

10.1 Study title: Six week oral (gavage) retinal function study of SCH 530348 in male rats with a two-week postdose period

Study number: SN 06554

Review in DARRTS dated: 08/20/09

The potential effects of SCH 530348 on retinal function were assessed in male rats that received single daily oral (gavage) doses of either vehicle or 50 mg/kg for six weeks. In this study the $AUC_{(0\text{-}24hr)}$ is 44400 ng*hr/mL, which the sponsor considers comparable to that in Study 05265 ($AUC_{(0\text{-}24hr)}$ of 52000 ng*hr/mL). Although minimal vacuolation was observed histopathologically in the retina of at least 5/10 rats treated with 50 mg/kg, no SCH 530348-related ophthalmoscopic findings were observed after six weeks of dosing. The sponsor's consultant electrophysiologist concluded that no changes in electroretinograms (b-wave onset latency, peak latency, peak-to-peak amplitude, and oscillatory amplitude) were observed at 50 mg/kg. When a clear outlier animal is excluded from the analysis, the mean oscillatory amplitude significantly decreased by 30% in the SCH 530348-treated compared to the mean in the control group. However, the consult review from DAIOP (dated 11/13/2009) concluded that the difference in mean oscillatory amplitude did not appear biologically significant even if the outlier animal is excluded.

10.2 Three day phototoxicity study to determine the effects of oral (gavage) administration of SCH 530348 on eyes and skin in pigmented rats

Study number: SN 06067

Review in DARRTS dated: 01/04/13

Summary: After three daily oral doses of 0, 3 or 30 mg/kg SCH 530348 or a single oral dose of the positive control 8-methoxypsoralen (8-MOP), male Long Evans pigmented

rats were exposed to simulated sunlight for 1 hour to determine the phototoxic effects on the eyes and skin. The skin was observed for 3 days post UV exposure. The animals were then sacrificed and their eyes examined microscopically.

The positive control, 8-MOP, induced cutaneous erythema and corneal epithelial and stromal edema indicative of phototoxicity. No cutaneous erythema was observed in SCH 530348-treated rats. Microscopy findings of corneal epithelial edema in a few SCH 530348-treated rats appeared to correlate with ophthalmology findings of corneal scarring attributed to manipulation of the eyes for UV exposure. The NOAEL for phototoxiclty in rats was >30 mg/kg

11 Integrated Summary and Safety Evaluation

Vorapaxar (SCH 530848), an inhibitor of the protease activated receptor-1 (PAR-1), is being developed as an anti-platelet agent. Under NDA 204886, vorapaxar is proposed for the prevention of atherothrombotic events in patients with a history of myocardial infarction. NDA 204886 for vorapaxar is approvable from a pharmacology and toxicology perspective because most of the toxicities identified in the non-clinical studies have adequate safety margins relative to the human exposure at the recommended human dose (RHD) or appear to be species specific. However, the NOAEL for decreased memory in F1 female rat offspring in the PPND study after SCH 530848 treatment of the F0 dams only has a 4-fold safety margin compared to human exposure at the RHD. The label needs to describe these potential effects for women of child-bearing age.

The submission focused on the effects of vorapaxar on PAR-1 receptors in the blood (platelets) and the cardiovascular system (smooth muscle cells). However, PAR-1 receptors are activated in many additional cell types and tissues (Macfarlane et al. 2001; Adams et al. 2012). These include epithelium in lung; osteoblasts in bone; fibroblasts in connective tissue; keratinocytes in the epidermis; monocytes and T cells in the immune system; smooth muscle cells in the intestine and stomach; glomerular mesangial cells in the kidney; glia, astrocytes and neurons in brain and nervous system; and myocytes in muscles.

The pharmacology studies in platelets and smooth muscle cells used α-thrombin or Thrombin Receptor Activating Peptides (TRAPs) as agonists. Specificity of vorapaxar for PAR-1 was examined versus PAR-2 and PAR-4 using peptide agonists. However, the specificity for PAR-1 versus PAR-3 has not been demonstrated. Specificity of vorapaxar for PAR-1 was examined versus $P2Y_{(12)}$ using ADP, TXA_2R using a thromboxane $A_{(2)}$ mimetic and GPVI using collagen. However, the effect of vorapaxar on platelet aggregation induced by other agonists used in clinical laboratory practice (Hayward 2001), such as epinephrine (α_2-adrenergic receptor), arachidonic acid, ristocetin, serotonin, and platelet activating factor (PAF), were not examined.

In addition, the ability of vorapaxar to inhibit activation of the PAR-1 receptor by biased agonists such as Activated Protein C/Endothelial Protein C receptor (APC/EPCR), has

not been examined. As biased activators of PAR 1, thrombin and APC/EPCR result in activation of different signaling pathways. Thrombin activates G protein-dependent signaling and RhoA activation, whereas APC/EPCR activates Rac1 through β3-arrestin 2-dependent signaling (Soh and Trejo et al. 2011). Thrombin and APC/EPCR result in different PAR 1-dependent effects on endothelial barrier function. APC/EPCR stabilizes endothelial barriers (Feistritzer and Riewald 2006; Finigan et al. 2005; Bir et al. 2011), whereas thrombin disrupts endothelial barrier G proteins (Bae et al. 2007; van Nieuw Amerongen et al. 2008). Mosnier et al. (2012) recently demonstrated that activation by APC/EPCR was dependent on PAR-I because the PAR-I antagonist SCH79797 inhibited Akt and glycogen synthase kinase 313 phosphorylation induced by TR47, a novel PAR1 N-terminal peptide beginning at residue Asn47 generated by APC cleavage at Arg46 of PAR-1. The peptide TR47 can activate Racl and stabilize endothelial barriers resulting in reduced vascular leakage. If SCH 530848, like SCH 79797, does inhibit PAR-1 activation by APC/EPCR, then the cytoprotective and anti-coagulant effects of thrombin on endothelial cells would be blocked and result in unintended effects. Thus, vorapaxar could inhibit both the prothrombotic effects of thrombin on platelets, but also inhibit the beneficial effects of the protein C system on vascular integrity.

SCH 530848 was not directly tested in a thrombosis model; however, ex vivo platelet aggregation induced by PAR-1 agonist peptides was inhibited by SCH 530848 administered orally to monkeys. The inhibition of ex vivo platelet aggregation of SCH 530848 was similar to that for a structurally similar analog, SCH 602539, which was evaluated in a Folts thrombosis model in monkeys. Similarity of SCH 530848 and SCH 602539 on platelet aggregation both in vitro and ex vivo suggests that SCH 530848 would also inhibit thrombosis in the Folts model.

In monkeys, SCH 530848 did not induce bleeding by itself nor did it exacerbate the prolonged bleeding observed following administration of a combination of aspirin and clopidogrel alone. The tested SCH 530848 doses would be expected to produce exposures greater than 20 times the human exposure at the RHD. These pharmacology studies were consistent with the lack of bleeding and hemorrhage observed in the rat, mouse, and monkey toxicology studies.

Although thrombin is a potent activator of platelets in all species, human and rodent platelets differ in the specific PAR isoforms that mediate thrombin signaling and platelet activation (Kahn et al. 1998). PAR-1 agonist $TRAP_6$ (SFLLRN-NH_2) induces aggregation of human, guinea pig and monkey platelets, but not aggregation of rat, mouse, and dog platelets (Derian et al. 1995; Connolly et al. 1994, 1996). Therefore, only non-human primates or humans can be used to demonstrate efficacy of a PAR-1 antagonist as an anti-thrombotic agent. The non-human primate is the more relevant species compared to the rat in toxicology studies.

The principal toxicology finding in all species was phospholipidosis (Table 122). However, phospholipidosis was observed only at exposures in monkeys and mice greater than 100 and 45 times, respectively, the human exposure at the recommended human dose. In rats, phospholipidosis was observed in the 6-month study at exposures less than 4 times the human exposure at the recommended human dose. Surprisingly,

phospholipidosis was not observed in the 2 year rat carcinogenicity study at similar and higher exposures.

In contrast to phospholipidosis, vacuolation of the inner nuclear layer of the retina was observed only in rats (Table 122). Moreover, retinal vacuolation was not found in the rat carcinogenicity study, in any mouse study, or in any monkey study. The finding is reversible after 4 weeks of recovery. After 6 weeks of dosing in rats, no effect was observed on retinal function in rats, although vacuolation was present histologically. SCH 602539, a close structural analog of SCH 530348, also induced retinal vacuolation in Sprague Dawley rats; however, two structurally distinct PAR-1 inhibitors (SCH 590709 and SCH 2490130) did not, suggesting that the induction of retinal vacuolation is not related to the mechanism of action of these PAR-1 inhibitors. Retinal vacuolation was observed when the eyes were fixed under a number of conditions when the fixative was aldehyde based, but not after 24 hours refrigeration in situ or in Carnoy's fixative (acetic acid fixative). The sponsor considers retinal vacuolation to be a drug-related exaggeration of common retinal fixation artifact that is associated with SCH 530348-treatment and aldehyde-based fixation. The finding appears to be species specific. It may also be rat strain specific, since it was not observed in Wistar rats, but only in Sprague Dawley rats.

In humans, the mono-hydroxy metabolite M20 (SCH 2046273) was found in plasma at levels above 10% of the parent SCH 530848. Although the levels of M20 in rats were very low, the levels in monkeys, mice, and rabbits were adequate to allow the M20 metabolite to be considered toxicologically qualified (Table 123).

Table 122: Reviewer's Summary – Retinal Vacuolation and Phospholipidosis

Species	Study	Duration	Dose	$AUC_{(0-24)}$ † (M, F)	Retinal vacuolation	Phospholipidosis
Rat	02125	1 month	3	1182, 1785	N	N
			30	10324, 23051	Y	Y
			100	41305, 73550	Y	Y
	02141	3 month	50	22500, 51900	Y	Y
			100	64900, 113000	Y	Y
			200	64300, 155000	Y	Y
	02138	6 month	3	2250, 3310	N	N
			10	5000, 9310	Y	Y
			30	13100, 37900	Y	Y
	02143	2 year	3	2250, 3310	N	N
			10	5000, 9310	N	N
			30	13100, 37900	N	N
Mouse	02142	3 month	25	61000, 75800	N	**M:** Y; F: N
			75	171000, 196000	N	Y
			150	571000, 490000	N	Y
	02144	2 year	1	2440, 3032	N	N
			5	12200, 15160	N	N
			15	36600, 45480	N	N
Monkey	02126	1 month	0.5	771, 866	N	N
			5	10093, 11804	N	N
			20	45016, 55426	N	N
	04056	3 month	30	121000, 112000	N	N
			60	146000, 235000	N	Y
			90	303000, 251000	N	Y
	02139	6 month	0.5	1370, 1306	N	N
			5	27525, 26100	N	N
			20	155250, 162500	N	N
	02140	12 month	0.5	1540, 1650	N	N
			5	27900, 27800	N	N
			20	106000, 112000	N	N

† $AUC_{(0-24)}$ = ng*hr/mL

Table 123: Summary of Animal to Human Exposure Ratios

			Exposure at NOAEL		Safety Margin	
Study/ Species	Sex	NOAEL (mg/kg)	SCH 530848 AUC (ng*hr/L)	Metabolite M20[†] AUC (ng*hr/L)	SCH 530848[‡]	Metabolite M20[§]
General toxicology – chronic studies						
6 month - rat	M	3	2250	12.4	1.7	0.05
	F	10	9310	7.4	7.0	0.03
12 month - monkey	M	5	27900	1283	21	4.9
	F	5	27800	1362	21	5.2
Carcinogenicity						
Rat	M	30	13100	72	10	0.3
	F	30	37900	30	29	0.1
Mouse	M	15	36600	1867	28	7.2
	F	15	45480	1956	34	7.5
Reproductive and Developmental Toxicology						
FEED – Rat Pre-mating to GD 6	Paternal	25	23460	129	18	0.5
	Maternal	25	41460	33	31	0.1
	Embryo toxicity	50	88300	71	67	0.3
	Fertility M	50	52700	290	40	1.1
	F	50	88300	71	67	0.3
EFD – Rat GD 6 to 17	Maternal	25	73500	59	56	0.2
	Fetal - toxicity	25	73500	59	56	0.2
	Malformations	25	73500	59	56	0.2
EFD – Rabbit GD 7 to 19	Maternal	20	117000	13455	89	52
	Fetal - toxicity	20	117000	13455	89	52
	Malformations	10	34600	3979	26	15
Pre/Post-natal – Rat GD 6 to weaning	F_0 -maternal	50	88300	71	67	0.3
	F_1 -prenatal	50	88300	71	67	0.3
	F_1 (perinatal)	25	41460	33	31	0.1
	F_1 (postnatal)	**50**	88300	71	67	0.3
	F_1 (behavior)	**25**	41460	33	31	0.1
	F_1 (female memory)	5	5025	4	4	0.02
	F_1 (mating/fertility)	50	88300	71	67	0.3
	F_2 prenatal fetal toxicity	25	41460	33	31	0.1

[†] Using % M20 as 0.55% for male rats, 0.08% for female rats, 11.5% for rabbits, 5.1% for male mice, 4.3% for female mice, 4.6% for male monkeys, 4.9% for female monkeys and 19.7% for human.
[‡] At the RHD of 2.5 mg, the vorapaxar total $AUC_{(0\text{-}24\ h)}$ value is 1320 ng•hr/mL (The sponsor's value for vorapaxar was obtained from Meta analysis for steady-state PK analysis (Section 5.3.5.3.4.3). [§] M20 $AUC_{(0\text{-}24\ h)}$ value is 260 ng•hr/mL

Approximately 50% of PAR1-deficient mouse embryos die due to fatal bleeding defects between embryonic days 9.5 and 10.5 (Connolly et al. 1996, Darrow et al. 1996). Based on the literature for PAR-1 knockout mice, the reviewer expected more severe embryo-fetal toxicity, since substantial SCH 530348 was shown to cross the placental barrier. The absence of severe fetal toxicity in neither the rat nor rabbit SCH 530348 embryo-fetal development studies suggests that either redundant pathways make up for the inhibition of PAR-1 by SCH 530848 or SCH 530848 did not distribute to and inhibit PAR-1 in critical areas at the appropriate times during embryo-fetal development. Alternatively, SCH 530848 radioactivity may have been transferred across the placenta in the form of an inactive metabolite.

In the embryo-fetal developmental toxicity in rats, fetal toxicity was observed in association with maternal toxicity. The occurrence of rare heart malformations in the rat study may be attributable to the maternal toxicity in the high dose group. In the rabbit embryo-fetal development study, a non-specific increase in total malformations also occurred in the high dose group, but in the absence of maternal toxicity. The reviewer's NOAELs for teratogenicity in both studies were more conservative than those of the sponsor. However, animal to human exposure ratios at the NOAEL doses were 56 and 26 times the human exposure at the RHD in rats and rabbits, respectively. These exposure ratios indicate a relatively low risk to humans.

Two pre-/postnatal (PPND) development studies were conducted. The first study was a standard PPND study in which pregnant F0 female Sprague-Dawley rats received single daily oral gavage doses of 0, 5, 25 or 50 mg/kg SCH 530348 from gestation day 6 through postnatal day (PND) 20. Adverse effects were observed in both F1 and F2 pups of the high dose group. To confirm and further evaluate these findings, a second PPND study was conducted using cross-fostering to compare pre-natal only (A3) and postnatal only (A4) exposure to both pre-and postnatal (A2) exposure of 50 mg/kg SCH 530348 and a control group (A1). The following paragraphs compare the results of the two PPND studies.

