Bacterial Strains	Nonactivation Phase (µg/plate)	Activation Phase (µg/plate)
Salmonella typhimurium		
TA1535 and TA100	Sodium azide (5)	2-Aminoanthracene (2.5)
TA97a	9-Aminoacridine (75)	2-Aminoanthracene (2.5)
TA98	2-Nitrofluorene (5)	2-Aminoanthracene (2.5)
TA102	Cumene hydroperoxide (200)	2-Aminoanthracene (5)
Escherichia coli		
WP2uvrA	N-Ethyl-N'-nitro-N-nitrosoguanidine (2)	2-Aminoanthracene (20)

Comments:
Exposure conditions/Study design: The plate incorporation method was used. The tester strains in the plate (in triplicate cultures) were exposed to the vehicle, drug, or positive controls. The cells were incubated for approximately 48 hrs at 37^{0}C on selective top agar, in both the presence and absence of S9 fraction. Colonies were counted manually or with automated colony counter.

Doses used in definitive study: 39-5000 µg/plate

Analysis:
No. of replicates: Duplicates cultures/dose
Counting method: Revertant colonies for a given tester strain were counted manually or with automated colony counter.

Criteria for positive results: If the drug induces an increase in revertant colonies compared to the solvent controls, in at least one of the six tester strains, and the increase is at least 2 times for strains TA97a, TA98, TA100, TA102, WP2 urvA, and 3 times for strain TA1535, compared to vehicle controls, the drug would be considered positive.

Summary of individual study findings:
Study validity: Appropriate dose selection was made for this study, and positive control responses were acceptable

Study outcome: The combination of SCH 58235 + lovastatin at a dose range of 39-5000 µg/plate in at least two independent assays was not mutagenic in any of the tester strains at any doses in the presence or absence of metabolic activation. Precipitate was generally observed from doses of 312 µg/plate in the presence or absence of metabolic activation in these assays. A significant increase in the number of revertant colonies was observed with the positive controls (with or without S9 mix). In conclusion, the AMES test was negative for combination of SCH 58235 + lovastatin.

Genetic toxicology summary: SCH 58235+ lovastatin co-administration was negative in AMES test in all tester strains.

4B. Effects of SCH 58235 + lovastatin (SCH 48176) on chromosome aberrations in human peripheral blood lymphocytes

Key findings: SCH 58235 + lovastatin was negative in the chromosome aberration assay in cultured whole blood human lymphocytes

Study no: 99015
Volume #, and page #: Volume 162, page 1 (reference 87)
Conducting laboratory and location: [redacted]

Date of study initiation: 3/19/1999
GLP compliance: Yes
QA reports: yes (X) no ( )

Basis of dose selection: The dose selection was based on cytotoxicity (or mitotic index). Mitotic index was ≥ 50% at the high dose in all assays

6.5.6. Chromosome Aberration Study of SCH 58235/SCH 48176 in Human Peripheral Blood Lymphocytes (SN 99015)

Methods/Design

Performed by:	[redacted]
Study Performed in Compliance with GLP:	Yes
Animals:	In vitro
Target Cells:	Human peripheral blood lymphocytes
Duration of Exposure:	≈4 and ≈19 hours (nonactivation); ≈4 hours (activation)
Sampling Times:	≈22-hour harvest
Test Articles/Formulation:	SCH 58235 and SCH 48176 in a 1:1 ratio by weight, prepared and delivered to the test system separately. All doses are presented as doses of the combination.
Batch Nos.:	SCH 58235: 98-58235-X-05 SCH 48176: 99-48176-X-01
Doses Analyzed:	Nonactivation: 2.5, 5, 10, 20 and 40 µg/mL Activation: 5, 10, 20, 30, 40, 45 and 50 µg/mL
No. of Independent Experiments:	Two
No. of Replicate Cultures:	Two/dose
No. of Cells Analyzed:	100/culture, 200/dose
Positive Controls:	Nonactivation: Mitomycin C (Sigma Lot No. 116H2511) Activation: Cyclophosphamide (Sigma Lot No. 073H0846)
Solvent and Final Concentration:	Dimethylsulfoxide (DMSO), 10 µL/mL in tissue culture medium

SCH 58235 + lovastatin (SCH 48176) results:

Results	
Genotoxic Effects:	No genotoxic effects were observed
Effect of the Positive Control:	All positive controls induced statistically significant increases above their respective vehicle controls ($p \leq 0.01$).

Conclusions

Coadministration of SCH 58235 and SCH 48176 (ratio of 1:1, by weight), was negative in inducing chromosome aberrations in cultured whole blood human lymphocytes in the presence or absence of an exogenous metabolic activation system under the conditions of this study.

Genetic toxicology summary: SCH 58235+ lovastatin co-administration was negative in the chromosome aberration assay in cultured whole blood human lymphocytes

4C. Effects of SCH 58235 + lovastatin (SCH 48176) on in Vivo Micronuclei in Mice.

Key findings: SCH 58235 + lovastatin (SCH 48176) was negative in vivo micronucleus test in mice

Study no: 99025
Volume #, and page #: Volume 162, page 1 (Reference 91)
Conducting laboratory and location: [redacted]

Date of study initiation: 8/27/1999
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug lot #, and % purity: Lot #: SCH 58235 97-58235-X-02, lovastatin batch # 99-48176-X-06. This drug combination was labeled as SCH 357015.

Formulation/vehicle: 0.4% aqueous methylcellulose

Methods:
Test strain and Cells: Mice (Crl:CD-1(CR)BR VAF/PLUS, 8-10 weeks of age.

Dose selection criteria:
Basis of dose selection: The dose selection was based on a previous in vivo micronucleus study in mice where combined doses of SCH 58235 + lovastatin (ratio 1:1 by weight) were 200, 400, 600, 800,1000, 1200 mg/kg/day, given ip once a day for two consecutive days.

Dose range finding study

Dosing Regimen for the Dose Range Finding Study with SCH 357015

Target Dose[a] (mg/kg/day)	Number of Animals Male	Female	Dosing Volume[b] (mL/kg/day)	Observation Duration[c] (Days)
0	6	6	20	4
200	6	6	20	4
400	6	6	20	4
600	-	6	20	4
800	6	6	20	[d]
1000	6	6	20	[d]
1200	6	6	20	[d]

[a] SCH 58235 was administered first, followed immediately by administration of lovastatin. The doses were administered once a day for two consecutive days.

[b] The dosing volume was 10 mL/kg per test article component; the vehicle was injected twice each day at 10 mL/kg.

[c] Three mice/sex/dose group were observed for clinical signs and survival for four days after the second dosing. For the evaluation of bone marrow toxicity, the three remaining mice/sex/dose group were euthanized 24 hours after the second dosing.

[d] Doses of 800 mg/kg and higher were lethal within 24 hours.

Based on mortality, clinical signs and on the bone marrow toxicity, doses of 0, 100, 125, 200, 250, 400, 500 mg/kg/day were chosen for the main micronucleus test. In the main micronucleus test, no mortality was observed in males and females up to 600 mg/kg/day. Excessive deaths were seen from the dose of 800 mg/kg/day. In the micronucleus test, clinical signs were noted in males (hunched posture, one eye sealed shut, rough hair coat) from the dose of 400 mg/kg/day, while in females (one or both eyes sealed shut, squinted eyes, tremors, ataxic, hunched posture, rough haircoat) from the dose of 125 mg/kg/day. In females at 500 mg/kg/day, 4/6 animals were found dead at 48 hrs harvest time, therefore additional replacement animals (n=6/sex) were used in high dose groups.

No. of animals used: 6/sex/group/sacrifice time.

Sponsor's summary of mouse bone marrow micronucleus test with SCH 58235 + lovastatin (SCH 48176):

Micronucleus Assay Results. The results of the micronucleus assay are presented in Section 12. As presented in the summary table (Table 4), administration of SCH 357015 caused statistically significant decreases in the PCE:NCE ratios, demonstrating that the test article was cytotoxic to the bone marrow. The decreases were noted at 200 mg/kg/day and higher for male mice and at 125 mg/kg/day and higher for the female animals. The marked depressions in the PCE:NCE ratios at the high dose levels for both sexes indicated that SCH 357015 was tested to acceptable cytotoxic doses.

SCH 357015 did not induce statistically significant increases in the frequency of micronucleated PCE for any dose group except for female mice administered 500 mg/kg/day, as measured at the 24-hour harvest. This statistical result was not considered to have biological significance for the following reasons: 1) the number of micronucleated PCE found for each female in the group was within the published and expected range for mice (0-4 micronucleated PCE /1000 PCE); and 2) the observed micronucleated PCE mean value, 0.18%, although elevated above the concurrent vehicle control group, was within the historical vehicle control range (0-0.20%) for recently conducted studies with female mice in this laboratory. In contrast, the administration of cyclophosphamide induced statistically significant increases in micronucleated PCE in male and female mice at both harvest times.

The number of NCE for the calculation of the frequency of micronucleated NCE was estimated from the number of PCEs screened and the PCE:NCE ratios. The percent micronucleated NCE were lower than the micronucleated PCE for all dose groups, although slight, but statistically significant, increases relative to the vehicle control animals were observed at the high dose for both sexes. These results were not considered to have biological significance for the same reasons as given for the micronucleated PCE above. Thus SCH 357015 is considered negative in this assay.

Table. Micronucleus test with SCH 58235 + lovastatin (SCH 48176):

TABLE 4: MICRONUCLEUS DATA SUMMARY TABLE

ASSAY: 20673 TEST ARTICLE: SCH 357015

TREATMENT	DOSE (MG/KG)	HARVEST TIME (HR)	MEAN % MICRONUCLEATED PCE PER ANIMAL ± S.E. MALES	MEAN % MICRONUCLEATED PCE PER ANIMAL ± S.E. FEMALES	MEAN ESTIMATED % MICRONUCLEATED NCE PER ANIMAL ± S.E. MALES	MEAN ESTIMATED % MICRONUCLEATED NCE PER ANIMAL ± S.E. FEMALES	RATIO PCE:NCE MEAN ± S.E. MALES	RATIO PCE:NCE MEAN ± S.E. FEMALES
CONTROLS:								
VEHICLE	0.4% MC	24	0.11 ± 0.04	0.07 ± 0.02	0.02 ± 0.01	0.04 ± 0.01	0.84 ± 0.10	0.78 ± 0.09
	(20 mL/kg)	48	0.07 ± 0.03	0.11 ± 0.03	0.04 ± 0.02	0.00 ± 0.00	0.75 ± 0.08	1.25 ± 0.27
POSITIVE	CP 50	24	2.66 ± 0.14*	3.01 ± 0.64*	0.23 ± 0.03*	0.22 ± 0.02*	0.42 ± 0.06**	0.68 ± 0.08
	CP 30	48	1.07 ± 0.20*	1.04 ± 0.20*	0.19 ± 0.03*	0.17 ± 0.05*	0.49 ± 0.06**	0.56 ± 0.07**
TEST ARTICLE	100	24	0.11 ± 0.03		0.03 ± 0.01		0.58 ± 0.09	
		48	0.05 ± 0.02		0.02 ± 0.01		0.63 ± 0.07	
	125	24		0.06 ± 0.02		0.01 ± 0.01		0.75 ± 0.08
		48		0.02 ± 0.01		0.02 ± 0.01		0.68 ± 0.12**
	200	24	0.09 ± 0.02		0.04 ± 0.02		0.54 ± 0.14	
		48	0.10 ± 0.06		0.07 ± 0.04		0.46 ± 0.07**	
	250	24		0.13 ± 0.03		0.04 ± 0.02		0.50 ± 0.04**
		48		0.07 ± 0.01		0.02 ± 0.01		0.39 ± 0.08**
	400	24	0.17 ± 0.06		0.11 ± 0.03*		0.28 ± 0.01**	
		48	0.07 ± 0.03		0.03 ± 0.01		0.13 ± 0.02**	
	500	24		0.18 ± 0.04*		0.09 ± 0.02*		0.31 ± 0.02**
		48		0.17 ± 0.09		0.03 ± 0.01*		0.17 ± 0.03**

* Significantly greater than the corresponding vehicle control, $p < 0.05$.
** Significantly less than the corresponding vehicle control, $p < 0.05$
0.4% MC = 0.4% methylcellulose
CP = Cyclophosphamide
PCE = Polychromatic erythrocytes
NCE = Normochromatic erythrocytes

Genetic toxicology summary: SCH 58235 + lovastatin (SCH 48176) was negative up to doses of 400-500 mg/kg/day in an in vivo micronucleus test in mice

In mouse micronucleus study with SCH 58235 alone, mortality in animals was observed at 2000 mg/kg/day, clinical signs at 1000 mg/kg/day and bone marrow toxicity was observed in males at 250 mg/kg/day and in females at 500 mg/kg/day. The drug did not increase micronucleated PCE in mice up to 800 mg/kg/day. The combination seems more cytotoxic to females vs the monotherapy in this study. With combination (SCH 58235 +lovastatin) bone marrow toxicity was noted at 200 mg/kg/day in males and at 125 mg/kg/day in females, while with monotherapy bone marrow toxicity was observed at 250 mg/kg/day in males and at 500 mg/kg/day in females. With the combination at 24 hrs, more cytotoxcity was noted in females at 125 mg/kg/day (76%) than in the positive control (87%).

