- Terminal and Necroscopic evaluations:
  - Dams:
  - Offspring:

# animals examined: ♂ ♀	21 22	24 24	22 26	25 23
# animals with abnormal findings: ♂ ♀	0 0	0 0	0 0	0 0
Organ weight (relative and absolute): Heart, lung, liver, kidney, spleen, testis/ovary	No significant difference observed			
Skeletal abnormality	0	0	0	0
Skeletal variation (%)	0	3/48 (6.3)	7/48 (14.6)	4/48 (8.3)
Accessory of sternebra	0	1	5	3
Lumbarization	0	1	1	0
Lumbar rib	0	0	0	1
14 ribs, accessory of sterbebra	0	1	0	0
Lumbar ribs, accessory of sterbebra	0	0	1	0
# animals examined: ♂ ♀	11 11	12 12	12 12	12 12
# animals with abnormal findings: ♂ ♀	0 0	0 0	0 0	0 0
Organ weight (relative and absolute): Heart, lung, liver, kidney, spleen, testis/ovary	No significant difference observed			
# animals examined: ♂ ♀	11 10	12 11	12 12	12 10
# animals with abnormal findings: ♂ ♀	0 0	1 0	1 0	0 0
Organ weight (relative and absolute): Heart, lung, liver, kidney, spleen, testis/ovary	No significant difference observed			

* significantly different from control $p<0.05$.

Summary and Evaluation:

S-4522 was repeatedly administered orally at doses of 25, 50 and 100 mkd to groups of 36 copulated rats during the fetal organogenesis period of pregnancy. Its effects on dams, fetuses, and offspring were evaluated.

- Effect on dams: No toxic symptoms nor death occurred. Relative liver weight increased 6% and 12% for 50 and 100 mkd groups, respectively. S-4522 had no effects on the establishment or duration of pregnancy, delivery and lactation conditions.
- Effects on fetuses and offspring: No embryo-fetolethal effect nor any growth suppressant or teratogenic effect on fetuses. No effects on viability, functional/behavioral development, reproductive function of the offspring.
- Dose selection: Preliminary study was conducted at doses of 100, 50, 25 and 12.5 mkd for 11 days. No adverse effect was observed in both dams and fetuses. Considering

death occurred at 150 mkd groups in the previous 2 week study, high dose was set at 100 mkd. In the present study, high dose (100 mkd) only induced minimal liver weight increases. The AUC at lower dose in rats (on day 1 of 60 mkd) was 1350 ng.hr/ml, that is about 4 times the AUC at the maximum proposed human dose of 80 mg. Therefore, 100 mkd appears to be acceptable as the high dose.

- Conclusion: NOAEL is 25 mg/kg/day for dams and 100 mg/kg/day for fetuses and offspring under the conditions tested.

Study title: Study on oral administration of S-4522 during the period of fetal organogenesis in rabbits

Submission: SN000 Vol 20 Page 1
Study No: S-4522-B-38-L (Contract No ——)
Study period: January 12, 1994 to November 30, 1994
Site and testing facility: ——
GLP compliance: Yes
QA- Reports Yes (X) No ( ):
Lot and batch numbers: Lot No. 56
Protocol reviewed by Division Yes ( ) No (X):

Methods:

- Species/strain: Rabbits (Kbl:JW, Japanese white, SPF)
- Doses employed: 0, 0.3, 1, 3 mg/kg/day
- Route of Administration: oral gavage
- Study Design: Successfully copulated females were treated orally with S-4522 at 0, 0.3, 1, 3 mkd for 13 days between pregnancy days 6 and 18. Dams were cesarean-sectioned on day 28 of pregnancy.
- Number of animals/dosing group: 14 to 16
- Parameters and endpoints evaluated:
  Dams: Clinical signs of toxicity, survival and death, body weight, food consumption, blood biochemistry, organ weight, histopathology.
  Fetuses: number of embryonic/fetal deaths, number of live fetuses, sex, body weight, placental weight, external abnormality, internal abnormality, skeletal abnormality/variation, ossification.
- Statistical evaluations: Treated and control groups were statistically compared at the 5% and 1% levels of significance.

Results:

- Clinical signs:
  Control and 0.3 mkd groups: No treatment-related changes.
  1 mkd group: hair loss in 1 animal, toe wound in 1 animal.
  3 mkd group: dead or killed moribund animals showed hypoactivity, weakness, loose feces, perianal and perigenital staining, bloodstains on the cage floor.
- Mortality:
  3 mkd group: 2 death and 2 moribund to kill between day 22 and day 25.
- Body weight:

Significant body weight gain reductions in 3 mkd group were due to the marked weight loss of the dead and killed moribund animals. When these animals were excluded, no significant difference was observed between the remaining 10 animals in 3 mkd group and controls.

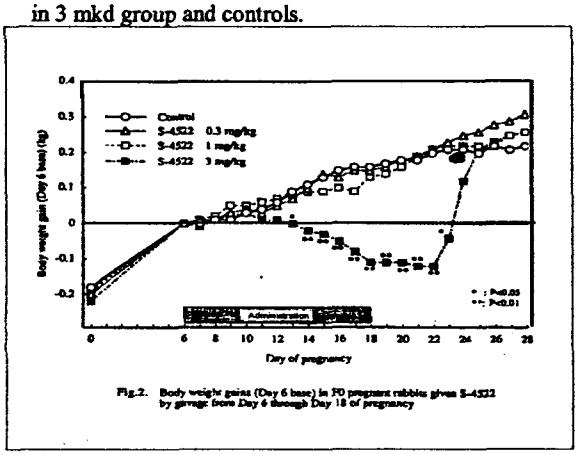


Fig.2. Body weight gains (Day 6 base) in FO pregnant rabbits given S-4522 by gavage from Day 6 through Day 18 of pregnancy

- Food consumption:

Significant food consumption decreases in 3 mkd group were due to the marked reductions in the dead and killed moribund animals. When these animals were excluded, no significant difference was observed between the remaining 10 animals in 3 mkd group and controls.

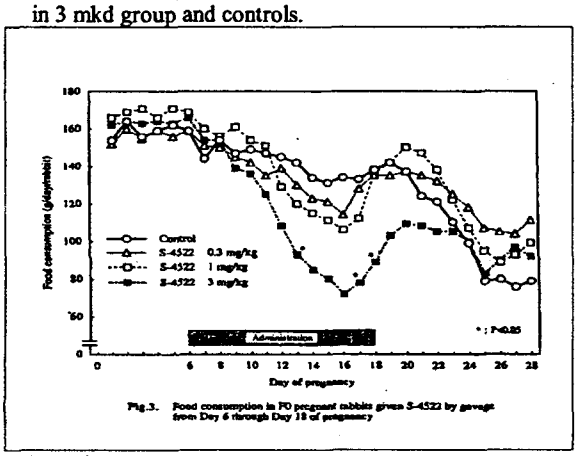


Fig.3. Food consumption in FO pregnant rabbits given S-4522 by gavage from Day 6 through Day 18 of pregnancy

- Embryo-fetal Development
  - In-life observations:
  - Terminal and Necroscopic evaluations:
    - Dams:

# of animals	14	16	14	10

Gross pathological findings	No significant changes			
Organ weight	No significant changes			
Histopathological findings	Changes only observed in dead animals in 3 mkd group, including necrosis/mineralization of myocardium and intercostal muscle fibers, hepatocellular vacuolation, ulceration in the gallbladder mucosa and epithelial necrosis of the renal cortical tubules.			
Blood biochemical findings	No significant changes, excepting total cholesterol ↓ in treated groups. Killed moribund animals exhibited increases in GOT, GPT, LDH, creatinine, total bilirubin, etc.			
Maintenance of pregnancy	Abortion occurred in 2 killed moribund animals.			
# of copora lutea/dam	11.1	11.4	10.6	11.6
# of implantations/dam	10.0	9.6	9.6	9.8
Implantation ratio (%)	87	86	90	85
# of live pups at birth/dam	8.8	8.9	8.6	8.5
Placental weight (g)	4.85	5.05	5.12	4.46

* significantly different from control $p<0.05$.

- Offspring:

# of live fetus/dam	8.8	8.9	8.6	8.5
Viability (%)	89	94	91	88
Sex ratio (♂/♀)	0.78	0.88	1.02	0.89
Body weight (g): ♂	32.8	36.7	34.3	34.6
♀	32.0	35.6	34.6	35.1
External abnormality (%)	0/123	0/143	0/121	0/85
Visceral abnormality (%)	3/57 (5.3)	4/67 (6.0)	3/56 (5.4)	0/40
Dilatation of lateral ventricle	0	0	1	0
Abnormal origin of a. from d. aorta	0	1	0	0
Left running of caudal vena cava	3	3	2	0
Skeletal abnormality (%)	0/65	0/76	3/65 (4.5)	1/45 (2.2)
Fusion between nasal bones	0	0	0	1
Fusion between strenebrae	0	0	2	0
Deformity of sternebrae	0	0	1	0
Curvature of scapula	0	0	1	0
Skeletal variation (%)				
Small bone at frontal suture	0	0	1	0
Small bone at sagittal suture	0	2	1	0
Lumbarization	7	4	11	2
Rudimentary cervical ribs	0	2	0	0
13th ribs	15	9	18	11
Rudimentary lumbar ribs	10	17	14	8
Asymmetry of sternebrae	0	1	0	0

Hyperplasia of acromion	0	1	0	1
Retarded Ossification				
# of coccygeal v.(Litter u; mean)	15.1	14.9	15.0	15.0
# and sites of retarded ossification				
Middle portion of sphenoid bone	1	4	0	1
Hyoid bone	13	4	1	4
Sternebrae I-VI	31	27	30	18
Proximal phalanges of fingers	2	1	0	1
Metacarpal bones (less than 5/5)	5	1	0	1

* significantly different from control $p<0.05$.

Summary and Evaluation:

S-4522 was repeatedly administered orally at doses of 0.3, 1 and 3 mkd to groups of 17 copulated rabbits during the fetal organogenesis period of pregnancy. Its effects on dams and fetuses were evaluated.

- Effect on dams:
  0.3 and 1 mkd groups: no significant changes observed.
  3 mkd group: 2 death and 2 killed moribund. Weight loss, food consumption decrease, abortion and histopathological changes in liver, kidney, gallbladder and muscle were observed in these animals.
- Effects on fetuses: No embryo-fetolethal effect nor any growth suppressant or teratogenic effect on fetuses were observed.
- Conclusion: NOAEL is 1 mg/kg/day for dams and 3 mg/kg/day for fetuses.

Summary and Evaluation of Reproductive Toxicology:

S-4522 was tested in teratology studies in rats and rabbits, and fertility study in rats.

High doses in all studies induced reasonable general toxicity, such as body weight gain reduction. Therefore, doses in these studies were considered appropriate.

S-4522 had no effects on dams, such as estrus cycle, copulation, establishment and duration of pregnancy, delivery and lactation conditions.

S-4522 had no effects on fetuses and offspring. No embryo-fetolethal effect nor any growth suppressant, or teratogenic effect on fetuses, no effects on viability, functional/behavioral development, reproductive function of the offspring were observed.

Study type	Teratology	Teratology	Fertility
Study number	F-11-L	B-38-L	F-03-L
Animal	Rat (Jcl:SD)	Rabbit (Kbl:JW)	Rat (Jcl:SD)
Route	Oral gavage	Oral gavage	Oral gavage
# and sex of animal	♀: 34/36	♀: 14/16	♂:24, ♀: 24
Duration of dosing	Day 7 to 17	Day 6 to 18	♂: 9 wks prior mating and throughout mating. ♀: 2 wks prior mating to day7 of pregnancy
Dose (mg/kg)	0, 25, 50, 100	0, 0.3, 1, 3	0, 5, 15, 50
Findings	**Effect on dams**: No toxic symptoms nor death occurred. 50 and 100 mkd groups exhibited liver weight increases. S-4522 had no effects on the establishment or duration of pregnancy, delivery and lactation conditions. **Effects on fetuses and offspring**: No embryo-fetolethal effect nor any growth suppressant or teratogenic effect on fetuses. No effects on viability, functional/behavioral development, reproductive function of the offspring.	**Effect on dams:** 0.3 and 1 mkd groups: no significant changes observed. 3 mkd group: 2 death and 2 killed moribund. Weight loss, food consumption decrease, abortion and histopathological changes in liver, kidney, gallbladder and muscle were observed in these animals. **Effects on fetuses**: No embryo-fetolethal effect nor any growth suppressant or teratogenic effect on fetuses were observed.	**General toxicity**: No toxic symptoms nor death occurred. 50 mkd female group exhibited persistent suppression of body weight gain and sporadic decreases in the food consumption. **Reproductive toxicity**: No effect on estrus cycle, copulation, male/female fertility, ovulation, implantation and maintenance of pregnancy. **Fetus development**: No embryo-fetolethal and teratogenic effect. Slight suppression of fetal body weight was observed in 50 mkd group.
Conclusion	NOAEL for dams and for fetuses and offspring is 25 mg/kg/day.	NOAEL for dams and for fetuses is 1 mg/kg/day.	NOAEL for parental animals and for embryos/fetuses is 15 mg/kg/day.

Labeling Recommendations:

S4522 is not teratogenic in rats and rabbits.

GENETIC TOXICOLOGY

Study Title: Reverse Mutation Test Of S-4522 With Bacteria
Study No.: B-011-L
Amendment #, Vol #, and Page #: SN000 Vol 20 Pg 226 and SN005 Vol 9 Pg 1

NOTE: Performed by Shionogi Research Laboratories, Shionogi & Co., Ltd., Japan. Study period: 5/92-7/92. Final study report dated July 2, 1992. Lot No. 54. QA and GLP statements provided.

EXPERIMENTAL DESIGN:

Strains:

Salmonella tyhimurium TA 100, TA 1535, TA 98 and TA 1537
Escherichia coli WP2*uvr*A

Dose selection criteria:

Preliminary dose-finding study shows that when tested in all above five strains with or without metabolic activation, S-4522 at doses of 156, 313, 625, 1250, 2500 and 5000 ug/plate did not inhibit the growth of bacteria. Therefore, same dose-range was used in the main test.

Test agent stability:

S-4522 was dissolved and diluted with DMSO just before use and was tested to be stable for three hours at room temperature.

Metabolic activation system:

S9 Mix containing S9 of liver homogenate from young male SD rats induced with phenobarbital and 5,6-benzoflavone.

Controls:

Vehicle: DMSO

Positive controls:

S9 Mix	Strains	Positive control	Solvent	Dose (ug/plate)
-	TA 98	AF2	DMSO	0.01
	TA100			0.1
	TA 1537	9AA		80
	TA 1535	ENNG		2
	WP2*uvr*A			5
+	TA 98	2AA		0.5
	TA 100			1
	TA 1535			2
	WP2*uvr*A			2
				10

AF2: 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
9AA: 9-Aminoacridine hydrochloride
ENNG: N-Ethyl-N'-nitro-N-nitrosoguanidine
2AA: 2-Aminoanthracene

Exposure conditions:

A 0.1 ml aliquot of the test or control solution, 0.5 ml of PBS (0.5 ml of S9 Mix for the metabolic activation assay) and 0.1 ml of the bacterial suspension were mixed and preincubated at 37°C for 20 min under shaking. 2 ml of the molten top agar was added and poured on the minimal glucose agar plate. The plate was incubated at 37°C for 48 hours.

Analysis:

Two plates were used for each group. The number of revertant colonies was counted. The growth inhibition of each tester strain and solubility of the test substance on the plate were also examined.

Criteria for positive results:

When the number of revertant colonies induced by test substance is more than 2-fold and tended to increase dose-dependently, the test substance was judged to be positive.

RESULTS:

Study validity:

Positive controls response appropriate, they induced markedly increase (>20 fold) in the number of revertant colonies than the negative control group with or without S9 Mix.

Study outcome:

S-4522 was judged to be negative in the Ames test, because it induced similar number of revertant colonies as the negative groups in all tester strains at all doses in the direct and metabolic activation assay, and there was no dose-dependent response.

SUMMARY

S-4522 is negative in reverse mutation test.

The number of revertant colonies induced by S-4522 was similar to that in the negative control plate in all strains (TA 100, TA 1535, TA 98, TA 1537, and WP2*uvr*A) and at all dose levels from 156 to 5000 ug/plate with or without S9 Mix.

Study Title: Micronucleus Test Of S-4522 With Mouse Bone Marrow Cells

Study No.: B-024-L

Amendment #, Vol #, and Page #: SN000 Vol 20 Pg 251 and SN005 Vol 9 Pg 36

NOTE: Performed by Shionogi Research Laboratories, Shionogi & Co., Ltd., Japan. Study period: 6/92-7/93. Final study report dated July 14, 1993. Lot No. 54. QA and GLP statements provided.

EXPERIMENTAL DESIGN:

Animal species:

Male Jcl:ICR mice from [redacted]. Mice were treated at age of 9 weeks. Pellet diet CA-1 and tap water were provided *ad libitum*.

Dose selection criteria:

Preliminary study with S-4522 at doses of 120 – 2000 mg/kg and sampling time from 24 – 72 hours shows that S-4522 at a single dose of 250, 500 and 1000 mg/kg or two-dose of 125, 250 and 500, with the sampling time of 24 hour result in peak frequency of micronuclei. Death occurred at 1500 and 2000 mg/kg in single dose group and 1000-2000 mg/kg in two-dose group.

Test agent stability:

S-4522 in 5% gum arabic is stable for six hours at room temperature and eight days at 4°C.