In the first study, overall F1 survival in the high dose group was lower from birth to pre-cull on PND 4 than the survival in the concurrent control group and was lower than the minimum reported in the historical control data (86.6%). The decrease in the high dose group survival from PND 0 to PND 1 was statistically significant. Through PND 7, F1 pup mortality/litter was more than 5-fold higher in the high dose group than in the control group. In the cross-fostering study, the F1 survival in Group A2 that received both pre- and postnatal exposure to SCH 530348 from birth to pre-cull on PND 4 was also below the minimum reported in the historical control data (86.6%). Statistical significance was not achieved, because the survival in the control A1 group also decreased. However, F1 mortality/litter increased at least 2-fold in Groups A2 and A4 from cross-fostering to PND 4 and from cross-fostering to PND 7.

In the first study on PND 7, the F1 male and female mean pup body weights in the high dose group were 12-13% lower than the mean pup body weights in the concurrent control group. The F1 male and female mean pup body weights in the high dose group were below the minimums of the historical control range on PND 1 and PND 4 as well as on PND 7. From PND 1 to 4 and from PND 1 to 21, the mean F1 pup body weight gains decreased 15.8% and 8.8%, respectively, in males and 22.2% and 11.9%, respectively, in females in the high dose group compared to the body weight gains in the control group. The decreases in female body weight gain were statistically significant. The cross-fostering study confirmed the decreased body weights not only in F1 pups receiving pre- and postnatal exposure (A2) to SCH 530348, but also F1 pups receiving pre-natal only exposure (A3) as well as F1 pups receiving pre-natal only exposure (A4). For the pre-weaning period PND 1-21, the overall F1 body weight gain decreased 14-15% in Groups A2 and A4, but only 7.6% in Group A3 compared to the control group. These results suggest that postnatal exposure to SCH 530348 had a greater effect on F1 body weight gain than did pre-natal exposure. Therefore, the

effects on F1 body weight gain observed in the first PPND study are more likely due either to non-overt changes in maternal care and/or postnatal pup exposure to SCH 530348 via the milk.

In the first study, the numbers of F2 pups born per litter and the live litter sizes on PND 0 were lower in the mid- and high dose groups than the numbers in the control group. Although the mean values were within the historical control range and the differences from control were not statistically significant, the sponsor considered the increased mortality and the decreased postnatal survival of F2 pups in the mid and high dose groups compared to the control group from PND 0-7 related to administration of SCH 530348 to F0 dams. The decrease in percent survival from PND 1 to 7 was statistically significant in the high dose group and the value was below the historical control range. In the second study, the mean number of F2 pups born and the mean F2 live litter size for the F1 animals receiving pre- and postnatal exposure (Group A2) prior to cross-fostering were 7.5% lower than the values for the concurrent control Group A1. Although these decreased values are within the historical control range, the decreases were statistically significant and consistent with the statistically significant decreases in the number of implantation sites in the F1 females from Group A2 compared to Group A1. In addition, similar decreases in the mean number of F2 pups born and the mean F2 live litter size were observed for the F1 animals from the F0 dams treated with 25 and 50 mg/kg SCH 580348 in the first PPND study. However, after cross-fostering, no clear difference was observed in F2 survival among the groups in the second study.

In the first study, mean F2 body weight gains in the high dose group decreased at least 20% from PND 1 to 7 compared to those the control group and resulted in decreased mean body weights in the high dose group on PND 4 and PND 7 that were below the minimum of the historical control range. However, in the second study, mean F2 body weights and mean F2 body weight gains were not significantly different among the groups. Because of the absence of a clear SCH 530348-related effect on F2 survival or growth in the second study the sponsor concluded that the effects on F2 survival or body weight gain observed in the first PPND study were incidental and not related to the administration of SCH 530348. The sponsor also extended this conclusion to the effects on F1 survival; however, the reviewer does not agree with this extension to F1 survival.

Sensory function and neurobehavioral development in the F1 pups were assessed in the first study, but not the second PPND study. In the acoustic startle assay on PND 20, both the high dose F1 males and females exhibited statistically significant increases in Tmax (the latency to Vmax). The Tmax values in both sexes were greater than the maximum historical control value, indicating a slower response to the auditory startle stimulus. In the locomotor assays on PND 21, the mean overall and cumulative total and ambulatory locomotor activity counts in the high dose F1 female group decreased compared to the counts in the control group, indicating a reduction in exploratory behavior. However, the high dose F1 females did display >95% habituation. In contrast, high dose F1 males did not display a decrease in overall total and ambulatory locomotor activity, but displayed only 50-54% habituation. Additional testing of acoustic startle and locomotor activity on PND 60 and 61 indicated that the treatment-related effects on auditory response and locomotor activity observed on PND 20 and 21 did not appear to continue into the post-weaning period.

Learning and memory were assessed from PND 22 to 27 using a Biel water-filled T maze. Treatment of F0 dams with SCH 530348 did not have a clear effect on learning in F1 pups in the first ten trials. However, a potential effect on memory exists in mid and high dose F1 female groups. The mean values for the time to escape and in number of errors/trial in memory Trial 11 for the mid and high dose F1 females are above the maximum historical control values and exhibit dose-dependent increases compared to the values in the control group. The difference from the control group is statistically significant in the high dose group based on the reviewer's calculations. Furthermore, the number of F1 females/group with values above the maximum historical control value increased with dose. However, the F1 male groups did not display these effects on memory.

All PARs, including PAR-1, are widely expressed in the central and peripheral nervous systems throughout development (Luo et al. 2007). PAR-1 mRNA detected by in situ hybridization is present at low levels and is widely distributed in the late embryonic and early postnatal nervous system (Niclou et al. 1998) with greater expression in some cells of the cerebellum, the thalamus, the hippocampus and the cortex. In the adult rat brain, PAR-1 protein detected by immunohistochemistry is abundant in the hippocampus, particularly in the pyramidal cell layers of the CA2 and CA3 region, while lower levels of expression are observed in cortex, thalamus, hypothalamus, striatum, and amygdala (Striggow et al. 2001).

Multiple studies indicate the direct involvement of PARs, particularly PAR-1, in brain development and function. PAR-1 activation induced by thrombin (10 pM–10 nM) or PAR-1 activating peptide protects rat hippocampal neurons and astrocytes from in vitro cell death in response to glutamate, hypoglycemia, oxidative stress, or β-amyloid aggregation (Gorbacheva et al. 2006; Pike et al. 1996; Striggow et al. 2000; Vaughan et al. 1995). PAR-1 was also documented to play a role in cell proliferation, differentiation, and migration during neural development (Debeir et al. 1998; Rohatgi et al. 2004).

The hippocampus is part of a system required for declarative memory in humans and spatial, as well as contextual, memory in rodents (Kandel 2009). Activation of PAR-1 either through proteolytic activity of thrombin or through a PAR-1 activating peptide potentiated hippocampal N-methyl-D-aspartate (NMDA) receptor responses in CA1 pyramidal cells of wild-type mice and rats (Gingrich et al. 2000). In addition, the potentiation of the NMDA receptor by thrombin was significantly attenuated in hippocampal neurons from PAR-1 -/- mice lacking PAR-1 function. Using PAR-1 knockout mice, Almonte et al. (2007) demonstrated that loss of PAR-1 leads to learning and memory deficits in passive avoidance, cued fear conditioning, and contextual fear conditioning tasks

Although NMDA receptor function or expression was normal in PAR -/- mice (Gingrich et al. 2000; Lee et al. 2007; Almonte et al. (2013), the loss of PAR-1 function impaired the induction and ceiling for NMDA receptor-dependent long-term potentiation (LTP), resulting in deficits in hippocampus-dependent memory formation and long-term synaptic plasticity in the hippocampus (Almonte et al. 2013). Both PAR-1 (Striggow et al. 2001), and NMDA receptor subunits (Ishii et al. 1993) are highly expressed in brain regions involved with emotional learning, including hippocampus and amygdala. Almonte et al. (2013) propose that PAR-1 is a novel regulator of synaptic responses and

PAR-1 activity is critical for NMDA receptor-dependent memory formation. These results are consistent with previous studies indicating that serine proteases can impact learning by acting through PAR-1 (Pang et al. 2004; Pawlak et al. 2002; 2005).

The finding that F1 females, but not F1 males, displayed decreases in memory in the SCH 530848 PPND study does not mean the finding can be ignored. First, sex differences exist in brain function and behavior (Mizuno and Geize 2010), including hippocampus-dependent learning and memory (Cahill 2006). For example, perinatal exposure to dexamethasone did not result in adverse clinical neurological outcomes, but did result in deficits in learning and memory functions with exposed females in all age groups more greatly affected than the exposed males (Machhor et al. 2004). Second, spatial maze test methods differ in their ability to detect deficits in learning and memory. Akaike et al. (1994) compared the usefulness of four spatial maze methods (single T-maze, Biel water maze, Morris water maze, and radial eight-arm maze) using F1 rats with different degrees of microcephaly induced by methylnitrosourea (MNU) on day 13 of gestation. Although the Biel water maze test detected increases in swimming time and number of errors in the 5 mg/kg group, but not the 3 mg/kg group, in the first trial path, no effect was observed in the retention and reverse trial path tests. Among the four maze tests, only the radial eight-arm maze test could detect the effect of both doses of MNU and the Biel test ranked below the Morris water maze, and radial eight-arm maze tests. Therefore, the Biel test used by the sponsor may not have been sensitive enough to detect deficits induced by SCH 530848 in males.

In a distribution study in pregnant female rats, substantial amounts of [^{14}C]-SCH 530348 transfer across the placenta into fetal blood and tissues. The distribution to fetal tissues was widespread and included the brain at levels higher than the level in fetal blood. Therefore, in the PPND studies in which F0 dams were dosed beginning on gestation day 6, the fetuses were exposed to SCH 530348 prenatally.

In another distribution study (DM27229), the sponsor demonstrated that exposure to [^{14}C]-SCH 530348-derived radioactivity in nursing pups was 34% of that in dams, based on comparison of plasma $AUC_{(0\text{-}48\ hr)}$ values, following a single oral dose of 30 mg/kg [^{14}C]-SCH 530348 to lactating, 12-day postpartum dams. The sponsor estimated exposure to SCH 530348 and/or its metabolites in human infants via milk consumption to be approximately 6% of the orally administered dose. Assuming a milk flow of 2.75 mL/hr (McGuire, 1995), the reviewer calculations indicated that approximately 7% of the maternal SCH 530348 dose is excreted into rat milk over a 24 hour period. A F0 dam receiving the high dose of 50 mg/kg in the PPND studies would transfer 1.05 mg of SCH 530348 to her pups through the milk. Assuming equal allocation of all milk supplied by the dam and the mean litter number, each pup would receive maximum doses of 11.7 mg/kg on PND 1 with 15 pup/litter and 16.4 mg/kg on PND 4 after culling to 8 pups/litter. On PND 12, the estimated dose would be 6.23 mg/kg or 12% of the maternal dose. This is less than half of the 34% expected based on the distribution study DM27229. However, drug exposures up to 10 fold higher in young pre-weaning rats, particularly between PND 10 and 15, compared to exposures in older post-weaning rats have been observed for other drugs, including rivaroxaban (NDA 202439) and apixaban (NDA 22512).

The principal drug-related compounds in rat plasma were the parent SCH 530348 and its amine metabolite (M19). Likewise the form of the [^{14}C]-SCH 530348 derived radioactivity excreted into rat milk was not specifically determined, but was most likely a mixture of the parent and the amine metabolite. The study in lactating, 12-day postpartum dams showed that levels of [^{14}C]-SCH 530348-derived radioactivity in milk were 6-fold higher than that in the plasma of the dams. Consequently, exposure to [^{14}C]-SCH 530348-derived radioactivity in nursing pups was 34% of that in dams based on comparison of plasma $AUC_{(0\text{-}48\ hr)}$ values. The decreased absorption of the [^{14}C]-SCH 530348-derived radioactivity in the pups may partially be due to the presence of the amine metabolite in milk. The amine metabolite is more polar than the parent SCH 530348 and is less likely to be absorbed. Study DM27219 with the intraduodenal administration of donor bile into recipient rats illustrated the lower absorption of the SCH 530348 metabolites in recipient rats.

The sponsor and reviewer estimated exposure to SCH 530348 and/or its metabolites in human infants via milk consumption to be approximately 6% to 7% of the orally administered dose. The adult maintenance dose of SCH 530348 in the Phase 3 trial was 2.5 mg/day or 42 µg/kg. If the transfer of SCH 530348 and/or its metabolites in humans is similar to that in rats, then a nursing mother would transfer 7% of the orally administered dose or 175 µg of SCH 530348 and/or its metabolites to her infant. Given body weight ranges for neonates and 1 year old infants of 2-5 kg and 7-11 kg, respectively, neonates and 1 year old infants would receive SCH 530348 doses of 35-88 µg/kg and 16-25 µg/kg, respectively, if all drug-related material in milk is in the form of the parent. The reviewer does not know whether the amine metabolite is pharmacologically active. However, the M20 metabolite was shown to be at least as active against PAR-1 as the parent. Furthermore, the sponsor has shown that repeated doses of 1 mg SCH 530348 to adult humans (1000 µg/60 kg = 16.6 µg/kg) results in inhibition of platelet aggregation by 50%. This means that infants up to 1 year of age, who consume milk from mothers being treated with SCH 530348, could likely have significantly decreased platelet aggregation. The reviewer recommends that mothers either not nurse while taking SCH 530348 or discontinue SCH 530348 treatment while nursing. The label should be appropriately worded.

The distribution study in rats clearly showed that SCH 530348 not only distributed to, but is retained for a long time by pigmented tissues – the skin and particularly the eye. PAR-1 receptors have been shown to be present and functionally active in the retina (Rohatgi et al. 2003), cornea (Lang et al. 2003; Satpathy et al. 2004), lens (James et al. 2005), retinal ganglion (Luo et al. 2005) and ocular conjunctiva (Nickel et al. 2006). However, the retention of SCH 530348 in the eye is unlikely to be the result of PAR-1 binding, since retention was only observed in the pigmented Long Evans rat, but not the Sprague Dawley albino rat. The sponsor concluded that SCH 530348 is bound to the melanin in pigmented tissues. SCH 530348 will likely distribute to and be retained by pigmented tissues in primates and humans.

Leblanc et al. (1998) maintain that the binding of drugs to eye melanin is not predictive of ocular toxicity. However, SCH 530348 has at least three of the four characteristics that are indicative of the potential to induce phototoxicity (Roberts 2002). It is a heterocyclic, tricyclic, lipophilic compound that is retained in the eye and skin by its

interaction with melanin. Furthermore, the UV-visible spectra of SCH 530348 in acidic, neutral, and alkaline media show absorption maxima at wavelengths greater than 290 nm. Therefore, SCH 530348 was evaluated for the potential to cause phototoxicity after three daily doses. In contrast to the positive control, 8-methoxypsoralen, SCH 530848 did not induce phototoxicity in either the eye or the skin.

12 References

Adams MN, Ramachandran R, Yau MK, Suen JY, Fairlie DP, Hollenberg MD, Hooper JD. 2011. Structure, function and pathophysiology of protease activated receptors. Pharmacol Ther.; 130(3): 248-82.

Ahn HS, Foster C, Boykow G, Arik L, Smith-Torhan A, Hesk D, Chatterjee M. 1997. Binding of a thrombin receptor tethered ligand analogue to human platelet thrombin receptor. Molecular Pharmacology, 51: 350-356.

Akaike M, Ohno H, Tsutsumi S, Omosu M. 1994. Comparison of four spatial maze learning tests with methylnitrosourea-induced microcephaly rats. Teratology; 49(2): 83-89.