V. Carcinogenicity studies

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET
Review of Carcinogenicity Study Results

Reviewer name: Indra Antonipillai, Ph.D.
Division name: Division of Metabolic and Endocrine Drug Products
HFD #: 510
Review completion date: March 15, 2002

IND/NDA: IND —— NDA 21,445
DRUG CODE NAME: SCH 58235
CAS#: N/A
DRUG NAME: ZEITA (Ezetimibe) tablets
CHEMICAL STRUCTURE:

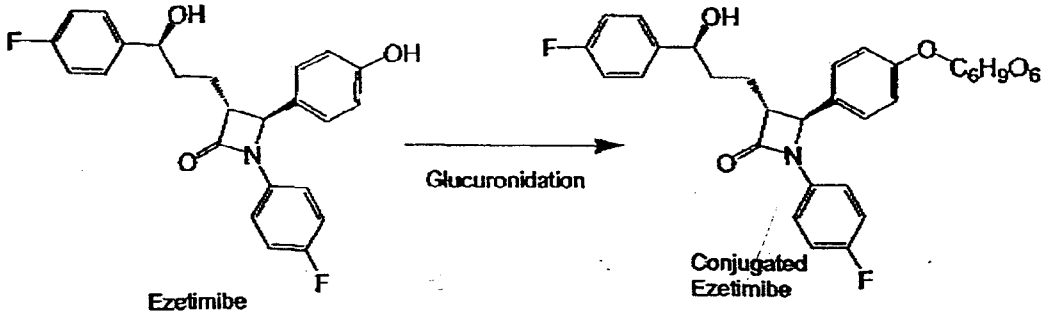


Figure 1 Structures of Ezetimibe and Conjugated Ezetimibe

SPONSOR: MPS Singapore CO., LLC, Singapore.
LABORATORY: Schering-Plough Research Institute, Lafayette, NJ
CARCINOGENICITY STUDY REPORT DATE: July 25, 2001

THERAPEUTIC CATEGORY: primary hypercholesterolemia (heterozygous ——— familial) and for homozygous familial sitosteolemia.

PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: Cholesterol absorption inhibitor ——— it blocks intestinal absorption of cholesterol. It will be used alone (monotherapy) or in combination with HMG CoA reductase inhibitors (statins such as lovastatin, pravastatin, atorvastatin, simvastatin)

MUTAGENIC/GENOTOXIC: negative in Ames test, micronucleus test in mice and chromosomal aberration test in cultured human whole blood lymphocytes.

Studies included Within This Submission: **Page**

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT COVER SHEET

MOUSE CARCINOGENICITY STUDY

MOUSE STUDY DURATION: 104 weeks
STUDY STARTING DATE: February 3, 1998
STUDY ENDING DATE: July 25, 2001
MOUSE STRAIN: Mice/Crl:CD-1(ICR)BR VAF/Plus strain from ———

ROUTE: oral in a diet
DOSING COMMENTS: daily dose, ad libitum for 104-105 weeks.

NUMBER OF MICE:	For Toxicity	Plasma analysis
	- Control-1 (C1): 50	0
	- Control-2 (C2): 50	0
	- Low Dose (T1): 50	6
	- Middle Dose (T2): 50	6
	- High Dose (T3): 50	6

MOUSE DOSE LEVELS* (mg/kg/day):
- Low Dose: 25
- Middle Dose: 100
- High Dose: 500

BASIS FOR DOSES SELECTED

The dose selection was based on saturation of exposure to the parent drug, which at 500 and 2000 mg/kg/day was 0.98 and 0.95 µg.h/ml in males, and 0.33 and 0.35 µg.h/ml in females respectively in a 3-month dose range study in mice. At 500 mg/kg/day, the exposure to parent compound and the major metabolite glucuronide (males 216, females 347 µg.h/ml) was 166-267 fold the human dose at 20 mg/day (1.3 µg.h/ml, based also on AUC of a parent + metabolite). The current clinical dose in humans is 10 mg/day. The major glucuronide metabolite was ≈99% of the total drug. Also the dietary route was chosen, as exposures of the parent drug + metabolite were higher by this route (——— µg.h/ml) vs gavage (——— µg.h/ml).

Plasma concentrations in a 2-year carcinogenicity study in mice: Plasma concentrations of SCH 58235 increased with increasing doses (males 212, 1775, and 14046 ng/ml, females 606, 5683 and 31289 ng/ml at 25, 100, 500 mg/kg/day respectively). Mean total and conjugated plasma concentration in females were 2.2-3.3 fold higher than in males. The drug was highly conjugated in plasma, but note that the conjugated drug has as much, or more drug activity than the active drug.

No AUC values were provided in the current 2-year study in mice to determine the saturation of exposure. It is also unknown if greater than 25 fold AUC of the parent + metabolite was achieved, as was observed in the 3-month mouse toxicity study. In the 3-month mouse study at 500 mg/kg/day, the exposure to parent compound and the major metabolite glucuronide (males 216, females 347 μg.h/ml) was 166-267 fold the human dose at 20 mg/day (1.3 μg.h/ml, based also on AUC of a parent + metabolite).

Pharmacokinetics of SCH 58235 in week 52 (obtained at 8:00 AM), in a 2-year cac study in mice

Table 1 Mean Total, Conjugated and Unconjugated SCH 58235 Plasma Concentrations Following Dietary SCH 58235 Administration to Mice (Week 52, n=6)

Dose (mg/kg)	Male	%CV	Female	%CV
Total SCH 58235 (ng/mL plasma)				
25	212	38	606	59
100	1775[a]	65	5683	42
500	14046	71	31321	58
Conjugated SCH 58235 (ng/mL plasma)				
25	208	39	524[a]	64
100	1749[a]	66	5678	42
500	14008	71	31289	59
Unconjugated SCH 58235 (ng/mL plasma)				
25	4.38	40	9.54[a]	216
100	26.0[a]	85	4.36	31
500	38.6	60	32.1	118

a: n=5

Plasma levels (ng/ml) in a 3-month dietary mouse toxicity study at 100, 500 and 2000 mg/kg/day are shown. Plasma samples were collected at 9-10, 18-19, 24-25 hrs after the start of the day 28 lighting cycle (approximately 6 AM was designated as 0 hour).

Pharmacokinetics of SCH 58235 on day 28, in a 3-month toxicity study in mice

Dose (mg/kg/day)	100	500	2000
Total SCH 58235 (conjugated + unconjugated) ng/ml			
9 hr			
Males	1389	4411	14322
Females	1448	9161	14784
18 hr			
Males	1771	14381	13769
Females	2944	15493	28846
24 hr			
Males	2190	9121	17605
Females	2323	19743	39416

Plasma concentrations of total drug at 100 mg/kg/day in animals were higher in week 52 in a cac study (males 1775, females 5683 ng/ml) than in week 4 (3-month mouse study males 1389, females 1448 ng/ml). Similarly, plasma concentrations at 500 mg/kg/day in animals were higher (by 3 fold) in week 52 (males 14,046, females 31,321 ng/ml) than in week 4 (males 4414, females 9161 ng/ml), suggesting accumulation of the drug over time. In a 3-month mouse toxicity study, Pk analysis was only performed in week 4, so it is unknown if the drug accumulated over time. However in dogs (in a 3-month and 1 year tox studies), 2-3 fold accumulation was observed over time. Similarly in rats (in a 6-month tox study), 1.5-2 fold accumulation was observed in week 25 vs week 4.

MOUSE CARCINOGENICITY: SCH 58235 tested negative (in both sexes, up to doses of 500 mg/kg/day) in the 2-year mouse carcinogenicity study. It is unknown if the saturation of absorption of the parent drug + glucuronide metabolite was achieved in the present study, as no AUC values were provided to determine if exposures at 500 mg/kg/day provide the safety margin over the FDA's approved doses and were adequate. However in the present study 3 fold higher plasma concentrations were achieved vs in the 3-month mouse study, which already showed exposures 166-267 fold the human doses.

MOUSE TUMOR FINDINGS: No neoplastic findings were observed with the drug compared to control. Oral dosing for 2 years at 25, 100 and 500 mg/kg/day did not result in significant increase in neoplastic or non-neoplastic findings in mice. In females, malignant histiocytic sarcoma (at undetermined primary site) was observed at a higher number in 25 mg/kg/day group (4, 7, 11, 3 and 6 at 0, 0, 25, 100, 500 mg/kg/day respectively), but no dose related trend was observed, and was not statistically significant. In males in the harderian gland, increased incidences of adenoma (benign tumors) were noted specially at low doses (0, 2, 9, 3, 4 at 0, 0, 25, 100, 500 mg/kg/day respectively, in females these incidences were 2, 3, 3, 1, 4 respectively), but were not statistically significant in the trend analysis.

Rat CARCINOGENICITY STUDY

Rat STUDY DURATION: 104-106 weeks
STUDY STARTING DATE: February 3, 1998
STUDY ENDING DATE: July 25, 2001
MOUSE STRAIN: Rat (Crl:CD(SD)BR VAF/Plus strain from [redacted]

ROUTE: oral in a diet
DOSING COMMENTS: daily dose was given for 104-106 weeks. **The rats were diet restricted and were offered 25% less food/day.**

NUMBER OF rats/dose/sex:	For Toxicity	Plasma analysis
- Control-1 (C1):	50	0
- Control-2 (C2):	50	0
- Low Dose (T1):	50	8
- Middle Dose (T2):	50	8
- High Dose (T3):	50	8

Rat DOSE LEVELS* (mg/kg/day):

	Males	Females
- Low Dose:	150	50
- Middle Dose:	750	250
- High Dose:	1500	500

BASIS FOR DOSES SELECTED

The dose selection was again based on saturation of exposure of a total drug i.e., parent + glucuronide (but not on the saturation of exposure to the parent drug alone). The Exe committee approved sponsor's doses for both males (150, 750, and 1500 mg/kg/days) and females (50, 250, and 500 mg/kg/day). The Committee concurred with the sponsors on the 2-year carcinogenicity study in diet restricted rats (25% less food/day), **based mainly on the fact that no differences in kinetics (TK) were observed during the 2-week of diet restriction. The concurrence was also contingent on the fact that no significant toxicity would be noted in animals as a consequence of diet restriction.**

Plasma concentrations in a 2-year carcinogenicity study in rats: Plasma concentrations of SCH 58235 poorly correlated with doses, except at 50-250 mg/kg/day in females, where some increase was noted with the dose. The drug was highly conjugated in plasma and unconjugated represented <1.3% of the total drug. Note that the conjugated drug has as much or more drug activity than the active drug itself. The AUC values (0-12 hrs) of only the total drug were provided which did not increase significantly in males with the dose (4131, 4434, 4775 ng.h/ml at 150, 750, 1500 mg/kg/day respectively). In females these values were 3326, 6017, 6659 ng.h/ml at 50, 250, 500 mg/kg/day respectively. This may be due to saturation of oral absorption following dietary administration. The values in females were in general similar to those seen in males, even when females received 3-fold lower doses. Overall, increases in plasma concentration were minimal with increases in doses, sponsor states that similar observations were noted in 1-month TK study in rats.

PK of SCH 58235 in weeks 4 and 52, in a 2-year bioassay in rats

Table 1 Mean Total, Conjugated and Unconjugated SCH 58235 Plasma Concentrations Following Dietary SCH 58235 Administration to Rats (n=4)

Dose (mg/kg) (Male/Female)	Week 4				Week 52			
	Male	%CV	Female	%CV	Male	%CV	Female	%CV
	Total SCH 58235 (ng/mL plasma)							
150/50	389	53	239	36	341[a]	10	349	17
750/250	354	22	692	23	458	40	744	39
1500/500	527	40	464	23	564	41	756	27
	Conjugated SCH 58235 (ng/mL plasma)							
150/50	387	53	236	36	339[a]	9	345	17
750/250	350	23	688	23	456	40	739	39
1500/500	524	40	459	23	562	41	753	28
	Unconjugated SCH 58235 (ng/mL plasma)							
150/50	2.22	57	3.01	41	2.15[a]	87	3.64	37
750/250	3.30	18	4.14	60	1.79	31	4.40	56
1500/500	3.66	33	5.25	9	1.76	92	3.44	54

a: n=3

AUC values (0-12 hrs) of the total drug (parent compound and the glucuronide metabolite) in the current cac study were 4.8 µg.h/ml at 1500 mg/kg/day in males, and 6.7 µg.h/ml in females at 500 mg/kg/day. In the 3-month dose range study in rats, the AUC exposures (0-24 hrs) were 11 and 12 µg.h/ml at 1500 and 500 mg/kg/day respectively in males and females. Exe cac had approved the doses for rat carcinogenicity study based on saturation of absorption of the drug which was achieved in the current study in male rats at the lowest dose of 150 mg/kg/day, as exposures did not further increase with increase in dose to 750-1500 mg/kg/day (4.1, 4.4, 4.8 µg.h/ml at 150, 750, 1500 mg/kg/day respectively). While in females, saturation of absorption was observed at a mid dose of 250 mg/kg/day (values were 3.3, 6.0, 6.7 µg.h/ml at 50, 250, 500 mg/kg/day respectively).

Rat CARCINOGENICITY: SCH 58235 tested negative in both sexes (up to doses of 1500 mg/kg/day in males, and 500 mg/kg/day in females) in the 2-year rat carcinogenicity study.