Controls:

Vehicle control: 5% aqueous solution of gum arabic by oral gavage.

Positive controls: MMC (mitomycin C) at 1 mg/kg once by ip.

Exposure conditions:

	Treatment	Dose (mg/kg)	Animal #
Negative control	Vehicle		5
Single	DMSA	250	5
		500	5
		1000	5
Two-dose	DMSA	125	5
		250	5
		500	5
Positive control	MMC	10	5

Mice were sacrificed 24 hours after the final dose and bone marrow smears were prepared according to the Schmid's original method.

Analysis:

The frequency of micronuclei was determined by scoring 1000 PCE (polychromatic erythrocytes)/animal.

Criteria for positive results:

When the frequency of micronuclei significant increased and increased dose-dependently, the test substance was judged positive.

RESULTS:

Study validity:

Positive controls response appropriate. The frequency of micronuclei markedly increase (>10 fold) in 1 mg/kg MMC treated group. The proportion of PCE in the total erythrocytes (PCE ratio) was comparable to that in the vehicle control group.

Study outcome:

S-4522 was judged to be negative in the Micronucleus test, because there is no significant increase in the frequency of micronuclei either in the single or two-dose groups.

SUMMARY

S-4522 is negative in micronucleus test.

The frequency of micronuclei either in the single or two-dose S-4522 treated groups is similar to that of vehicle control group.

Study Title: Chromosomal Aberration Test Of S-4522 In Cultured Chinese Hamster Cells

Study No.: B-025-L

Amendment #, Vol #, and Page #: SN000 Vol 20 Pg 287 and SN005 Vol 9 Pg 79

NOTE: Performed by Shionogi Research Laboratories, Shionogi & Co., Ltd., Japan. Study period: 6/92-3/93. Final study report dated March 17, 1993. Lot No. 54. QA and GLP statements provided.

EXPERIMENTAL DESIGN:

Cell line:

Cultured Chinese hamster (CHL/IU) fibroblastic cells from [redacted]

Dose selection criteria:

Preliminary cell growth inhibition test of S-4522 determines the ED_{50} value (concentration causing 50% inhibition of cell growth) to be 6.4 ug/ml in the non-activation assay and 76 ug/ml in the metabolic activation assay. These ED_{50} values are used as the maximal concentration in the chromosomal aberration test.

Test agent stability:

S-4522 in the culture medium is stable for 3 hours at room temperature.

Metabolic activation system:

S9 Mix containing S9 of liver homogenate from male SD rats induced with phenobarbital and 5,6-benzoflavone.

Controls:

Negative control:	culture medium.
Positive controls:	MMC (mitomycin C)
	CPA (cyclophosphamide)

Exposure conditions:

5 ml of the CHL cell suspension was inoculated at 37°C for 2 days. For Non-activation assay, S-4522 (1.6, 3.2, and 6.4 µg/ml) was added the cells and the chromosomal specimens were made after 24 and 48 hours treatment. For Metabolic activation assay, S-4522 (19, 38, and 76 µg/ml) and S9 mix replaced culture medium and incubated for 6 hrs. Then, cell layers were washed with PBS and incubated with fresh medium for additional 18 hours.

Analysis:

Types of chromosomal aberrations were classified according to "Atlas of Chromosomal Aberrations induced by Chemicals". 50 well-spread metaphases per slide, and a total of 4 slides per dose were observed, and the presence or absence of structural aberrations was examined and recorded for a total of 200 metaphases per dose. The presence and absence of polyploidy was observed for 250 metaphases per slide, for a total of 4 slides.

Fisher's exact probability test was used for testing the statistical significance in the frequency of cells with chromosomal aberrations between the negative control and S-4522 treated groups.

Criteria for positive results:

When the frequency of chromosome aberrations was statistically significantly different from that in the negative control group, the test substance was judged positive.

RESULTS:

Study validity:

Positive controls response appropriate. In MMC treated group without metabolic activation, TA (total number of aberration cells excluding gaps) is 75/200 in 24 hours treatment and 79/200 in 48 hours treatment. In CPA treated group in metabolic activation assay, TA is 1/200 without S9 mix and 76/200 with S9 mix.

Study outcome:

S-4522 was judged to be negative in the chromosomal aberration test, because there is no significant increase in the frequency of chromosomal aberration either with or without S9 mix. The frequency of polypoid cells in S-4522 treated group is similar to that of negative control group.

SUMMARY

S-4522 is negative in chromosomal aberration test in cultured CHL cells.

The frequency of chromosomal aberration in S-4522 treated groups with or without S9 mix is similar to that of vehicle control group.

Summary of Genetic Toxicology

S-4522 was testedin a bacterial mutagenicity assay, a micronucleus test in the mouse and in an in vitro cytogenetic assay using cultured Chinese hamster lung cells. The results were all negative, indicating that S-4522 has no mutagenic potential..

SPECIAL TOXICITY STUDIES

Study Title: Supplement Toxicity Studies Of S-4522 In Rats And Mice: Gallbladder Toxicity Of HMG CoA Reductase Inhibitors In Mice

Study No.: A1-01-01

Amendment #, Vol #, and Page #: SN000 Vol 17 Page 1 and SN005 Vol 5 Page 128

NOTE: Study period: 8/93-10/93. Final study report dated November 5, 1993. Translated from non-GLP report.

EXPERIMENTAL DESIGN: Male mice (Jcl:ICR) were obtained from [redacted]. Dosing started at 6 weeks of age. Mice were administered S-4522 (Lot No. 55), simvastatin, lovastatin and fluvastatin orally by gavage in 5% gum arabic solution daily for 14 days.

Group	Dose (mg/kg)	Dosing volume (ml/10g)	♂ #
Control	0	0.1	5
S-4522	250	0.05	5
S-4522	500	0.1	5
Simvastatin	500	0.05	5
Simvastatin	1000	0.1	5
Lovastatin	500	0.05	5
Lovastatin	1000	0.1	5
Fluvastatin	250	0.05	5
Fluvastatin	500	0.1	5

RESULTS:

CLINICAL SIGNS (daily):

No dose-related changes.

MORTALITY:

Group	Dose (mg/kg)	Mortality	Days after dosing
Control	0	0	
S-4522	250	1/5 (1)	10
S-4522	500	5/5 (2)	4-5
Simvastatin	500	4/5 (2)	5-6
Simvastatin	1000	5/5 (1)	4-6
Lovastatin	500	1/5	8
Lovastatin	1000	2/5 (1)	7-8
Fluvastatin	250	3/5 (1)	6-12
Fluvastatin	500	5/5 (2)	3-6

Numbers in ( ) are No. of mice killed in moribund state.

BODY WEIGHT (daily):

No treatment-related changes.

GROSS PATHOLOGY AND HISTOPATHOLOGY:

Group	Dose (mg/kg)	Gallbladder Submucosal edema				Liver Degeneration/necrosis of hepatocyte				Forestomach Hyperkeratosis			
		±	+	++	L	±	+	++	L	±	+	++	L
Control	0												
S-4522	250			1		1	3	1		2			
S-4522	500	1	1		2	1		4		1			
Simvastatin	500		2		2		2	3		4	1		
Simvastatin	1000	1			4			5		4	1		
Lovastatin	500	1						1					
Lovastatin	1000	1			1			2		2			
Fluvastatin	250	1		1	1	2	1	2		2	3		
Fluvastatin	500	1	1		3		1	4			4	1	

Empty cell: no change; ±: slight; +: moderate; ++:severe; L: autolysis

SUMMARY

Title	SUPPLEMENT TOXICITY STUDIES OF S-4522 IN RATS AND MICE (A1-01-01:							
Animal	Male mice (Jcl:ICR), 6 weeks of age							
Route	Oral gavage							
Drug	S-4522		Simvastatin		Lovastatin		Fluvastatin	
Dose (mg/kg/day)	250	500	500	1000	500	1000	250	500
# of animal	5	5	5	5	5	5	5	5
Mortality	1	5	4	5	1	2	3	5
Body weight	-							
Histopathology								
Gallbladder: submucosal edema	1	4	4	5	1	2	3	5
Liver: degeneration/necrosis	5	5	5	5	1	2	5	5
Forestomach: hyperkeratosis	2	1	5	5		2	5	5
Conclusion	S-4522 induces gallbladder, liver, and forestomach damage in mice. Other HMG reductase inhibitors have similar effects as S-4522.							

*: sacrificed in extremis. -: No remarkable findings.

Study Title: Supplement Toxicity Studies Of S-4522 In Rats: Toxicological Characterization Of Effective Compounds

Study No.: A1-01-01

Amendment #, Vol #, and Page #: sub-report, SN005 Vol 5 Page 146

NOTE: Study period: 8/94-10/94. Final study report dated October 31, 1994. Translated from non-GLP report.

EXPERIMENTAL DESIGN: Male SD rats were obtained from ———

Dosing started at 6 weeks of age. Rats were administered S-4522 (Lot No. 56) orally by gavage in 5% gum arabic solution daily for 8 days. Four diets were compared in this study.

Group	Dose (mg/kg)	Diet	Ca (%)	♂ #
Control		CA-1,	1.80	10
S-4522	150	CA-1	1.80	10
S-4522	150	MM-6,	1.02	10
S-4522	150	F-2,	0.74	6
S-4522	150	MF,	1.17	6

RESULTS:

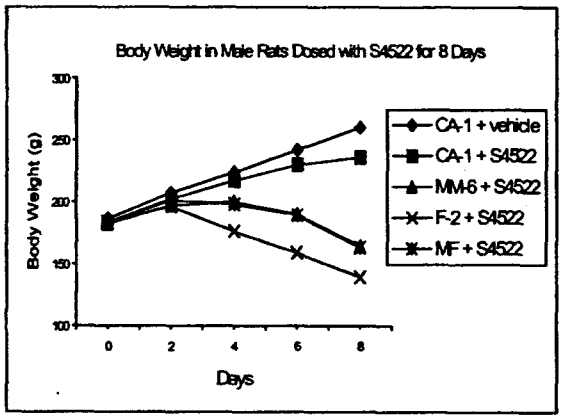
CLINICAL SIGNS (daily):

Hypoactivity and body weight decreases occurred earlier in F-2 group, then MM-6 and MF group. No changes in CA-1 group.

MORTALITY:

None.

BODY WEIGHT (daily):



GROSS PATHOLOGY AND HISTOPATHOLOGY:

Group	Liver									Forestomach								
	Eosinophilic change			Single cell necrosis			Bile duct proliferation			Hyper-keratosis			Submucosal cell infiltration			Submucosal edema		
	±	+	++	±	+	++	±	+	++	±	+	++	±	+	++	±	+	++
CA-1 + Vehicle																		
CA-1 + S4522	8	2		3			1						1					
MM-6 + S4522		9	1	5	3		3			2	4	4	7	1		2	3	
F-2 + S4522		4	2	5	1		1					6	2	3	1	1	5	
MF + S4522		6		5	1		2	1		1	5		2	1	1			2

Empty cell: no change; ±: slight; +: moderate; ++:severe

SUMMARY

Title	SUPPLEMENT TOXICITY STUDIES OF S-4522 IN RATS: TOXICOLOGICAL CHARACTERIZATION OF EFFECTIVE COMPOUNDS				
Animal	Male SD rats, 6 weeks of age				
Route	Oral gavage				
Diet	CA-1	CA-1	MM-6	F-2	MF
Vitamin A (IU/100g)	1867	1867	1000	1000	880
Nicotinamide (mg/100g)	17.2	17.2	10	10	8.6
Ca (g/100g)	1.8	1.8	1.02	0.74	1.17
P (g/100g)	1.38	1.38	0.88	0.65	0.91
S4522 (mg/kg/day)	0	150	150	150	150
# of animal	10	10	10	5	5
Mortality	None				
Body weight gain		↓10%	↓50%	↓64%	↓51%
Histopathology					
Liver:					
Eosinophilic change		10	10	6	6
Single cell necrosis		3	8	6	6
Bile duct proliferation		1	3	1	3
Forestomach:					
Hyperkeratosis			10	6	6
Submucosal cell infiltration		1	8	6	4
Submucosal edema			5	6	2
Ulceration				2	1
Conclusion	Diets can affect S-4522 toxicity significantly. The reason is unclear.				

-: No remarkable findings.

Study Title: Supplement 3-Month Repeated Oral Dose Toxicity Study Of S-4522 In Dogs (Examination Of Effects On Gallbladder)
Study No.: B-033-L
Amendment #, Vol #, and Page #: SN000 Vol 17 Page 20

NOTE: Performed by ——— Study period: 2/93-11/94. Final study report dated November 8, 1994. Lot No. 55. GLP statements provided.

EXPERIMENTAL DESIGN: Beagle dogs (— Beagles) were obtained from ——— Japan. Dosing started at 7-8 months of age. Dogs were administered S-4522 orally by gavage in 10-fold triturate with lactose daily for 91 days.

S-4522 Dose (mg/kg)	♂ #	♀ #
1	3	3
2	3	3
4	3	3

RESULTS:

CLINICAL SIGNS (daily):
No dose-related changes.

MORTALITY:
None.

BODY WEIGHT (every 14 days):
No dose-related changes.

FOOD CONSUMPTION (daily):
No dose-related changes.

BLOOD CHEMISTRY EXAMINATION (days –20, -5, 27, 55 and 89):
Cholesterol decreases 29% - 42% in males and 13% - 31% in females.
ALP decreases 29% - 43% in males and 22% - 28% in females.

TOXICOKINETICS (Non-GLP, days 0, 43, and 82):
T_{max} ranges from 1.2 to 2.2 hr.
No accumulation.
No sex difference

GROSS PATHOLOGY AND HISTOPATHOLOGY:
No dose-related changes.

SUMMARY

Title	SUPPLEMENT 3-MONTH REPEATED ORAL DOSE TOXICITY STUDY OF S-4522 IN DOGS (Examination of Effects on Gallbladder)					
Animal	Beagle dogs (beagles), 7-8 months of age					
Route	Oral gavage					
Dose (mg/kg/day)	1		2		4	
# of animal	♂	♀	♂	♀	♂	♀
	3	3	3	3	3	3
Mortality	None					
Body weight	-					
Food consumption	-					
Blood chemistry	Cholesterol ↓ 13% - 42%, ALP ↓ 22% - 43%					
Toxicokinetics	T_{max} ranges from 1.2 to 2.2 hr. No accumulation. No sex difference					
Histopathology	-					
Conclusion	NOAEL is 4 mg/kg/day					

-: No remarkable findings.

Study Title: Preventive Effect Of Mevalonate Or Farnesol On The Toxicity Induced By S-4522 In Rats
Study No.: T-YAHARA 1-001
Amendment #, Vol #, and Page #: SN000 Vol 17 Pg 102 and SN003 Vol 5 pg 157

NOTE: Performed by _____. Study period: 9/92-11/92. Final study report dated December 2, 1992. Lot No. 56. Non-GLP study.
EXPERIMENTAL DESIGN: Rats (Jcl:SD) (6-weeks old at dosing start). Rats were administered 250 mkd S-4522 orally by gavage in 5% aqueous gum arabic for 14 days. Mevalonate (D,L-mevalono-1,5-lactone, MV) and Farnesol (FN) were administered twice daily at 30 min and 4 hour after S-4522. CA-1 diet and tap water were provided *ad libitum*.

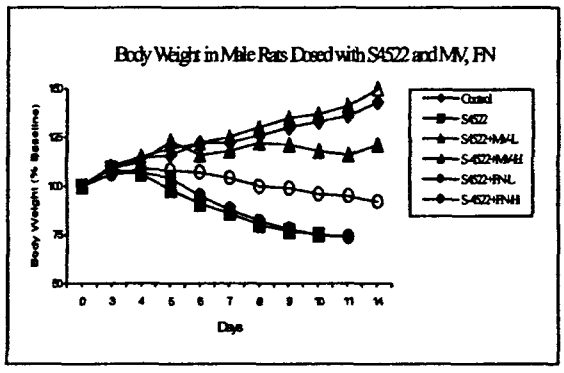
Group	Treatment	♂
Control	Vehicle control	3
S-4522	S-4522 (250 mkd)	3
S-4522 + MV-L	S-4522 (250 mkd) + MV (50 x2 mkd)	3
S-4522 + MV-H	S-4522 (250 mkd) + MV (200 x2 mkd)	3
S-4522 + FN-L	S-4522 (250 mkd) + FN (50 x2 mkd)	3
S-4522 + FN-H	S-4522 (250 mkd) + FN (200 x2 mkd)	3

RESULTS:
CLINICAL SIGNS (daily):
S-4522 and S-4522+FN-L groups revealed slight hypoactivity and death.

MORTALITY:

Group	Total #	Death (or killed on moribund)
S-4522	3	3 on day 8,9 and 10
S-4522 + FN-L	3	3 on day 10, 11 and 11
S-4522 + FN-H	3	1 on day 10

BODY WEIGHT (daily):



FOOD CONSUMPTION (weekly):

Group	Day 0-7 (g)	Day 8-14 (g)
Control	24.8	26.7
S-4522	13.9 (56%)	0.4 (1%)
S-4522 + MV-L	22.8 (92%)	19.9 (75%)
S-4522 + MV-H	26.3 (106%)	29.0 (109%)
S-4522 + FN-L	15.8 (64%)	1.2 (4%)
S-4522 + FN-H	19.0 (77%)	9.2 (34%)

Values in ( ) are % of control.