Almonte AG, Hamill CE, Chhatwal JP, Wingo TS, Barber JA, Lyuboslavsky PN, David Sweatt J, Ressler KJ, White DA, Traynelis SF. 2007. Learning and memory deficits in mice lacking protease activated receptor-1. Neurobiol Learn Mem.; 88(3): 295-304.

Almonte AG, Qadri LH, Sultan FA, Watson JA, Mount DJ, Rumbaugh G, Sweatt JD. 2013. Protease-activated receptor-1 modulates hippocampal memory formation and synaptic plasticity. J Neurochem.; 124(1): 109-22.

Andrade-Gordon P, Derian CK, Maryanoff BE, Zhang HC, Addo MF, Cheung Wm, Damiano BP, D'Andrea MR, Darrow AL, de Garavilla L, Eckardt AJ, Giardino EC, Haertlein BJ, McComsey DF. 2001. Administration of a potent antagonist of protease activated receptor-1 (PAR-1) attenuates vascular restenosis following balloon angioplasty in rats. J Pharmacol Exp Ther.; 298(1): 34-42.

Austin KM, Covic L, Kuliopulos A. 2013. Matrix metalloproteases and PAR1 activation. Blood. ; 121(3): 431-9.

Bae JS, Yang L, Manithody C, Rezaie AR. 2007. The ligand occupancy of endothelial protein C receptor switches the protease-activated receptor 1-dependent signaling specificity of thrombin from a permeability-enhancing to a barrier-protective response in endothelial cells. Blood; 110(12): 3909-16.

Biel WC. 1940. Early age differences in maze performance in the albino rat. J. Genet. Psychol.; 56: 439-53.

Bir N, Lafargue M, Howard M, Goolaerts A, Roux J, Carles M, Cohen MJ, Iles KE, Fernández JA, Griffin JH, Pittet JF. Cytoprotective-selective activated protein C attenuates Pseudomonas aeruginosa-induced lung injury in mice. Am J Respir Cell Mol Biol.; 45(3): 632-41

Blackburn JS, Brinckerhoff CE. 2008. Matrix metalloproteinase-1 and thrombin differentially activate gene expression in endothelial cells via PAR-1 and promote angiogenesis. Am J Pathol.; 173(6): 1736-46.

Brass LF, Vassallo RR Jr, Belmonte E, Ahuja M, Cichowski K, Hoxie JA. 1992. Structure and function of the human platelet thrombin receptor. Studies using monoclonal antibodies directed against a defined domain within the receptor N terminus. J. Biol. Chem. 267: 13795–13798.

Cahill L. 2006. Why sex matters for neuroscience. Nat. Rev. Neurosci.; 7: 477–484

Cheung WM, D'Andrea MR, Andrade-Gordon P, Damiano BP. 1999. Altered vascular injury responses in mice deficient in protease-activated receptor-1. Arterioscler Thromb Vasc Biol. 19(12):3014-24.

Chintala M, Strony J, Yang B, Kurowski S, Li Q. 2010. SCH 602539, a protease-activated receptor-1 antagonist, inhibits thrombosis alone and in combination with cangrelor in a Folts model of arterial thrombosis in cynomolgus monkeys. Arterioscler Thromb Vasc Biol.; 30(11): 2143-9.

Connolly AJ, Ishihara H, Kahn ML, Farese RV Jr, Coughlin SR. 1996. Role of the thrombin receptor in development and evidence for a second receptor. Nature. 381: 516-519.

Connolly TM, Condra C, Feng DM, Cook JJ, Stranieri MT, Reilly CF, Nutt RF, Gould RJ. 1994 Species variability in platelet and other cellular responsiveness to thrombin receptor- derived peptides. Thromb. Haemost. 72: 627– 633.

Côté HC, Bajzar L, Stevens WK, Samis JA, Morser J, MacGillivray RT, Nesheim ME. 1997. Functional characterization of recombinant human meizothrombin and Meizothrombin(desF1). Thrombomodulin-dependent activation of protein C and thrombin-activatable fibrinolysis inhibitor (TAFI), platelet aggregation, antithrombin-III inhibition. J Biol Chem.; 272(10): 6194-200.

Coughlin SR. 2000. Thrombin signalling and protease-activated receptors. Nature 407: 258-264.

Darrow AL, Fung-Leung WP, Ye RD, Santulli R3, Cheung WM, Derian CK, Burns CL, Damiano RP, Zhou L, Keenan CM, Peterson PA, Andrade-Gordon P. 1996. Biological consequences of thrombin receptor deficiency in mice. Thromb Haemost. 76: 860–866.

Davey MG, Luscher EF 1967. Actions of thrombin and other coagulant and proteolytic enzymes on blood platelets. Nature 216: 857-858.

Debeir T, Benavides J, Vigé X. 1998. Involvement of protease-activated receptor-1 in the in vitro development of mesencephalic dopaminergic neurons. Neuroscience; 82(3): 739-52.

Derian CK, Damiano BP, Addo MF, Darrow AL, D'Andrea MR, Nedelman M, Zhang HC, Maryanoff BE, and Andrade-Gordon P. 2003. Blockade of the thrombin receptor protease- activated receptor-1 with a small-molecule antagonist prevents thrombus formation and vascular occlusion in nonhuman primates. J Pharmacol Exp Ther.; 304: 855– 861.

Derian CK, Santulli RJ, Tomko KA, Haertlin BJ, Andrade-Gordon P. 1995. Species differences in platelet responses to thrombin and SFLLRN. Receptor-mediated calcium mobilization and aggregation, and regulation by protein kinases. Thrombosis Research. 78: 505-519

Feistritzer C, Riewald M. 2005. Endothelial barrier protection by activated protein C through PAR1-dependent sphingosine 1-phosphate receptor-1 crossactivation. Blood.; 105(8): 3178-84.

Finigan JH, Dudek SM, Singleton PA, Chiang ET, Jacobson JR, Camp SM, Ye SQ, Garcia JG. 2005. Activated protein C mediates novel lung endothelial barrier enhancement: role of sphingosine 1-phosphate receptor transactivation. J Biol Chem.; 280(17): 17286-93.

(b) (4)

Gingrich MB, Junge CE, Lyuboslavsky P, Traynelis SF. 2000. Potentiation of NMDA receptor function by the serine protease thrombin. J Neurosci.; 20(12): 4582-4595.

Gorbacheva LR, Storozhevykh TP, Pinelis VG, Ishiwata S, Strukova SM. 2006 Modulation of hippocampal neuron survival by thrombin and factor Xa. Biochemistry(Mosc.); 71: 1082–1089.

Hackeng TM, Tans G, Koppelman SJ, de Groot PG, Rosing J, Bouma BN. 1996. Protein C activation on endothelial cells by prothrombin activation products generated in situ: meizothrombin is a better protein C activator than alpha-thrombin. Biochem J.; 319 (Pt 2): 399-405.

Hollenberg MD, Compton SJ. 2002. International Union of Pharmacology. XXVIII. Proteinase-activated receptors. Pharmacol Rev. 54(2):203-17.

Hayward CP. 2011. Diagnostic evaluation of platelet function disorders. Blood Rev.; 25(4): 169-73.

Hung DT, Vu TH, Nelken NA, and Coughlin SR. 1992.Thrombin induced events in non-platelet cells are mediated by the unique proteolytic mechanism established for the cloned platelet thrombin receptor. J Cell Biol.; 116: 827–832.

Ishii T, Moriyoshi K, Sugihara H, Sakurada K, Kadotani H, Yokoi M, Akazawa C, Shigemoto R, Mizuno N, Masu M, Nakanishie S. 1993. Molecular characterization of the family of the N-methyl-D-aspartate receptor subunits. J Biol Chem.; 268(4): 2836-43.

James C, Collison DJ, Duncan G. 2005. Characterization and functional activity of thrombin receptors in the human lens. Invest Ophthalmol Vis Sci.; 46(3): 925-32.

Kahn ML, Nakanishi-Matsui M, Shapiro MJ, Ishihara H, Couglin SR. 1999 Protease activated receptors 1 and 4 mediate activation of human platelets by thrombin. J. Clin Invest.; 103: 879-887.

Kahn ML, Zheng YW, Huang W, Bigornia V, Zeng D, Moff S, Farese RV Jr, Tam C, Coughlin SR. 1998. A dual thrombin receptor system for platelet activation. Nature.; 394(6694): 690-4.

Kahn ML, Nakanishi-Matsui M, Shapiro MJ, Ishihara H, Coughlin SR. 1999. Protease-activated receptors 1 and 4 mediate activation of human platelets by thrombin. J Clin Invest.; 103(6): 879-87.

Kandel ER. 2009. The biology of memory: a forty-year perspective. J. Neurosci.; 29: 12748–12756.

Kaufmann R, Hoffmann J, Ramakrishnan V, Nowak G. 1998. Intermediates of prothrombin activation induce intracellular calcium mobilization in rat aortic smooth muscle cells. Thromb Haemost.; 80(6): 1018-21.

Keenan KP, Laroque P, Ballam GC, Soper KA, Dixit R, Mattson BA, Adams SP, Coleman JB. 1996. The effects of diet, ad libitum overfeeding, and moderate dietary restriction on the rodent bioassay: the uncontrolled variable in safety assessment. Toxicol Pathol.; 24(6):757-68.

Lang R, Song PI, Legat FJ, Lavker RM, Harten B, Kalden H, Grady EF, Bunnett NW, Armstrong CA, Ansel JC. 2003. Human corneal epithelial cells express functional PAR-1 and PAR-2. Invest Ophthalmol Vis Sci.; 44(1): 99-105

Leblanc B, Jezequel S, Davies T, Hanton G, Taradach C. 1998. Binding of drugs to eye melanin is not predictive of ocular toxicity. Regul Toxicol Pharmacol. ; 28(2): 124-32.

Lee CJ, Mannaioni G, Yuan H, Woo DH, Gingrich MB, Traynelis SF. 2007. Astrocytic control of synaptic NMDA receptors. J Physiol.; 581(Pt 3): 1057-81.

Luo W, Wang Y, Reiser G. 2007 Protease-activated receptors in the brain: Receptor expression, activation, and functions in neurodegeneration and neuroprotection. Brain Research Reviews; 56: 331–345

Luo W, Wang Y, Reiser G. 2005. Two types of protease-activated receptors (PAR-1 and PAR-2) mediate calcium signaling in rat retinal ganglion cells RGC-5. Brain Res.; 1047(2): 159-67.

Macdonald RL, Olsen RW. 1994. GABAA receptor channels. Annu Rev Neurosci. 17: 569-602

MacFarlane SR, Seatter MJ, Kanke T, Hunter GD, Plevin R, 2001. Proteinase-activated receptors. Pharmacol Reviews 53: 245-282.

Machhor N, Balaji T, Raju TN. 2004. Postnatal dexamethasone and long term learning and memory functions in developing rats: Effect of postnatal age and gender. Life Sci.; 74(15): 1925-35.

Martin BM, Feinman RD, Detwiler TC. 1975. Platelet stimulation by thrombin and other proteases. Biochemistry 14(6):1308-14.

McGuire MK, Littleton AW, Schulze KJ, Rasmussen KM. 1995. Pre- and postweaning food restrictions interact to determine reproductive success and milk volume in rats. J Nutr.; 125(9): 2400-6.

Mizuno K, Giese KP. 2010. Towards a molecular understanding of sex differences in memory formation. Trends Neurosci.; 33(6): 285-91.

Mosnier LO, Sinha RK, Burnier L, Bouwens EA, Griffin JH. 2012. Biased agonism of protease-activated receptor 1 by activated protein C caused by noncanonical cleavage at Arg46. Blood.; 120(26): 5237-46

Nelken NA, Soifer SJ, O'Keefe J, Vu TH, Charo IF, Coughlin SR. J. 1992. Thrombin receptor expression on normal and atherosclerotic arteries. J Clin. Invest. 90: 1614-621.

Nickel TJ, Kabir MH, Talreja J, Stechschulte DJ, Dileepan KN. 2006. Constitutive expression of functionally active protease-activated receptors 1 and 2 in human conjunctival epithelial cells. Mediators Inflamm.; 2006(3): 61359.

Niclou SP, Suidan HS, Pavlik A, Vejsada R, Monard D, 1998. Changes in the expression of protease-activated receptor 1 and protease nexin-1 mRNA during rat nervous system development and after nerve lesion. Eur. J. Neurosci.; 10: 1590–1607

(b) (4)

Offermanns S, Toombs CF, Hu YH, and Simon MI. 1997.Defective platelet activation in G alpha(q)-deficient mice. Nature 389: 183–186.

Olsen RW. 1982. Drug interactions at the GABA receptor-ionophore complex. Annu Rev Pharmacol Toxicol.; 22: 245-77.

Ossovskaya VS, Bunnett NW. 2004 Protease-activated receptors: contribution to physiology and disease. Physiol Rev.; 84(2): 579-621.

Pang PT, Teng HK, Zaitsev E, Woo NT, Sakata K, Zhen S, Teng KK, Yung WH, Hempstead BL, Lu B. 2004. Cleavage of proBDNF by tPA/plasmin is essential for long term hippocampal plasticity. Science; 306: 487–491.

Pawlak R, Nagai N, Urano T, Napiorkowska-Pawlak D, Ihara H, Takada Y, Collen D, Takada A. 2002. Rapid, specific and active site-catalyzed effect of tissue plasminogen activator on hippocampus-dependent learning in mice. Neuroscience; 113: 995–1001.

Pawlak R, Rao BS, Melchor JP, Chattarji S, McEwen B, Strickland S. 2005. Tissue plasminogen activator and plasminogen mediate stress-induced decline of neuronal and cognitive functions in the mouse hippocampus. Proc. Natl. Acad. Sci. U. S. A.; 102: 18201–18206.

Pike CJ, Vaughan PJ, Cunningham DD, Cotman CW. 1996. Thrombin attenuates neuronal cell death and modulates astrocyte reactivity induced by β-amyloid in vitro. J. Neurochem.; 66: 1374–1382.

Rajagopal S, Ahn S, Rominger DH, Gowen-MacDonald W, Lam CM, Dewire SM, Violin JD, Lefkowitz RJ. 2011. Quantifying ligand bias at seven-transmembrane receptors. Mol Pharmacol.; 80(3): 367-77.

Ramachandran R, Noorbakhsh F, Defea K, Hollenberg MD. 2012. Targeting proteinase-activated receptors: therapeutic potential and challenges. Nat Rev Drug Discov.; 11(1): 69-86.

Roberts JE. 2002. Screening for ocular phototoxicity. Int J Toxicol.; 21(6): 491-500.

Rohatgi T, Sedehizade F, Reymann KG, Reiser G. 2004. Protease-activated receptors in neuronal development neurodegeneration, and neuroprotection: thrombin as signaling molecule in the brain. Neuroscientist; 10: 501–512.

Rozmiarek H. 1999. Convulsions in rodents related to frequent handling. Lab Anim Sci. 49(5): 468-9.

Sambrano GR, Weiss EJ, Zheng YW, Huang W, Couglin SR. 2001. Role of thrombin signaling in plateletes in haemostatsis and thrombosis. Nature 413: 74-78.