APPEARS THIS WAY
ON ORIGINAL

RAT TUMOR FINDINGS: In females, hepatocellular adenomas were observed in 2/50 animals (or 4%) at a high dose vs none in control or other groups. Sponsor states that these are in the range of historical control values (range 1-5.5%). However the reference for historical control data appears to be in the rats which are not diet restricted (following reference was provided: Spontaneous neoplastic lesions and selected non-neoplastic lesions in the Crl:CDBR rats, ——————— Feb, 1992). Sponsor has not provided the historical control data for diet restricted rats, but the reference in diet restricted rats (Spontaneous neoplastic lesions and survival in the Crl:CD(SD) BR rats maintained on dietary restriction, ——————— March, 1998) shows that incidence for hepatocellular adenomas in female rats is 2.2% (range 1.3%-2%), which may show hepatocellular adenomas of 4% to be significant in female rats. In the large intestine, malignant lymphoma (in 1/50 control male rats and 1/50 female rats at mid dose vs none in other groups) and fatal fibrosarcoma, mesentery (in 1/50 males at mid dose vs none in other groups) were observed. **Sponsor states that no statistically significant trend in the incidence of tumor-bearing rats was observed with increases in drug doses.** In summary, no neoplastic findings were observed with the drug compared to control. Oral dosing for 2 years at 150, 750, 1500 mg/kg/day in males and 50, 250, and 500 mg/kg/day in females did not result in significant increase in neoplastic or non-neoplastic findings. A decrease in BW (of 4-7%) and weight gains (of 7-10%) was observed in males at mid/high doses. In contrast in a 3-month dose range study in non–diet restricted rats (at doses up to doses of 1500 mg/kg/day), in a 6-month dietary toxicity study in rats (at 150, 750, 1500 mg/kg/day in males and 50, 250, and 500 mg/kg/day in females), or in a 2-week TK study in diet restricted rats (at 2000 mg/kg/day), no effects on BW or weight gains were observed. However, in the present cac study a decrease in BW (of 4-7%) and weight gains (of 7-10%) was observed in males at 750-1500 mg/kg/day during most of the study weeks.

In a T-con on 5/23/2002, sponsor was asked to provide the historical tumor incidences in their diet restricted rats, as there was a concern of a significant increase in hepatocellular adenomas at a high dose in female rats. In a subsequent 7/3/2002 submission, sponsor has provided the historical tumor incidences dataset in control diet restricted rats. No hepatocellular adenomas were observed in male or female animals in above control diet restricted rats. Sponsor also states in the above submission that the ——— databases are considered more appropriate historical control dataset for ezetimibe studies. The ——— databases in the diet restricted rats show that incidence of hepatocellular adenomas in female rats are in the range of 0-8% (mean 2.2%), which is derived from 26 total studies, and in 20 studies lesions were identified. This suggests that hepatocellular adenomas of 4% in the current CAC study are incidental in female rats.

The Exe. CAC committee after reviewing both the sponsor's historical control dataset and ——— dataset in diet restricted rats concluded that 4% increase in incidences of hepatocellular adenomas in female rats at a high dose of 500 mg/kg/day is incidental. In conclusion the committee concurred that there was no significant tumor finding in a 2-year diet restricted rat CAC study.

Study title: 104 Week Oral Dietary Oncogenicity Study in the Mouse

Key study findings: SCH 58235 tested negative in the 2-year mouse carcinogenicity study.

Study number: SN 96458, Document # 31623
Volume #, and page #: 1.43, page # 1. Electronic submission, folder/file name: pharm\tox\Sn96458.pdf
Conducting laboratory and location: Conducting laboratory is Schering-Plough Research Institute, Lafayette, NJ. Sponsor is MPS Singapore CO., LLC, Singapore. However, the drug is a joint venture of Schering-Plough and Merck Co.
Date of study initiation: February 3, 1998
GLP compliance: Yes
QA report: yes (X) no ( )

Drug, lot #, and % purity: SCH 58235: 97-58235-X-01, 98-58235-X-05

CAC concurrence:
CaC concurrence was obtained after initiation of the study. The 2-year carcinogenicity study in mice was initiated on 2/3/1998. The sponsor submitted dose selection document for 2-year mouse carcinogenicity study on 7/20/1998. Executive CAC committee concurred with the dose selection on 9/8/1998.

Study Type: 2-year oral dietary bioassay
Species/strain: Mice/Crl:CD-1(ICR)BR VAF/Plus strain from

Table 1. Number/sex/group:

Oral (Diet) Oncogenicity Study of SCH 58235 in Mice (SN 96458): **Study Design**						
			Number of Mice			
		Estimated Total Daily Dose	Toxicity Portion		Plasma Analysis Portion[a]	
Group	Test/Control Article	(mg/kg)	M	F	M	F
C1	Vehicle Control (Rodent Diet)	0	50	50	0	0
C2	Vehicle Control (Rodent Diet)	0	50	50	0	0
T1	Low-Dose (SCH 58235)	25	50	50	6	6
T2	Mid-Dose (SCH 58235)	100	50	50	6	6
T3	High-Dose (SCH 58235)	500	50	50	6	6
a: These animals were evaluated for plasma exposure at Week 52 only.						

Age and weight at start of study: Animals at the start of the study were 6 weeks old. In the toxicity study animals weighed 23.8-31.9 g (males) and 18.4-25.6 g (females). In PK study animals weighed 27.2-31.5 g (males) and 18.7-22.4 g (females).
Animal housing: mice were housed individually in suspended stainless-steel cages, and in a separate room form animals of other studies. The temperature and relative humidity of the room ranged of 72°F and 40-70% respectively. They had 12 hours light/dark cycles.

Formulation/vehicle:

The drug was given orally in a diet: The diet was [redacted] (meal). The dietary admixture and tap water were offered ad libitum to animals.

Drug stability/homogeneity:

SCH 58235 at concentrations of 0.1-15 g/kg is stable and homogenous in above rodent diet feed [redacted] meal) for 15 days at ambient temperatures and light. The appropriate amounts of the drug were admixed in a diet weekly, at conc. estimated to attain the intended doses. These were based on the most recent mean body weights and food consumption data for the dosing intervals

Methods:

Doses: 0, 0, 25, 100, and 500 mg/kg

Basis of dose selection:

Dose selection was based on the results of a 2-week oral (dietary vs gavage) toxicokinetic study, and a 13 week oral dietary dose-range study in Crl:CD-1 mice.

A 2-week oral (dietary vs gavage) toxicokinetic study in mice showed that exposures of the total drug were higher by this route vs gavage [redacted] vs [redacted] µg.h/ml).

In the 3-month dietary dose range toxicity study in mice, the drug (at 100, 500 and 2000 mg/kg/day) at 2000 mg/kg/day decreased body weights by 6-7% and caused toxicity (vacuolation in liver, and focal tubular atrophy in testes). The MTD was based on saturation of exposure to the parent drug, which at 500 and 2000 mg/kg/day was 0.98 and 0.95 µg.h/ml in males, and 0.33 and 0.35 µg.h/ml in females respectively. At 500 mg/kg/day, the exposure to parent compound and the major metabolite glucuronide (males 216, females 347 µg.h/ml) was 166-267 fold the human dose at 20 mg/day (1.3 µg.h/ml, based also on AUC of a parent + metabolite). The major glucuronide metabolite was ≈99% of the total drug.

The drug was not genotoxic in the Ames test and chromosome aberration in human lymphocytes. Based on the above end points (saturation of absorption, and exposures greater than 25 fold of a parent+metabolite), the high doses of 500 mg/kg/day were approved for mice carcinogenicity study by Exe CAC Committee. Also the dietary route was chosen for cac studies, as exposures of the parent drug + metabolite were higher by this route. The Committee also proposed that the duration of the mouse cac study be increased from 92 weeks to 104 weeks.

Restriction paradigm for dietary restriction studies:

Mice had access *ad libitum* to [redacted] (meal, [redacted]

Water was provided *ad libitum* via an automatic watering system.

Route of administration: Dietary

Frequency of drug administration: Ad libitum for 104-105 weeks

Dual controls employed: yes

Interim sacrifices: There were no interim sacrifices. However in a PK study, at 100 mg/kg, one male animal was found dead on day 349 and this animal was cremated

without necropsy

Satellite PK or special study group(s):
6 animals/sex/ group. Blood was obtained during week 52 from all mice assigned to PK study, except in the 100 mg/kg/day group, because of one male, which was found dead as indicated above.

Deviations from original study protocol: None.

Statistical methods:

Male and female mouse data were analyzed separately. Tumor incidence patterns were compared over the length of entire study. The palpable, and nonpalpable (both fetal and incidental) tumors were analyzed using the methods by Peto et al. Non-palpable-incidental tumors were analyzed using fixed intervals of 1-52, 53-78, 79-104 weeks, and a separate startum for mice which were terminally sacrificed. Results for palpable, non-palpable and non-palpable incidental tumors were then combined in accordance with the Peto et al (IARC Monographs on the evaluation of the carcinogenic risk of chemicals to Humans suppl. 2, 365, 1980).

Trend analysis was used which is defined as a progressiveness of response with increasing dose of the test compound, with the control included as a zero dose. One tailed positive p-values were reported since the primary object was to determine whether the drug increases the incidence of tumor in mice.

For tumor sites at which 10 or fewer tumor-bearing mice were observed in any time startum, a small-sample, discrete, permutation test was used. This method supposedly incorporates time to tumor detection, time to death without tumor, context of tumor observation (i.e palpable vs non-palpable tumors) and a cause of death in a similar manner as the procedure described above. The significance level for all statistical tests was set at 0.05.

When applying a trend test simultaneously to many tumor sites, a multiplicity adjustment method was used. Two multiplicity adjustment procedures were chosen. 1) the standard method used by Merck and Co. Inc. using a procedure described by Hayse and Rom (Biochem J 30:883, 1998) and by Harter (Biometrics13:511, 1957). 2) [redacted] method used by Schering Plough Research Institute uses [redacted] for common tumor types and [redacted] for rare tumor types. In this method [redacted] For study # 96458, all of the tumor types were considered to be common tumors, except for the following tumors that were considered rare: a) brain-choroid plexus carcinoma, b) epididymides-leiomyosarcoma, c) heart-mesothelioma d) lung-osteosarcoma and e) seminal vesciles-mesenchymal tumor.

For mortality, trend was evaluated using the log rank test. This approach supposedly compares the entire life-table incidence patterns by summarizing the survival data at, and cumulating over, each day an unscheduled death or sacrifice occurs. In case of tumor incidence, one-tailed P values were used in the statistical evaluation since the primary concern was to determinine

whether treatment with the test compound increases mortality. Also, cumulative percent mortality or 'life-table' plots were constructed as described by Cutler and Ederer (J of Chronic Disease 8:699, 1958).

Observations and times:

Clinical signs: daily.

Body weights: day -4, weekly from week 2 through 13, and once every other week thereafter through week 104.

Food consumption: weekly from week 2 through 13, and once every other week thereafter through week 104.

Test Article intake: weekly from week 2 through 13, and once every other week thereafter through week 104.

Ophthalmoscopy: pre-treatment and once during weeks 52 and 104 in all toxicity animals.

Hematology: At sacrifice. Red blood cell count, hemoglobin (calculated), hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin conc. calculated, reticulocyte count, platelet count, mean platelet volume, total and differential leukocyte count, and blood smear morphology were measured.

Clinical chemistry: Not performed.

Organ weights: Not performed.

Gross pathology: At sacrifice.

Histopathology: It was performed on tissues shown in the table below from all main test animals in the toxicity study. These were evaluated by the pathologist, and a peer review was conducted. All tissues were preserved in the appropriate fixatives.

Table 2. Tissues collected for histopathology in 2-year cac study

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

a: Bone marrow smears were prepared for all mice sacrificed prior to and at the scheduled necropsies but were not evaluated because it was not warranted by changes in the peripheral blood.
b: Collected but not processed
c: Examined histopathologically when present in routine section

Toxicokinetics: Plasma samples were collected during week 52 at 8:00 AM from the drug treated mice (5-6 mice/sex/group), and assayed for unconjugated, and total (conjugated + unconjugated) SCH 58235, using ———————— by

Results:
Mortality: No significant mortality was observed in the drug treated mice vs controls during the 104 week treatment. Number of mice found dead or sacrificed were as follows: Males 24, 28, 28, 29, 25 at 0, 0, 25, 100, 500 mg/kg/day respectively. In females, these values were 20, 26, 22, 20, 23 respectively (Table 3).

Table 3: Number of mice found dead or sacrificed prior to the scheduled necropsy in 2-year mouse cac study:

Incidental Mortality										
Dose (mg/kg):	0		0		25		100		500	
Sex:	M	F	M	F	M	F	M	F	M	F
No. Animals:	50	50	50	50	50	50	50	50	50	50
Number of mice found dead or sacrificed prior to the scheduled necropsy	24	20	28	26	28	22	29	20	25	23

Percent survival to scheduled sacrifice (i.e terminal sacrifice, Table 4) for males was 52%, 44%, 44%, 42%, 50% at 0, 0, 25, 100 and 500 mg/kg/day respectively. These numbers in females were 60, 48, 56, 60, 54% respectively. Over the entire length of the study, in both sexes there was no statistically significant increase in mortality with increasing doses (Table 4). There were no significant drug related unscheduled deaths. In Table 4a, the two control groups are combined and mortality in drug treated vs controls is shown.