BLOOD CHEMISTRY EXAMINATION (at sacrifice):

Group	No. rats	Trigly ceride	GOT	GPT	ALP	LDH	CPK	Biliru bin	Creati nine	Urea-N	Amyl ase
S-4522	1	13	4886	2079	319	1319	1145	800	260	256	280
S-4522 + MV-L	3	32	211	174	175	100	91	140	85	100	94
S-4522 + MV-H	3	87	103	105	107	86	92	100	91	107	112
S-4522 + FN-L	1	6	3828	1474	238	1319	2590	520	296	504	322
S-4522 + FN-H	2	6	1011	934	159	537	419	480	96	122	78

Values are % of control in all groups except control group. Values in control group are real values.

Killed moribund animals exhibited marked increases in GOT, GPT, LDH, CPK, creatinine, ALP and bilirubin.

GROSS PATHOLOGY AND HISTOPATHOLOGY:

	S-4522	S-4522 +MV-L	S-4522 +MV-H	S-4522 +FN-L	S-4522 +FN-H
No. of animal observed	2	3	3	2	2
Eosinophilic homogenous cytoplasm in hepatocyte	-+	---	---	--	+++
Irregular hepatic cell cord	-++	---	---	+++	+++
Eosinophilic inclusion body in hepatocyte	-++	---	---	-+	++
Hydropic degeneration in centrilobular hepatocyte	+++	---	---	-+	-+
Hypertrophy with solid cytoplasm in perilobular hepatocyte	--	+±±	---	-+	+±
Single cell necrosis of hepatocyte	+++	---	---	++	-++
Nuclear enlargement with large nucleolus in hepatocyte	++	---	---	++	++
Hyperkeratosis in forestomach	-+	+++	-+-	++	++
Submucosal inflammatory cell infiltration	--	--+	-+-	--	--
Submucosal edema	-+	---	---	++	--
Increase of zymogen granule in acinor cell	+++	--+	---	+++	++
Necrosis/vacuole in tubular epithelium	--	---	---	++	--

-: no change; ±: slight; +: moderate; ++: marked

SUMMARY

Title	PREVENTIVE EFFECT OF MEVALONATE OR FARNESOL ON THE TOXICITY INDUCED BY S-4522 IN RATS (T-YAHARA 1-001)					
Animal	Rats (Jcl:SD), 6-weeks of age					
Route	Oral gavage					
Group	control	S-4522	S-4522 +MV-L	S-4522 +MV-H	S-4522 +FN-L	S-4522 +FN-H
# of animal	3	3	3	3	3	3
Mortality		3			3	1
Body weight gain (day 8)	-	↓46%	↓4%	↑5%	↓44%	↓25%
Food consumption (d 0-7)	-	↓46%	↓8%	↑6%	↓46%	↓23%
Blood chemistry						
Triglyceride	-	↓87%	↓8%	↓6%	↓46%	↓23%
GOT, GPT, ALP	-	↑↑	↑	-	↑↑	↑↑
LDH, CPK	-	↑↑	-	-	↑↑	↑
TB, CT, UN, AL	-	↑	-	-	↑	-
Histopathology	-					
Conclusion	S-4522 induced toxicity can be blocked by mevalonate					

-: No remarkable findings.

Study Title: Supplement Toxicity Study Of S-4522 In Rabbits
Study No.: B-052-N
Amendment #, Vol #, and Page #: SN000 Vol 17 Pg 146 and SN003 Vol 5 Pg 221

NOTE: Performed by [redacted] Study period: 9/94-4/95. Final study report dated April 7, 1995. Lot No. R39001. Non-GLP study.

EXPERIMENTAL DESIGN: Male Japanese white rabbits (Kbl:JW, SPF) were obtained from [redacted] Dosing started at 17 weeks of age. Dogs were administered S-4522 orally by gavage in 5% aqueous gum arabic daily for 14 days.

Vehicle	0	-	5
Vehicle	0	40	5
S-4522	5	-	5
S-4522	10	-	5
S-4522	5	40	5
S-4522	10	40	5
Simvastatin	20	-	5
Simvastatin	40	-	5
Fluvastatin	10	-	5
Fluvastatin	20	-	5

RESULTS:
CLINICAL SIGNS (daily):
Dead animals: ↓ motor activity, diarrhea, ↓ food consumption, ↓ body weight.
Survived animals: unremarkable.

MORTALITY:

Vehicle Control	5	-
Mevalonic acid	5	-
S-4522 5 mg/kg	5	1 on day 14
S-4522 10 mg/kg	5	-
S-4522 5 mkd + Mevalonic acid 40 mkd	5	1 on day 7#
S-4522 10 mkd + Mevalonic acid 40 mkd	5	1 on day 5#
Simvastatin 20 mkd	5	-
Simvastatin 40 mkd	5	2 on day 12, 13*
Fluvastatin 10 mkd	5	-
Fluvastatin 20 mkd	5	1 on day 13

-: no death. *: Killed moribund. #: Dosing error

BODY WEIGHT and FOOD CONSUMPTION (daily):

Vehicle Control	5	102.4	-
Mevalonic acid	5	103.3	-
S-4522 5 mg/kg	5	98.6	↓(3*)
S-4522 10 mg/kg	5	92.8	↓(3)
S-4522 5 mkd + Mevalonic acid 40 mkd	5	102.4	-
S-4522 10 mkd + Mevalonic acid 40 mkd	5	101.3	-
Simvastatin 20 mkd	5	89.0	↓(3)
Simvastatin 40 mkd	5	93.3	↓(5)
Fluvastatin 10 mkd	5	94.5	↓(3)
Fluvastatin 20 mkd	5	93.0	↓(4)

*: Value in ( ) is the number of animals exhibiting reduction of food consumption.

BLOOD CHEMISTRY EXAMINATION (days -5, -1, 2, 5, 9 and 14):

Vehicle Control	5	↑(1)	↑(1)	-	-		
Mevalonic acid	5	↑(1)	-	-	-		
S-4522 5 mg/kg	5	↑(1)	↑(1)	↑(4)	↑(2)	↑(1)	↑(1)
S-4522 10 mg/kg	5	↑(1)	↑(1)	↑(2)	↑(3)	↑(2)	↑(3)
S-4522 5 mkd + Mevalonic acid 40 mkd	5	↑(1)	-	-	-		
S-4522 10 mkd + Mevalonic acid 40 mkd	5	-	-	-	-		
Simvastatin 20 mkd	5	↑(2)	↑(2)	↑(2)	↑(3)		↑(2)
Simvastatin 40 mkd	5	↑(3)	↑(2)	↑(3)	↑(5)	↑(2)	↑(3)
Fluvastatin 10 mkd	5	↑(1)	↑(2)	↑(2)	↑(2)		↑(2)
Fluvastatin 20 mkd	5	↑(2)	↑(2)	↑(3)	↑(3)	↑(3)	↑(3)

*: Value in ( ) is the number of animals exhibiting marked changes.

BLOOD LEVEL OF FARNESYL PYROPHOSPHATE (profiling on days 0, 6, and 13; monitoring on days 2 and 9)

Vehicle Control	2.0-4.1 ng/ml
Mevalonic acid	25-50 times higher than control at 1 hr after dosing
S-4522 5 mg/kg	Below the detection limit
S-4522 10 mg/kg	
S-4522 5 mkd + Mevalonic acid 40 mkd	Equal or higher than mevalonic acid group one hour after mevalonic acid dosing
S-4522 10 mkd + Mevalonic acid 40 mkd	

Simvastatin 20 mkd	Below the detection limit
Simvastatin 40 mkd	
Fluvastatin 10 mkd	
Fluvastatin 20 mkd	

*: Value in ( ) is the number of animals exhibiting marked changes.

ELECTROCARDIOGRAPHY (at the day of autopsy)

No dose-related changes.

TOXICOKINETICS (profiling on days 0, 6 and 13; monitoring daily):

S-4522: T_{max} = 15-30 min. and then decreases below or around detection limit at 24 hours
C_{max} increases with repeated dose.

Simvastatin: T_{max} = 30 min. and then decreases below or around detection limit at 24 hours
C_{max} dose not increase with repeated dose.

Fluvastatin: T_{max} = 30 min. and then decreases below or around detection limit at 24 hours
C_{max} increases with repeated dose at high dose group.

ORGAN WEIGHT

Vehicle Control	5	-	-	-	-
Mevalonic acid	5	-	-	-	-
S-4522 5 mg/kg	5	-	↓(1)	↑(1)	-
S-4522 10 mg/kg	5	-	↓(2)	↑(3)	-
S-4522 5 mkd + Mevalonic acid 40 mkd	5	-	-	-	-
S-4522 10 mkd + Mevalonic acid 40 mkd	5	-	-	-	-
Simvastatin 20 mkd	5	-	↓(2)	-	-
Simvastatin 40 mkd	5	-	↓(2)	-	-
Fluvastatin 10 mkd	5	-	↓(1)	-	-
Fluvastatin 20 mkd	5	-	↓(1)	↑(2)	-

GROSS PATHOLOGY AND HISTOPATHOLOGY:

Vehicle Control	5	-	-	-	-	-
Mevalonic acid	5	-	-	-	-	-
S-4522 5 mg/kg	5	1	-	1	1	-
S-4522 10 mg/kg	5	1	1	1	3	-
S-4522 5 mkd + Mevalonic acid 40 mkd	5	-	-	-	-	-
S-4522 10 mkd + Mevalonic acid 40 mkd	5	-	-	-	-	-
Simvastatin 20 mkd	5	1	1	2	3	-
Simvastatin 40 mkd	5	1	2	3	3	-
Fluvastatin 10 mkd	5	-	-	1	1	-
Fluvastatin 20 mkd	5	2	1	3	3	1

(a) Cardiac pathology: perivascular myocardium focal degeneration and necrosis, with cell infiltration and calcification.

(b) Skeletal muscles: degeneration and necrosis of the skeletal muscle fibers, with cell infiltration and calcification.

(c) Liver: periportal hepatocytes fatty degeneration and single cell necrosis.

(d) Kidney: necrosis of the proximal renal tubule epithelium.

(e) Testis: hypospermatogenesis.

*: Value in table is the number of animals exhibiting marked changes.

SUMMARY

Title	SUPPLEMENT TOXICITY STUDY OF S-4522 IN RABBITS (B-052-N)									
Animal	Male Japanese white rabbits (Kbl:JW, SPF)									
Route	Oral gavage									
Group	Contr	MA	S-4522+MA		S-4522		Simvastatin		Fluvastatin	
Dose (mg/kg)	0	40	5+40	10+40	5	10	20	40	10	20
# of animal	5	5	5	5	5	5	5	5	5	5
Mortality	-	-	1*	1*	1	-	-	2	-	1
Body weight	↑2.4	↑3.3%	↑2.4%	↑1.3%	↓1.4%	↓7.2%	↓11%	↓6.7%	↓5.5%	↓7%
Food consumption	-	-	-	-	↓	↓	↓	↓	↓	↓
Blood chemistry	-		-		CPK↑, LDH↑, GOT↑, GPT↑, BUN↑,					
Blood FPP (x of control)	1	25-50	> 25-50		Below limit of detection					
Toxicokinetics	T_{max} ranges from 15-30 min. Cmax increases with repeated dose. No accumulation.									
Organ weight	-				Liver ↓, kidney ↑					
Histopathology	-				Changes in heart, liver, kidney, skeletal muscle					
Conclusion	1. All three statins causes similar toxicity. 2. Mevalonic acid prevents S-4522 induced toxicity. 3. Three statins have similar toxicokinetic profiles. 4. FPP levels are below the limit of detection in statins alone treated animals.									

-: No remarkable findings. *:dose error

Study Title: Effects Of Mevalonic Acid On Toxicities Of S-4522 In Dogs
Study No.: B-034-N
Amendment #, Vol #, and Page #: SN000 Vol 17 Pg 252

NOTE: Performed by) ——— Study period: 2/93-11/93. Final study report dated November 30, 1993. Lot No. 30207. Non-GLP study.

EXPERIMENTAL DESIGN: Male beagle dogs — Beagles) were obtained from ——— Dosing started at 8-9 months of age. Dogs were administered S-4522 orally by gavage in 10-fold triturate with lactose daily for 30 days.

S-4522	50	-	6
Mevalonic Acid	-	50	6
S-4522 + MA	50	10	6
S-4522 + MA	50	50	6

RESULTS:

CLINICAL SIGNS (daily):
No treatment-related changes.

MORTALITY:
None.

BODY WEIGHT (every 10 days):
No treatment-related changes.

FOOD CONSUMPTION (daily):
No treatment-related changes.

HEMATOLOGY (days -19, -5, 8, 17 and 29):

WBC ↑ in 2/6 S-4522 group, 1/6 mevalonate group and 2/6 S-4522 + 50 mg/kg mevalonate group.

BLOOD CHEMISTRY EXAMINATION (days –19, -5, 8, 17 and 29):

S-4522 50 mkd	6	↓	↓	↑ (1)	↑ (3)	↑ (1)
Mevalonate 50 mkd	6	-	-	-	-	-
S-4522 50 mkd + Mevalonate 10 mkd	6	↓	↓	↑ (2)	↑ (3)	↑ (2)
S-4522 50 mkd + Mevalonate 50 mkd	6	↓	↓	-	-	-

*: Value in ( ) is the number of animals exhibiting marked changes.

TOXICOKINETICS (days 0, 13 and 28):

The blood concentration profiles for S-4522 were not affected by the combination of mevalonate.

GROSS PATHOLOGY AND HISTOPATHOLOGY:

No. of animal observed	6	6	6	6
Thickening of mucosa with red points or sports in the fundus through corpus and collum	6	-	6	1
Hemorrhage, edema and inflammatory cell infiltration in the lamina propria mucosae and hyperplasia of the mucosal epithelium	6	-	6	1
Erosion of mucosa	-	-	2	-
Hemorrhage and inflammatory cell infiltration in the lamina propria mucosae of the common bile duct	-	-	1	-

SUMMARY

Title	EFFECTS OF MEVALONIC ACID ON TOXICITIES OF S-4522 IN DOGS (B-034-N)			
Animal	Male beagle dogs — Beagles)			
Route	Oral gavage			
Group	Mevalonate	S-4522	S-	S-
Dose (mg/kg)	50	50	50 + 10	50 + 50
# of animal	6	6	6	6
Mortality	None			
Body weight	-			
Food consumption	-			
Hematology	WBC↑ (1)	WBC↑ (2)	-	WBC↑ (2)
Blood chemistry		CHO↓ TRG↓ GOT↑ GPT↑ ALP↑		
Toxicokinetics	S-4522 PK profiles not affected by mevalonate			
Histopathology	-	Gallbladder changes		
Conclusion	S-4522 induced gallbladder toxicity is due to its pharmacological action in blocking mevalonate biosynthesis.			

-: No remarkable findings. *:dose error

OVERALL SUMMARY AND EVALUATION

Introduction

ZD4522 was developed by the Japanese pharmaceutical company Shionogi and in-licensed to Zeneca Limited intended for the treatment of primary hypercholesterolemia and mixed dyslipidemias. Phase I and Phase II clinical trials have been conducted for up to 8 weeks at up to 80 mg/kg by oral administration. An End of Phase II meeting was held on February 24, 1999.

ZD4522 is a novel member of the statin class of lipid lowering agents. It is a synthetic 3-hydroxy 3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor. By inhibiting hepatic cholesterol biosynthesis at the level of HMG CoA, ZD4522 produces compensatory increases in hepatic low-density lipoprotein receptors, resulting in an increased uptake of low density lipoprotein cholesterol from the blood and the subsequent lowering of circulating cholesterol levels. Statins have proven to be clinically effective in the reduction of plasma levels of LDL and VLDL, and are marketed world-wide for the lowering of total cholesterol/LDL-cholesterol levels. First generation statins (lovastatin, pravastatin and simvastatin) are prodrug derivatives of fungal metabolites, whereas ZD4522 is structurally similar to the synthetic second generation statins (super statins, such as, atorvastatin, fluvastatin and cerivastatin). The toxicology profiles of statins include toxicity on liver, gallbladder, kidney, non-glandular, eye, testis, CNS, skeletal muscle, adrenal glands and intestines.

Pre-clinical safety evaluation studies of ZD4522 include toxicology studies in rats, dogs, and monkeys from single dose to up to 12 months, carcinogenicity sighting studies and on-going 2-year carcinogenicity studies in rats and mice, teratology studies in rats and rabbits, a fertility study in rats, mutagenicity assays and antigenicity studies. In general, the toxicology profile of ZD4522 shows only some of the effects reported for others statins and no new toxicities have been found.

ZD4522 is of low acute toxicity with lethal dose > 2000 mg/kg in rats and dogs. No mutagenic activity was observed in *in vitro* and *in vivo* assays. No adverse effect on fetal development was observed in rat fertility study at 10 mkd. No teratogenic activity was observed in rats at 25 mkd and rabbits at 1 mkd. The NOAELs are 1 mkd for rabbits, 2 mkd for rats, 3 mkd for dogs, and 10 mkd for monkeys.

Safety Evaluation

In rats, the major target organ of toxicity is the liver. Histopathological changes observed in the 1, 3 and 6 months studies include hypertrophy in the perilobular hepatocytes, proliferation of the bile ducts, increased foci of cellular alteration and single cell necrosis. The liver toxicity of ZD4522 is attributable to its pharmacological effect of inhibition of HMG-CoA reductase. This was proven in the studies of co-administration of ZD4522 and mevalonic acid. In these studies, mevalonic acid attenuated the ZD4522 induced toxicity in rats, dogs and rabbits. Forestomach is another target organ in rat, but it is not important for its lack of clinical significance.