Satomoto K, Kuroiwa Y, Masubuchi Y, Uemura H, Oshima Y, Okazaki S. 2012. Spontaneous convulsions in Sprague-Dawley rats in carcinogenicity studies. J Toxicol Sci.; 37(3): 645-7

Satpathy M, Gallagher P, Lizotte-Waniewski M, Srinivas SP. 2004.Thrombin-induced phosphorylation of the regulatory light chain of myosin II in cultured bovine corneal endothelial cells. Exp Eye Res.; 79(4): 477-86

Schuepbach RA, Madon J, Ender M, Galli P, Riewald M. 2012. Protease-activated receptor-1 cleaved at R46 mediates cytoprotective effects. J Thromb Haemost.; 10(8): 1675-84.

Soh UJ, Trejo J. 2011. Activated protein C promotes protease-activated receptor-1 cytoprotective signaling through β-arrestin and dishevelled-2 scaffolds. Proc Natl Acad Sci U S A.; 108(50): E1372-80.

Striggow F, Riek M, Breder J, Henrich-Noack P, Reymann KG, Reiser G, 2000. The protease thrombin is an endogenous mediator of hippocampal neuroprotection against ischemia at low concentrations but causes degeneration at high concentrations. Proc. Natl. Acad. Sci. U. S. A.; 97: 2264–2269

Striggow F, Riek-Burchardt M, Kiesel A, Schmidt W, Henrich-Noack P, Breder J, Krug M, Reymann KG, Reiser G. 2001. Four different types of protease-activated receptors are widely expressed in the brain and are upregulated in hippocampus by severe ischemia. The European Journal of Neuroscience; 14(4): 595–608.

Takada M, Tanaka H, Yamada T, Ito O, Kogushi M, Yanagimachi M, Kawamura T, Musha T, Yoshida F, Ito M, Kobayashi H, Yoshitake S, Saito I. 1998. Antibody to thrombin receptor inhibits neointimal smooth muscle cell accumulation without causing inhibition of platelet aggregation or altering hemostatic parameters after angioplasty in rat. Circ Res.; 82(9): 980-7.

Tello-Montoliu A, Tomasello SD, Ueno M, Angiolillo DJ. 2011. Antiplatelet therapy: thrombin receptor antagonists. Br J Clin Pharmacol.; 72(4): 658-71.

Tennekes H, Kaufmann W, Dammann M, van Ravenzwaay B. 2004. The stability of historical control data for common neoplasms in laboratory rats and the implications for carcinogenic risk assessment. Regul Toxicol Pharmacol.; 40(3): 293-304.

Trivedi V, Boire A, Tchernychev B, Kaneider NC, Leger AJ, O'Callaghan K, Covic L, Kuliopulos A. 2009. Platelet matrix metalloprotease-1 mediates thrombogenesis by activating PAR1 at a cryptic ligand site. Cell.; 137(2): 332-43.

Vaughan PJ, Pike CJ, Cotman CW, Cunningham DD. 1995. Thrombin receptor activation protects neurons and astrocytes from cell death produced by environmental insults. J Neurosci.; 15: 5389−5401.

van Nieuw Amerongen GP, Musters RJ, Eringa EC, Sipkema P, van Hinsbergh VW.2008. Thrombin-induced endothelial barrier disruption in intact microvessels: role of RhoA/Rho kinase-myosin phosphatase axis. Am J Physiol Cell Physiol.; 294(5): C1234-41

van Ravenzwaay B, Tennekes H. 2002. A Wistar rat strain prone to spontaneous liver tumor development: implications for carcinogenic risk assessment. Regul Toxicol Pharmacol.; 36(1): 86-95.

Vu TH, Hung DT, Wheaton VI, Coughlin SR. 1991 Molecular cloning of a functional thrombin receptor reveals a novel proteolytic mechanism of receptor activation. Cell 64: 1057-1068.

Zhang C, Srinivasan Y, Arlow DH, Fung JJ, Palmer D, Zheng Y, Green HF, Pandey A, Dror RO, Shaw DE, Weis WI, Coughlin SR, Kobilka BK. 2012. High-resolution crystal structure of human protease-activated receptor 1. Nature; 492(7429): 387-92.

13 Appendix/Attachments

Appendix 1: Reviewer's Summary of Impurities

(b) (4)

Batch used in indicated toxicology study	3-mo monkey 3-mo rat, 6-mo rat	12-mo monkey, 2 yr rat & mouse	2 yr rat & mouse.	1-mo rat with impurities			
Maximum (NOAEL) animal dose, mg/kg	(b) (4)						
HED (mg/kg) based on mg/m^2							

[T] [Value stated by sponsor in Table 1, CMC Impurities 3.2.S.3.2] Value based on human dose of 2.5 mg QD vorapaxar sulfate = 2.08 mg vorapaxar base, [‡] Value based on % in bold text for animal toxicology study indicated, dash (-) = less than limit of quantification, NI = not indicated; NT = not tested

Sources: Data from 3.2.S.4.4 BATCH ANALYSES, Table 1, 4, 5, 6, 7. Results from HPLC 2

Appendix 2: Nonclinical Study Reports submitted to NDA 204886

Number	Title
	The reports reviewed under IND 71394 are in bold text with a shaded background
D46293	**Pharmacology Of A Selective Orally Active Thrombin Receptor Antagonist, SCH 530348**
D49206	Pharmacology Of A Potent, Orally Active Thrombin Receptor Antagonist, SCH 602539
D56013	Effects of SCH 2046273, a metabolite of the PAR 1 antagonist SCH 530348, on calcium efflux in human coronary artery smooth muscle cells
PD001	Characterization Of SCH 530348 (Vorapaxar) Binding Kinetics
D-46311	**Biochemical Pharmacology Of SCH 530348, Thrombin Receptor Antagonist**
D-47153	**SPRI Counterscreening Of SCH 530348 At G Protein-Coupled Receptors**
D44255	**Ancillary Pharmacology Studies on SCH 530348: Cardiovascular Effects in Conscious Cynomolgus Monkeys, In Vitro Effects on hERG Current and Effects on CNS, Respiraory, Renal and Gastrointestinal Function in Rats**
SN 02127	**A Single Oral (Gavage) Dose Cadiovascular Safety Study of SCH 530348 in Male Cynomolgus Monkeys**
SN 02128	**the Acute Central Nervous System Pharmacological Profile of SCH 530348 Following Oral Administration in Rats**
SN 02129	**Effect of Single Oral Dose Administration of SCH 530348 on Respiratory Parameters in Rats**
SN 02203	**Effect of SCH 530348 on Action Potential Parameters in Dog Isolated Cardiac Purkinje Fibres**
SN 03128	**Assessment of Potential Bleeding Liability of SCH 530348 Co-Administered with Aspirin and Clopidogrel in Anesthesized Cynomolgus Monkeys**
SN 06077	**Two-week bleeding liability study of SCH 530348 in Cynomolgus Monkeys**
DM27719	Validation of a 96-Well Sample Processing and Liquid Chromatographic-Tandem Mass Spectrometic Method for the Determination of SCH 530348 and SCH 2046273 Concentrations in Rat Plasma
DM27720	Validation of a 96-Well Sample Processing and Liquid Chromatographic-Tandem Mass Spectrometic Method for the Determination of SCH 530348 and SCH 2046273 Concentrations in Mouse Plasma
DM27722	Validation of a 96-Well Sample Processing and Liquid Chromatographic-Tandem Mass Spectrometic Method for the Determination of SCH 530348 and SCH 2046273 Concentrations in Monkey Plasma
DM27723	Validation of a 96-Well Sample Processing and Liquid Chromatographic-Tandem Mass Spectrometic Method for the Determination of SCH 530348 and SCH 2046273 Concentrations in Rabbit Plasma
SN 02613	**SCH 530348: Validation of a Liquid Chromatographic-Tandem Mass Spectrometric Method for the Determination of SCH 530348 in Rat Plasma**
SN 02614	**SCH 530348: Validation of a High Performance Liquid Chromatographic-Tandem Mass Spectrometric Method for the Determination of SCH 530348 in Monkey Plasma**
SN 03043	**SCH 530348: In Vivo Stability Of Radiolabel After Administration**
SN 03077	SCH 530348: Method Development for the Profiling and Structural Characterization of Metabolites in Various Biological Matrices
SN 03136	**SCH 530348: Validation of a 96-Well Liquid Chromatographic-Tandem**

Number	Title
	Mass Spectrometric Method for the Determination of SCH 530348 in Rabbit Plasma
SN 03137	SCH 530-348: Validation of a 96-Well Liquid Chromatographic-Tandem Mass Spectrometric Method for the Determination of SCH 530348 in Mouse Plasma
DM 28074	SCH 530348: Pharmacokinetics Of SCH 530348 Following A Single Oral Dose Of Various Capsule Or Tablet Formulations To Male Cynomolgus Monkeys
SN 03223	SCH 530348: Pharmacokinetic Evaluation in Mice Following a Single Oral Gavage Administration
SN 03329	**Exploratory Nonclinical Pharmacokinetics and Metabolism of SCH 530348**
SN 04317	Single-dose oral (gavage) comparative toxicokinetic study of SCH 530348 in rats
SN 05003	Single-dose oral (gavage) comparative toxicokinetic study of SCH 530348 in mice
SN 08257	Toxicokinetic Study of SCH 530348 Administered Orally by Gavage in Pregnant Rats
SN 08378	**Two Week Toxicokinetic Study of SCH 530348 and SCH 204273 (a Metabolite of SCH 530348) in Rats**
SN 08379	**Two Week Toxicokinetic Study of SCH 530348 and SCH 2046273 (a Metabolite of SCH 530348) in Mice**
SN 08380	Toxicokinetic Study Of SCH 530348 And SCH 2046273 (A Metabolite Of SCH 530348) Administered Orally By Gavage In Pregnant Rabbits
SN 08381	A Two-Week Oral (Nasogastric) Gavage Toxicokinetic Study Of SCH 530348 In Cynomolgus Monkeys
DM27226	**SCH 530348: Placental transfer of 14C-SCH 530348-derived radiocarbon following a single oral dose to pregnant rats**
DM27463	**SCH 530348: In Vitro Binding Of SCH 530348 To Purified Human Serum Proteins By Equilibrium Dialysis**
PK005	**SCH530348: In vitro binding of SCH 530348 (L-002409410) and SCH 2046273 (L-003189067) to human plasma proteins using equilibrium dialysis**
PK006	**SCH 530348: In vitro binding of a metabolite of SCH 530348, SCH 2046273 (L-003189067), to pregnant New Zealand white rabbit, cynomolgus monkey, and CD1-mouse plasma proteins using equilibrium dialysis**
SN 03342	**SCH 530348: Tissue Distribution and Excretion Pattern of 14C-SCH 530348-Derived Radiocarbon After a Single Oral Dose to Male and Female, Albino and Pigmented Rats**
SN 03358	Pilot protein binding studies for SCH 530348 (thrombin receptor antagonist)
SN 03359	**SCH 530348: In Vitro Binding of SCH 530348 to Mouse, Rat, Rabbit, Monkey and Human Plasma Proteins Using Equilibrium Dialysis**
DM27220	**SCH 530348: excretion and metabolism of 14C-SCH 530348-derived radioactivity after a single 75-mg/kg oral suspension administration to male mice**
DM27633	Metabolic Profiling of SCH 530348 Following Multiple Oral Doses of 20 mg/kg SCH 530348 to Non-Fasted Female New Zealand White Rabbits
DM28002	**An In vitro Enzymology Study of SCH 2046273 (M20 metabolite)**
PK007	**Incubation Of SCH 530348 (Mk-5348) With Recombinant Human CYP2C8 (PK007)**
SN 03343	**Identification of Human Cytochrome P450 Enzyme(s) Capable of Metabolizing SCH 530348**
SN 04025	**SCH 530348: Identification of human cytochrome P450 enzyme(s)**

Number	Title
	responsible for the metabolism of SCH 530348
SN 04919	**Metabolism Of 14C-SCH 530348 After Oral Administration Of 14-SCH 530348 Suspension To Male And Female Rats**
DM27219	**SCH 530348: Biliary excretion, enterohepatic circulation, and metabolism of 14C-SCH 530348-derived radioactivity after a single oral 10-mg/kg dose to male and female rats**
DM27229	**Transfer of radioactivity into milk following a single oral administration of 14C-SCH 530348 suspension to 12-day postpartum rats**
SN 03327	**SCH 530348: Mass Balance Study of 14C-SCH 530348 in Male and Female Sprague Dawley Rats Following a Single Oral or Intravenous Administration**
SN 03328	**SCH 530348: mass balance study of 14C-SCH 530348 in male and female cynomolgus monkeys following a single oral or intravenous administration**
DM27351	**In Vitro Evaluation of SCH 530348 as an Inhibitor of Human Cytochrome P450 Enzymes**
DM27413	In Vitro Evaluation Of SCH 530348 As An Inducer Of Cytochrome P450 Expression In Cultured Human Hepatocytes
DM27415	**SCH 530348: Evaluation Of SCH 530348 As A P-Glycoprotein (P-Gp, MDR1) Inhibitor using Caco-2 Bi-Directional Permeability Assay**
DM27476	**SCH 530348: Caco-2 bi-directional permeability study**
PK008	**Interactions Of MK-5348 With The Human Liver Uptake Transporters, OATP1B1 And Oatp1B3, The Human Renal Uptake Transporters OAT1, OAT3, AND OCT2, And The Human Efflux Transporter BCRP (PK008)**
PK009	**Interactions Of L-003189067-000X002 With The Human Liver Uptake Transporters, OATP1B1 AND OATP1B3, The Human Renal Uptake Transporters OAT1, OAT3, AND OCT2, And The Human Efflux Transporter Bcrp (PK009)**
PK010	**Evaluation Of L-003189067 As A Reversible Inhibitor Of Five Cytochrome P450 Activities In Pooled Human Liver Microsomes (Study 120872)**
PK012	**Passive Permeability of L-003189067 Across LLC-PK1 Monolayers**
PK013	**Evaluation of Vorapaxar and SCH 2046273 as an Inhibition of Selective Gut, Liver, and Renal Transporters (PK013)**
SN 02137	**Acute Rising-Dose Toxicity Study of SCH 530348 in Cynomolgus Monkeys**
SN 02133	**Acute Intraperitoneal Toxicity Study of SCH 530348 in Rats**
SN 02132	**Acute Oral (Gavage) Toxicity Study of SCH 530348 in Rats**
SN 02142	**Three-Month Oral (Gavage) Dose Range-Finding Study of SCH 530348 in Mice**
SN 02139	Six-Month Oral (Gavage) Toxcity and Toxicokinetic Study of SCH 530348 in Cynomolgus Monkeys
SN 02140	**Twelve-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 530348 in Cynomolgus Monkeys**
SN 04056	**Three-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 530348 in Cynomolgus Monkeys**
SN 02126	**One-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 530348 in Cynomolgus Monkeys**
SN 02138	**Six-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 30348 in Rats**
SN 02141	**Three-month Oral (Gavage) Dose Range-Finding Toxicity and Toxicokinetic Study of SCH 530348 in Rats**
SN 02125	**One-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH**