Table 4: Summary of Mortality

Table 1 Summary of Mortality										
Group:	C1		C2		T1		T2		T3	
Dose (mg/kg):	0		0		25		100		500	
Sex:	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
No. Animals:	50	50	50	50	50	50	50	50	50	50
Type of Mortality	Incidence									
Unscheduled Sacrifice	7 (14%)	8 (16%)	10 (20%)	13 (26%)	12 (24%)	7 (14%)	10 (20%)	6 (12%)	8 (16%)	8 (16%)
Found Dead	17 (34%)	12 (24%)	18 (36%)	13 (26%)	16 (32%)	15 (30%)	19 (38%)	14 (28%)	17 (34%)	15 (30%)
Terminal Sacrifice	26 (52%)	30 (60%)	22 (44%)	24 (48%)	22 (44%)	28 (56%)	21 (42%)	30 (60%)	25 (50%)	27 (54%)

APPEARS THIS WAY ON ORIGINAL

Table 4a. Mortality in drug treated vs both controls

Summary of Mortality Analysis for Study No. 96458

Sex		SCH 58235 C[a]	L[b]	M[c]	H[d]
Female	R	46	22	20	23
	NT	100	50	50	50
Percent Dead		46%	44%	40%	46%
Log-Rank P-value[e]					0.581
Male	R	52	28	29	25
	NT	100	50	50	50
Percent Dead		52%	56%	58%	50%
Log-Rank P-value[e]					0.499

Key:

R = Number of animals dying prior to scheduled sacrifice.
NT = Number of animals tested in the study.

a = Control group.
b = 25 mg/kg/day of SCH 58235.
c = 100 mg/kg/day of SCH 58235.
d = 500 mg/kg/day of SCH 58235.
e = One-tailed log-rank P-value was computed using the "life-table" analysis. (see text)

The majority of the deaths were due to acute or chronic urinary tract obstruction. These were observed at necropsy or during histopath examinations and included renal pelvic dilatation, urinary bladder distension, thinning of the urinary bladder wall and/or evidence of penile obstruction. Some mice had several of these findings, while others only had one finding. There was an increased incidence of urinary tract obstructions in males with the drug vs controls, but it was not dose related and sponsor states that obstructive uropathy is a common cause of death in male mice in chronic studies. The specific cause of death or unscheduled sacrifice is shown in Tables 5 and 6.

Table 5. The specific cause of death or unscheduled sacrifice in 2-year mouse cac study

Probable Cause of Early Death/Unscheduled Sacrifice										
Sex:	Males					Females				
Dose (mg/kg):	0	0	25	100	500	0	0	25	100	500
Probable Cause	Incidence[a]									
Cause Unknown	8	9	7	7	6	4	7	3	4	6
Urinary Tract Obstruction	9	9	11	15	13	1			1	
Brain	(23)[b]	(28)	(28)	(29)	(25)	(20)	(26)	(22)	(20)	(23)
- Choroid plexus carcinoma (M)										1
Harderian Glands	(24)	(28)	(28)	(29)	(25)	(20)	(26)	(22)	(20)	(22)
- Adenocarcinoma (M)							1			
Heart	(24)	(28)	(28)	(29)	(25)	(20)	(26)	(22)	(20)	(23)
- Polyarteritis nodosa							1			
- Thrombus(i), atrial	2	2	2		2	1		2		1
Kidneys	(24)	(28)	(28)	(29)	(25)	(20)	(26)	(22)	(20)	(23)
- Cellular infiltration, neutrophilic				1						
- Nephritis, chronic	1			1				3	1	1
- Amyloidosis, glomerular						1				1
Liver	(24)	(28)	(28)	(29)	(24)	(20)	(26)	(22)	(20)	(23)
- Hepatocellular adenoma (B)			1		1					
- Hemangiosarcoma (M)			1			1				
- Angiectasis					1					
Lungs	(24)	(28)	(28)	(29)	(25)	(20)	(26)	(22)	(20)	(23)
- Bronchiolo-alveolar carcinoma (M)	1	2	1				2	1	2	1
- Bronchiolo-alveolar adenoma (B)				1						
- Thrombosis	1									
- Metaplasia, osseus		1								
Mammary Glands	(1)				(1)	(20)	(25)	(20)	(17)	(20)
- Adenocarcinoma (M)						2		1	1	1
Ovaries						(20)	(25)	(22)	(20)	(23)
- Cyst(s)									1	
Pituitary Gland	(23)	(28)	(27)	(28)	(25)	(19)	(26)	(21)	(20)	(23)
- Adenoma (B)			1				1			
Skeletal Muscle	(24)	(28)	(28)	(29)	(25)	(20)	(24)	(22)	(19)	(23)
- Hemorrhage(s)						1				
- Hemangiosarcoma (M)								1		

a: Incidence = Number affected
b: ( ) = Number examined
M = Malignant
B = Benign

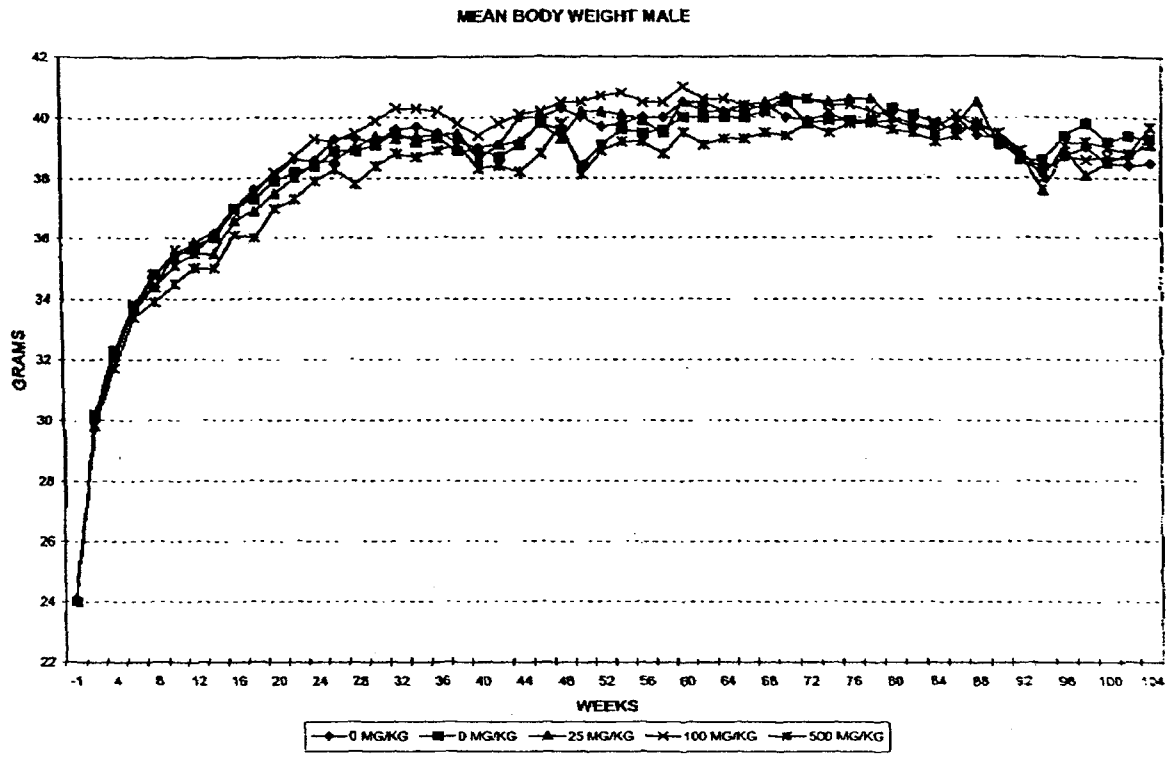
Table 6. The specific cause of death or unscheduled sacrifice continued

Probable Cause of Early Death/Unscheduled Sacrifice										
Sex:	Males					Females				
Dose (mg/kg):	0	0	25	100	500	0	0	25	100	500
Probable Cause	Incidence[a]									
Skin	(24)[b]	(28)	(28)	(29)	(25)	(20)	(26)	(22)	(20)	(23)
- Basal cell carcinoma (M)							1			
- Malignant fibrous histiocytoma (M)							2			
- Hemangioma (B)							1			
- Fibrosarcoma (M)	1									
- Inflammation		1								
Small Intestine	(21)	(26)	(27)	(28)	(23)	(19)	(25)	(21)	(18)	(20)
- Necrosis, intestinal	1	1								
Spleen	(24)	(28)	(28)	(29)	(24)	(20)	(26)	(22)	(20)	(22)
- Hemangiosarcoma (M)			1			1	1			
Stomach	(24)	(28)	(28)	(29)	(24)	(20)	(26)	(22)	(20)	(23)
- Sarcoma (M), undifferentiated		1								
- Leiomyosarcoma (M)					1					
- Adenoma (B)						1				
Urinary Bladder	(24)	(28)	(28)	(29)	(25)	(20)	(24)	(22)	(19)	(21)
- Papilloma (B)				1						
Uterus						(20)	(26)	(22)	(20)	(23)
- Cystic endometrial hyperplasia								1	1	
- Endometrial stromal sarcoma (M)										1
- Hemorrhage						1			1	
Primary Site Undetermined	(24)	(28)	(28)	(29)	(25)	(20)	(26)	(22)	(20)	(23)
- Histiocytic Sarcoma (M)			1			3	6	4	2	5
- Lymphoma (M)		2	2	1		3	3	5	5	4
Leukemia (M)				1	1			1		
- Fibrosarcoma (M)									1	
- Mesothelioma (M)				1						
- Sarcoma (M)										1

a: Incidence – Number affected
b: ( ) = Number examined
M = Malignant
B = Benign

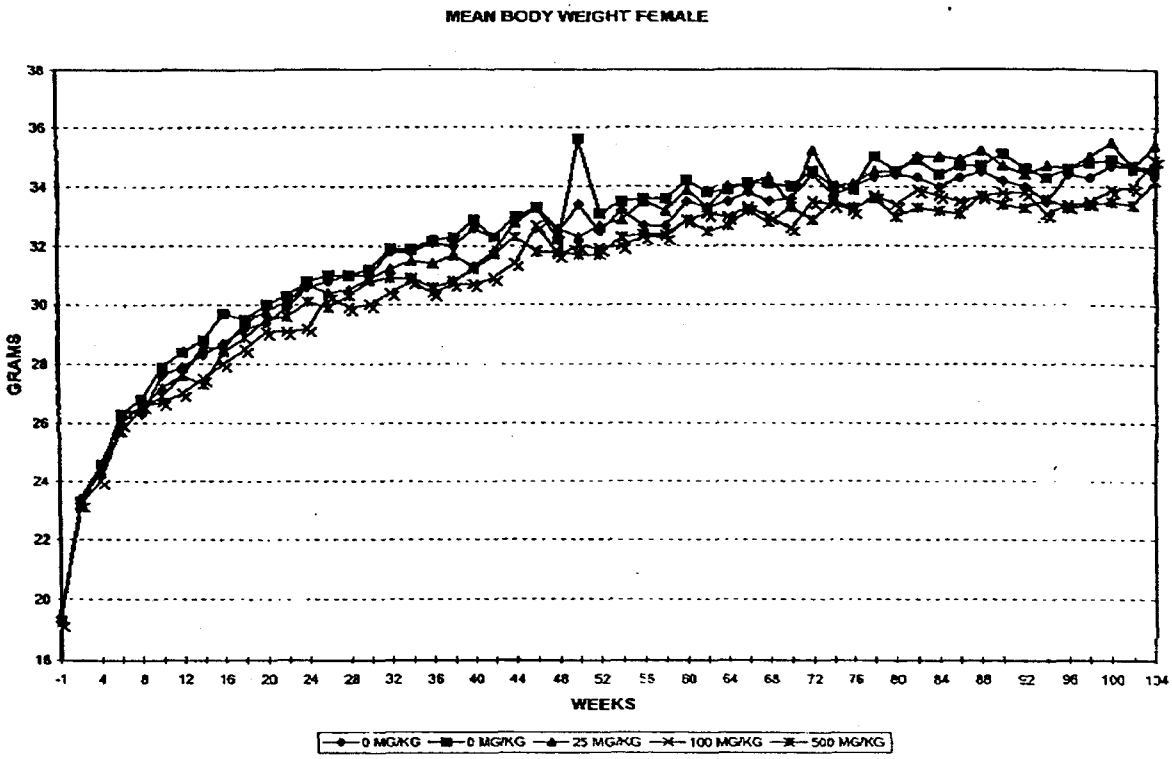
Clinical signs: No treatment related clinical signs were noted at ≤ 500 mg/kg/day in males or females.
Palpable masses: The incidence, timing and number of palpable masses were not drug related
Body weights: No treatment related changes were noted in body weights or weight gains, see figures 1 and 2.