In dogs, the target organ is the gallbladder and to a lesser extent the testis. The gallbladder toxicity of ZD4522, including hemorrhage, edema or inflammatory cell infiltration, was

attributable to the high concentration of ZD4522 in gallbladder, since bile is the major excretory pathway of ZD4522. The toxicity on testis includes a small number of giant cells, and the mechanism is unclear.

In monkeys, testis changes (including decrease of germ cells and appearance of giant cells in seminiferous tubules) were the only treatment related changes at 10 and 30 mkd. The mechanism is unclear.

In mice, the target organs are liver, gallbladder and forestomach.

These ZD4522 induced toxicities were reversible upon withdrawal of treatment.

Clinical Relevance of Safety Issues

Based on NOAELs (1 mkd for rabbits, 2 mkd for rats, 3 mkd for dogs, 10 mkd for monkeys), the body surface area based HEDs are 0.33, 0.33, 1.5, and 3.3 mg/kg for rabbits, rats, dogs and monkeys, respectively. For a 60 kg human, the HEDs are 20, 20, 90 and 200 mg/day. The proposed doses in clinical trial, 40 or 80 mg, are within the range of HEDs based on different animal species. It is difficult to determine which is the superior animal model for ZD4522 toxicity, but since the proposed doses are above the rat and rabbit based HEDs, special attention should be paid to relevant toxicities in clinical trial, especially liver toxicity. For other statins, dogs appears to be the preferred model.

Other Clinical Relevant Issues

Conclusions from studies related to labeling:
Mutagenicity: ZD4522 has no mutagenic potential based on available genetic toxicology studies.
Reproduction: ZD4522 has no teratogenic potential based on available reproductive toxicology studies.

Conclusions

Pharmacology has no objection to the proposed clinical trial doses of 40 and 80 mg. Liver function should be closely monitored in patients.

On the dose selection for carcinogenicity studies, the Executive CAC conditionally concurred with the mouse carcinogenicity study and did not concur with the rat carcinogenicity study (please refer to the carcinogenicity section of this review).

Recommendations

--Internal comments (to Medical Officer):

Diet could significantly affect ZD4522 induced toxicity in rats. Sponsor proposed that this effect is due to the difference of the calcium concentration in the diet. Since some patients participated in the clinical trials may take calcium tablets regularly as nutritional supplement, it may be appropriate to take the diet (especially calcium) effect into account in clinical trial design, if possible.

--External Recommendations (to Sponsor):

The Executive CAC recommendations for dose selection of carcinogenicity studies have been communicated to Sponsor.

Reviewer signature: /S/

John Zhaolong Gong, Ph.D. Date
Pharmacologist

Team leader signature [Concurrence/Non-concurrence]

/S/

Ronald W. Steigerwalt, Ph.D. Date
Pharmacology Team Leader

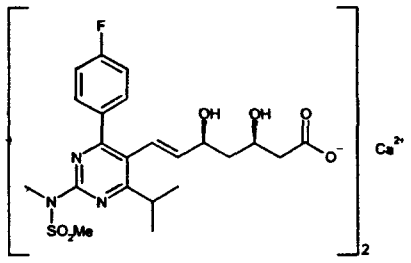
cc: IND Arch
HFD 510
HFD 510/Simoneau/Gong/Steigerwalt

Continuation of the Pharmacology/Toxicology review, starting at page 169, contains pertinent pages (1 through 108 out of 143). The reviewer incorporated pages 1 through 108 of the CAC summaries. Therefore, there are two page numbers reflected on each page, top to bottom, from that point. All pages for this review are accounted for.

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

Reviewer name: John Zhaolong Gong, Ph.D.
Division name: Division of Metabolic and Endocrine Drug Products
HFD #: 510
Review completion date: January 2, 2002
Date of eCAC meeting: January 29, 2002 (minutes attached on page 96)

IND/NDA: IND 56,385, NDA 21,366
DRUG CODE#: ZD4522, S4522
CAS#: 147098-20-2
DRUG NAME: CRESTOR™ (rosuvastatin calcium) tablets
CHEMICAL STRUCTURE:



SPONSOR: ZENECA Pharmaceuticals Inc., Wilmington, DE 19850.
LABORATORY:
CARCINOGENICITY STUDY REPORT DATE: June 26, 2001

THERAPEUTIC CATEGORY: primary hypercholesterolemia and mixed dyslipidemias
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: HMG CoA reductase inhibitor

MUTAGENIC/GENOTOXIC: negative in Ames test, micronucleus test in mice, and chromosomal aberration test in cultured Chinese hamster cells.

Studies included Within This Submission:	**Page**
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MOUSE CARCINOGENICITY STUDY

MOUSE STUDY DURATION: 107 weeks
STUDY STARTING DATE: June 10, 1998
STUDY ENDING DATE: 12 July, 2000
MOUSE STRAIN: Mice/B6C3F1 strain from [redacted]
ROUTE: oral gavage
DOSING COMMENTS: daily dose at a dose volume of 10 ml/kg.

NUMBER OF MICE:
- Control-1 (C1): 51
- Control-2 (C2): 51
- Low Dose (LD): 51
- Middle Dose (MD): 51
- High Dose-1 (HD1): 51
- High Dose-2 (HD2): 51

MOUSE DOSE LEVELS (mg/kg/day):
- Low Dose: 10
- Middle Dose: 60
- High Dose-1: 200
- High Dose-2: 400, terminated in week 3 due to mortality and deteriorating condition.

BASIS FOR DOSES SELECTED:

AUC: Based on the AUC values from the repeated human studies and the 2-year mouse study, the high dose of 200 mg/kg/day only provides 10 fold margin over the sponsor proposed MRHD of 80 mg/day. Therefore, AUC values can not support the adequacy of the high dose used in the 2-year mouse study. However, based on the tentatively FDA approved MRHD of 10 mg, 200 mg/kg in mice can provide about 100 fold margin. Therefore, the 200 mg/kg appears to be an acceptable high dose for the 2-year study.

However, since there is high inter-animal variability in plasma concentration, we should be cautious in using the AUC value to support the adequacy of the carcinogenicity study.

Pharmacokinetic parameters after administration of multiple oral-dose rosuvastatin to healthy volunteers (pooled data)

Dose mg	N	C_{max} ng/ml gmean (CV%)		t_{max} h Median (range)		AUC(0-24) ng.h/ml gmean (CV%)		$t_{½}$ h Mean (SD)	
10[a]	49	4.09	(49.3)	3.0	[redacted]	40.1	(46.7)	29.7[b]	(14.0)
20[c]	10	9.87	(53.3)	3.0		87.9	(50.0)	14.5[d]	(2.63)
40[e]	42	24.1	(57.0)	4.0		201	(47.0)	20.8[f]	(12.8)
80[g]	22	53.1	(79.3)	4.5		436	(70.7)	13.4[f]	(2.04)

Pharmacokinetic parameters in the 2-year carcinogenicity study in mice

	10 mg/kg/day		60 mg/kg/day		200 mg/kg/day	
Parameter	Male	Female	Male	Female	Male	Female
C_{max} (ng/ml)	87.8	38.9	273	165	3180	3320
t_{max} (h)	0.5	1.5	0.5	0.5	0.5	0.5
AUC(0-t) (ng.h/ml)	120	152	580	779	4270	4900
AUC(0-24) (ng.h/ml)	120	158	580	779	4270	4900
λ_z (/h)	0.101	0.293	0.210	0.274	0.204	0.240
$t_{½}$ (h)	6.84	2.37	3.30	2.53	3.39	2.89

MTD: MTD can be determined based on the results of the two preliminary 2-week studies and a 13-week sighting study in the B6C3F1 mouse, as well as the result of the completed 2-year study.

In the first preliminary study in the ICR mouse, all animals given 500 mg/kg/day and one animal given 250 mg/kg/day died. Histological examination of the surviving animals given 250 mg/kg/day revealed eosinophilic changes associated with single cell necrosis in periportal hepatocytes.

In the second 2-week study, ZD4522 was administered orally by gavage to groups of B6C3F1 mice at doses of 20, 60 and 200 mg/kg/day. There were no deaths related to ZD4522, no adverse clinical signs and no effect on body weight or food consumption. There was an increase in liver weight and minimal centrilobular hepatocyte hypertrophy at 200 mg/kg/day.

In the 13-week study, doses administered were 20, 60 and 200 mg/kg/day. No deaths or adverse clinical signs and no effect on body weight or food consumption were observed. An increase in liver weight of 24 and 16% in males and females respectively dosed 200 mg/kg/day was accompanied by minimal centrilobular hepatocyte hypertrophy. Centrilobular hepatocyte hypertrophy was also seen in a proportion of males dosed 60 mg/kg/day, but there was no effect on liver weight. A 16% increase in liver weight was seen in females dosed 60 mg/kg/day. In the 13 week study, the high dose of 200 mg/kg/day produced minimal histological changes in the liver. Based on this and data from the short term studies 500 mg/kg/day not tolerated, a high dose of 400 mg/kg/day was selected for the 2-year study.

However, during weeks 1 and 2 of the 2-year study, the deteriorating clinical condition of the animals dosed at 400 mg/kg/day, together with the rapid histopathological assessment of six decedent animals which indicated hepatocyte vacuolation with single cell necrosis in the liver, squamous cell hyperplasia with/ without hyperkeratosis and in addition gastritis in the stomach and tubular degeneration in the kidneys of two animals caused this group to be prematurely terminated in week 3. The findings at 400 mg/kg were considered drug-related. Therefore, the group dosed at 200 mg/kg/day was considered as the high dose group.

PRIOR FDA DOSE.CONCURRENCE:

The sponsor submitted dose selection document for rats and mice 2-year carcinogenicity studies on November 25, 1998 and June 21, 1999. The 2-year carcinogenicity study in mice was initiated in June 10, 1998. The eCAC concurred with the dose selection on January 18, 2000.

MOUSE CARCINOGENICITY:

Crestor tested positive in both sexes at dose of 200 mg/kg in the 2-year carcinogenicity study. The exposure level at 200 mg/kg in mice is about 100 fold the human exposure based on the tentatively FDA approved MRHD of 10 mg.

MOUSE TUMOR FINDINGS:

The spectrum of neoplastic findings in the control groups was consistent with that expected in mice of this age, excepting those in the liver.

In the liver of mice of the 200 mg/kg/day groups of both sexes, there was a clear increase in incidence of both hepatocellular adenomas and carcinomas which correlated with the masses and focal discolorations described at necropsy. In many cases, the tumors were also multiple. The histology of the tumors varied from small well-differentiated masses in which only the lobular architecture had been lost (adenoma) to large atypical and pleomorphic cellular masses with organoid and trabecular architecture, necrosis and metastases (carcinoma). The incidence of liver tumors in other groups was comparable to controls.

Generally, higher incidence of hepatocellular adenoma/carcinoma was observed in males than females. Increased hepatocellular adenoma were noted at 60 mg/kg in both sexes, with significant increases was observed at 200 mg/kg in both sexes. Higher incidence of hepatocellular carcinoma was only observed at 200 mg/kg in both sexes. These results are consistent with the findings with other statins, where higher incidence of hepatocellular adenoma/carcinoma was also observed in both sexes.

Incidence of salient neoplastic findings

		Males					Females				
Finding		1M	2M	3M	4M	6M	1F	2F	3F	4F	6F
Liver	No. examined	51	51	51	51	51	51	51	51	51	51
hepatocellular adenoma	Absent	38	39	32	26	35	48	48	45	42	48
	Present	13	12	19	25	16	3	3	6	9	3
hepatocellular carcinoma	Absent	43	41	40	35	41	51	50	51	47	51
	Present	8	10	11	16	10	0	1	0	4	0
Total tumour bearers		19	20	25	34	23	3	4	6	12	3

MOUSE STUDY COMMENTS:

The statistical review performed by Cynthia Liu is generally consistent with the above conclusion. The summary table from the statistical review is attached below. Significant cases determined at $p < 0.05$ mentioned in the sponsor's report are listed. When the new decision rules of $p \leq 0.005$ for common and $p \leq 0.025$ for rare tumor types are applied, some of the cases are no longer significant. In addition, the significant negative trends are not of concern in this review.

Sex	Organ-Tumor Finding	p-value	Reviewer's Comment
M	Liver – Hemangioma	0.015 ↓	No Concern
[redacted]			
M	Liver – Hepatocellular Carcinoma	0.028 ↑	NS
[redacted]			
M	Lung – Bronchiolo-Alveolar Adenoma	0.025 ↑	Common Tumor, NS
M	Blood Vessel Tumor	0.019 ↓	No Concern
M	Histiocytic Sarcoma	0.031 ↑	NS, Common
F	Liver – Hepatocellular Adenoma	0.010 ↑	Common Tumor, NS
[redacted]			

S = Significant; NS = Not significant; ↑ = Positive trend; ↓ = Negative trend.

RAT CARCINOGENICITY STUDY

RAT STUDY DURATION: 104 weeks
STUDY STARTING DATE: May 5, 1998
STUDY ENDING DATE: May 12, 2000
RAT STRAIN: Sprague Dawley rats (Crl:(IGS)CD) from ———
ROUTE: oral gavage
DOSING COMMENTS: daily dose at a dose volume of 10 ml/kg.

NUMBER OF RATS:
- Control-1 (C1): 50
- Control-2 (C2): 50
- Low Dose (LD): 50
- Middle Dose (MD): 50
- High Dose-1 (HD1): 50
- High Dose-2 (HD2): 50

RAT DOSE LEVELS (mg/kg/day):
- Low Dose: 2
- Middle Dose: 20
- High Dose-1: 60
- High Dose-2: 80

BASIS FOR DOSES SELECTED:

AUC: Based on the AUC values from the repeated human studies and the 2-year rat study, the high dose of 80 mg/kg/day only provides 9 – 11 fold margin over the sponsor proposed MRHD of 80 mg/day. Therefore, AUC values can not support the adequacy of the high dose used in the 2-year rat study. However, based on the tentatively FDA approved MRHD of 10 mg, 80 mg/kg in rats can provide about 100 fold margin. Therefore, the 80 mg/kg appears to be an acceptable high dose for the 2-year study.

However, since there is high inter-animal variability in plasma concentration, we should be cautious in using the AUC value to support the adequacy of the carcinogenicity study.

Pharmacokinetic parameters after administration of multiple oral-dose rosuvastatin to healthy volunteers (pooled data)

Dose mg	N	C_{max} ng/ml gmean (CV%)		t_{max} h Median (range)	AUC(0-24) ng.h/ml gmean (CV%)		$t_{½}$ h Mean (SD)	
10[a]	49	4.09	(49.3)	3.0	40.1	(46.7)	29.7[b]	(14.0)
20[c]	10	9.87	(53.3)	3.0	87.9	(50.0)	14.5[d]	(2.63)
40[e]	42	24.1	(57.0)	4.0	201	(47.0)	20.8[f]	(12.8)
80[g]	22	53.1	(79.3)	4.5	436	(70.7)	13.4[f]	(2.04)

D4522.KPR009. Pharmacokinetic parameters of ZD4522 in male and female rats following repeated oral (gavage) administration of ZD4522 at 80 mg/kg/day

	Male Rats			Female Rats		
Parameter	Day 1	1 Month	1 Year	Day 1	1 Month	1 Year
C_{max} (ng/ml)	944	7975	1976	4407	828	2990
t_{max} (h)	0.5	0.5	0.5	0.5	0.5	0.5
AUC(0-t) (ng.h/ml)	3558	9836	3903	5805	1801	4636
AUC (ng.h/ml)	3564	9857	4001	5818	1822	NC
λ_z (/h)	0.266	0.271*	0.138	0.205	0.196*	NC
$t_{½}$ (h)	2.61	2.56*	5.04	3.38	3.53*	NC

NC = Not calculated
* = Unreliable estimate; only 3 data points used in regression analysis

MTD: MTD could not be established based on the 1- and 3-month studies in SD rats, because great variation was observed in these two studies. In the 1-month study, 150 mg/kg did not induce any dose-limiting effect. However, in the 3-month study, 100 mg/kg induced animal death. A third dose-range finding study can not be used, because F344 rats were used.

As recommended by FDA, additional 3-month dose range finding studies were conducted. In the first study, only a single dose level of 160 mg/kg/day was used. In the initial 5 weeks, body weight loss was noted in 7/20 males (-6% to -23%) and 3/20 females (-14% to -28%). These 10 animals were terminated early due to weight loss and poor overall condition. Histopathological findings in these animals included minimal changes in stomach (squamous cell hyperplasia), liver (diffuse hepatocyte cytoplasmic basophilia, together with cytomegaly/karyomegaly, single cell necrosis, increased mitoses and Kupffer cell pigment), kidney (tubular cell degeneration/regeneration), duodenum (villous atrophy), and spleen (lymphoid atrophy). The rest of the animals appeared to be in good condition throughout the whole study duration. Histopathological findings in terminal kill animals were similar to the early terminated animals. The greater variation in toxicity between the terminal kill animals and the remaining animals limited the value of this study to determine MTD.

A second 3-month study was conducted with doses of 80, 160, 240, and 320 mg/kg. Significant numbers of animal deaths were observed at ≥ 160 mg/kg. In the 80 mg/kg group, 2/24 males died or were killed *in extremis*, indicating 80 mg/kg was above MTD. However, the AUC values at 80 mg/kg group in the 3-month study were generally 2 times the value in the 2-year study, indicating these two studies are not fully comparable, i.e., at the same dose level of 80 mg/kg, rats in the 3 month study were exposed to higher levels of compound than rats in the 2-year study, leading to the severe toxicity observed in the 3-month study.