Number	Title
	530348 in Rats
SN 02038	**Exploratory Bacterial Mutagenicity Study of SCH 530348**
SN 02130	**Bacterial Mutagenicity Study of SCH 530348**
SN 02131	**Chromosome Aberration Study of SCH 530348 in Human Peripheral Blood Lymphocytes**
SN 02149	**Mouse Bone Marrow Erythrocyte Micronucleus Study of SCH 530348**
SN 02144	104-Week Carcinogenicity Study of SCH 530348 in Mice
SN02144.xpt	Tumor Tables - Mouse
SN 02143	104-Week Carcinogenicity Study of SCH 530348 in Rats
SN02143.xpt	Tumor Tables - Rat
SN 02134	**Pilot Fertility and Early Embryonic Developmental Toxicity Study of SCH 530348 Administered Orally by Gavage in Rats**
SN 02145	**Fertility and Early Embryonic Developmental Toxicity Study of SCH 530348 Administered Orally by Gavage in Rats**
SN 02135	**Pilot Embryo-Fetal Developmental Toxicity Study of SCH 530348 Administered Orally by Gavage in Rats**
SN 02136	**Dose Range-Finding and Pilot Embryo-Fetal Developmental Toxicity Study of SCH 530348 Administered Orally by Gavage in Rabbits**
SN 02146	**Embryo-Fetal Developmental Toxicity Study of SCH 530348 Administered Orally by Gavage in Rats**
SN 02147	**Embryo-Fetal Developmental Toxicity And Toxicokinetic Study Of SCH 530348 Administered Orally By Gavage In Pregnant Rabbits**
SN 02148	**A prenatal and postnatal developmental toxicity and maternal function study SCH 530348 administered orally by gavage in rats.**
SN 07358	**Cross Fostering Study Of SCH 530348 Administered Orally By Gavage In Rats Repeat Study**
SN 05265	**One-Month Oral (Gavage) Toxicity and Toxicokinetic Study of SCH 530348 with Impurities in Rats**
SN 06042	Chromosome Aberration Study of SCH 530348 with Impurities in Human Peripheral Blood Lymphocytes
SN 06043	**Bacterial Mutagenicity Study of SCH 530348 With Impurities**
SN 8378	Two week toxicokinetic study of SCH 530348 and SCH 2046273 (a metabolite of SCH 530348) in rats
SN 06067	**Three-Day Phototoxicity Study to Determine the Effects of Oral (Gavage) Administration of SCH 530348 on Eyes and Skin in Pigmented Rats**
SN 06068	**Salmonella-Escherichia reverse mutation assay of SCH 530348 in presence of solar stimulated light**
SN 06316	**One-Month Oral (Gavage) Toxicity Study Of SCH 530348 In Male Rats With 4-Week And 12-Week Postdose Periods**
SN 06527	**3-, 7- and 14-Day Oral (gavage) time course toxicity study of SCH 530348 in male rats**
SN 6528	**A 29-day comparative oral (gavage) toxicity study of SCH 530348 in rats with different tissue fixatives**
SN 06554	**Six Week Oral (Gavage) Retinal Function Study Of SCH 530348 In Male Rats With A Two-Week Postdose Period**
SN 10119	Two-Week Oral (Gavage) Investigative Study Of SCH 530348 In Young And Older Male Rats.
SN 10805	Investigative Two-Week Oral (Gavage) Study Of SCH 590709, SCH 2490130 And SCH 602539 In Male Rats
TT#11-1513	Fourteen-day exploratory oral toxicity study of L-003959712 in male Wistar rats with an interim necropsy

Appendix 3: Exec CAC Meeting Minutes - Rat Protocol

cc:\
/Division File, HFD 110
/A. Defelice, Team leader, HFD-110
/P. Harlow, Reviewer, HFD-110
/M. Pease-Fye, CSO/PM, HFD-110
/A. Seifried, HFD-024

Appendix 4: Sponsor's Summary of Tumor Incidence – Study 02143

104-WEEK CARCINOGENICITY STUDY OF SCH 530348 IN RATS

Histopathology (Microscopic Observations)

SN 0214
Page : 1

FINDINGS	TREATMENT	INCIDENCE OF TUMORS (NUMERIC)									
		Males					Females				
		0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3
ADRENAL GLANDS		(50)	(49)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
PHEOCHROMOCYTOMA [M].		1			2						1
(Probably incidental)								1	1		
(Fatal)				1					1		
PHEOCHROMOCYTOMA [B].		4	1	2	6	2	1	1		1	1
(Incidental)				2					1		
(Probably incidental)			1								
ADENOMA [B].		1	2	4	4	1	3	1	1	3	5
(Incidental)			1	1	3	1	5	4	4	1	2
ADENOCARCINOMA [M], cortical.			1								
BONE		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
OSTEOSARCOMA [M].											
(Fatal)									1	1	
BONE MARROW		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
HEMANGIOMA [B].											1
BRAIN		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
GRANULAR CELL TUMOR [B].						1	1				
ASTROCYTOMA [M].					1						
(Probably incidental)					1						
(Fatal)		1			1						
HEART		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
SCHWANNOMA [M].											
(Fatal)				1							
SCHWANNOMA [B].											
(Probably incidental)						1					
KIDNEYS		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(49)	(50)	(49)
ADENOMA [B], tubular cell.									1		
(Incidental)										1	
LIVER		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA [B].					2	1				1	2

	INCIDENCE OF TUMORS (NUMERIC)									
	Males					Females				
FINDINGS / TREATMENT	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3
LIVER	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA [B].										
(Incidental)			1	1			1			2
LUNGS	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
BRONCHIOLO-ALVEOLAR CARCINOMA [M].										
(Probably incidental)		1								
BRONCHIOLO-ALVEOLAR ADENOMA [B].										
(Incidental)			1							
MAMMARY GLANDS	(47)	(43)	(43)	(43)	(45)	(48)	(49)	(49)	(50)	(50)
FIBROMA [B].			1	1				1	1	1
(Incidental)				1					1	
FIBROADENOMA [B].						7	7	6	8	9
(Incidental)	1					5	5	12	8	5
(Probably incidental)						1	1	2		
(Probably fatal)		1							1	
(Fatal)							1	1	1	2
ADENOMA [B].			1			6	6	4	3	4
MAMMARY GLANDS	(47)	(43)	(43)	(43)	(45)	(48)	(49)	(49)	(50)	(50)
ADENOMA [B].										
(Incidental)						6	7	8	7	7
(Probably incidental)								3		
(Probably fatal)								1		
(Fatal)						1				
ADENOCARCINOMA [M].						3	3	1	3	3
(Incidental)	1					1			1	
(Probably incidental)								1	2	1
(Fatal)						4	2	3	1	2
OVARIES						(50)	(50)	(50)	(49)	(50)
SERTOLI CELL TUMOR [B].										
(Incidental)								1		
PANCREAS	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(50)
ISLET CELL CARCINOMA [M].						2	1			
ISLET CELL ADENOMA [B].	2	7	6	3	3	2	1		3	
(Incidental)	2	1		1	5					
PANCREAS	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(50)
ADENOMA [B], acinar cell.	2			1						
(Incidental)								1		
(Probably incidental)				1						
ADENOCARCINOMA [M], acinar cell.										
(Fatal)			1							
PARATHYROID GLANDS	(46)	(41)	(48)	(49)	(46)	(48)	(43)	(45)	(46)	(44)
ADENOMA [B].	1			4			1			
(Incidental)					1		1			
PITUITARY GLAND	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
PARS DISTALIS CARCINOMA [M].	1			1			4			2
(Fatal)	1				3	6	4	4	3	3
PARS DISTALIS ADENOMA [B].	11	11	11	11	9	9	7	10	14	8
(Incidental)	3	3	3	2	7	3	1	4	3	4
(Probably incidental)	2		2	2	2	3	1	7	3	4
(Probably fatal)		1						1		1
(Fatal)	8	5	9	5	5	14	17	12	18	16

		INCIDENCE OF TUMORS (NUMERIC)									
		Males					Females				
FINDINGS	TREATMENT	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3
PITUITARY GLAND		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
PARS INTERMEDIA ADENOMA [B].						1					
(Incidental)					1		1				
(Probably incidental)		1									
PROSTATE GLAND		(50)	(50)	(49)	(50)	(50)					
ADENOCARCINOMA [M].											
(Fatal)		1									
SALIVARY GLANDS		(50)	(49)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
ADENOCARCINOMA [M].											
(Fatal)							1				
SKELETAL MUSCLE		(50)	(49)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)
OSTEOSARCOMA [M].			1								
HEMANGIOSARCOMA [M].											
(Fatal)							1				
SKIN		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LIPOMA [B].				1							
(Incidental)										1	
BASAL CELL TUMOR [B].				1	1	1					
(Incidental)						1					
TRICHOEPITHELIOMA [B].									1		
SARCOMA [M], not otherwise specified.											
(Probably incidental)										1	
(Fatal)								1			
RHABDOMYOSARCOMA [M].											
(Fatal)						1					
PAPILLOMA [B].		1					1				
OSTEOSARCOMA [M].									1		
SCHWANNOMA [B].											
(Fatal)								1			
MAST CELL TUMOR [B].							1				
MALIGNANT FIBROUS HISTIOCYTOMA [M].											
(Fatal)									2		
KERATOACANTHOMA [B].		2	1	1			1				1
(Incidental)		1		1			1				
SKIN		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA [M].											
(Fatal)					1						
HEMANGIOMA [B].											
(Incidental)						1		1			
FIBROSARCOMA [M].					1						
(Probably incidental)							1	1			
(Fatal)		2	1			1			1		
FIBROMA [B].			1			1					
(Incidental)			1		1	1					
CARCINOMA [M], Zymbal's gland.					1						
(Fatal)				1				1			
SMALL INTESTINE		(49)	(48)	(47)	(48)	(50)	(50)	(50)	(48)	(49)	(50)
NEUROENDOCRINE CELL TUMOR [M].											
(Fatal)				1							
LEIOMYOSARCOMA [M].									1		
ADENOCARCINOMA [M].											
(Fatal)						1					

		INCIDENCE OF TUMORS (NUMERIC)									
		Males					Females				
FINDINGS	TREATMENT	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3
STOMACH		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(49)	(49)	(50)
PAPILLOMA [B], squamous cell.											
(Incidental)						1					
HEMANGIOSARCOMA [M].						1					
FIBROSARCOMA [M].											
(Fatal)		1									
TESTES		(50)	(50)	(50)	(50)	(49)					
SERTOLI CELL TUMOR [B].											
(Incidental)		1									
MESOTHELIOMA [M].					1						
INTERSTITIAL CELL ADENOMA [B].											
(Incidental)			1	1	1						
THYMUS		(44)	(44)	(45)	(47)	(42)	(47)	(46)	(44)	(46)	(48)
THYMOMA [M].											
(Probably incidental)							1				
SARCOMA [M].											
(Fatal)									1		
THYROID GLAND		(49)	(48)	(49)	(48)	(50)	(50)	(49)	(50)	(50)	(50)
FOLLICULAR CELL CARCINOMA [M].								1			
(Probably incidental)									1		
FOLLICULAR CELL ADENOMA [B].			1			1					1
(Incidental)				2							
C-CELL CARCINOMA [M].							1			1	
C-CELL ADENOMA [B].		3	6	4	1	3	2		1	4	1
(Incidental)		5		2	1		1	3	2	3	1
URINARY BLADDER		(50)	(50)	(47)	(50)	(49)	(50)	(50)	(50)	(50)	(50)
TRANSITIONAL CELL PAPILLOMA [B].					1						
UTERUS							(50)	(50)	(50)	(50)	(50)
ENDOMETRIAL STROMAL POLYP [B].							1	2		2	2
(Incidental)							1	1	2		1
(Probably incidental)										1	
(Fatal)									1	1	1
GRANULAR CELL TUMOR [B].											
(Incidental)									1		
UTERUS							(50)	(50)	(50)	(50)	(50)
ENDOMETRIAL STROMAL SARCOMA [M].								1		2	1
(Fatal)							1	2		1	1
LEIOMYOSARCOMA [M].										1	
HEMANGIOMA [B].											
(Fatal)								1			
ADENOMA [B].											1
(Incidental)											1
VAGINA							(50)	(50)	(50)	(50)	(50)
POLYP [B].											
(Incidental)									1		
PRIMARY SITE UNDETERMINED		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
HISTIOCYTIC SARCOMA [M].					1						
(Incidental)				1						1	
(Probably incidental)			1								1
(Fatal)					2	2		1	1		

		INCIDENCE OF TUMORS (NUMERIC)									
		Males					Females				
FINDINGS	TREATMENT	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3	0 mg/kg C1	0 mg/kg C2	3 mg/kg T1	10 mg/kg T2	30 mg/kg T3
PRIMARY SITE UNDETERMINED		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
LARGE GRANULAR-CELL LYMPHOMA [M]. (Fatal)				1							
LIPOMA [B].					1						
SQUAMOUS CELL CARCINOMA [M]. (Fatal)			1								
MESOTHELIOMA [M]. (Incidental)						1					
LYMPHOMA [M]. (Incidental)										1	1
FIBROSARCOMA [M]. (Fatal)									1		
ADENOCARCINOMA [M]. (Probably incidental)									1		

[B] Benign tumor
[M] Malignant tumor
Figures in ( ) represent the number of animals in which the tissue was examined microscopically.
The absence of a numeral indicates that the finding specified was not present.

9-MAY-08 16:15
Places 2000 V1.400

Appendix 5: Sponsor's Statistical Evaluation of Tumor Incidences - Study 02143

Sex: Males

Sponsor's Tables

Table 3 Tumor Frequencies and Unadjusted Peto p-Values for Tumors in Male Animals

Organ:Tumor	Dose Group C1	C2	T1	T2	T3	p-Value
Adrenal Glands: Adenoma [B]	1	3	5	7	2	0.2356
Adrenal Glands: Pheochromocytoma [B]	4	2	4	6	2	0.4491
Adrenal Glands: Pheochromocytoma [M]	1	0	1	2	0	0.5153
Brain: Astrocytoma [M]	1	0	0	3	0	0.3606
Liver: Hepatocellular adenoma [B]	0	0	1	3	1	0.0851
Mammary Glands: Fibroma [B][a]	0	0	1	2	0	0.3051
Pancreas: Adenoma [B], acinar cell	2	0	0	2	0	0.6677
Pancreas: Islet cell adenoma [B]	4	8	6	4	8	0.3369
Parathyroid Glands: Adenoma [B]	1	0	0	4	1	0.1471
Pituitary Gland: Pars distalis adenoma [B]	24	20	25	20	23	0.4843
Pituitary Gland: Pars distalis carcinoma [M]	2	0	0	1	3	0.1200
Primary Site Undetermined: Histiocytic sarcoma [M][a]	0	1	1	3	2	0.0897
Skin: Basal cell tumor [B]	0	0	1	1	2	0.0544
Skin: Fibroma [B][a]	0	2	0	1	2	0.2780
Skin: Fibrosarcoma [M][a]	2	1	0	1	1	0.6964
Skin: Keratoacanthoma [B][a]	3	1	2	0	0	0.9771
Thyroid Gland: C-cell adenoma [B]	8	6	6	2	3	0.9794
Thyroid Gland: Follicular cell adenoma [B]	0	1	3	0	1	0.5421

a: Typically detected as a palpable mass during the in-life phase

Table 4 Tumor Frequencies and Unadjusted Peto p-Values for Pooled Tumors in Male Animals

Organ:Tumor	Dose Group C1	C2	T1	T2	T3	p-Value
Adrenal Glands: Adenoma [B] + Adenocarcinoma [M], cortical	1	4	5	7	2	0.3186
Adrenal Glands: Pheochromocytoma [M] + Pheochromocytoma [B]	5	2	5	7	2	0.4919
Mammary Glands: Fibroma [B] + Fibroadenoma [B][a]	1	1	1	2	0	0.6782
Pancreas: Adenoma [B], acinar cell + Adenocarcinoma [M], acinar cell	2	0	1	2	0	0.6822
Pituitary Gland: Pars distalis carcinoma [M] + Pars distalis adenoma [B]	26	20	25	21	26	0.2819
Skin: Fibroma [B] + Fibrosarcoma [M][a]	2	3	0	2	3	0.4286

a: Typically detected as a palpable mass during the in-life phase

Females

Table 5 Tumor Frequencies and Unadjusted Peto p-Values for Tumors in Female Animals