Figure 1. Mean body weights in male mice



APPEARS THIS WAY
ON ORIGINAL

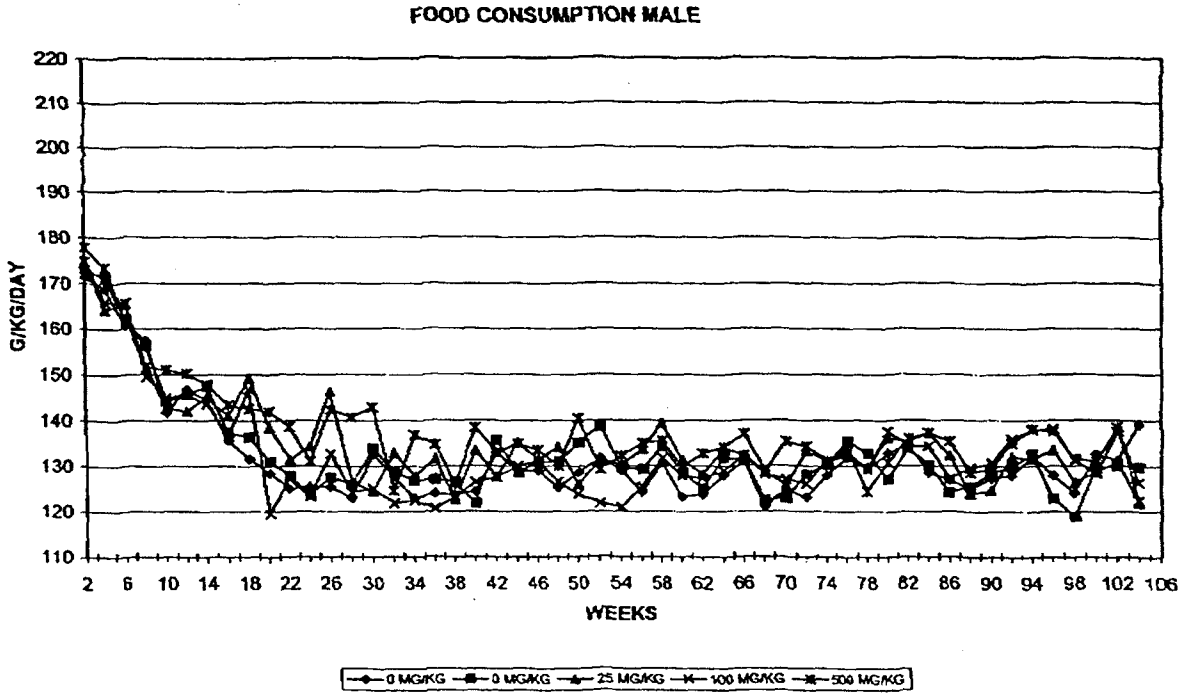
Figure 2. Mean body weights in female mice



APPEARS THIS WAY
ON ORIGINAL

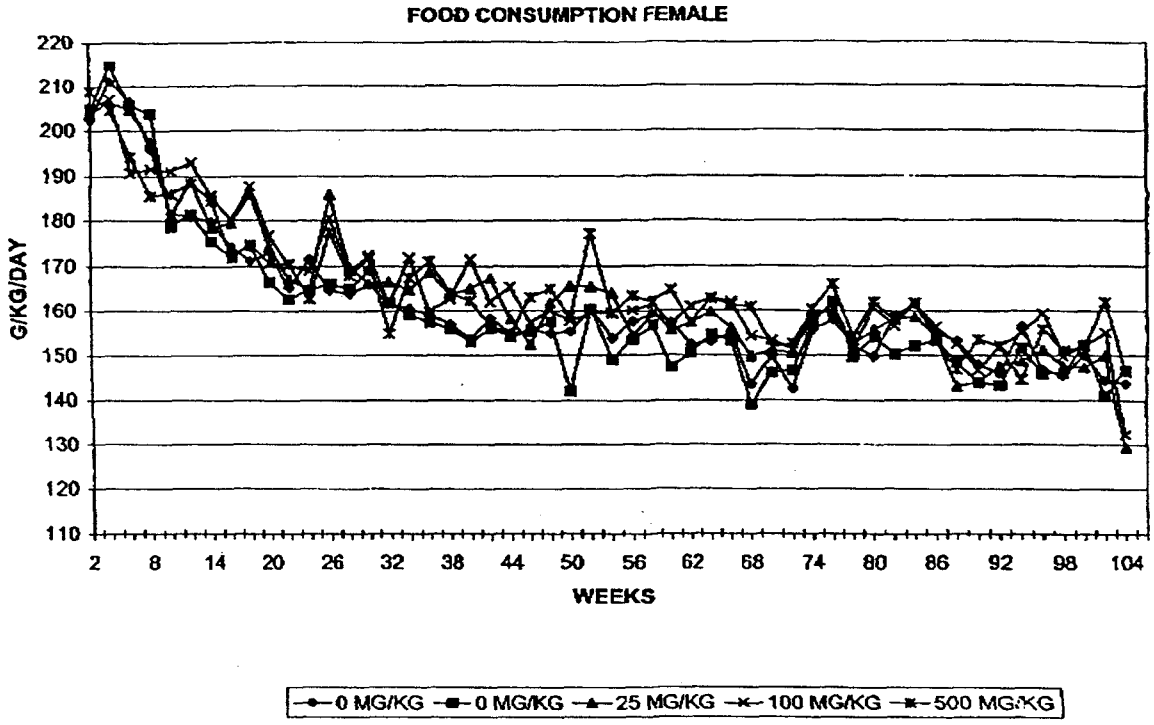
Food consumption: No apparent treatment related changes in food consumption were observed, figures 3 and 4.

Figure 3. Mean Food consumption in male mice



APPEARS THIS WAY
ON ORIGINAL

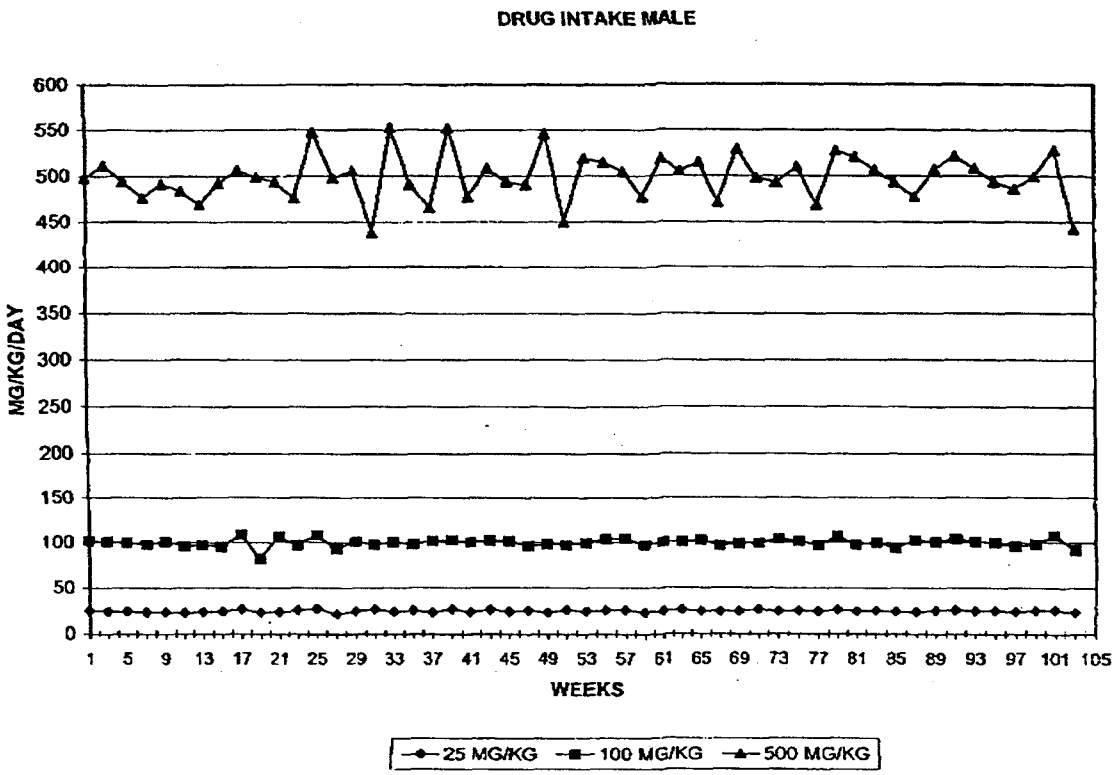
Figure 4. Mean Food consumption in female mice



APPEARS THIS WAY
ON ORIGINAL

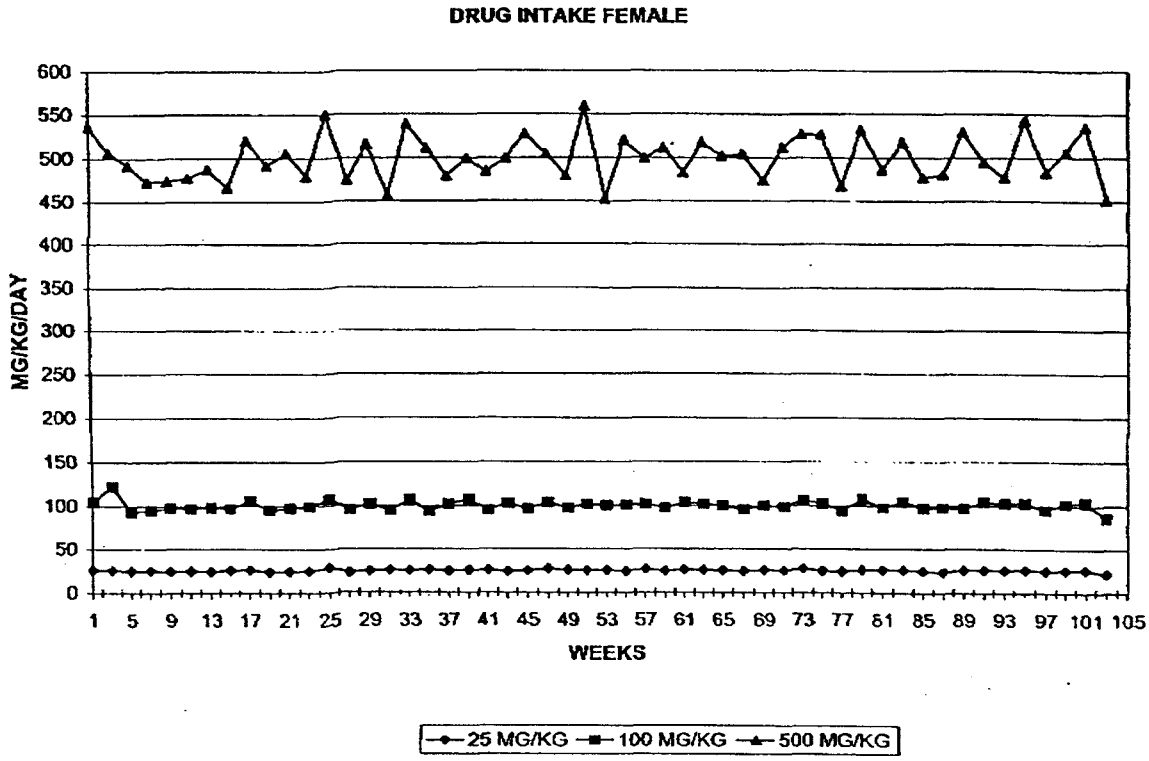
Test Article Intake : The mean drug intake was within ±20% in all groups throughout the study, except at one interval in females at 100 mg/kg/day (mean intake on day 21 in toxicity and PK study was +21.8% and 26.2% respectively), figures 5 and 6.

Figure 5. Mean Drug intake in male mice



APPEARS THIS WAY
ON ORIGINAL

Figure 6. Mean Drug intake in female mice



Ophthalmologic Examinations: No treatment related changes were observed

Hematology:
In control group (one female in week 105), at 25 mg/kg/day (two males in week 69 and 84), and at 500 mg/kg/day (one male in week 101), animals had hematologic evidence of leukemia. This was based on high total leukocyte counts (40.2-113 K/ul) and lymphocyte count (24.5-92.1 K/Ul) and/or presence of atypical lymphocytes. Sponsor states that leukemia of lymphoid type is not rare in mice. Therefore it was not considered drug related. No other treatment related hematological changes were observed.

Gross pathology:
No remarkable findings were observed and most findings seen were generally consistent with the expected pattern of background findings seen in mice of this age.

Histopathology:
Non-neoplastic:
There were no drug related non-neoplastic findings. These microscopic findings were generally considered incidental.

In drug treated males, thymus had an increased incidence of lymphoid atrophy (or involution/regression, males 27/30, 26/33, 29/33, 36/38, 37/40 respectively, females 27/45, 20/40, 23/40, 26/41, 25/42 respectively), but sponsor states that these were also high in both male controls (27/30, and 26/33 respectively), Table 7. There was no dose

related effect in females. Additionally, histopathologic examinations of the spleen, mandibular/mesenteric lymph nodes, gut-associated lymphoid tissue, and thymus revealed no evidence of the effect of the drug on immune systems. In spleen, lymphoid atrophy of minimal to severe degree was noted in all animals (males 4/50, 6/50, 3/50, 6/50, 6/49, females 6/50, 7/50, 7/50, 3/50, 3/49 respectively in C1, C2, and at 25, 100 and 500 mg/kg/day), Table 8. Sponsor claims that thymus atrophy is a common finding in most species with age, including in mice.