PRIOR FDA DOSE CONCURRENCE:

Six eCAC meetings and a number of T-con had been held before the final report was submitted to discuss the dose selection and the adequacy of the 2-year study. No final concurrence had been reached.

RAT CARCINOGENICITY:

Crestor tested positive in females in the 2-year rat carcinogenicity study. The exposure level at the high dose of 80 mg/kg is about 100 fold the human exposure based on the tentatively FDA approved MRHD of 10 mg.

RAT TUMOR FINDINGS (details):

The spectrum of neoplasia in both the control and treated groups was generally consistent with that expected in rats of this strain and age.

There was no increase in neoplasia in the forestomach and liver associated with the non-neoplastic treatment-related changes seen in these tissues.

The incidence of uterine stromal polyps in females dosed at 80 mg/kg/day was outside the historical control reference range and was statistically significant when compared with the study control group ($P<0.05$). The incidence of uterine stromal polyps in the other treated groups was comparable with the controls and within the normal historical control reference range for this strain of animals. However, malignant uterine stromal polyp/sarcoma is a rare tumor with statistical significant increase at 80 mg/kg.

Two squamous cell carcinoma were recorded for the skin of males dosed at 80 mg/kg/day and this achieved statistical significance, $P<0.05$, when compared with the control group, where no squamous cell carcinomas were recorded. The overall incidence of benign and malignant squamous cell tumors in the skin of the high dose males was comparable with the control group, and none were present in the females. Squamous cell carcinoma was considered a rare tumor, but did not reach statistical significance, when compared with historical control.

The incidence of the combined pancreatic islet cell tumors (adenoma + carcinoma) in females dosed at 60 and 80 mg/kg/day was within the normal historical control reference range for this strain of animals but achieved statistical significance, $P<0.05$, when compared with the control group.

In summary, statistical significant increases of pancreatic islet cell adenoma/carcinoma were observed in females. However, this significant finding by trend test would unlikely be demonstrated significant based on a pairwise comparison. Therefore, this findings are not considered to be clearly related to drug treatment. In contrast, the increased (not statistically significant) incidence of uterine stromal polyps at $\geq$ 60 mg/kg, including stromal sarcoma in a female at 80 mg/kg was considered as drug related.

In other statins, forestomach squamous papilloma/carcinoma, hepatocellular tumors, thyroid tumors, pancreatic tumors, and testicular interstitial cell tumors were observed (see Page 11).

Findings		Males						Females					
		1M	2M	3M	4M	5M	6M	1F	2F	3F	4F	5F	6F
	# examined	50	50	50	50	50	50	50	50	50	50	50	50
Pancreas													
Islet cell adenoma	Present	2	1	4	2	4	2	0	0	1	2	1	0
Islet cell carcinoma	Present	0	0	0	0	2	2	1	0	1	1	2	0
Uterus													
Stromal polyp	Present	0	0	0	0	0	0	5	6	0	8	12	6
Stromal sarcoma	Present	0	0	0	0	0	0	0	0	0	0	1	0
adenocarcinoma	Present	0	0	0	0	0	0	0	0	0	0	1	0

RAT STUDY COMMENTS:

The statistical review was performed by Cynthia Liu. The summary table from the statistical review is attached below. Significant cases determined at $p < 0.05$ mentioned in the sponsor's report are listed. When the new decision rules of $p \leq 0.005$ for common and $p \leq 0.025$ for rare tumor types are applied, some of the cases are no longer significant. In addition, the significant negative trends are not of concern in this review.

The eCAC Committee concluded that the increased (not statistically significant) incidence of uterine stromal polyp/sarcoma was drug related. However, the increased (statistically significant) incidence of pancreatic islet cell adenoma/carcinoma was not considered to be clearly drug related.

Sex	Organ-Tumor Finding	p-value	Reviewer's Comment
M	HAEM/LYMPH/RETIC – Lymphocytic Leukemia	0.036 ↓	No Concern
M	Skin + Subcutis – Squamous Cell Carcinoma	0.037 ↑	NS
M	Glial Cell Tumor	0.025 ↓	No Concern
F	Mammary Gland – Fibroadenoma	0.036 ↓	No Concern
F	Mammary Gland – Adenocarcinoma	0.045 ↓	No Concern
F	Mammary Gland – Fibroadenoma/Adenocarcinoma/ Adenoma	0.018 ↓	No Concern
F	Pituitary – Adenoma	0.023 ↓	No Concern
F	Pituitary – Adenoma/Carcinoma	0.007 ↓	No Concern
F	Pancreas – Islet Cell Adenoma/Carcinoma	0.025 ↑	Rare Tumor, S
F	Uterus – Stromal Polyp	0.028 ↑	NS
F	Uterus – Stromal Polyp/Sarcoma	0.015 ↑	Common Tumor, NS

NS = Not significant; ↑ = Positive trend; ↓ = Negative trend.

The results of carcinogenicity studies of other approved statins are listed below. Some statins also tested positive in carcinogenicity tests.

Drug name	Sponsor	Approval date	Rat -male	Rat -female	Mouse -male	Mouse -female
Cerivastatin	BAYER	JUN 26, 1997	- (104 wks)	- (104 wks)	+ (104 wks)	+ (104 wks)
Fluvastatin	NOVARTIS	DEC 31, 1993	- (104 wks)	- (104 wks)	- (84 wks)	- (93 wks)
Lovastatin	MERCK	MAR 28, 1991	+ (104 wks)	- (104 wks)	+ (84 wks)	+ (84 wks)
Pravastatin	BRISTOL MYERS SQUIBB	OCT 31, 1991	+ (104 wks)	- (104 wks)	- (95 wks)	- (89 wks)
Simvastatin	MERCK	DEC 23, 1991	+ (104 wks)	+ (104 wks)	+ (72, 92 wks)	+ (72, 92 wks)
Atorvastatin	PFIZER	DEC 17, 1996	- (104 wks)	+ (104 wks)	+ (104 wks)	+ (104 wks)
Fenofibrate	ABBOTT	FEB 09, 1998	+ (104 wks)	+ (104 wks)	+ (91 wks)	+ (91 wks)

Tumors observed in other statins

Drug name	Rat -male	Rat -female	Mouse -male	Mouse -female
Cerivastatin	-	-	hepatocellular adenomas (3X), Hepatocellular carcinomas (1X)	hepatocellular adenomas (3X)
Fluvastatin	forestomach squamous papillomas, carcinoma of the forestomach , thyroid follicular cell adenomas and carcinomas (35X)	forestomach squamous papillomas, carcinoma of the forestomach (35X)	forestomach squamous cell papillomas (7X)	forestomach squamous cell papillomas (2X)
Lovastatin	hepatocellular carcinogenicity (2-7X) thyroid neoplasms	hepatocellular carcinogenicity (2-7X) thyroid neoplasms	hepatocellular carcinomas and adenomas (3-4X) papilloma in the non-glandular mucosa of the stomach (1-2X)	hepatocellular carcinomas and adenomas, pulmonary adenomas (3-4X), papilloma in the non-glandular mucosa of the stomach (1-2X)
Pravastatin	hepatocellular carcinomas (6-10X)	-	hepatocellular carcinomas (30-40X)	hepatocellular carcinomas (30-40X)
Simvastatin	thyroid follicular adenomas, hepatocellular adenomas and carcinomas (7-15X)	thyroid follicular adenomas, hepatocellular adenomas and carcinomas (22-25X)	Liver carcinomas (4X), lung adenomas (4X)	Liver carcinomas (8X), lung adenomas (4X)
Atorvastatin	-	Rhabdomyosarcoma, fibrosarcoma (16X)	liver adenomas (6X)	liver carcinomas (6X)
Fenofibrate	liver carcinoma (6X), pancreatic carcinomas (1X), pancreatic adenomas and benign testicular interstitial cell tumors (6X)	liver carcinoma (6X)	liver carcinoma (3X)	liver carcinoma (3X)
[redacted]				

* Values in ( ) represent fold of human exposure based on AUC.

Study title: 107 Week Oral (Gavage Administration) Oncogenicity Study in the Mouse.

Key study findings: Crestor tested positive in the 2-year carcinogenicity study. Higher incidence of hepatocellular tumors (both adenomas and carcinomas) were observed at the high dose of 200 mg/kg in both sexes.

Study number: —— Study Number 88/233. Sponsor Reference Number TCM/1088
Volume #, and page #: Electronic submission, file name: tcm1088.pdf
Conducting laboratory and location: ——

Date of study initiation: 22 April 1998
GLP compliance: Yes
QA report: yes (X) no ( )

Drug, lot #, and % purity:

lot number	Sponsor's analytical reference number	Quantity supplied (g)	Purity (%)	Date of receipt at
2	00518198		96.86	1 April 1998
4	00518198		96.86	26 August 1998
5	03516E98		96.7	25 November 1998
6	60414K99		96.1	19 February 1999
7	03516E98		96.5	13 August 1999
8	64725E99		96.2	3 December 1999
9	62413K99		95.6	2 March 2000
10	70888E00		98.3	11 April 2000

CAC concurrence:
The sponsor submitted dose selection document for rats and mice 2-year carcinogenicity studies on November 25, 1998 and June 21, 1999. The 2-year carcinogenicity study in mice was initiated in June 10, 1998. CAC concurred with the dose selection on January 18, 2000.

Study Type: 2-year bioassay
Species/strain: Mice/B6C3F1 strain from
Number/sex/group:

Group number	Group description	Dose level (mg/kg/day)	Animals/group Main test		Satellites	
			Male	Female	Male	Female
1	Control 1	0	51	51	24	24
2	Low	10	51	51	24	24
3	Intermediate 1	60	51	51	24	24
4	Intermediate 2	200	51	51	24	24
5	High	400	51	51	24	24
6	Control 2	0	51	51	0	0

Age and weight at start of study: aged 8 weeks old and weighed 17.0 to 28.8 g (males) and 15.5 to 24.0 g (females).

Animal housing: mice were housed in a single, air-conditioned, exclusive room with the temperature and relative humidity ranges of 19 to 25°C and 40 to 70% respectively. Fluorescent lighting was controlled automatically to give a cycle of 12 hours light (0600 to 1800) and 12 hours dark.

Formulation/vehicle:
The control article and vehicle for the test article was 5% w/v aqueous Gum Arabic.

Drug stability/homogeneity:
The suspensions were homogeneous and stable during the 14 day storage period.

Methods:
Doses: 0, 10, 60, 200, 400, and 0 mg/kg
Basis of dose selection:
Dose selection was based on the results of two preliminary two week studies and a 13 week sighting study in the B6C3F1 mouse.

In the first preliminary study in the ICR mouse, all animals given 500 mg/kg/day and one animal given 250 mg/kg/day died. Histological examination of the surviving animals given 250 mg/kg/day revealed eosinophilic changes associated with single cell necrosis in periportal hepatocytes.

In the second two week study, ZD4522 was administered orally by gavage to groups of B6C3F1 mice at doses of 20, 60 and 200 mg/kg/day. There were no deaths related to ZD4522, no adverse clinical signs and no effect on body weight or food consumption.

There was an increase in liver weight and minimal centrilobular hepatocyte hypertrophy at 200 mg/kg/day.

In the 13-week study, doses administered were 20, 60 and 200 mg/kg/day. Again there were no deaths or adverse clinical signs related to ZD4522 and no effect on body weight or food consumption. An increase in liver weight of 24 and 16% in males and females respectively dosed 200 mg/kg/day was accompanied by minimal centrilobular hepatocyte hypertrophy. Centrilobular hepatocyte hypertrophy was also seen in a proportion of males dosed 60 mg/kg/day, but there was no effect on liver weight. A 16% increase in liver weight was seen in females dosed 60 mg/kg/day.

In the 13 week study, the high dose of 200 mg/kg/day produced minimal histological changes in the liver. Based on this and data from the short term studies 500 mg/kg/day not tolerated, a high dose of 400 mg/kg/day was selected for the 2-year study.

However during weeks 1 and 2 of the 2-year study, the deteriorating clinical condition of the animals dosed at 400 mg/kg/day, together with the rapid histopathological assessment of six decedent animals which indicated hepatocyte vacuolation with single cell necrosis in the liver, squamous cell hyperplasia with/ without hyperkeratosis and in addition gastritis in the stomach and tubular degeneration in the kidneys of two animals caused this group to be prematurely terminated in week 3. Therefore, the group dosed at 200 mg/kg/day was considered as the high dose group.

Restriction paradigm for dietary restriction studies:
Mice had access *ad libitum* to SQC Rat and Mouse Maintenance Diet No 1, Expanded ——— Water was provided *ad libitum* via an automatic watering system or water bottles.

Route of administration: oral gavage
Frequency of drug administration: daily
Dual controls employed: yes
Interim sacrifices: the group dosed at 400 mg/kg was terminated in week 3 due to mortality and deteriorating clinical condition.

Satellite PK or special study group(s): 3 animals/sex/time point.
Deviations from original study protocol: None.

Statistical methods:
Body weight gains, food and water consumption were analyzed using one-way analysis of variance (ANOVA), separately for each sex. Pairwise comparisons with control were made using Dunnett's test. A regression test was performed to determine whether there was a relationship between increasing dose and response. Where it showed a significant result ($p<0.05$) and any of the pairwise comparisons were also significant, the regression result was not reported. Levene's test for equality of variances among the groups was also

performed, and where this showed evidence of heterogeneity ($p<0.01$), the data were re-analyzed using non-parametric methods.

The non-parametric methods employed were the Kruskal-Wallis ANOVA, the Terpstra-Jonckheere test for a dose related trend and the Wilcoxon rank sum test for pairwise comparisons. Where the Kruskal-Wallis ANOVA was not significant, the pairwise comparisons were not reported.

Male and female survival data were analyzed separately. Survival probability functions were estimated for each group by the Kaplan-Meier technique. Survival curves were compared to the start of the terminal kill phase (during week 108).

Permutational tests were performed with a one-sided risk for increasing mortality with dose. Tests were performed for an overall dose-response and where this was significant ($P<0.05$), the dose response test was repeated, excluding the highest dose level, until no significant dose response was found ($P\geq0.05$).

An overall dose response test was also performed with a one-sided risk for decreasing mortality with dose.

The tests were performed in accordance with the IARC annex, using the dose levels as weighting coefficients. The number of tumor bearing animals were analyzed separately for males and females, for tumor types found in at least three animals of the given sex. Tumors of similar histogenic origin were merged, as requested by the Pathologist. At the request of the sponsor, the separate tumor types contributing to a merged type were also analyzed wherever they were found in at least three animals.

Permutational tests were performed with a one-sided risk for increasing incidence with dose. Tests were performed for an overall dose-response and where this was significant ($P<0.05$), the dose response test was repeated, excluding the highest dose level, until no significant dose response was found ($P\geq0.05$).

An overall dose response test was also performed with a one-sided risk for decreasing incidence with dose.

The tests were performed in accordance with the IARC annex, using the dose levels as weighting coefficients. Non-fatal tumors were analyzed using fixed intervals of 1 to 50 weeks, 51 to 80 weeks, 81 to 107 weeks and the terminal kill phase. The fatal and non-fatal results were combined in accordance with the IARC annex.

Observations and times:

Clinical signs: daily.

Body weights: day 0, weekly for first 16 weeks, and once every four weeks thereafter.

Food consumption: weekly for the first 16 weeks, then one week in every four thereafter.

Ophthalmoscopy: pre-treatment and in weeks 26, 52, 78 and 104 in 20 animal/sex in both control groups and the high dose group.

Hematology: at sacrifice. Red blood cell count, white cell count and differential were measured.

Clinical chemistry: no data provided.

Organ weights: at sacrifice.

Gross pathology: at sacrifice.

Histopathology: all tissues listed in the table below from all main test animals, all group 1 satellite animals, nine group 4 satellite animals per sex and decedents(satellite and main test) were preserved in the appropriate fixatives. Histopathology was performed on tissues denoted by Š in the table below from all main test animals, all group 1 satellite animals, nine group 4 satellite animals per sex and decedents (satellite and main test).

Adrenals		§	Optic nerves		§
Animal identification			Ovaries		§
Aorta			Pancreas		§
Brain		§	Pituitary		§
Caecum		§	Prostate		§
Colon		§	Rectum		§
Duodenum		§	Salivary glands		§
Eyes	b	§	Sciatic nerves		§
Femur with bone marrow and articular surface		§	Seminal vesicles		§
Gall bladder		§	Skin		§
Gross lesions		§	Spinal cord cervical		§
Harderian glands	d	§	Spinal cord lumbar		§
Head			Spinal cord thoracic		§
Heart		§	Spleen		§
Ileum		§	Sternum with bone marrow		§
Jejunum		§	Stomach		§
Kidney		§	Testes + epididymides		§
Lacrimal glands	d		Thymus		§
Larynx			Thyroids + parathyroids		§
Liver		§	Tissue masses		§
Lungs (including mainstem bronchi)		§	Tongue		§
Mammary	f	§	Trachea		§
Mandibular lymph nodes		§	Trachea bifurcation		§
Mesenteric lymph nodes		§	Urinary bladder		§
Muscle (quadriceps)		§	Uterus		§
Nasal turbinates	d		Vagina		§
Nasopharynx	d		Zymbal glands	d	
Oesophagus		§			

Fixative 10% neutral buffered formalin except where indicated by: b Davidson's fluid

d preserved with the head *in situ* f female only

Bone designated for histopathological examination was decalcified using Kristenson's fluid.