Organ:Tumor	Dose Group C1	C2	T1	T2	T3	p-Value
Adrenal Glands: Adenoma [B]	8	5	5	4	7	0.5836
Adrenal Glands: Pheochromocytoma [M]	0	1	2	0	1	0.5483
Liver: Hepatocellular adenoma [B]	0	1	0	1	4	0.0150
Mammary Glands: Adenocarcinoma [M][a]	8	5	5	7	6	0.5531
Mammary Glands: Adenoma [B][a]	13	13	16	10	11	0.8428
Mammary Glands: Fibroma [B][a]	0	0	1	2	1	0.1448
Mammary Glands: Fibroadenoma [B][a]	13	14	21	18	16	0.2544
Pancreas: Islet cell adenoma [B]	2	1	0	3	0	0.7514
Pancreas: Islet cell carcinoma [M]	2	1	0	0	0	1.0000
Parathyroid Glands: Adenoma [B]	0	2	0	0	0	1.0000
Pituitary Gland: Pars distalis adenoma [B]	29	26	34	38	33	0.0766
Pituitary Gland: Pars distalis carcinoma [M]	6	8	4	3	5	0.9022
Skin: Keratoacanthoma [B][a]	2	0	0	0	1	0.7200
Skin: Malignant fibrous histiocytoma [M][a,b]	0	0	2	0	0	0.6996
Thyroid Gland: C-cell adenoma [B]	3	3	3	7	2	0.4252
Uterus: Adenoma [B]	0	0	0	0	2	0.0428
Uterus: Endometrial stromal polyp [B]	2	3	3	4	4	0.2432
Uterus: Endometrial stromal sarcoma [M]	1	3	0	3	2	0.4431

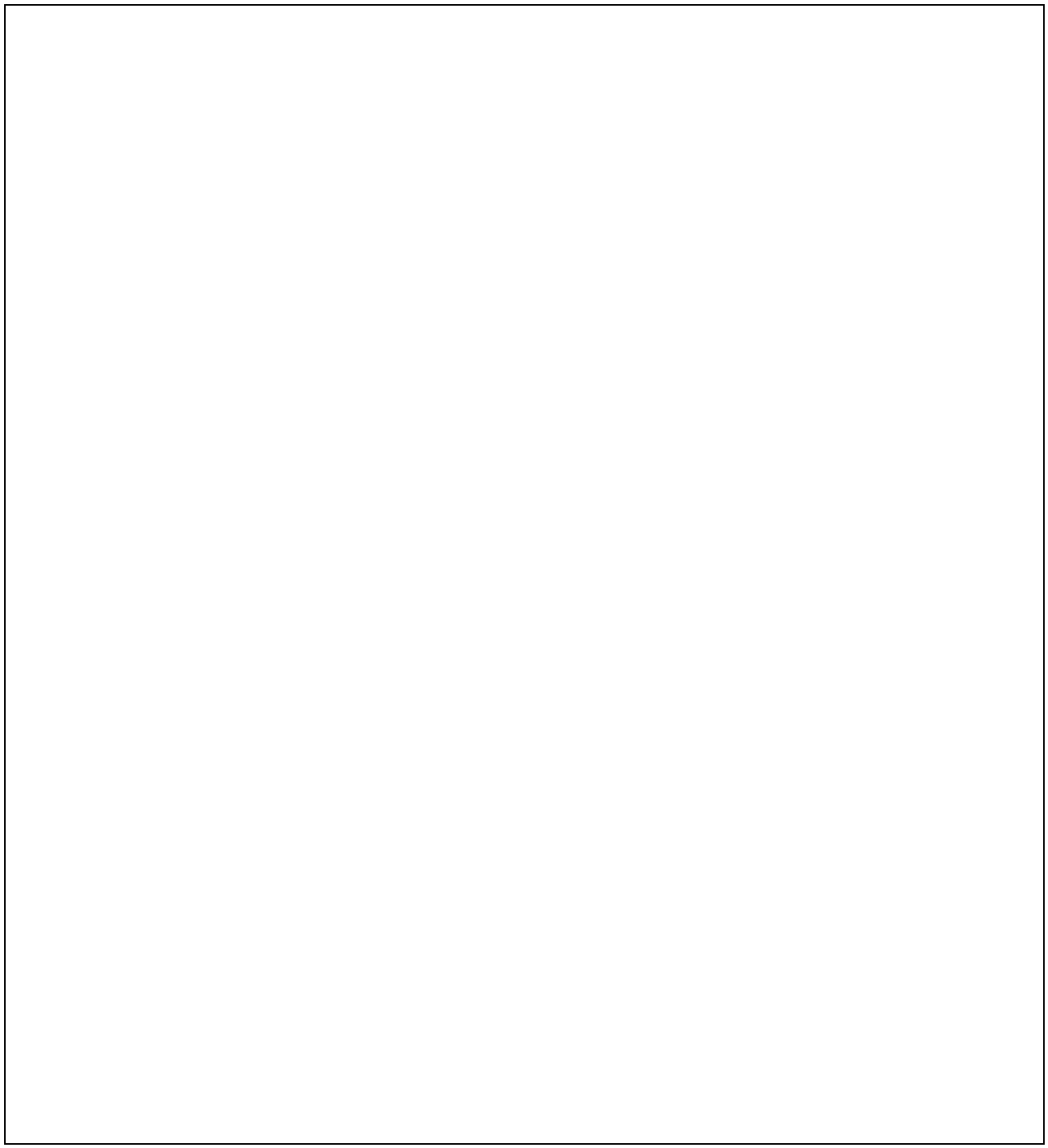
a: Typically detected as a palpable mass during the in-life phase
b: Rare tumor

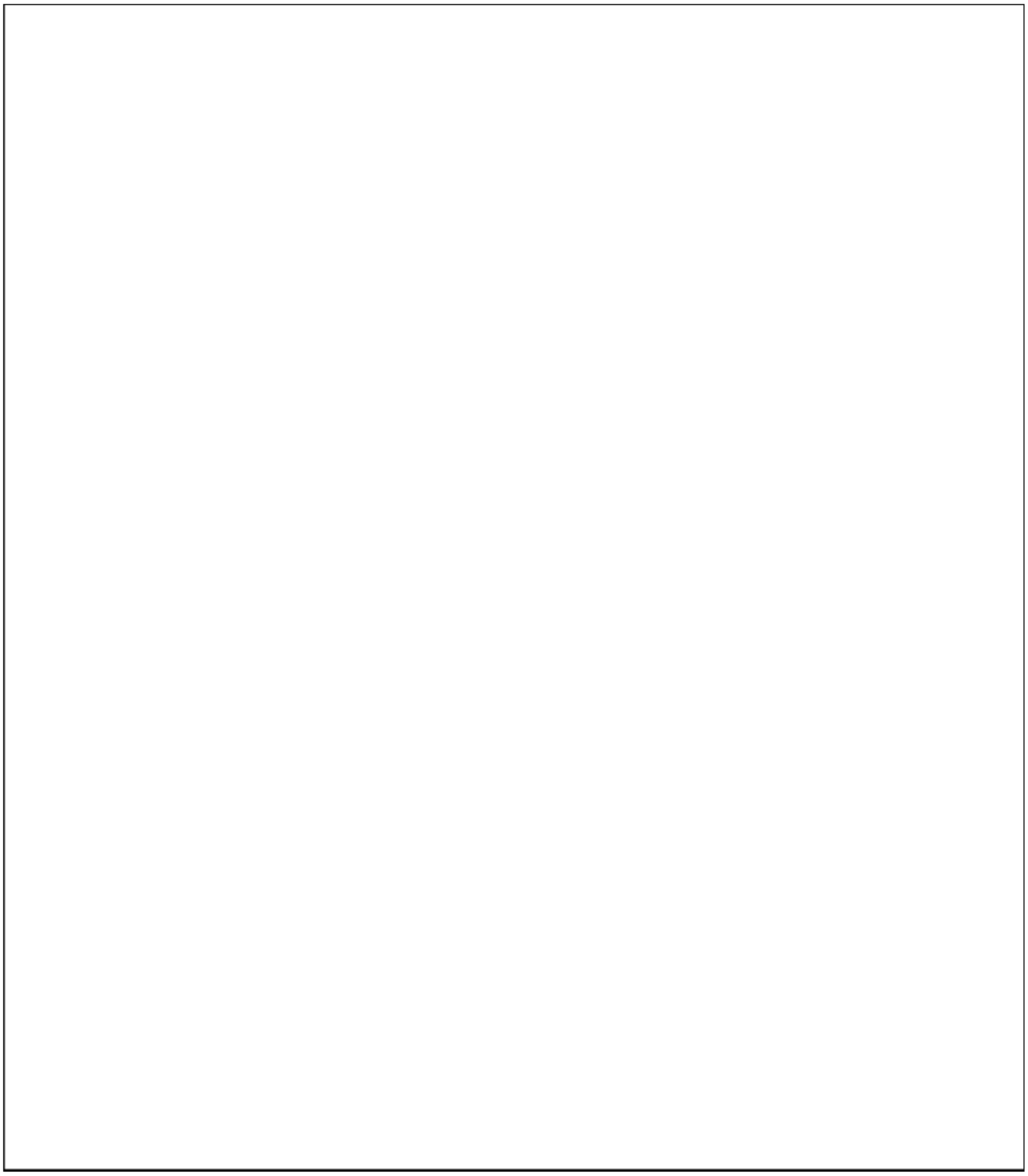
Table 6 Tumor Frequencies and Unadjusted Peto p-Values for Pooled Tumors in Female Animals

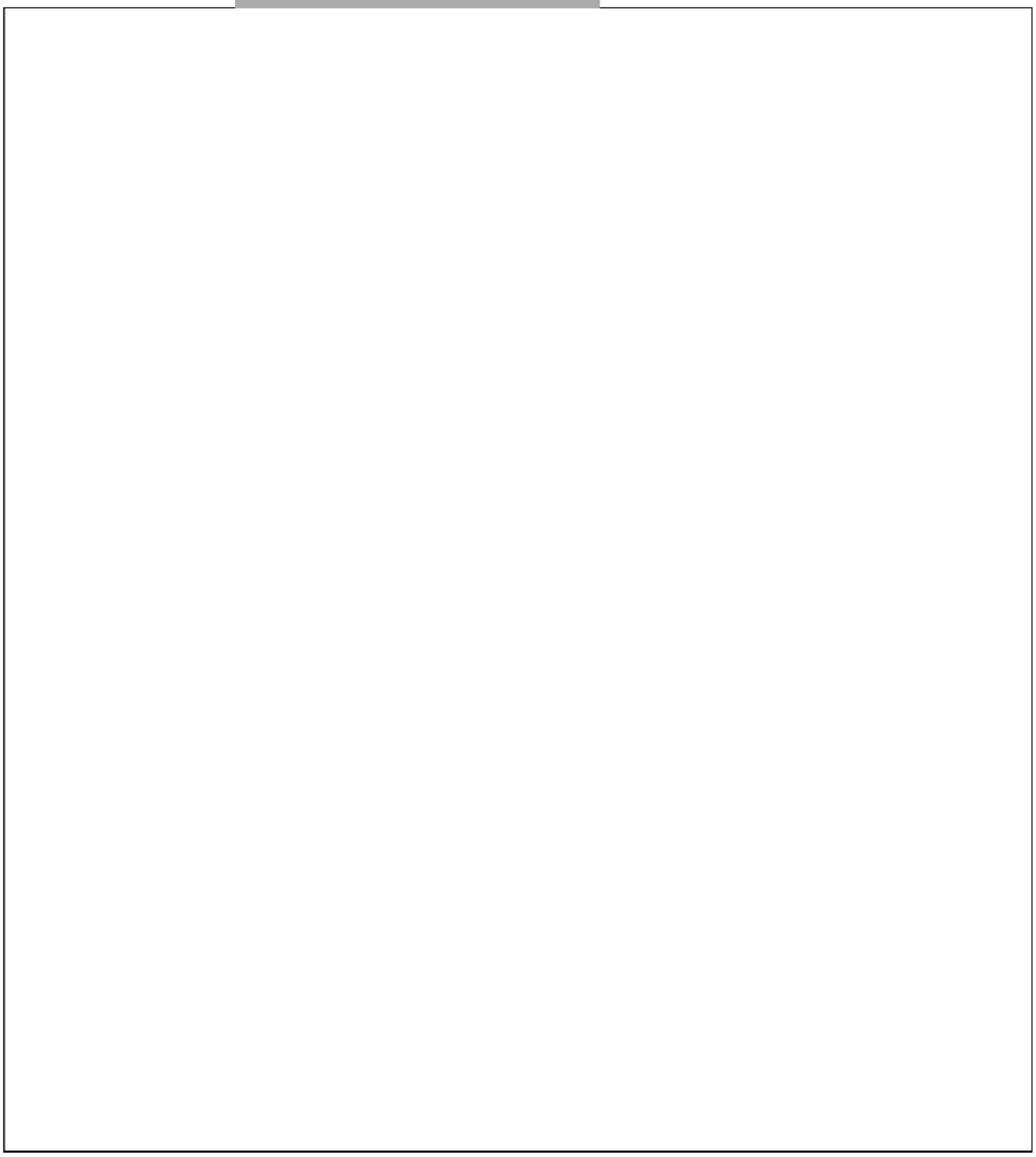
Organ:Tumor	Dose Group C1	C2	T1	T2	T3	p-Value
Adrenal Glands: Pheochromocytoma [M] + Pheochromocytoma [B]	1	2	2	1	2	0.5342
Mammary Glands: Adenoma [B] + Adenocarcinoma [M][a]	18	15	18	17	16	0.5972
Mammary Glands: Fibroma [B] + Fibroadenoma [B][a]	13	14	22	19	16	0.2264
Pancreas: Islet cell carcinoma [M] + Islet cell adenoma [B]	4	2	0	3	0	0.9574
Pituitary Gland: Pars distalis carcinoma [M] + Pars distalis adenoma [B]	35	34	38	41	38	0.2148
Thyroid Gland: C-cell carcinoma [M] + C-cell adenoma [B]	4	3	3	8	2	0.4673
Uterus: Endometrial stromal polyp [B] + Endometrial stromal sarcoma [M]	3	6	3	7	6	0.2326