Table 7: Histopathologic findings in thymus in mice

Histopathology (Microscopic Observations)
Incidence Table with Severity (Numeric)

		Incidence of Findings									
		Males					Females				
FINDINGS	TREATMENT	C1	C2	T1	T2	T3	C1	C2	T1	T2	T3
THYMUS		(30)	(33)	(33)	(38)	(40)	(45)	(40)	(40)	(43)	(42)
Cyst(s).		5		1	4	7		1	1		1
Congestion.											
moderate									1		
Atrophy, lymphoid.											
minimal				1		2		1			3
mild		8	5	6	1	5	8	5	5	7	4
moderate		11	8	13	17	13	13	8	11	14	7
severe		8	13	9	18	17	6	5	7	5	21
Amyloidosis.											
mild			1								
THYROID GLAND		(50)	(50)	(50)	(50)	(49)	(49)	(49)	(50)	(50)	(50)
Not Remarkable		34	28	36	36	34	30	23	30	33	31
Polyarteritis nodosa.											
minimal		1		1				1	1	1	
Cellular infiltration.											
minimal			3	1	3	1	3	5	7	2	4
mild									1	1	

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.

14-MAR-01 05:59
Places 2000 V1.400

APPEARS THIS WAY
ON ORIGINAL

Table 8: Histopathologic findings in spleen of mice

Histopathology (Microscopic Observations)
Incidence Table with Severity (Numeric)

		Incidence of Findings									
		Males					Females				
FINDINGS	TREATMENT	C1	C2	T1	T2	T3	C1	C2	T1	T2	T3
SPLEEN		(50)	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(49)
Hyperplasia, lymphoid.											
mild		1			1	3	2		2	4	1
Hematopoiesis, extramedullary.											
minimal		6	4	2	2	5	5	12	3	7	8
mild		1	2	3	5	1	10	8	6	5	5
moderate			4	1	2		2	3		4	1
severe										1	
HEMANGIOSARCOMA [M].			1	1			1			1	
(Incidental)		2	1		2		1				1
(Fatal)				1			1	1			
Fibrosis.											
minimal					1	1	1				
mild		1	3		1				1		
Atrophy, lymphoid.											
minimal		2			1		1		1		
mild		1		2	4	2	2	3	2	1	
moderate			5	1	1	4	1	3	4	2	2
severe		1	1				2	1			1

[M] Malignant tumour
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.

14-MAR-01 09:59
Places 2000 V1.400

Neoplastic:

The neoplastic findings were considered incidental in the drug treated groups. These in general were not different from the control groups. In females, malignant histiocytic sarcoma (at undetermined primary site) were observed at a higher number in 25 mg/kg/day group (4, 7, 11, 3 and 6 at 0, 0, 25, 100, 500 mg/kg/day respectively), but these showed no dose related trend, Table 12. Also in males in the harderian gland, increased incidences of adenoma (benign tumors) were noted specially at low doses (0, 2, 9, 3, 4 at 0, 0, 25, 100, 500 mg/kg/day respectively, in females these incidences were 2, 3, 3, 1, 4 respectively), but were not statistically significant in the trend analysis. Sponsor states that no statistically significant trend in the incidence of tumor-bearing mice was observed with increases in drug doses. These are summarized in Tables 9-12. In Tables 12a-12d, the tumor incidences and trend p-values for these tumors are described.

APPEARS THIS WAY
ON ORIGINAL

Table 9. Incidental neoplastic tumors in mice

Incidental Tumors										
Sex:	Males					Females				
Dose (mg/kg):	0	0	25	100	500	0	0	25	100	500
Organ/Finding	Incidence[a]									
Adrenal Glands	(49)[b]	(50)	(50)	(49)	(49)	(50)	(50)	(50)	(50)	(50)
- Pheochromocytoma (M)					1					
- Pheochromocytoma (B)							2			
- Carcinoma (M), cortical										1
- Adenoma (B), cortical			1	1		1			1	1
Brain	(49)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Choroid plexus carcinoma (M)										1
Epididymides	(50)	(50)	(50)	(50)	(50)					
- Leiomyosarcoma (M)			1	1						
Eyes	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Schwannoma (M)	1									
Harderian Glands	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(49)
- Adenocarcinoma (M)							1			
- Adenoma (B)		2	9	3	4	2	3	3	1	4
Heart	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Mesothelioma (B)				1						
Kidneys	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Adenoma (B)			2							
Large Intestine	(50)	(49)	(50)	(50)	(49)	(49)	(49)	(50)	(50)	(48)
- Leiomyosarcoma (M)		1								
- Leiomyoma (B)										1
Liver	(50)	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)
- Hepatocellular carcinoma (M)			1							
- Hepatocellular adenoma (B)	12	8	14	13	11	1	1	1	4	2
- Hemangiosarcoma (M)		1	2		2	2	1			
Lungs	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Bronchiolo-alveolar carcinoma (M)	1	4	4	2			2	1	3	3
- Bronchiolo-alveolar adenoma (B)	11	12	11	9	8	15	8	8	8	9
- Osteosarcoma (M)						1				
Mammary Glands	(1)	(1)			(1)	(45)	(44)	(44)	(37)	(46)
- Adenocarcinoma (M)						3	1	2	1	1

a: Incidence = Number affected
b: ( ) = Number examined
M = Malignant tumor
B = Benign tumor

Table 10. Incidental neoplastic tumors in mice continued.

Incicental Tumors										
Sex:	Males					Females				
Dose (mg/kg):	0	0	25	100	500	0	0	25	100	500
Organ/Finding	Incidence[a]									
Ovaries						(50)[b]	(49)	(50)	(50)	(50)
- Sarcoma (M), undifferentiated										1
- Granulosa cell tumor (B)							1		1	
- Cystadenoma (M)						1	1			
- Sertoli cell tumor (B)						1				
- Luteoma (B)						1				
- Leiomyoma (B)							1			
- Hemangioma (B)						1				
Pancreas	(50)	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)
- Islet cell adenoma (B)									1	
Parathyroid Glands	(47)	(44)	(46)	(43)	(41)	(42)	(43)	(46)	(47)	(44)
- Carcinoma (M)							1			
- Adenoma (B)								1		
Pituitary Gland	(49)	(50)	(48)	(49)	(50)	(48)	(50)	(49)	(50)	(48)
Adenoma (B), pars anterior	1		2	1		3	4	4	4	3
- Adenoma (B), pars intermedia								1		
Seminal Vesicles	(50)	(50)	(50)	(50)	(49)					
- Mesenchymal tumor (B)			1							
Skeletal Muscle	(50)	(50)	(50)	(50)	(50)	(50)	(48)	(50)	(47)	(49)
- Hemangiosarcoma (M)								1		
Skin	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(49)
- Sebaceous cell carcinoma (M)					1					
- Mast cell tumor (M)									1	
- Osteosarcoma (M)					1					
- Malignant fibrous histiocytoma (M)	1						2	1		
- Myxosarcoma (M)							1			1
- Fibrosarcoma (M)	2		1			1	1			
- Basal cell carcinoma (M)							1			
- Hemangioma (M)		1		1			1			
Small Intestine	(47)	(48)	(49)	(49)	(48)	(49)	(49)	(49)	(48)	(47)
- Adenocarcinoma (M)							1			
- Adenoma (B)									1	

a: Incidence = Number affected
b: ( ) = Number examined
M = Malignant tumor
B = Benign tumor

Table 11. Incidental neoplastic tumors in mice continued.

Incidental Tumors										
Sex:	Males					Females				
Dose (mg/kg):	0	0	25	100	500	0	0	25	100	500
Organ/Finding	Incidence[a]									
Spleen	(50)[b]	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(49)
- Hemangiosarcoma (M)	2	2	2	2		3	1		1	1
Stomach	(50)	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)
- Sarcoma (M), undifferentiated		1				1				
- Papilloma (B), nonglandular									1	
- Leiomyosarcoma (M)					1					
- Adenoma (B)						1				1
Testes	(50)	(50)	(50)	(50)	(50)					
- Sertoli cell tumor (B)					1					
- Interstitial cell adenoma (B)	4	1			1					
- Hemangioma (B)				1						
Thymus	(30)	(33)	(33)	(38)	(40)	(45)	(40)	(40)	(41)	(42)
- Thymoma (B)							1			
Trachea	(50)	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(50)
- Papilloma (B)								1		
Urinary Bladder	(50)	(50)	(50)	(50)	(50)	(48)	(48)	(50)	(49)	(47)
- Mesenchymal tumor (B)	1		1	1	2	1			1	1
- Papilloma (B)				1						
Uterus						(50)	(50)	(50)	(50)	(50)
- Endometrial stromal sarcoma (M)						1		1		1
- Endometrial stromal polyp (B)						6	4	5	3	4
- Leiomyosarcoma (M)									2	
- Leiomyoma (B)							2	2	4	
- Hemangiosarcoma (M)									1	
- Hemangioma (B)						1				
- Fibrosarcoma (M)									1	
- Fibroma (B)							2	1	1	1
- Adenocarcinoma (M)							1		2	1
- Granular cell tumor (B)						1				1
Vagina						(50)	(48)	(49)	(49)	(50)
- Squamous cell carcinoma (M)						1			1	
- Leiomyoma (B)						1				

a: Incidence = Number affected
b: ( ) = Number examined
M = Malignant tumor
B = Benign tumor

Table 12. Incidental neoplastic tumors in mice continued.

Incidental Tumors										
Sex:	Males					Females				
Dose (mg/kg):	0	0	25	100	500	0	0	25	100	500
Organ/Finding	Incidence[a]									
Primary Site Undetermined	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Histiocytic sarcoma (M)		1	1			4	7	11	3	6
- Sarcoma (M), undifferentiated										1
- Mesothelioma (M)				1						
- Lymphoma (M)	2	4	3	2		9	8	7	7	6
- Leukemia (M)				1	1			1		
- Hemangiosarcoma (M)										1
- Fibrosarcoma (M)									1	
a: Incidence = Number affected b: ( ) = Number examined M = Malignant tumor										

Table 12a. Tumor incidences in drug treated vs controls.

Table 1: Oral (Diet) Oncogenicity Study of SCH 58235 in Mice: Summary of Tumor Incidence for Study No. 96458

ORGAN/TUMOR TYPE	Males C1	C2	T1	T2	T3	Trend P-value	Females C1	C2	T1	T2	T3	Trend P-value
LUNGS	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(50)	(50)	(50)	
Bronchiolo-Alveolar Carcinoma (M)	1	4	4	2	0	0.979	0	2	1	3	3	0.117
Bronchiolo-Alveolar Adenoma (B)	11	12	11	9	8	0.852	15	8	8	8	9	0.553
PRIMARY SITE UNDETERMINED	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(50)	(50)	(50)	
Leukemia (M)	0	0	0	1	1	0.134	0	0	1	0	0	NA
Histiocytic Sarcoma (M)	0	1	1	0	0	0.840	4	7	11	3	6	0.499
Lymphoma (M)	2	4	3	2	0	0.978	9	8	7	7	6	0.699
URINARY BLADDER	(50)	(50)	(50)	(50)	(50)		(48)	(48)	(50)	(49)	(47)	
Mesenchymal Tumor (B)	1	0	1	1	2	0.155	1	0	0	1	1	0.273
HARDERIAN GLANDS	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(50)	(50)	(49)	
Adenoma (B)	0	2	9	3	4	0.404	2	3	3	1	4	0.173
ADRENAL GLANDS	(49)	(50)	(50)	(49)	(49)		(50)	(50)	(50)	(50)	(50)	
Adenoma (B), cortical	0	0	1	1	1	0.205	1	0	0	1	1	0.272
Pheochromocytoma (B)	0	0	0	0	0	NA	0	2	0	1	0	0.761

LEGEND:
C1 = Control 1
C2 = Control 2
T1 = 25 mg/kg/day SCH 58235
T2 = 100 mg/kg/day SCH 58235
T3 = 500 mg/kg/day SCH 58235
B = Benign Tumor
M = Malignant Tumor
NA = No Analysis Performed.