Toxicokinetics: during week 52 (pre-dose and at 0.5, 1.5, 4, 8, 12 and 24 hours after dosing).

Results:

Mortality:

During weeks 1 and 2, the deteriorating condition of the animals dosed at 400 mg/kg/day, together with the rapid histopathological assessment of six decedent animals which indicated hepatocyte vacuolation with single cell necrosis in the liver, squamous cell hyperplasia with/ without hyperkeratosis and gastritis in the stomach and tubular degeneration in the kidneys of two animals caused this group to be prematurely terminated in week 3. Therefore, from this point the group dosed at 200 mg/kg/day was considered as the high dose group.

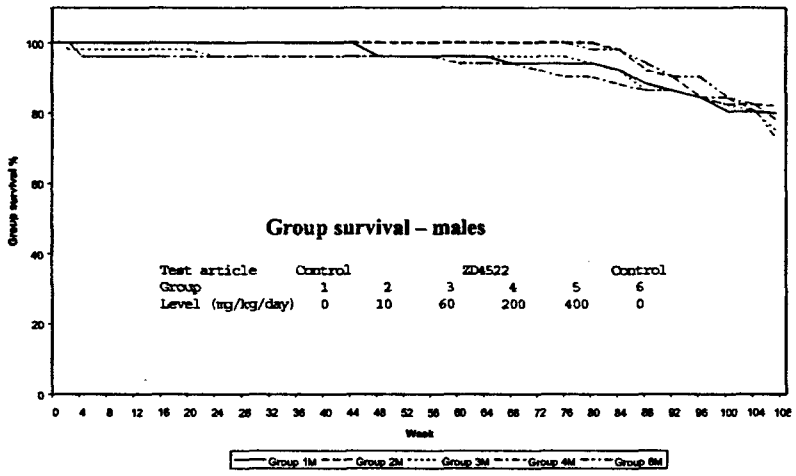
Generally the mortality was comparable between controls and treated groups during the 52 week treatment. There was no significant dose response in mortality (P> 0.05).

The majority of the deaths were due to tumors. The most common cause of mortality in females was haemolymphoreticular tumors and in males liver tumors.

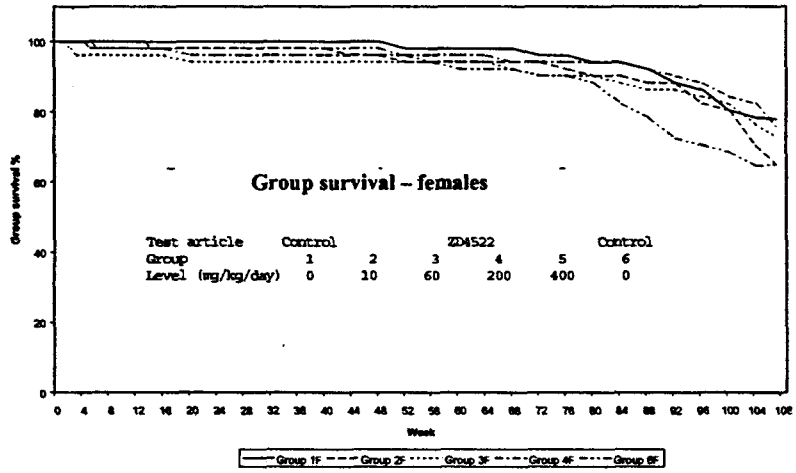
Survival at terminal kill

Group number	Dose levels (mg/kg/day)	Number of Animals/sex	Survival (%) Male	Female
1	0	51	80	78
2	10	51	82	65
3	60	51	75	73
4	200	51	78	76
5	400	51	-	-
6	0	51	73	65

- animals removed prematurely



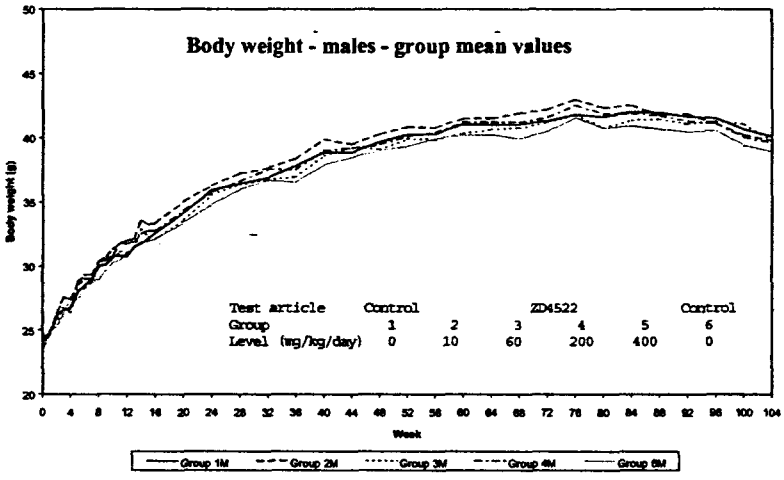
All Group 5 terminated beginning of week 3; data not presented



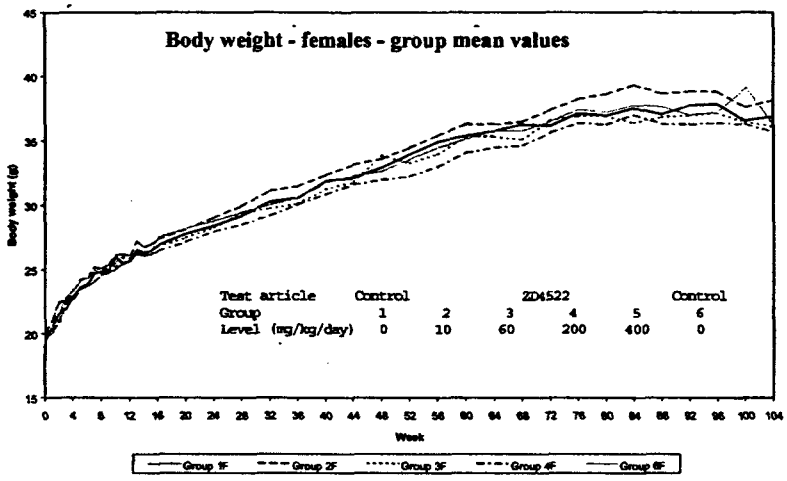
All Group 5 terminated beginning of week 3; data not presented

Clinical signs: No treatment related clinical signs were noted at ≤ 200 mg/kg/day.

Body weights: no treatment related changes were noted in body weight or body weight gain.

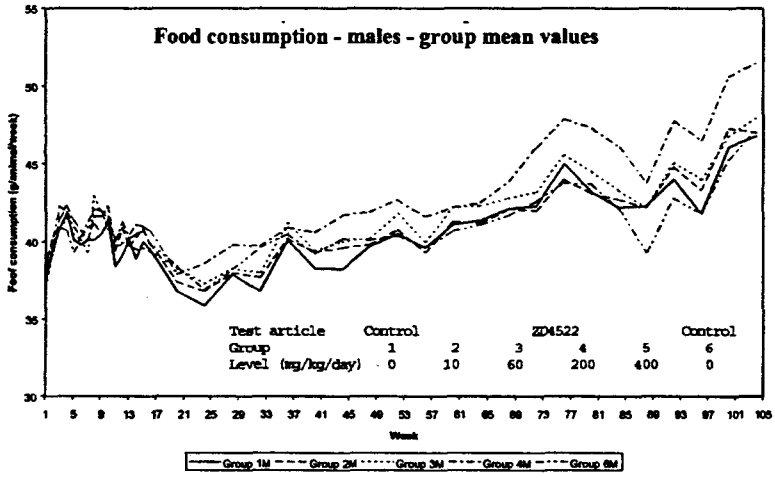


All Group 5 terminated beginning of week 3; data not presented

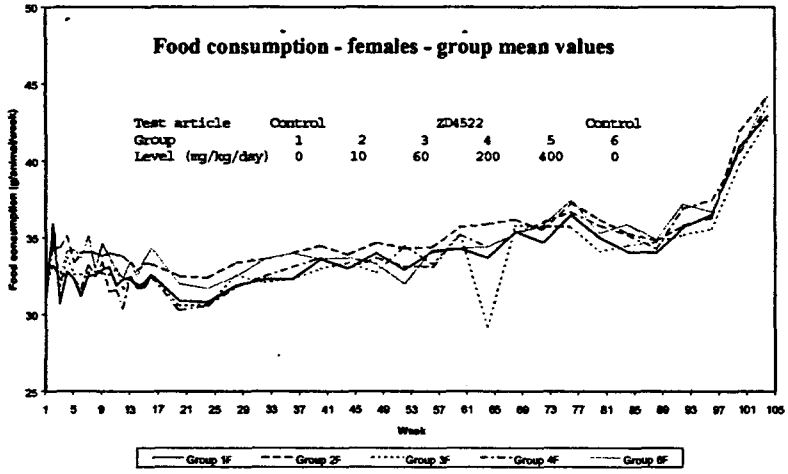


All Group 5 terminated beginning of week 3; data not presented

Food consumption: no apparent treatment related changes.



All Group 5 terminated beginning of week 3; data not presented



All Group 5 terminated beginning of week 3; data not presented

Hematology: no treatment related changes.

Clinical chemistry: no data provided.

Organ weights: no data provided.

Gross pathology:

Most tissues in the control group mice were macroscopically unremarkable and most findings seen were generally consistent with the expected pattern of background findings seen in mice of this age.

There were dose-related increases in incidence of macroscopic findings in the liver. In the livers of animals of both sexes in groups given 200 mg/kg/day, there was an increased incidence of pale foci, pale areas and masses. The 60 mg/kg/day dose group was comparable with the control range.

Incidence of salient macroscopic findings

		Males					Females				
Tissue and finding		1M	2M	3M	4M	6M	1F	2F	3F	4F	6F
Liver	No. examined:	51	51	51	51	51	51	51	51	51	51
pale focus		1	2	1	2	0	0	2	1	4	1
pale area		4	5	3	8	3	1	1	3	7	2
mass		19	19	15	19	8	2	2	3	7	2
multiple mass		2	0	3	7	8	1	1	0	2	0

Histopathology:

Non-neoplastic:

The spectrum of non-neoplastic microscopic findings in the control groups was generally consistent with that expected in mice of this age.

There were dose-related findings in the liver, stomach, thyroid and kidney. In the liver, diffuse hepatocellular hypertrophy was noted in the 60 and 200 mg/kg/day male groups and 200 mg/kg female group. The lesion was characterized by enlargement of hepatocytes throughout the lobule. In these groups, there were also increases in incidence of foci of cellular alteration. The foci were characterized by areas of hepatocytes distinct from the surrounding normal tissues. The most affected variant was foci of vacuolated cells, but the incidence of eosinophilic and basophilic cell foci was also increased compared with controls. The no effect level for the liver changes in males was 10 mg/kg/day and in females 60 mg/kg/day.

In the keratinised forestomach in the 200 mg/kg/day group there was slightly higher incidence of hyperkeratosis in males and of squamous cell hyperplasia in females. The hyperkeratosis consisted of focal to diffuse thickening of the superficial keratin of the forestomach. The squamous cell hyperplasia was characterized by focal thickening of the epithelium with folding of the basement epithelium and sometimes associated with superficial erosions of the epithelium. The 60 mg/kg/day group was comparable with controls.

In the thyroid gland of females of the 200 mg/kg/day there was a higher incidence of follicular cell hyperplasia. The lesion consisted of focal increases in cell density around follicles, with slight papillary formations in some individual animals. The 60 mg/kg/day females were in the control range. There was no increase in thyroid follicular cell tumors associated with these focal hyperplasia in females and no increased thyroid follicular cell hyperplasia or neoplasia were seen in males.

In the kidney of male mice of the 60 and 200 mg/kg/day group there was a dose-related reduction in the normal vacuolation of the cortical tubules found in control males in this strain. The 10 mg/kg/day male group was comparable with controls.

Summary of the non-neoplastic findings:

Incidence of salient non-neoplastic findings

		Males					Females				
Tissue and finding		1M	2M	3M	4M	6M	1F	2F	3F	4F	6F
Liver	No. examined:	51	51	51	51	51	51	51	51	51	51
hepatocellular hypertrophy	Absent	51	51	14	3	51	51	51	51	42	51
	Minimal	0	0	32	17	0	0	0	0	9	0
	Slight	0	0	5	26	0	0	0	0	0	0
	Moderate	0	0	0	5	0	0	0	0	0	0
focal vacuolation	Absent	50	48	48	39	50	51	51	48	44	51
	Present	1	3	3	12	1	0	0	3	7	1
eosinophilic focus	Absent	49	46	47	43	51	51	50	51	45	50
	Present	2	5	4	8	0	1	1	0	6	1
basophilic focus	Absent	41	41	46	39	41	51	48	48	44	49
	Present	10	10	5	12	10	0	3	3	7	2
Stomach	No. examined:	51	51	51	51	51	50	51	50	50	51
hyperkeratosis	Absent	46	49	44	39	44	38	37	44	40	43
	Minimal	4	2	5	7	7	9	11	2	8	8
	Slight	1	0	2	5	0	3	3	3	2	0
	Moderate	0	0	0	0	0	0	0	1	0	0
squamous cell hyperplasia	Absent	48	50	51	45	45	45	44	43	38	43
	Minimal	2	0	0	1	1	1	2	1	1	1
	Slight	0	1	0	4	1	1	2	3	5	4
	Moderate	1	0	0	1	4	3	3	3	6	3
Thyroid	No. examined:	51	51	51	51	51	51	51	51	51	51
follicular cell hyperplasia	Absent	50	50	51	50	51	48	49	48	36	42
	Minimal	0	1	0	1	0	2	2	1	12	7
	Slight	1	0	0	0	0	0	0	0	1	2
	Moderate	0	0	0	0	0	1	0	0	2	0
	Moderately severe	0	0	0	0	0	0	0	2	0	0
Kidney	No. examined:	51	51	51	51	51	51	51	51	51	51
tubular vacuolation	Absent	0	1	1	24	0	51	51	51	51	51
	Minimal	2	3	34	27	7	0	0	0	0	0
	Slight	47	46	16	0	42	0	0	0	0	0
	Moderate	2	1	0	0	2	0	0	0	0	0

Details of the non-neoplastic findings:

study number 88/233. Sponsor reference number TCM/1088.
Microscopic findings - group incidence - non-neoplastic data - all animals

Test article	Control		ED4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	10	60	200	400	0

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STUDY NUMBER: 88233

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
TABLE INCLUDES:											
SEX=ALL;GROUP=ALL;WEEKS=ALL	SEX:	---------MALE--------					---------FEMALE-------				
DEATH=ALL;FIND=P;SUBSET=T											
	GROUP:	-1-	-2-	-3-	-4-	-6-	-1-	-2-	-3-	-4-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	51	51	51	51	51	51	51	51	51	51
** TOP OF LIST **											
ABDOMINAL CAVITY	NUMBER EXAMINED:	0	0	0	4	2	1	1	0	2	1
--FAT NECROSIS		0	0	0	0	0	0	1	0	1	0
--ABSCESS		0	0	0	0	0	0	0	0	0	1
ADRENAL	NUMBER EXAMINED:	51	51	51	50	51	51	51	50	51	51
--CYST		0	0	0	1	0	0	0	0	0	0
--HAEMORRHAGE		0	0	0	0	0	1	0	0	0	0
--HAEMOPOIESIS		0	0	0	0	0	1	0	0	0	0
--HAEMANGIECTASIS		0	0	0	0	0	0	0	0	1	0
--MEDULLARY HYPERTROPHY		0	1	0	0	0	0	0	0	0	0
--CORTICAL HYPERTROPHY		0	0	0	0	0	0	0	0	1	0
--BASOPHILIC FOCUS		0	1	0	0	0	0	0	0	0	0
--EOSINOPHILIC FOCUS		12	5	17	7	15	4	1	0	3	1
--EOSINOPHILIC NODULE		0	1	0	0	0	0	0	0	0	0
--MEDULLARY HYPERPLASIA - FOCAL		0	0	0	2	0	1	1	0	0	3
--SUBCAPSULAR CELL HYPERPLASIA		46	47	43	46	45	50	51	49	51	50
BRAIN	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--MINERALISATION		40	44	40	36	41	34	38	36	35	40
--VENTRICULAR DILATATION		0	0	0	1	1	0	0	0	2	0
--COMPRESSION		0	0	0	0	0	2	1	1	2	2
--INFLAMMATORY CELL FOCI		0	0	0	0	0	1	1	0	0	0
--MENINGITIS		0	0	0	0	0	0	0	1	0	0
--ARTERITIS		0	0	0	0	0	0	0	0	1	0
--GLIOSIS		0	0	0	0	0	1	0	0	0	0
--NECROSIS		0	0	0	0	0	0	0	0	0	1
BRONCHIAL LN	NUMBER EXAMINED:	0	0	0	0	0	0	1	0	1	0
--LYMPHOID HYPERPLASIA		0	0	0	0	0	0	0	0	1	0
CAECUM	NUMBER EXAMINED:	50	50	51	49	50	49	50	49	49	51
--HABITUAL LYSIS		0	0	0	0	0	1	0	0	0	0
COLON	NUMBER EXAMINED:	50	51	51	50	51	50	51	50	50	51
--DISTENSION		0	0	0	0	0	0	0	1	0	0
CONNECTIVE TISS	NUMBER EXAMINED:	1	1	1	0	0	0	1	0	1	0
--FAT NECROSIS		0	1	0	0	0	0	0	0	0	0
DIAPHRAGM	NUMBER EXAMINED:	0	0	0	0	1	0	0	1	0	0
--ADHESION		0	0	0	0	0	0	0	1	0	0
DUODENUM	NUMBER EXAMINED:	51	51	51	49	50	49	49	49	50	50
--HABITUAL LYSIS		0	0	0	0	0	0	0	0	1	0
--VILLOUS ATROPHY		0	0	0	1	0	0	1	1	0	0
--BRUNNER'S GLAND ADENITIS/ATROPHY		0	0	0	0	1	0	0	0	1	0
--EROSION/ULCER		0	0	0	0	0	0	0	1	0	0
--HYPERPLASIA - AVILLOUS		1	1	0	0	0	0	0	0	1	1
EPIDIDYMIS	NUMBER EXAMINED:	51	51	51	51	51	0	0	0	0	0
--INFLAMMATORY CELL FOCI		7	11	11	10	8	0	0	0	0	0
--ARTERITIS		0	1	0	1	0	0	0	0	0	0
--SPERM GRANULOMA		0	1	0	1	0	0	0	0	0	0