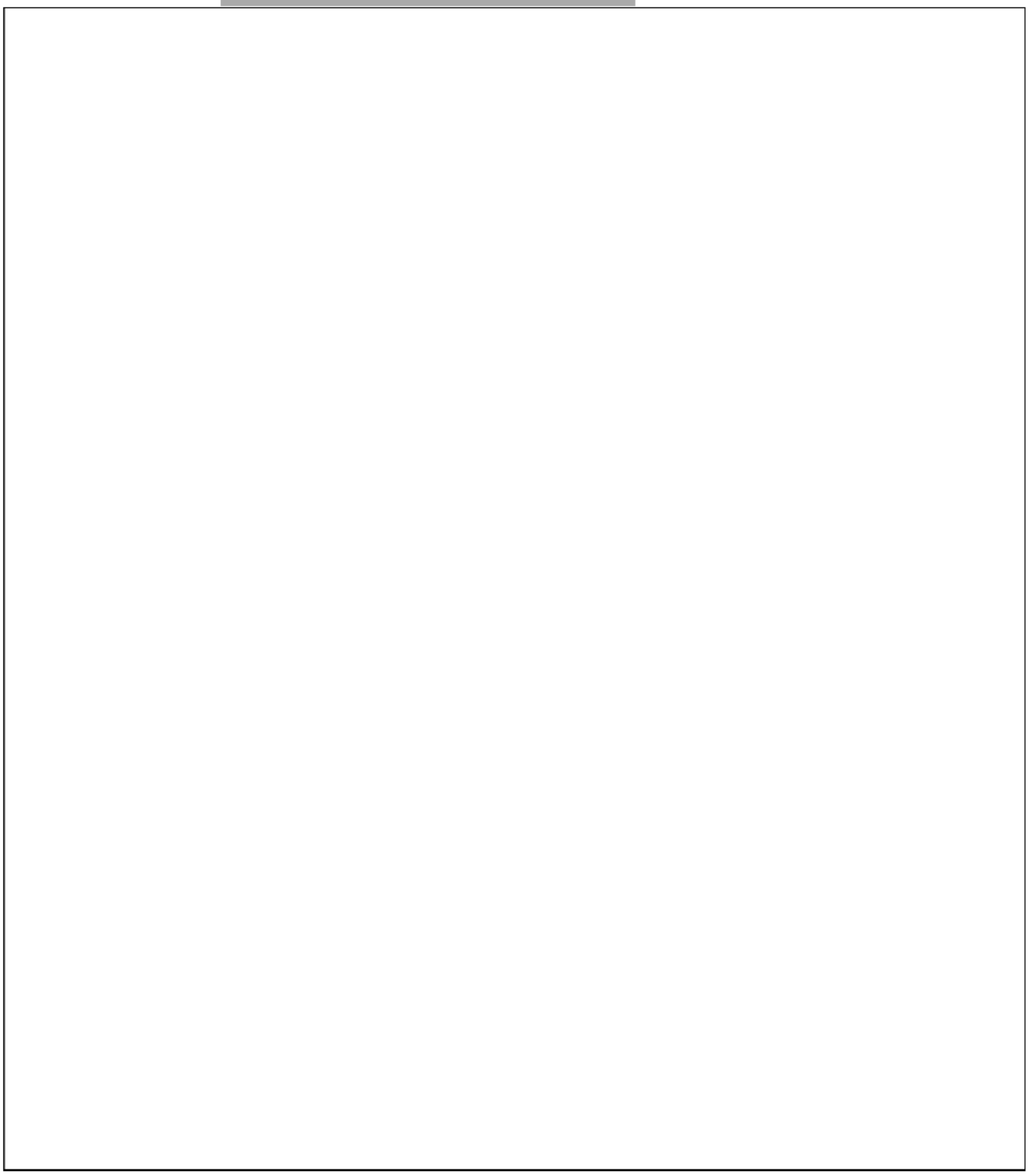
a: Typically detected as a palpable mass during the in-life phase

Appendix 6: Sponsor's Historical Control Ranges - Rat Tumors









Primary Site Undetermined		
Adenocarcinoma [M]	0 to 2	0 to 2
Carcinoma [M]	0 to 2	0 to 0
Granulocytic Leukemia [M]	0 to 2	0 to 0
Hibernoma [B]	0 to 0	0 to 2
Histiocytic Sarcoma [M]	2 to 12	0 to 6
Leukemia, granulocytic [M]	0 to 2	0 to 0
Lymphoma [M]	0 to 8	0 to 4
Mesothelioma [M]	0 to 2	0 to 2
Paraganglioma [M]	0 to 2	0 to 0
Sarcoma, Undifferentiated [M]	0 to 2	0 to 2

a: In rats, the overall historical control range is based on data from 7 carcinogenicity studies (950 male rats, 950 female rats; 50 rats/group) necropsied between 1999 and 2008. Percent range is presented as lowest to highest percentage seen in any of the 7 rat studies. [B] = Benign; [M] = Malignant

Appendix 7: Sponsor's Table Historical Control Data - Liver Tumor Data (Lafayette, NJ)

Study	SN 01304		SN 00261		SN 00121		SN 96459		SN 95088	
Necropsy (Mon/Year)	Mar-08		Jul-05		Jun-05		Mar-00		Dec-99	
Sex	M	F	M	F	M	F	M	F	M	F
Group(s)	C1/C2	C1/C2	C1/C2	C1/C2	C1/C2	C1/C2	C1/C2	C1/C2	C1/C2	C1/C2
Feeding Regimen	Diet Restricted (21 g (M); 17 g (F))		Diet Restricted (21 g (M); 17 g (F))		Diet Restricted (21 g (M); 17 g (F))		Diet Restricted (21 g (M); 17 g (F))		Diet Restricted (21 g (M); 17 g (F))	
N	100	100	100	100	100	100	100	100	100	100
ORGAN, FINDING										
Liver, Hepatocellular Carcinoma [M]	0	0	1	0	0	0	0	0	0	0
Liver, Hepatocellular Adenoma [B]	0	0	2	2	0	0	0	0	0	0

Study	SN 00065											
Necropsy (Mon/Year)	Jun-02											
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Group(s)	All	All	C1		C2		C3		C4		C5	
Feeding Regimen	Mixed	Mixed	Ad lib		Diet Restricted (21 g (M); 17 g (F))		Diet Restricted (21 g (M); 17 g (F))		Diet Restricted (21 g (M); 17 g (F))		Diet Restricted (21 g (M); 17 g (F))	
N	250	250	50	50	50	50	50	50	50	50	50	50
ORGAN, FINDING												
Liver, Hepatocellular Carcinoma [M]	7	0	5	0	0	0	0	0	2	0	0	0
Liver, Hepatocellular Adenoma [B]	14	1	4	0	1	0	4	0	2	1	3	0

Study	SN 99328									
Necropsy (Mon/Year)	Dec-01									
Sex	M	F	M	F	M	F	M	F	M	F
Group(s)	All	All	C1		C2		C3		C4	
Feeding Regimen	Mixed	Mixed	Ad lib		Diet Restricted (20 g (M); 15 g (F))		Diet Restricted (20 g (M); 15 g (F))		Diet Restricted (20 g (M); 15 g (F))	
N	200	200	50	50	50	50	50	50	50	50
ORGAN, FINDING										
Liver, Hepatocellular Carcinoma [M]	2	0	2	0	0	0	0	0	0	0
Liver, Hepatocellular Adenoma [B]	3	1	0	0	0	0	2	1	1	0

Appendix 8: Exec CAC Minutes - Review of NDA 204886 Carcinogenicity Studies

Executive CAC
Date of Meeting: October 15, 2013

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair
Abigail Jacobs, Ph.D., OND -IO, Member
Paul Brown, Ph.D., OND-IO, Member
Aisar Atrakchi Ph.D., DPP, Alternate Member
Thomas Papoian, Ph.D., DCRP, Supervisor
Patricia Harlow, Ph.D., DCRP, Presenting Reviewer

Author of Draft: Patricia Harlow, Ph.D.

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

NDA: 204-886
Drug Name: Vorapaxar (SCH 530848)
Sponsor: Merck (Schering Plough)

Background:
Vorapaxar is an inhibitor of the protease activated receptor 1 (PAR-1), also known as the thrombin receptor. In the Phase 3 trial for reduction of atherothrombotic events in patients with a history of myocardial infarction, the daily vorapaxar dose was 2.5 mg.

Rat Carcinogenicity Study:
Sprague Dawley rats (50/sex/group) received daily oral doses of 0, 3, 10, and 30 mg/kg/day of vorapaxar administered by oral gavage in 0.4% (w/v) aqueous methylcellulose for 105-106 weeks. As specified in the Exec CAC's concurrence of the protocol, the male and female rats were fed 21 gm and 17 gm, respectively, of food per day, as was done in the 3-month and 6-month dose-ranging studies. The total exposures to vorapaxar in the high dose males and females were 10 and 28 fold, respectively, the mean total exposure in patients receiving the recommended human dose (RHD) of 2.5 mg.

No significant treatment-related effects were observed on mortality, and food consumption. However, the mean body weight gain decreased up to 16% and 17% in the high dose males and females, respectively, compared to the control groups.

The high dose females had increased incidences of uterine adenoma and the high dose males had increased incidences of basal cell tumor of the skin and histiocytic sarcoma. However, the p values for these tumors did not attain the significance level required for the neoplams to be considered drug related.

Although the high dose female rats had an increased incidence of hepatocellular adenoma that was 4-fold above the maximum of the sponsor's historical control range (0-2%), the p values for both the trend test and the pairwise test for this tumor did not attain the criteria (p_t<0.005 and p_p<0.01) required for a common tumor to be considered positive. It

should be noted that the incidence of hepatocellular adenoma in the concurrent control group was 1%, the lower threshold for being considered a common tumor (≥1%).

Mouse Carcinogenicity Study:
CD-1 mice (50/sex/group) received daily oral doses of 0, 1, 5, and 15 mg/kg/day of vorapaxar administered by oral gavage in 0.4% (w/v) aqueous methylcellulose for 103 to 104 weeks. The total exposures to vorapaxar in the high dose males and females were 28 and 34 fold, respectively, the mean total exposure to vorapaxar in patients receiving the RHD of 2.5 mg. A metabolite of vorapaxar, SCH 2046273, represents about 25% of the vorapaxar plasma concentration in humans. The exposures to SCH 2046273 in the high dose males and females were 5.5 and 6.3-fold the mean exposure to SCH 2046273 in patients receiving the RHD of 2.5 mg.

No significant treatment-related effects were observed on mortality or food consumption. However, the high dose male and female groups gained 16% and 14%, respectively, less bodyweight than the control group.

The incidence of bronchiolo-alveolar adenoma increased in the high dose females and the incidence of bronchiolo-alveolar carcinoma increased in the high dose males. However, the p values for each of these tumors and their combination in the trend test did not attain the significance level of $pt < 0.005$ required for these common tumors to be considered positive.

Executive CAC Recommendations and Conclusions:

Rat:

The Committee considered that the study was adequate, noting prior Exec CAC concurrence with the protocol.

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

Mouse:

The Committee considered that the study was adequate, noting prior Exec CAC concurrence with the protocol.

The Committee concurred that there were no drug-related neoplasms in male or female mice.

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

cc:\
/Division File, DCRP
/T. Papoian, Supervisor, DCRP
/P. Harlow, Reviewer, DCRP
/A. Blaus, CSO/PM, DCRP
/A.Seifried, OND-IO

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

/s/

ADELE S SEIFRIED
10/16/2013

DAVID JACOBSON KRAM
10/16/2013

Appendix 9: Exec CAC Minutes - Review of Mouse Protocol

/s/

David Jacobson-Kram
6/29/05 09:40:04 AM

Appendix 10: Sponsor's Summary of Tumor Incidence - Study 02144

104-WEEK CARCINOGENICITY STUDY OF SCH 530348 IN MICE

Histopathology (Microscopic Observations)

SN 02144
Page : 1

		INCIDENCE OF TUMORS (NUMERIC)									
		Males					Females				
FINDINGS	TREATMENT	0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3	0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3
ADRENAL GLANDS		(48)	(50)	(49)	(49)	(49)	(50)	(50)	(50)	(50)	(50)
SUBCAPSULAR CELL CARCINOMA [M].							1				
SUBCAPSULAR CELL ADENOMA [B].		2					1	1			
(Incidental)								1		1	1
PHEOCHROMOCYTOMA [B].											
(Incidental)									1		
BONE		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
OSTEOSARCOMA [M].							1				
FIBROSARCOMA [M].								1			
(Incidental)								1			
BRAIN		(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(51)	(50)
OLIGODENDROGLIOMA [M].											
(Probably fatal)			1								
GALLBLADDER		(41)	(43)	(35)	(44)	(44)	(43)	(42)	(38)	(39)	(43)
PAPILLARY ADENOMA [B].						1					
HARDERIAN GLANDS		(50)	(49)	(50)	(50)	(50)	(50)	(50)	(49)	(51)	(50)
ADENOMA [B].		7	3	4	2	4	2	1			
(Incidental)		1		3	1	1		1		1	
KIDNEYS		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
RENAL TUBULE ADENOMA [B].											
(Incidental)		1									
LIVER		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
HEPATOCELLULAR CARCINOMA [M].			1			1					
(Probably fatal)				1		1					
(Fatal)			1								
HEPATOCELLULAR ADENOMA [B].		4	5	2	7	3					
(Incidental)		1	1	3							1
(Probably fatal)				2							
HEMANGIOSARCOMA [M].											
(Probably fatal)				1							
HEMANGIOMA [B].		1				1	1	1			
(Incidental)		1		1				1			

	INCIDENCE OF TUMORS (NUMERIC)									
	Males					Females				
FINDINGS / TREATMENT	0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3	0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3
LIVER	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
HEMANGIOMA [B].										
(Probably incidental)						1				
(Probably fatal)										1
(Fatal)			1							
LUNGS	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
BRONCHIOLO-ALVEOLAR CARCINOMA [M].	1					2			1	
(Incidental)					1			1		
(Probably incidental)									1	
(Fatal)		1	1	1	3		2		2	
BRONCHIOLO-ALVEOLAR ADENOMA [B].	6	3	6	7	6	5	5	4	3	6
(Incidental)	5	5	10	5	3	1	2	2	4	4
SARCOMA [M].										
(Probably incidental)									1	
MAMMARY GLANDS	(11)	(5)	(6)	(2)	(3)	(46)	(46)	(43)	(45)	(48)
ADENOCARCINOMA [M].										
(Probably fatal)									1	
MAMMARY GLANDS	(11)	(5)	(6)	(2)	(3)	(46)	(46)	(43)	(45)	(48)
ADENOCARCINOMA [M].										
(Fatal)								1		
OVARIES						(50)	(49)	(50)	(51)	(49)
TUBULOSTROMAL ADENOMA [B].								1		
(Incidental)						1	1			
GRANULOSA CELL TUMOR [M].						1		1		
(Incidental)								1		
(Probably incidental)								1		
(Fatal)									1	
CYSTADENOMA [B].									1	
(Incidental)								1		
LUTEOMA [B].										
(Incidental)							1			
HEMANGIOMA [B].							1			
(Probably fatal)								1		
PANCREAS	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
ACINAR CELL ADENOCARCINOMA [M].										
(Fatal)	1									
ISLET CELL ADENOMA [B].	1									
PITUITARY GLAND	(50)	(50)	(48)	(49)	(49)	(48)	(47)	(49)	(49)	(48)
PARS DISTALIS ADENOMA [B].										
(Fatal)								1		
SALIVARY GLANDS	(50)	(50)	(50)	(50)	(50)	(49)	(50)	(50)	(51)	(50)
LEIOMYOMA [B].	1									
SKELETAL MUSCLE	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(49)	(51)	(50)
RHABDOMYOSARCOMA [M].										
(Probably fatal)			1		1					