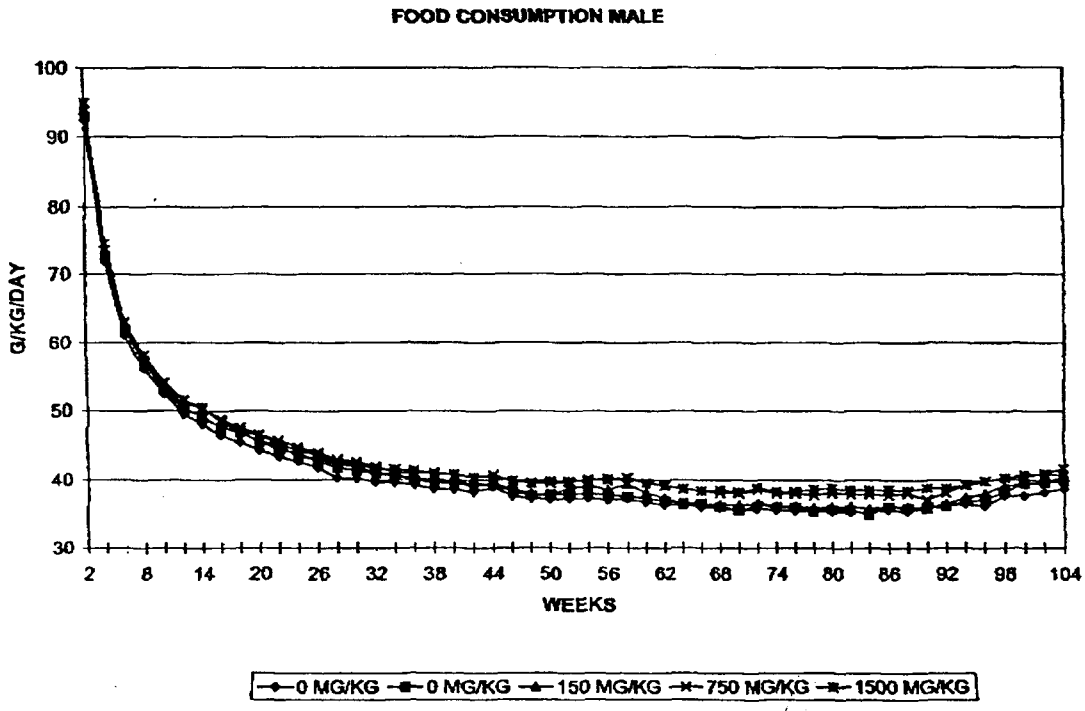
NOTE: For purpose of analysis, the control groups were combined into one group. Also, the parenthetical numbers are the number of animals examined for that organ. The P-values are one-sided and age-adjusted. When P ≤ 0.05, an adjustment for multiplicity is used (but there are none in Table 1). No tumor types in Table 1 are statistically significant by the Schering-Plough Research Institute (page 6)

APPEARS THIS WAY
ON ORIGINAL

Table 12b. Tumor incidences in drug treated vs controls, contnued.

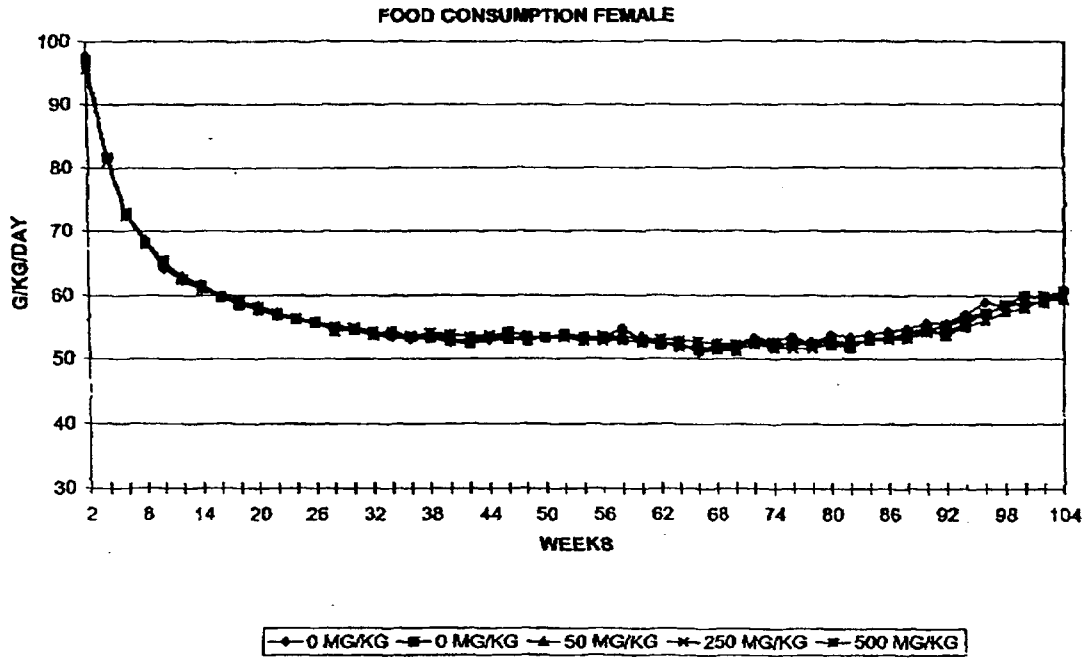
mg/kg/day appeared to consume more food than controls or 150 mg/kg/day group when normalized for body weight (g/kg/day), however this was attributed to lower body weights in two high groups

Figure 9. Mean Food consumption in male rats



APPEARS THIS WAY
ON ORIGINAL

Figure 10. Mean food consumption in female rats



Test Article Intake : The mean drug intake was within ±7.1% in all groups throughout the study.

APPEARS THIS WAY
ON ORIGINAL

Figure 11. Mean drug intake in male rats

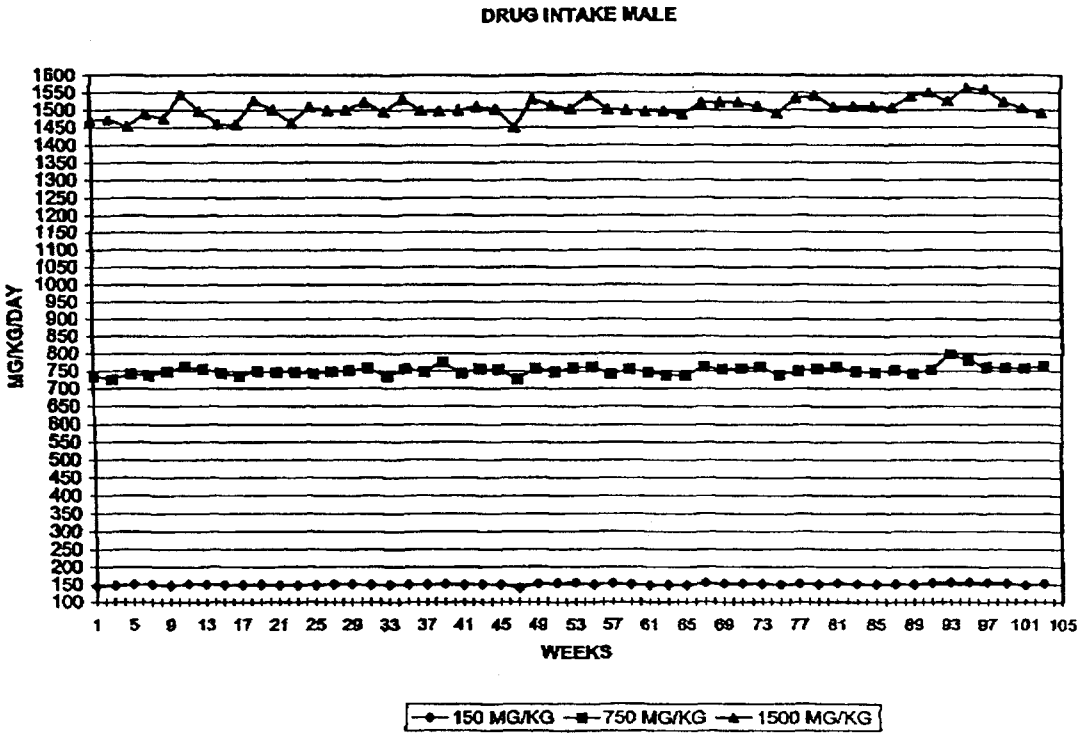
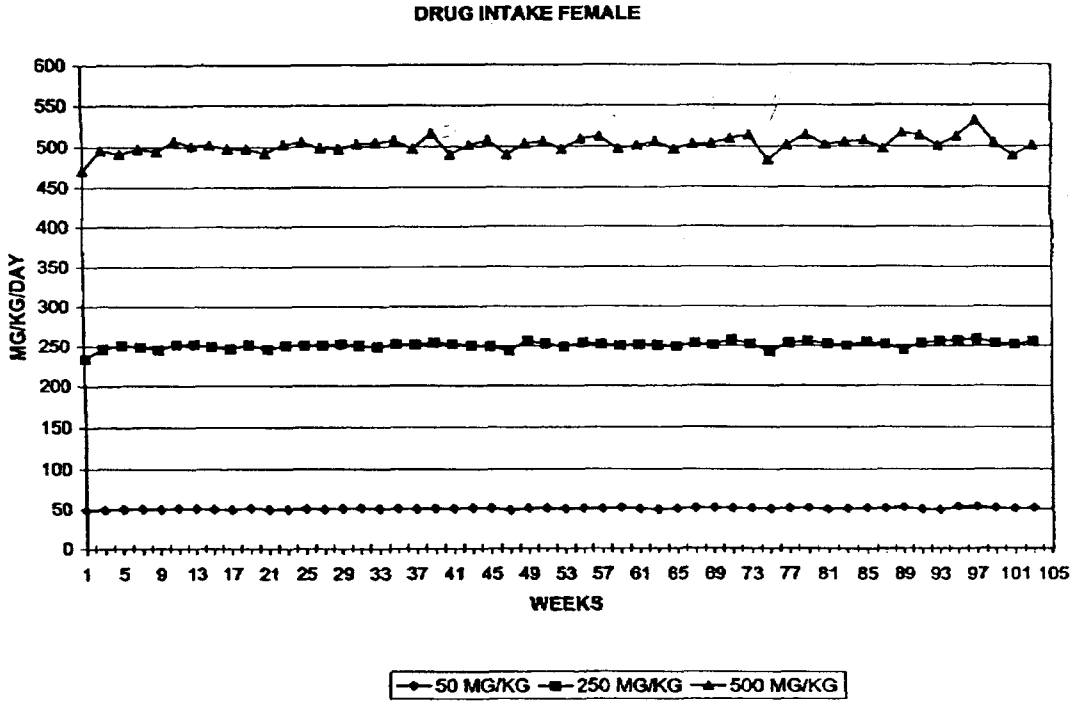


Figure 12. Mean drug intake in female rats



Ophthalmologic Examinations: The most frequent identified incidental finding was pale ocular fundi, which was noted in all animals including in controls. These were

examined by focal illumination and indirect ophthalmoscopy. Mydriasis was produced with 1% atropine and the eyes examined in subdued light. These eye findings were so extensive in some cases that retinal degeneration if present could not be detected. Pathologist report suggests that it may be an indicator of anemia and therefore not a primary ocular condition. Most of these rats also had hematocrit and/or hemoglobin values at week 105 that were lower than the group mean values. No summary data or severity of eye findings were provided in week 52 or 103. Also the mean hematocrit and/or hemoglobin values in week 105 in these animals were not provided to determine how low these values were, and if there were differences between control and drug treated animals. **It is unknown if ophthalmosopic or hematologic findings were more severe in drug treated vs controls.**

Table 20. Ophthalmosopic exams with SCH 58235 in male (0, 0, 150, 750, 1500 mg/kg/day) and female (0, 0, 50, 250, 500 mg/kg/day) rats in a 2-year dietary cac study:

	(n=50/sex/dose) Males	Females
Eyes (pale ocular fundi)		
Week 52	0, 1, 0, 1, 0	0, 0, 2, 1, 1
Week 103	6, 7, 13, 10, 9	15, 26, 18, 19, 21

Hematology:
Sponsor states that no significant differences in group mean were observed between controls and drug treated animals, there was a lot of variation in individual rats. Incidences found were similar in drug treated vs controls, not dose related, did not occur consistently and were consistent with biologic variations in this species.

At scheduled sacrifice, the mean hemoglobin (12.7, 13.1, 12.6, 12.8, 12.6 g/dl at 0, 0, 150, 500, 1500 mg/kg/day respectively) and hematocrit (32.9, 34.2, 32.9, 33.4, 33.2% respectively) values in males were not significantly different in drug treated vs controls. Similarly in females these were not different from controls (mean hemoglobin 11.1, 10.4, 10.9, 11.5, 11.2 g/dl respectively, mean hematocrit 28.4, 26.4, 27.9, 29.7, 28.6 % respectively)

Gross pathology:
No remarkable findings were observed and most findings seen were generally consistent with the expected pattern of background findings seen in rats of this age.

Histopathology:
Non-neoplastic:
There were no drug related non-neoplastic findings. These microscopic findings were generally considered incidental. The incidence of selected hyperplasia is shown in Tables 21 and 22. In the large intestine, malignant lymphoma (in 1/50 control male rats and 1/50 female rats at mid dose vs none in other groups) and fatal fibrosarcoma, mesentery (in 1/50 males at mid dose vs none in other groups) were observed, Table 22a. Histopath exams of spleen, mandibular and mesenteric lymph nodes, gut associated lymphoid tissue and thymus did not show any evidence of drug related effect on immune systems.