—— study number 88/233. Sponsor reference number TCM/1088.
Microscopic findings - group incidence - non-neoplastic data - all animals

Test article Control ED4522 Control
Group 1 2 3 4 5 6
Level (mg/kg/day) 0 10 60 200 400 0

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STUDY NUMBER: 88233

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	---------MALE---------					---------FEMALE---------				
ORGAN AND FINDING DESCRIPTION	GROUP: -1-	-2-	-3-	-4-	-6-	-1-	-2-	-3-	-4-	-6-	
	NUMBER: 51	51	51	51	51	51	51	51	51	51	
** FROM PREVIOUS PAGE **											
EPIDIDYMIS ..... NUMBER EXAMINED:	51	51	51	51	51	0	0	0	0	0	
--OLIGOSPERMIA	0	0	1	3	5	0	0	0	0	0	
EAR ..... NUMBER EXAMINED:	0	1	2	0	2	0	1	0	0	0	
--DERMATITIS	0	0	1	0	0	0	1	0	0	0	
--ACANTHOSIS	0	0	1	0	0	0	0	0	0	0	
EYE ..... NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51	
--RETINAL ATROPHY	0	0	0	0	0	0	0	0	1	0	
--CORNEAL MINERALISATION	0	2	1	2	2	5	8	5	9	7	
--LENTICULAR DEGENERATION	1	0	0	0	0	0	1	0	0	0	
--KERATITIS	1	1	1	0	3	1	2	1	0	1	
--PANOPHTHALMITIS	0	0	0	1	0	0	0	0	1	0	
--PHTHISIS BULBI	0	0	0	0	0	1	0	0	0	0	
FEMUR + MARROW ..... NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51	
--MARROW ATROPHY	0	0	0	1	0	0	0	0	0	0	
--FIBRO-OSSEOUS LESION	2	2	2	0	4	34	33	31	34	34	
--THROMBOSIS	0	1	0	0	1	0	0	0	0	0	
--ARTHRITIS/ARTHROPATHY	0	1	1	0	0	0	0	3	2	0	
--ARTERITIS	1	1	0	0	0	0	0	0	0	0	
--MARROW HYPERPLASIA	4	3	6	5	5	5	8	7	5	11	
--MEGAKARYOCYTIC HYPERPLASIA	1	0	0	0	1	0	0	0	0	0	
FOOT/LEG ..... NUMBER EXAMINED:	0	1	0	0	1	0	1	2	0	0	
--PODODERMATITIS	0	0	0	0	0	0	1	0	0	0	
FOOT/LEG ..... NUMBER EXAMINED:	0	1	0	0	1	0	1	2	0	0	
--ARTHRITIS	0	0	0	0	0	0	0	2	0	0	
GALL BLADDER ..... NUMBER EXAMINED:	50	51	51	49	49	48	50	48	49	50	
--INFLAMMATORY CELL FOCI	0	3	2	1	1	5	2	6	5	4	
--DISTENSION	1	0	0	1	0	0	2	1	0	2	
--HAEMOLYTIC LYSIS	0	0	0	1	0	0	0	0	0	0	
--PIGMENT	0	0	0	0	0	0	1	0	0	0	
HARDERIAN GLAND ..... NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51	
--VACCULATION	0	0	1	0	0	0	0	0	0	0	
--CYST	0	0	0	0	0	0	0	0	1	0	
--INFLAMMATORY CELL FOCI	16	28	25	25	34	22	30	31	30	30	
--ADENITIS	0	1	0	0	0	1	0	0	0	0	
--HYPERPLASIA	4	2	4	2	2	6	4	4	0	3	
HEART ..... NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51	
--MINERALISATION	0	0	0	0	0	0	0	1	1	0	
--FIBROSIS/DEGENERATION	1	0	0	0	1	1	0	0	0	0	
--MURAL THROMBUS	0	0	0	0	1	0	0	0	0	0	
--VALVULAR ENDOCARDITIS	0	0	0	0	0	1	0	0	0	1	
--INFLAMMATORY CELL FOCI	0	0	0	0	0	2	5	1	2	4	
--ARTERITIS	1	2	1	1	3	0	0	1	1	0	
--EPICARDITIS	0	1	2	1	0	0	0	4	1	0	
--MYOCYTOTOX HYPERPLASIA	1	0	0	0	0	0	0	0	0	0	

study number 88/233. Sponsor reference number TCM/1088.
Microscopic findings - group incidence - non-neoplastic data - all animals

Test article	Control		ED4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	10	60	200	400	0

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STUDY NUMBER: 88233

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=P;SUBSET=T

			--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	----------MALE----------					----------FEMALE----------					
	GROUP:	-1-	-2-	-3-	-4-	-6-	-1-	-2-	-3-	-4-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	51	51	51	51	51	51	51	51	51	51
JEJUNUM	NUMBER EXAMINED:	50	51	51	50	50	50	49	50	49	49
--DISTENSION		0	0	0	0	0	1	0	0	0	0
--EROSION/ULCER		1	0	0	0	0	0	0	0	0	0
KIDNEY	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--CYST		10	14	12	12	12	1	0	0	1	0
--INFLAMMATORY CELL FOCI		5	7	6	8	7	18	10	13	8	11
--NECROSIS		1	1	2	1	1	0	0	0	0	0
--PYELITIS		1	0	1	0	0	0	0	0	0	0
--PYELONEPHRITIS		0	1	0	0	1	0	0	0	0	1
--CORTICAL MINERALISATION		46	47	42	41	40	0	0	0	2	0
--PAPILLARY MINERALISATION		9	5	7	4	10	2	4	0	2	5
--CORTICAL SCAR		2	3	2	2	1	0	0	3	1	0
--CAPSULAR SCAR		0	0	0	0	1	0	0	0	0	0
--TUBULAR DILATION		1	0	0	0	0	0	2	0	1	0
--GLOMERULONEPHROPATHY		3	3	4	2	6	3	3	3	2	1
--FOCAL NEPHROPATHY		43	46	43	44	41	24	19	26	22	23
--NEPHROSIS		1	1	0	0	1	1	4	3	1	0
--HYALINE DROPLETS		0	0	0	1	1	2	4	1	1	8
--TUBULAR VACUOLATION		51	50	50	27	51	0	0	0	0	0
--TUBULAR NECROSIS		0	0	0	0	0	1	0	0	0	1
--TUBULAR CELL HYPERPLASIA		1	1	1	2	4	0	0	0	0	0
--OSSEOUS METAPLASIA		1	1	0	0	1	0	1	1	1	2
LIVER	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--BARBITURATE LYSIS		0	0	0	0	0	1	0	2	1	2
LIVER	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--CAPSULAR FIBROSIS/ADHESION		0	0	0	0	0	0	0	0	1	0
--PIGMENT		0	0	0	0	0	0	0	1	0	0
--CYST		0	0	0	0	0	0	1	0	0	0
--BILIARY CYST		0	0	0	1	0	1	0	0	0	0
--TELANGIECTASIS		0	0	0	0	0	0	0	0	1	0
--HAEMOPOIESIS		1	0	2	0	0	0	4	3	1	2
--INFLAMMATORY CELL FOCI		46	51	46	49	45	40	37	33	39	37
--HEPATOCYTE HYPERTROPHY		0	0	37	48	0	0	0	0	9	0
--CENTRILOBULAR VACUOLATION		1	0	0	0	0	0	1	1	0	0
--HEPATOCYTE VACUOLATION		19	18	27	21	22	36	31	32	30	27
--SINGLE CELL NECROSIS		1	0	0	0	0	0	0	0	0	0
--FOCAL NECROSIS		1	0	4	1	6	3	5	1	3	4
--LOBAR NECROSIS		1	1	0	2	0	0	0	0	0	0
--CENTRILOBULAR NECROSIS		1	0	1	1	1	0	1	1	3	0
--BASOPHILIC FOCUS		10	18	5	12	10	0	3	3	7	2
--EOSINOPHILIC FOCUS		2	5	4	8	0	1	1	0	6	1
--FOCAL VACUOLATION		1	3	3	12	1	0	0	3	7	1
--OVAL CELL HYPERPLASIA		0	0	0	0	1	0	0	0	0	0
--MUCINOUS METAPLASIA/CYSTIALE		1	0	0	0	0	0	0	0	0	0
LUNG	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--ALVEOLAR CONGESTION/HAEMORRHAGE		1	1	0	3	0	1	2	2	1	0
--CYST		0	0	0	0	0	0	0	1	0	0
--PLEURAL FIBROSIS/ADHESION		0	0	2	2	0	0	0	0	1	1	0
--CONGESTION		0	0	0	0	0	0	0	0	0	1

——— study number 88/233. Sponsor reference number TCM/1088.
Microscopic findings - group incidence - non-neoplastic data - all animals

Test article	Control		ZD4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	10	60	200	400	0

———

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STUDY NUMBER: 88233

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
TABLE INCLUDES:											
SEX=ALL;GROUP=ALL;NUMBER=ALL	SEX:	----------MALE----------					----------FEMALE----------				
DEATH=ALL;FIND=P;SUBSET=T	GROUP:	-1-	-2-	-3-	-4-	-6-	-1-	-2-	-3-	-4-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	51	51	51	51	51	51	51	51	51	51
** FROM PREVIOUS PAGE **											
LUNG	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--HAEMORRHAGE		0	0	1	1	1	2	1	0	0	0
--INFLAMMATORY CELL FOCI		49	51	46	49	50	47	40	41	43	39
--PNEUMONITIS		0	1	1	0	0	0	0	0	1	0
--FOAMY HISTIOCYTES		0	0	1	1	1	0	1	1	0	0
--PIGMENTED HISTIOCYTES		1	4	3	8	4	2	1	2	0	2
--ABSCESS		0	0	1	1	0	0	1	3	0	2
--OSSEOUS METAPLASIA		0	0	0	0	0	0	0	1	0	0
--BRONCHIOLO-ALVEOLAR HYPERPLASIA		1	4	1	0	1	1	2	0	1	1
MAMMARY GLAND	NUMBER EXAMINED:	0	0	0	0	0	50	50	51	51	51
--CYSTIC CHANGE		0	0	0	0	0	1	2	0	2	1
--INFLAMMATORY CELL FOCI		0	0	0	0	0	0	1	0	2	0
--HYPERPLASIA - CYSTIC		0	0	0	0	0	0	0	0	1	0
--HYPERPLASIA - ACINAR		0	0	0	0	0	0	1	1	1	1
--HYPERPLASIA - ATYPICAL		0	0	0	0	0	1	0	1	0	0
MANDIBULAR LN	NUMBER EXAMINED:	51	50	51	51	51	51	51	51	51	51
--PIGMENT		0	1	0	0	1	0	0	1	0	0
--HAEMORRHAGE		0	0	0	0	0	0	0	0	1	0
--MASTOCYTOSIS		0	0	0	0	0	0	0	0	1	0
--LYMPHOID HYPERPLASIA		0	0	1	1	3	5	6	9	4	9
MESENTERIC LN	NUMBER EXAMINED:	50	51	51	51	51	51	51	50	50	49
--INJECTION LESION		0	0	1	0	0	0	0	0	0	0
--PIGMENT		1	0	2	1	0	0	0	0	0	1
MESENTERIC LN	NUMBER EXAMINED:	50	51	51	51	51	51	51	50	50	49
--BARBITURATE LYSIS		0	1	0	0	0	0	0	0	0	0
--HAEMANGIECTASIS		4	8	8	5	3	1	2	1	8	1
--LYMPHANGIECTASIS		0	0	0	1	1	0	0	0	0	1
--HAEMORRHAGE		1	4	2	10	4	0	0	1	2	1
--ATROPHY		0	0	0	0	0	0	0	1	0	0
--ARTERITIS		0	1	0	1	0	0	0	0	0	0
--LYMPHOHISTIOCYTIC HYPERPLASIA		1	0	0	0	0	0	1	0	0	0
--LYMPHOID HYPERPLASIA		3	3	1	3	8	7	4	5	2	5
MUSCLE	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--MYOPATHY		0	0	0	0	0	0	0	0	0	1
--INFLAMMATORY CELL FOCI		4	9	8	6	4	11	10	12	6	10
NASAL CAVITY	NUMBER EXAMINED:	0	3	1	0	1	0	0	0	0	1
--GINGIVAL EROSION		0	1	1	0	0	0	0	0	0	0
--NODAL ABSCESS		0	1	0	0	0	0	0	0	0	0
OESOPHAGUS	NUMBER EXAMINED:	50	51	51	51	51	51	51	51	51	51
--RUPTURE		0	0	0	0	0	0	0	0	1	0
--DISTENSION		1	0	0	0	0	0	0	0	0	0
--OESOPHAGITIS		0	0	0	0	0	0	0	1	0	0
--INFLAMMATORY CELL FOCI		1	1	0	0	0	0	0	0	0	0
OPTIC NERVE	NUMBER EXAMINED:	51	50	51	51	51	51	48	50	49	50
--NEUROPATHY		2	3	0	2	3	5	2	4	5	7

[redacted] study number 88/233. Sponsor reference number TCM/1088.
Microscopic findings - group incidence - non-neoplastic data - all animals

Test article	Control		ED4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	10	60	200	400	0

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STUDY NUMBER: 88233

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;[redacted]=ALL
DEATH=ALL;FIND=P;SUBSET=T

						--- NUMBER-OF-ANIMALS-AFFECTED ---					
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-6-	-1-	-2-	-3-	-4-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	51	51	51	51	51	51	51	51	51	51
OVARY	NUMBER EXAMINED:	0	0	0	0	0	51	51	50	51	51
--INFLAMMATORY CELL FOCI		0	0	0	0	0	0	0	1	0	1
--FIBROSIS		0	0	0	0	0	1	0	0	0	0
--HAEMANGIECTASIS		0	0	0	0	0	0	0	0	1	1
--HAEMORRHAGE		0	0	0	0	0	0	1	0	1	3
--CYSTIC BURSA		0	0	0	0	0	1	2	1	1	4
--CYST		0	0	0	0	0	20	22	11	23	16
--MINERALISATION		0	0	0	0	0	0	1	0	1	0
--ARTERITIS		0	0	0	0	0	1	0	0	0	0
--ABSCESS		0	0	0	0	0	0	1	1	2	3
--ACYCLIC		0	0	0	0	0	6	1	2	1	1
--SEX CORD STROMAL HYPERPLASIA		0	0	0	0	0	0	0	0	1	1
--TUBULOSTROMAL HYPERPLASIA		0	0	0	0	0	0	0	1	0	1
PANCREAS	NUMBER EXAMINED:	51	51	51	51	51	50	51	51	51	51
--CYST		0	1	0	0	0	0	1	1	1	0
--DUCT ECTASIA		0	1	0	0	0	1	2	0	1	1
--INFLAMMATORY CELL FOCI		3	6	2	9	6	13	4	7	10	7
--ARTERITIS		0	0	0	0	0	1	0	0	0	0
--PANCREATITIS		0	1	0	0	0	0	1	0	0	1
--ACINAR CELL HYPERTROPHY		1	0	1	0	4	0	0	1	0	0
--ACINAR CELL ATROPHY		0	0	0	0	0	0	1	0	2	0
--LOBULAR ATROPHY		0	1	0	1	0	2	2	1	0	0
--FATTY ATROPHY		0	1	0	0	0	0	1	0	0	0
--ISLET CELL HYPERPLASIA		2	5	1	2	3	0	0	2	4	2
PARATHYROID	NUMBER EXAMINED:	48	47	46	51	49	48	46	46	49	47
--CYST		2	1	1	2	1	3	0	1	0	3
--ECTOPIC THYMUS		0	0	0	0	0	2	1	2	0	0
--INFLAMMATORY CELL FOCI		0	0	0	0	0	1	0	1	0	1
--HYPERPLASIA - DIFFUSE		0	0	1	0	0	0	0	0	0	0
--HYPERPLASIA - FOCAL		0	0	0	0	0	0	0	0	0	1
PITUITARY	NUMBER EXAMINED:	51	51	50	51	51	51	50	51	51	51
--ACINAL CONGESTION/HAEMORRHAGE		0	0	0	1	0	0	0	0	0	0
--CYST		1	0	0	1	0	4	0	3	1	0
--HYPERPLASIA - FOCAL		0	4	1	2	0	8	7	15	15	16
PREPUT/CLIT GL	NUMBER EXAMINED:	11	15	13	8	11	1	0	0	0	0
--DUCT ECTASIA		7	11	10	6	8	0	0	0	0	0
--ADENITIS		2	2	1	2	0	0	0	0	0	0
--ABSCESS		3	3	6	3	3	0	0	0	0	0
PROSTATE	NUMBER EXAMINED:	51	51	51	51	51	0	0	0	0	0
--INFLAMMATORY CELL FOCI		20	38	34	36	38	0	0	0	0	0
--ARTERITIS		1	3	0	0	0	0	0	0	0	0
--PROSTATITIS		1	2	1	0	1	0	0	0	0	0
RECTUM	NUMBER EXAMINED:	51	51	51	51	51	50	51	51	51	51
--INFLAMMATORY CELL INFILTRATION		0	0	0	1	0	1	0	0	0	0
--PROCTITIS		0	0	0	0	0	1	0	0	1	2
--EROSION/ULCER		0	0	0	1	0	0	0	0	0	0

study number 88/233. Sponsor reference number TCM/1088.
Microscopic findings - group incidence - non-neoplastic data - all animals