FINDINGS	TREATMENT	INCIDENCE OF TUMORS (NUMERIC) Males 0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3	Females 0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3
SKIN		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
SEBACEOUS CELL ADENOMA [B].					2	1					
(Incidental)					1						
SQUAMOUS CELL CARCINOMA [M].											
(Incidental)						1					
FIBROSARCOMA [M].				1			3		1		
(Incidental)		1									
(Probably fatal)		1						1			1
(Fatal)				1	1			1	1		
FIBROMA [B].				1		1					
(Incidental)					1						
SMALL INTESTINE		(46)	(44)	(39)	(45)	(45)	(46)	(45)	(41)	(43)	(45)
HEMANGIOSARCOMA [M].											
(Incidental)					1						
ADENOMA [B].								1			
SPLEEN		(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
HEMANGIOSARCOMA [M].		1				1					
SPLEEN		(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
HEMANGIOSARCOMA [M].											
(Fatal)		1		1	1						
STOMACH		(49)	(47)	(45)	(46)	(47)	(50)	(49)	(47)	(46)	(46)
PAPILLARY ADENOMA [B].											
(Incidental)			1								
TESTES		(50)	(50)	(50)	(50)	(50)					
SERTOLI CELL TUMOR [B].			1								
(Incidental)						1					
INTERSTITIAL CELL ADENOMA [B].					1	1					
HEMANGIOMA [B].											
(Incidental)				1							
URINARY BLADDER		(49)	(48)	(49)	(46)	(48)	(50)	(47)	(48)	(43)	(47)
TRANSITIONAL CELL PAPILLOMA [B].		1									
URINARY BLADDER		(49)	(48)	(49)	(46)	(48)	(50)	(47)	(48)	(43)	(47)
HEMANGIOMA [B].											
(Incidental)										1	
FIBROMA [B].											
(Incidental)								1			
UTERUS							(50)	(50)	(50)	(51)	(50)
ENDOMETRIAL STROMAL POLYP [B].											
(Incidental)							1	1	1		
GRANULAR CELL TUMOR [M].								1			
LEIOMYOSARCOMA [M].							1		1		
(Fatal)							1			2	1
LEIOMYOMA [B].							2	2	1	2	1
(Incidental)							2		1	1	1
(Probably fatal)							1		1		1
(Fatal)										1	
HEMANGIOMA [B].								1			
(Incidental)							1		1		
(Probably fatal)										1	1

FINDINGS	TREATMENT	INCIDENCE OF TUMORS (NUMERIC)									
		Males					Females				
		0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3	0 mg/kg C1	0 mg/kg C2	1 mg/kg T1	5 mg/kg T2	15 mg/kg T3
UTERUS							(50)	(50)	(50)	(51)	(50)
FIBROMA [B].											
(Incidental)										1	
CARCINOMA [M].											
(Fatal)										1	
ADENOCARCINOMA [M].											
(Probably fatal)								1			
VAGINA							(50)	(49)	(50)	(50)	(49)
FIBROSARCOMA [M].											
(Probably fatal)								1			
PRIMARY SITE UNDETERMINED		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
HISTIOCYTIC SARCOMA [M].											
(Fatal)			1								1
MAST CELL TUMOR [M].					1						
LYMPHOMA [M].			1	1			3	1		3	3
(Incidental)								1		1	
(Probably fatal)							2				
PRIMARY SITE UNDETERMINED		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(51)	(50)
LYMPHOMA [M].											
(Fatal)		6	6	7	6	4	8	9	17	10	10

[M] Malignant tumor
Figures in ( ) represent the number of animals in which the tissue was examined microscopically.
The absence of a numeral indicates that the finding specified was not present.

2-JUL-08 08:08
Places 2000 V1.400

Appendix 11: Sponsor's Statistical Analysis - Study 02144

Sex: Males

Sponsor's Tables

Organ:Tumor	Dose Group C1	C2	T1	T2	T3	p-Value
Adrenal Glands: Subcapsular Cell Adenoma [B]	2	0	0	0	0	1.0000
Harderian Glands: Adenoma [B]	8	3	7	3	5	0.8082
Liver: Hemangioma [B]	2	0	2	0	1	0.7158
Liver: Hepatocellular Adenoma [B]	5	6	7	7	3	0.8186
Liver: Hepatocellular Carcinoma [M]	0	2	1	0	2	0.4596
Lungs: Bronchiolo-Alveolar Adenoma [B]	11	8	16	12	9	0.5400
Lungs: Bronchiolo-Alveolar Carcinoma [M]	1	1	1	1	4	0.0840
Primary Site Undetermined: Lymphoma [M][a]	6	7	8	6	4	0.8491
Skin: Fibrosarcoma [M][a]	2	0	2	1	0	0.8332
Skin: Sebaceous Cell Adenoma [B][a]	0	0	0	3	1	0.0939
Spleen: Hemangiosarcoma [M]	2	0	1	1	1	0.6051

a: Analyzed using the onset rate method

Organ:Tumor	Dose Group C1	C2	T1	T2	T3	p-Value
Liver: Hepatocellular Carcinoma [M] + Hepatocellular Adenoma [B]	5	7	8	7	5	0.7103
Liver: Hemangiosarcoma [M] + Hemangioma [B]	2	0	3	0	1	0.7267
Lungs: Bronchiolo-Aveolar Carcinoma [M] + Bronchiolo-Aveolar Adenoma [B]	12	9	17	13	13	0.2372
Skin: Fibrosarcoma [M] + Fibroma [B][a]	2	0	3	2	1	0.5763

a: Analyzed using the onset rate method

Females

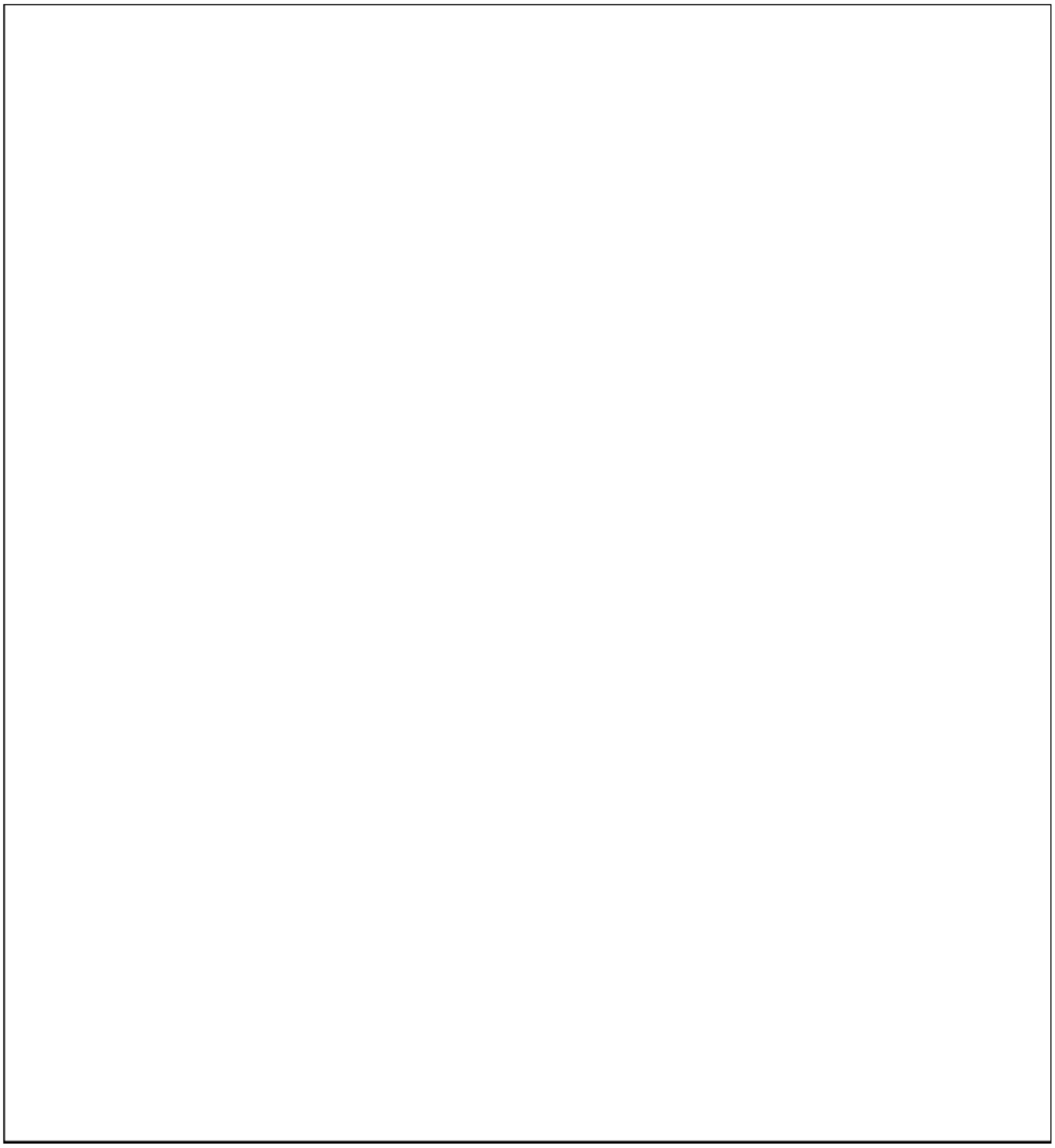
Organ:Tumor	Dose Group C1	C2	T1	T2	T3	p-Value
Adrenal Glands: Subcapsular Cell Adenoma [B]	1	2	0	1	1	0.6864
Bone: Fibrosarcoma [M]	0	2	0	0	0	1.0000
Harderian Glands: Adenoma [B]	2	2	0	1	0	0.9554
Liver: Hemangioma [B]	2	2	0	0	1	0.9055
Lungs: Bronchiolo-Alveolar Adenoma [B]	6	7	6	7	10	0.1166
Lungs: Bronchiolo-Alveolar Carcinoma [M]	2	2	1	4	0	0.6943
Ovaries: Granulosa Cell Tumor [M]	1	0	3	1	0	0.6834
Primary Site Undetermined: Lymphoma [M][a]	13	11	17	14	13	0.2990
Skin: Fibrosarcoma [M][a]	3	2	2	0	1	0.9273
Uterus: Leiomyoma [B]	5	2	3	4	3	0.5321
Uterus: Leiomyosarcoma [M]	2	0	1	2	1	0.4131

a: Analyzed using the onset rate method

Organ:Tumor	Dose Group C1	C2	T1	T2	T3	p-Value
Adrenal Glands: Subcapsular Cell Carcinoma [M] + Subcapsular Cell Adenoma [B]	2	2	0	1	1	0.8031
Lungs: Bronchiolo-Alveolar Carcinoma [M] + Bronchiolo-Alveolar Adenoma [B]	8	9	7	10	10	0.2044
Uterus: Leiomyosarcoma [M] + Leiomyoma [B]	7	2	4	6	4	0.4468

Appendix 12: Sponsor's Historical Control Ranges

ORGAN/TUMOR TYPE	PERCENT INCIDENCE	
	MALES	FEMALES
Lymph Nodes		
Hemangiosarcoma [M]	0 to 0	0 to 2
Mammary Glands		
Adenoacanthoma [M]	0 to 0	0 to 4
Adenocarcinoma [M]	0 to 0	0 to 6
Adenoma [B]	0 to 0	0 to 3
Carcinoma [M]	0 to 0	0 to 4
Ovaries		
Adenoma [B]	-	0 to 2
Adenocarcinoma [M]	-	0 to 2
Granulosa Cell Tumor [B]	-	0 to 4
Granulosa Cell Tumor [M]	-	0 to 4
Hemangioma [B]	-	0 to 2
Hemangiosarcoma [M]	-	0 to 2
Leiomyoma [B]	-	0 to 2
Luteoma [B]	-	0 to 4
Sertoli Cell Tumor [B]	-	0 to 2
Tubulostromal Adenoma [B]	-	0 to 2
Pancreas		
Adenoma [B] acinar cell	0 to 2	0 to 0
Parathyroid Glands		
Adenoma [B]	0 to 0	0 to 2
Carcinoma [M]	0 to 0	0 to 2
Pituitary Gland		
Adenoma [B]	0 to 2	0 to 8
Seminal Vesicles		
Sarcoma [M]	0 to 2	-
Skeletal Muscle		
Hemangiosarcoma [M]	0 to 2	0 to 0
Fibrosarcoma [M]	0 to 0	0 to 2



ORGAN/TUMOR TYPE	PERCENT INCIDENCE	
	MALES	FEMALES
Uterus		
Adenocarcinoma [M]	-	0 to 8
Carcinoma, Endometrial [M]	-	0 to 2
Endometrial Stromal Polyp [B]	-	0 to 12
Endometrial Stromal Sarcoma [M]	-	0 to 8
Fibroma [B]	-	0 to 4
Granular Cell Tumor [B]	-	0 to 2
Hemangioma [B]	-	0 to 2
Hemangiosarcoma [M]	-	0 to 4
Leiomyoma [B]	-	2 to 8
Leiomyosarcoma [M]	-	0 to 2
Vagina		
Endometrial Stromal Polyp [B]	-	0 to 2
Fibroma [B]	-	0 to 2
Leiomyoma [B]	-	0 to 2
Papilloma [B]	-	0 to 2
Squamous Cell Carcinoma [M]	-	0 to 2
Primary Site Undetermined		
Fibrosarcoma [M]	0 to 0	0 to 4
Granulocytic Leukemia [M]	0 to 2	0 to 2
Hemangioma [B]	0 to 2	0 to 0
Hemangiosarcoma [M]	0 to 2	0 to 0
Histiocytic Sarcoma [M]	0 to 6	4 to 14
Lymphoma [M]	4 to 14	10 to 18

a: In mice, the overall historical control range is based on data from 5 carcinogenicity studies (550 male mice, 550 female mice; 50 mice/group) necropsied between 1999 and 2005. Percent range is presented as lowest to highest percentage seen in any of the 5 mouse studies. [B] = Benign; [M] = Malignant

---

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

/s/

PATRICIA P HARLOW
12/16/2013

THOMAS PAPOIAN
12/17/2013
Concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204886 **Applicant: Merck** **Stamp Date: 5/10/2013**

Drug Name: Vorapaxar sulfate **NDA/BLA Type: NDA commercial**

On **initial** overview of the NDA/BLA 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?	Yes		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	Yes		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	Yes		
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)?	Yes		
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).		No	All of the toxicology studies were conducted with vorapaxar free base, whereas the clinical trials were conducted with vorapaxar sulfate. The sponsor needs to justify why a toxicology or bridging study was not conducted with vorapaxar sulfate.
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?	Yes		
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?	Yes		Statements are included with individual study reports that were conducted as GLP studies.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	Yes		A functional electroretinography (ERG) assessment in the eyes of rats after repeated dosing and a long-term ocular safety Phase 3 clinical sub-study were conducted.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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?	Yes		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	Yes*		Yes* = Partially addressed. All of the toxicology studies were conducted with vorapaxar batches made using the (b) (4) Although these processes result in drug substance lots with different impurity profiles, most of the impurities are qualified toxicologically, except for the (b) (4) degradants for which no toxicology or safety assessment study was conducted. In addition, statements concerning genotoxic impurities require clarification.
11	Has the applicant addressed any abuse potential issues in the submission?	Yes		The sponsor only briefly addressed abuse potential in the CTD Clinical Overview. Although vorapaxar does have distribution to the brain in adult rats, the sponsor's single dose safety pharm studies indicated no effects on behavioral, neurological, or autonomic function at a maximum dose of 100 mg/kg with systemic exposures at least 3-fold that in the human at steady state.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _NDA 204866 is fileable from the pharmacology/toxicology perspective_

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

1. All of the toxicology studies were conducted with vorapaxar free base, whereas the clinical trials were conducted with vorapaxar sulfate. Please justify why a toxicology or bridging study was not conducted with vorapaxar sulfate.

2. Please justify the specifications for the (b) (4) degradants in the drug product given that these impurities were not found in any lot of vorapaxar used in a toxicology study. Please confirm that (b) (4) degradants are not genotoxic.

3. Please clarify what genotoxic impurities are present in the drug substance even if they are controlled to be present at levels less than the TTC of (b) (4) /day.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Patricia Harlow, Ph.D.	6/12/2013
Reviewing Pharmacologist	Date
Thomas Papoian, Ph.D.	6/12/2013
Team Leader/Supervisor	Date

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

/s/

PATRICIA P HARLOW
06/12/2013

THOMAS PAPOIAN
06/12/2013
Concur.