Table 21: Selected incidental hyperplastic findings in rats

Incidence of Selected Incidental Hyperplastic Findings										
Group:	C1		C2		T1		T2		T3	
Sex	M	F	M	F	M	F	M	F	M	F
Dose (mg/kg):	0	0	0	0	150	50	750	250	1500	500
Organ/Finding	Incidence[a]									
Adrenal Glands	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Hyperplasia, cortex, focal										
minimal		1		1		2		4		2
mild	3	5	3	8	4		2	1	1	
- Hyperplasia, medulla										
minimal	2	4		4	1	5	2			
mild	3	3		4	2	1		1	1	3
moderate		1	1							
Liver	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Focus (i) of cellular alteration, basophilic										
minimal	4	4	1	7	4	5	1	5	6	1
mild	1	2		1			1		1	
- Focus (i) of cellular alteration, clear cell										
minimal	4	3	2	2	2	1	5	2	4	3
mild		1	1	1		2	1		1	2
- Focus (i) of cellular alteration, eosinophilic										
minimal			1				1			2
mild			1				1			
- Focus (i) of cellular alteration, mixed cell										
minimal										1
Pancreas	(50)	(50)	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)
- Hyperplasia, islet cell, focal										
minimal					1					
mild	1				1					
Pituitary Gland	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(49)	(50)
- Hyperplasia, pars anterior, focal										
minimal	4	4	9		4	3	4	2	8	
mild	2	3	2	3	4	2	3	3	4	4
moderate	1	1		1					1	
- Hyperplasia, pars intermedia, focal										
minimal	1									
mild			1			1				

a: Incidence = Number affected
b: ( ) = Number examined

Table 22: Selected incidental hyperplastic findings in rats continued

Incidence of Selected Incidental Hyperplastic Findings										
Group:	C1		C2		T1		T2		T3	
Sex:	M	F	M	F	M	F	M	F	M	F
Dose (mg/kg):	0	0	0	0	150	50	750	250	1500	500
Organ/Finding	Incidence[a]									
Testes	(50)[b]		(50)		(50)		(50)		(49)	
- Hyperplasia, interstitial cell, focal										
minimal	1									
mild			1							
- Hyperplasia, interstitial cell, diffuse										
mild							1			
Thyroid Gland	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Hyperplasia, C-cell, focal										
minimal	3	2	2	3	1	1	1	4	3	2
mild	2	2	1	2	1		2	3		2
moderate			1		1				1	
- Hyperplasia, C-cell, diffuse										
minimal	1									
mild										1

a: Incidence = Number affected
b: ( ) = Number examined

APPEARS THIS WAY
ON ORIGINAL

Table 22a. Histopath findings in the large intestine

Histopathology (Microscopic Observations)
Incidence Table with Severity (Numeric)

		Incidence of Findings									
		Males					Females				
FINDINGS	TREATMENT	C1	C2	T1	T2	T3	C1	C2	T1	T2	T3
KIDNEYS		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
Cast(s), hyaline.											
minimal		3	3	1	3	4	4		5	2	2
mild		1		1							
Basophilia, cortical tubule, focal.											
minimal		13	8	8	9	14	4	3	3	5	2
mild			1	1							
Atrophy, glomerular.											
minimal				1		1					
LARGE INTESTINE		(50)	(50)	(50)	(50)	(50)	(50)	(50)	(49)	(50)	(50)
Not Remarkable		49	50	50	49	50	50	48	49	49	50
CHOLANGIOCARCINOMA [M], mesentery, metastatic site.								1			
Accumulation, lamina propria, histiocyte.											
minimal								1			
LYMPHOMA [M], metastatic site.		1								1	
FIBROSARCOMA [M], mesentery.											
(Fatal)					1						

[M] Malignant tumour
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.

1-MAR-01 08:33
Places 2000 V1.400

Neoplastic:

The neoplastic findings were considered incidental in the drug treated groups. These in general were not different from the control groups. In females, hepatocellular adenomas were observed in 2/50 animals (or 4%) at a high dose vs none in control or other groups, Table 23, which sponsor states is in the range of historical controls values (range 1-5.5%). The reference for historical control data was following: Spontaneous neoplastic lesions and selected non-neoplastic lesions in the Crl:CDBR rats, ——— ——————— and appears to be in the rats which are not diet restricted. Also in pancreas, benign islet cell adenomas were increased in males at low and high doses (0, 0, 2, 0, 2 at 0, 0, 150, 750, 1500 mg/kg/day respectively). The historical control data for diet restricted rats are not provided, but the reference in diet restricted rats (Spontaneous neoplastic lesions and survival in the Crl:CD(SD) BR rats maintained on dietary restriction ———————————) shows that incidence for hepatocellular adenomas in female rats is 2.2% (range 1.3-2%) and for benign islet cell adenoma incidence in male rats is 9.7% (range 1.7-32%), which would suggest that heptocellular adenomas in females may be significant. In the large intestine, malignant lymphoma (1/50 female rats at mid dose vs none in control or other groups) and fatal fibrosarcoma, mesentery (in 1/50 males at mid dose vs none in other groups) were observed. **Sponsor states that no statistically significant trend in the incidence of tumor-bearing rats was observed with increases in drug doses.** The primary neoplasm incidences are summarized in
Tables 23-24. In Tables 25-27, the tumor incidences and trend p-values for these tumors are shown.
Table 23. Incidences of primary neoplastic findings in 2-year rat study

Incidence of Incidental Primary Neoplasms

Group:	C1		C2		T1		T2		T3	
Sex:	M	F	M	F	M	F	M	F	M	F
Dose (mg/kg):	0	0	0	0	150	50	750	250	1500	500
Organ/Finding	Incidence[a]									
Adrenal Glands	(50)[b]	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Cortical-cell adenoma (B)	1	5	1		1	1	1			2
- Cortical-cell carcinoma (M)				1						
- Ganglioneuroma (B)				1						
- Pheochromocytoma (B)	3	2	6	2	2	3	3	4	3	2
- Pheochromocytoma (M)	1				3			1		
Bone Marrow	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Sarcoma (M), undifferentiated	1									
Brain	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Astrocytoma (B)			1							
- Astrocytoma (M)		1					1			
- Oligodendroglioma (B)						1				
- Oligodendroglioma (M)	1									
Eyes	(50)	(49)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Meningioma (B)										1
- Schwannoma (B)			1							
Harderian Glands	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Adenocarcinoma (M)			1							
Heart	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Paraganglioma (B)						1				
Kidneys	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Hemangiosarcoma (M)	1									
Large Intestine	(50)	(50)	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)
-Fibrosarcoma (M), *mesentery*							1			
Liver	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Cholangiocarcinoma (M)				1						
- Hemangioma (B)					1					
- Hepatocellular adenoma (B)										2
Lymph Nodes	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Hemangioma (B)					1					

a: Incidence = Number affected
b: ( ) = Number examined
M = Malignant tumor
B = Benign tumor

APPEARS THIS WAY
ON ORIGINAL

Table 24. Incidences of primary neoplastic findings in 2-year rat study

Incidence of Incidental Primary Neoplasms										
Group:	C1		C2		T1		T2		T3	
Sex:	M	F	M	F	M	F	M	F	M	F
Dose (mg/kg):	0	0	0	0	150	50	750	250	1500	500
Organ/Finding	Incidence[a]									
Mammary Glands	(46)[b]	(49)	(43)	(50)	(42)	(50)	(43)	(48)	(44)	(50)
- Adenoma (B)		5		3		2		1		3
- Adenocarcinoma (M)		10		4		8		8		4
- Adenocarcinoma arising in fibroadenoma (M)				2				1		
- Fibroma (B)	1									
- Fibroadenoma (B)		14		17		18		17		11
- Lipoma (B)					1					
Pancreas	(50)	(50)	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)
- Islet cell adenoma (B)				1	2	1		1	2	1
- Carcinoma (M), acinar cell			1				1			
Pituitary Gland	(50)	(50)	(50)	(49)	(50)	(50)	(50)	(50)	(49)	(50)
Adenoma (B)	30	34	20	41	28	28	28	34	23	34
Skin	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Fibroma (B)	2	2	1	1				4	1	1
- Fibrosarcoma (M)						1				
- Hemangiosarcoma (M), subcutis			1							
- Sarcoma (M), undifferentiated									1	
- Squamous cell carcinoma (M)					1					
- Squamous cell papilloma (B)					1		1		1	
Testes	(50)		(50)		(50)		(50)		(49)	
- Interstitial cell adenoma (B)			3				1			
Thyroid Gland	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- C-cell adenoma (B)	5	10	5	3	4	5	3	1	3	3
- Follicular cell adenoma (B)				1		1				
- Follicular cell carcinoma (M)									1	
Urinary Bladder	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(48)	(50)
- Papilloma (B)				1						
Uterus		(50)		(50)		(50)		(50)		(50)
-Endometrial stromal polyp (B)		2		2		2		2		1
- Fibroma (B)				1		1		2		1
- Granular cell tumor (B)		1								
- Leiomyoma (B)				1		1				
Primary Site Undetermined	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)	(50)
- Histiocytic sarcoma (M)	1		2			1	1	1	1	
- Lymphoma (M)	1		1	1			1	1	1	1

a: Incidence = Number affected
b: ( ) = Number examined
M = Malignant tumor
B = Benign tumor

Table 25.Tumor incidences in drug treated vs both controls

Table 1: Oral (Diet) 104 Week Oncogenicity Study of SCH 58235 in Rats: Summary of Tumor Incidence for Study No. 96459

ORGAN/TUMOR TYPE	Males C1	C2	T1	T2	T3	Trend P-value	Females C1	C2	T1	T2	T3	Trend P-value
LIVER	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(50)	(50)	(50)	
Hepatocellular Adenoma (B)	0	0	0	0	0	NA	0	0	0	0	2	0.044 (0.446)
PANCREAS	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(49)	(50)	(50)	
Islet Cell Adenoma (B)	0	0	2	0	2	0.125	0	1	1	1	1	0.344
Carcinoma (M), acinar cell	0	1	0	1	0	0.677	0	0	0	0	0	NA
SKIN	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(50)	(50)	(50)	
Squamous Cell Papilloma (B)	0	0	1	1	1	0.184	0	0	0	0	0	NA
Fibroma (B)	2	1	0	0	1	0.742	2	1	0	4	1	0.367
PRIMARY SITE UNDETERMINED	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(50)	(50)	(50)	
Lymphoma (M)	1	1	0	1	1	0.466	0	1	0	1	1	0.287
Histiocytic Sarcoma (M)	1	2	0	1	1	0.614	0	0	1	1	0	0.478

LEGEND:
C1 = Control 1
C2 = Control 2
T1 = 150 mg/kg/day SCH 58235 For Male Rats And 50 mg/kg/day SCH 58235 For Female Rats
T2 = 750 mg/kg/day SCH 58235 For Male Rats And 250 mg/kg/day SCH 58235 For Female Rats
T3 = 1500 mg/kg/day SCH 58235 For Male Rats And 500 mg/kg/day SCH 58235 For Female Rats
B = Benign Tumor
M = Malignant Tumor
NA = No Analysis Performed.

NOTE: For purpose of analysis, the control groups were combined into one group. Also, the parenthetical numbers are the number of animals examined for that organ. The P-values are one-sided and age-adjusted. When P ≤ 0.05, an adjustment for multiplicity is used. The P-value in parentheses is a one-sided, multiplicity-adjusted P-value calculated using the Merck & Co., Inc. multiplicity adjustment procedure (pages 5 and 6). No tumor types in Table 1 are statistically significant by the Schering-Plough Research Institute (page 6) or by the Merck & Co., Inc. multiplicity adjus

Table 26.Tumor incidences in drug treated vs both controls continued

Table 1: (Continued)

ORGAN/TUMOR TYPE	Males C1	C2	T1	T2	T3	Trend P-value	Females C1	C2	T1	T2	T3	Trend P-value
UTERUS							(50)	(50)	(50)	(50)	(50)	
Fibroma (B)							0	1	1	2	1	0.313
Endometrial Stromal Polyp (B)							2	2	2	2	1	0.723
Leiomyoma (B)							0	1	1	0	0	0.828
ADRENAL GLANDS	(50)	(50)	(50)	(50)	(50)		(50)	(50)	(50)	(50)	(50)	
Pheochromocytoma (B)	3	6	2	3	3	0.750	2	2	3	4	2	0.458
Cortical-Cell Adenoma (B)	1	1	1	1	0	0.763	5	0	1	0	2	0.685
Pheochromocytoma (M)	1	0	3	0	0	0.909	0	0	0	1	0	NA
PITUITARY GLAND	(50)	(50)	(50)	(50)	(49)		(50)	(49)	(50)	(50)	(50)	
Adenoma (B)	30	20	28	28	23	0.849	34	41	28	34	34	0.670
MAMMARY GLANDS	(46)	(43)	(42)	(43)	(44)		(49)	(50)	(50)	(48)	(50)	
Adenoma (B)	0	0	0	0	0	NA	5	3	2	1	3	0.733
Adenocarcinoma Arising in Fibroadenoma (M)	0	0	0	0	0	NA	0	2	0	1	0	0.778
Adenocarcinoma (M)	0	0	0	0	0	NA	10	4	8	8	4	0.856
Fibroadenoma (B)	0	0	0	0	0	NA	14	17	18	17	11	0.888

LEGEND:
C1 = Control 1
C2 = Control 2
T1 = 150 mg/kg/day SCH 58235 For Male Rats And 50 mg/kg/day SCH 58235 For Female Rats
T2 = 750 mg/kg/day SCH 58235 For Male Rats And 250 mg/kg/day SCH 58235 For Female Rats
T3 = 1500 mg/kg/day SCH 58235 For Male Rats And 500 mg/kg/day SCH 58235 For Female Rats
B = Benign Tumor
M = Malignant Tumor
NA = No Analysis Performed.

NOTE: For purpose of analysis, the control groups were combined into one group. Also, the parenthetical numbers are the number of animals examined for that organ. The P-values are one-sided and age-adjusted. When P ≤ 0.05, an adjustment for multiplicity is used. No tumor types in Table 1 are statistically significant by the Schering-Plough Research Institute (page 6) or by the Merck & Co., Inc. multiplicity ad