Test article	Control		ZD4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	10	60	200	400	0

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STUDY NUMBER: 88233

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;MEMBS=ALL
DEATH=ALL;FIND=P;SUBSET=T

ORGAN AND FINDING DESCRIPTION		SEX: MALE					FEMALE				
		GROUP: -1-	-2-	-3-	-4-	-6-	-1-	-2-	-3-	-4-	-6-
	NUMBER:	51	51	51	51	51	51	51	51	51	51
SALIVARY GLAND	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--ATROPHY		0	1	0	0	0	5	0	2	1	0
--INFLAMMATORY CELL FOCI		36	39	35	34	39	41	40	41	38	37
--SIALODENITIS		0	0	0	0	0	0	0	0	0	1
SCIATIC NERVE	NUMBER EXAMINED:	50	51	51	51	51	51	51	51	51	51
--NEURONOPATHY		25	31	25	28	34	38	39	37	41	34
--INFLAMMATORY CELL FOCI		0	1	0	0	1	1	2	3	4	2
--ARTERITIS		1	1	0	0	0	0	0	0	0	0
SEMINAL VESICLE	NUMBER EXAMINED:	51	51	51	51	51	0	0	0	0	0
--DISTENSION		2	4	3	1	2	0	0	0	0	0
--CONTRACTION		2	1	3	5	3	0	0	0	0	0
--INFLAMMATORY CELL FOCI		4	4	12	9	10	0	0	0	0	0
--VESICULITIS		1	0	0	0	0	0	0	0	0	0
SPINAL CORD	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--SQUAMOUS CYST		0	0	0	0	0	0	1	0	0	1
--INFLAMMATORY CELL FOCI		0	0	0	0	0	1	0	0	1	2
--MINERALISATION		1	0	0	0	0	0	0	0	0	0
--MENINGITIS		0	0	0	0	0	0	0	1	0	0
SKIN + SUBCUTIS	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--CYST		1	0	0	0	1	0	0	0	0	0
--ADNEXAL ATROPHY		2	4	6	1	4	21	23	23	21	17
--ACANTHOSIS		0	0	0	1	0	0	2	6	2	4
SKIN + SUBCUTIS	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--ONCHIA		0	0	0	1	0	0	1	0	0	0
--DERMATITIS		2	4	6	4	4	2	4	2	2	5
--ABSCESS		1	1	1	0	1	0	0	0	1	0
--FAT DEPOT		0	2	0	0	0	1	0	0	0	0
SPLEEN	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--HAEMATURATE LYSIS		0	0	0	0	0	0	0	2	1	2
--CAPSULAR FIBROSIS		0	1	0	0	0	0	0	0	0	0
--HAEMOPOIESIS		7	10	9	10	8	10	16	16	16	16
--HAEMANGIECTASIS		0	2	0	1	1	0	0	0	1	0
--HAEMORRHAGE		0	0	0	1	0	1	0	0	0	0
--ATROPHY		1	3	0	0	0	0	0	0	2	0
--LYMPHOID ATROPHY		0	0	0	0	1	0	0	0	0	0
--LYMPHOID HYPERPLASIA		5	3	1	1	1	9	8	6	9	10
--STROMAL HYPERPLASIA		0	2	0	0	0	0	0	0	0	0
--ANGIOMATOUS HYPERPLASIA		1	0	0	0	0	1	0	0	0	0
STERNUM + MARROW	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--DEFORMITY		1	1	0	0	0	0	0	0	0	0
--FIBRO-OSSEOUS LESION		1	0	1	1	3	44	44	43	44	40
--MARROW HYPERPLASIA		5	3	6	4	5	6	8	9	5	11
--MEGAKARYOCYTE HYPERPLASIA		0	0	0	0	0	0	0	1	0	0
STOMACH	NUMBER EXAMINED:	51	51	51	51	51	50	51	50	50	51
--MINERALISATION		0	0	0	0	0	0	0	0	1	0

[redacted] study number 88/233. Sponsor reference number TCM/1088.
Microscopic findings - group incidence - non-neoplastic data - all animals

Test article	Control		ED4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	10	60	200	400	0

[redacted]

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STUDY NUMBER: 88233

---NUMBER-OF-ANIMALS-AFFECTED

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;MEMBR=ALL
DEATH=ALL;FIXD=F;SUBSET=T

	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-6-	-1-	-2-	-3-	-4-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	51	51	51	51	51	51	51	51	51	51
** FROM PREVIOUS PAGE **											
STOMACH	NUMBER EXAMINED:	51	51	51	51	51	50	51	50	50	51
--FIBROSIS/ADHESION		0	0	0	1	0	0	0	0	0	0
--INFLAMMATORY CELL FOCI		8	5	2	1	2	2	0	0	1	0
--EROSION/ULCER		2	1	2	2	2	1	3	2	7	3
--CYSTIC GLANDS		2	3	1	0	0	1	0	2	0	0
--MUCOSAL HYPERTROPHY		1	0	0	0	0	0	0	0	0	0
--HYPERKERATOSIS		5	2	7	12	7	12	14	6	10	8
--JUNCTIONAL METAPLASIA		2	7	7	1	7	7	8	8	2	5
--SQUAMOUS CELL HYPERPLASIA		3	1	0	6	6	5	7	7	12	8
--MAST CELL HYPERPLASIA		0	0	0	0	0	0	0	0	0	1
--HYPERPLASIA - GLANDULAR		0	0	0	0	0	0	1	1	0	0
TAIL	NUMBER EXAMINED:	9	14	13	13	5	6	5	6	4	2
--FRACTURE/DISLOCATION		9	13	13	13	4	6	4	6	4	2
--DERMATITIS/FOLLICULITIS		0	1	0	0	0	0	0	0	0	0
TESTIS	NUMBER EXAMINED:	51	51	51	51	51	0	0	0	0	0
--HAEMORRHAGE		0	0	0	1	0	0	0	0	0	0
--TUBULAR MINERALISATION		0	0	0	0	1	0	0	0	0	0
--TUBULAR ATROPHY		11	5	6	6	9	0	0	0	0	0
--INTERSTITIAL CELL HYPERPLASIA - FOCAL		1	0	0	1	0	0	0	0	0	0
THORACIC CAVITY	NUMBER EXAMINED:	0	0	2	2	1	1	1	0	0	2
--ABSCESS		0	0	2	1	0	0	1	0	0	1
THYMUS	NUMBER EXAMINED:	47	48	41	49	47	51	50	46	49	49
--CYST		12	10	8	13	11	6	8	7	5	6
--ARTERITIS		2	1	0	0	0	1	0	0	0	0
--ABSCESS		0	0	0	1	0	0	0	0	0	0
--ATROPHY		5	2	8	11	4	5	6	1	5	2
--HAEMANGIECTASIS		0	0	0	0	0	0	0	1	0	2
--LYMPHANGIECTASIS		0	0	0	0	1	0	0	1	0	0
--LYMPHOCYTOLYSIS		1	0	0	0	0	0	0	0	0	0
--EPITHELIAL HYPERPLASIA		0	0	0	0	0	0	0	1	0	0
--LYMPHOID HYPERPLASIA		1	2	1	4	1	15	13	13	20	17
THYROID	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--CYSTIC FOLLICLES		5	4	7	4	4	11	16	5	16	9
--INFLAMMATORY CELL FOCI		2	1	2	2	5	3	4	6	3	4
--ARTERITIS		0	2	0	0	0	0	0	1	1	0
--FOLLICULAR CELL HYPERPLASIA		1	1	0	1	0	3	2	3	15	9
TONGUE	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--CYST		0	0	0	0	0	0	1	0	0	0
--INFLAMMATORY CELL FOCI		1	0	0	0	1	1	1	1	0	0
--ARTERITIS		1	2	0	0	0	0	0	0	2	2
TRACHEA	NUMBER EXAMINED:	51	50	51	51	51	51	51	51	51	51
--HAEMORRHAGE		0	0	0	1	0	0	0	0	0	0
--ABSCESS		0	0	2	0	0	0	0	2	0	0
--SQUAMOUS CELL METAPLASIA		0	1	0	1	0	0	0	0	0	0

[redacted] study number 88/233. Sponsor reference number TCM/1088.
Microscopic findings - group incidence - non-neoplastic data - all animals

Test article	Control		ED4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	10	60	200	400	0

[redacted]

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STUDY NUMBER: 88233

		--- NUMBER-OF-ANIMALS-AFFECTED ---									
TABLE INCLUDES:											
SEX=ALL;GROUP=ALL;WEEKS=ALL	SEX:	--[redacted]----MALE--------					---------FEMALE--------				
DEATH=ALL;FIND=P;SUBSET=T											
	GROUP:	-1-	-2-	-3-	-4-	-6-	-1-	-2-	-3-	-4-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	51	51	51	51	51	51	51	51	51	51
URINARY BLADDER	NUMBER EXAMINED:	51	51	51	51	51	51	51	50	51	51
--HABITUATE LYSIS		2	0	2	0	0	0	0	0	0	1
--DISTENSION		4	3	2	4	2	3	0	0	6	1
--INFLAMMATORY CELL FOCI		25	35	29	28	37	38	43	41	35	41
--ARTERITIS		1	0	0	0	0	0	0	0	0	0
--CYSTITIS		0	1	1	0	1	0	0	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	51	51	51	51	51
--INTUSSUSCEPTION		0	0	0	0	0	0	0	1	0	0
--MINERALISATION		0	0	0	0	0	0	1	0	0	0
--HAEMANGIECTASIS		0	0	0	0	0	1	0	1	3	0
--HYDROMETRA		0	0	0	0	0	4	8	4	4	6
--CYST		0	0	0	0	0	2	0	0	1	0
--CYSTIC GLANDS		0	0	0	0	0	1	1	4	3	7
--ADENOMYOSIS		0	0	0	0	0	0	0	1	1	2
--ARTERITIS		0	0	0	0	0	1	0	0	1	0
--ENDOMETRITIS		0	0	0	0	0	4	4	5	1	6
--METRITIS		0	0	0	0	0	0	1	0	0	1
--ABSCESS		0	0	0	0	0	0	0	0	0	2
--SQUAMOUS METAPLASIA		0	0	0	0	0	2	1	1	5	4
--STROMAL HYPERPLASIA		0	0	0	0	0	0	1	2	0	1
--ENDOMETRIAL HYPERPLASIA		0	0	0	0	0	46	44	43	45	39
VAGINA	NUMBER EXAMINED:	0	0	0	0	0	51	51	51	51	50
--EROSION/ULCER		0	0	0	0	0	0	0	1	0	0
--ARTERITIS		0	0	0	0	0	1	0	1	0	0
VAGINA	NUMBER EXAMINED:	0	0	0	0	0	51	51	51	51	50
--VASCULITIS		0	0	0	0	0	1	0	0	2	0
VULVA	NUMBER EXAMINED:	0	0	0	0	0	0	0	1	0	0
--ACANTHOSIS		0	0	0	0	0	0	0	1	0	0
** END OF LIST **											

Neoplastic:

The spectrum of neoplastic findings in the control groups was consistent with that expected in mice of this age, excepting those in the liver.

In the liver of mice of the 200 mg/kg/day groups of both sexes, there was a clear increase in incidence of both hepatocellular adenomas and carcinomas which correlated with the masses and focal discolorations described at necropsy. In many cases, the tumors were also multiple. The histology of the tumors varied from small well-differentiated masses in which only the lobular architecture had been lost (adenoma) to large atypical and pleomorphic cellular masses with organoid and trabecular architecture, necrosis and metastases (carcinoma). The incidence of liver tumors in other groups was comparable to controls.

Incidence of salient neoplastic findings

		Males					Females				
Finding		1M	2M	3M	4M	6M	1F	2F	3F	4F	6F
Liver	No. examined	51	51	51	51	51	51	51	51	51	51
hepatocellular adenoma	Absent	38	39	32	26	35	48	48	45	42	48
	Present	13	12	19	25	16	3	3	6	9	3
hepatocellular carcinoma	Absent	43	41	40	35	41	51	50	51	47	51
	Present	8	10	11	16	10	0	1	0	4	0
Total tumour bearers		19	20	25	34	23	3	4	6	12	3

[redacted] study number 88/233. Sponsor reference number TCM/1088.
Microscopic findings - group incidence - neoplastic data - all animals

Test article	Control		ZD4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	10	60	200	400	0

[redacted]

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		--- NUMBER-OF-ANIMALS-AFFECTED ---									
TABLE INCLUDES:											
SEX=ALL;GROUP=ALL;WEEKS=ALL	SEX:	---------MALE---------					---------FEMALE---------				
DEATH=ALL;FIND=B,M;SUBSET=ALL											
	GROUP:	-1-	-2-	-3-	-4-	-6-	-1-	-2-	-3-	-4-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	51	51	51	51	51	51	51	51	51	51
** TOP OF LIST **											
ADRENAL	NUMBER EXAMINED:	51	51	51	50	51	51	51	50	51	51
--B-SUBCAPSULAR CELL ADENOMA		0	1	1	1	1	0	0	0	0	0
--B-CORTICAL ADENOMA		5	2	1	1	0	0	0	0	0	0
BONE	NUMBER EXAMINED:	0	1	0	0	1	0	1	0	0	0
--B-OSTEOMA		0	1	0	0	0	0	0	0	0	0
CAECUM	NUMBER EXAMINED:	50	50	51	49	50	49	50	49	49	51
--B-ADENOMA		0	0	0	0	0	0	0	0	1	0
CONNECTIVE TISS	NUMBER EXAMINED:	1	1	1	0	0	0	1	0	1	0
--B-HAEMANGIOMA		1	0	0	0	0	0	0	0	0	0
--M-SARCOMA - NOS		0	0	1	0	0	0	0	0	0	0
DUODENUM	NUMBER EXAMINED:	51	51	51	49	50	49	49	49	50	50
--B-ADENOMA		0	0	0	0	0	0	0	1	0	0
EPIDIDYMIS	NUMBER EXAMINED:	51	51	51	51	51	0	0	0	0	0
--M-HISTIOCYTIC SARCOMA		0	0	1	0	0	0	0	0	0	0
FIBER - MARROW	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--B-HAEMANGIOMA		0	0	0	0	0	0	0	1	0	0
--M-HAEMANGIOSARCOMA		0	0	0	0	0	1	0	0	0	0
HAEM/LYMPH/RETIC	NUMBER EXAMINED:	5	5	5	3	5	20	16	21	18	18
--M-MALIGNANT LYMPHOMA - PLEOMORPHIC		3	5	4	1	1	17	13	19	16	13
HAEM/LYMPH/RETIC	NUMBER EXAMINED:	5	5	5	3	5	20	16	21	18	18
--M-MALIGNANT LYMPHOMA - LYMPHOCYTIC		0	0	1	1	2	2	1	2	2	3
--M-HISTIOCYTIC SARCOMA		1	0	0	0	1	0	2	0	0	1
--M-MALIGNANT LYMPHOMA - NOS		0	0	0	0	0	0	0	0	0	1
--M-MASTOCYTOSARCOMA		1	0	0	0	0	0	0	0	0	0
HARDERIAN GLAND	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--B-ADENOMA		5	7	6	3	8	4	5	0	3	4
--M-ADENOCARCINOMA		0	0	0	2	0	1	1	1	1	0
JEJUNUM	NUMBER EXAMINED:	50	51	51	50	50	50	49	50	49	49
--M-SARCOMA - NOS		0	0	0	0	1	0	0	0	0	0
LIVER	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--B-HAEMANGIOMA		2	1	0	0	3	0	0	0	0	1
--B-HEPATOCELLULAR ADENOMA		13	12	19	25	16	3	3	6	9	3
--M-HEPATOCELLULAR CARCINOMA		8	10	11	16	10	0	1	0	4	0
--M-HISTIOCYTIC SARCOMA		0	0	0	2	0	0	0	0	0	0
--M-HAEMANGIOSARCOMA		1	0	0	0	0	0	0	0	1	0
LUNG	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--B-BRONCHIOLO-ALVEOLAR ADENOMA		9	5	6	13	8	3	3	1	1	3
--M-BRONCHIOLO-ALVEOLAR CARCINOMA		0	4	1	1	2	0	0	1	0	0
MAMMARY GLAND	NUMBER EXAMINED:	0	0	0	0	0	50	50	51	51	51
--M-ADENOCARCINOMA		0	0	0	0	0	0	2	3	2	3