TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
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
MESENTERIC LN	NUMBER EXAMINED:	50	51	51	51	51	51	51	50	50	49
--B-HAEMANGIOMA		0	0	0	0	1	0	1	0	0	0
MUSCLE	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--M-RHABDOMYOSARCOMA		0	0	0	0	0	0	1	0	0	0
OVARY	NUMBER EXAMINED:	0	0	0	0	0	51	51	50	51	51
--B-TUBULOSTROMAL ADENOMA		0	0	0	0	0	0	0	1	0	0
--B-HAEMANGIOMA		0	0	0	0	0	0	0	0	0	1
--B-CYSTADENOMA		0	0	0	0	0	0	0	1	0	0
PANCREAS	NUMBER EXAMINED:	51	51	51	51	51	50	51	51	51	51
--B-ISLET CELL ADENOMA		0	0	1	0	0	0	0	0	0	1
--M-ISLET CELL CARCINOMA		0	1	0	0	0	0	0	0	0	0
PITUITARY	NUMBER EXAMINED:	51	51	50	51	51	51	50	51	51	51
--B-ADENOMA		0	0	0	0	1	7	4	8	8	3
PREPUT/CLIT GL	NUMBER EXAMINED:	11	15	13	8	11	1	0	0	0	0
--B-ADENOMA		1	0	0	0	0	0	0	0	0	0
--M-SQUAMOUS CELL CARCINOMA		1	0	0	0	0	0	0	0	0	0
SEMINAL VESICLE	NUMBER EXAMINED:	51	51	51	51	51	0	0	0	0	0
--B-ADENOMA		0	0	0	1	0	0	0	0	0	0
SKIN + SUBCUTIS	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--B-SEBACEOUS CELL ADENOMA		0	0	0	0	1	0	0	0	0	0
--B-BENIGN HISTIOCYTOMA		0	0	0	1	0	0	0	0	0	0
--B-BENIGN MAST CELL TUMOUR		0	0	0	0	0	1	0	0	0	0
--M-FIBROSARCOMA		0	0	0	0	0	1	2	1	0	1
--M-SQUAMOUS CELL CARCINOMA		1	0	0	0	0	0	1	0	0	0
--M-MALIGNANT FIBROUS HISTIOCYTOMA		0	0	0	0	0	0	0	1	0	0
SPLEEN	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--B-HAEMANGIOMA		0	0	2	0	0	0	0	0	0	0
--M-HAEMANGIOSARCOMA		0	0	0	0	1	2	0	0	0	0
STOMACH	NUMBER EXAMINED:	51	51	51	51	51	50	51	50	50	51
--B-SQUAMOUS CELL PAPILLOMA		0	1	0	0	0	0	0	0	0	0
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	0	0	0	0	1	0
--M-ADENOCARCINOMA		0	0	0	0	1	0	0	0	0	0
TESTIS	NUMBER EXAMINED:	51	51	51	51	51	0	0	0	0	0
--B-INTERSTITIAL CELL ADENOMA		0	0	1	0	0	0	0	0	0	0
--B-HISTIOCYTOMA		0	1	0	0	0	0	0	0	0	0
THYROID	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--B-FOLLICULAR CELL ADENOMA		1	0	1	1	0	2	0	2	3	2
--M-FOLLICULAR CELL CARCINOMA		0	0	0	1	0	0	0	0	0	0
TONGUE	NUMBER EXAMINED:	51	51	51	51	51	51	51	51	51	51
--M-SQUAMOUS CELL CARCINOMA		0	0	1	1	0	0	0	0	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	51	51	51	51	51
--B-STROMAL POLYP		0	0	0	0	0	1	2	2	4	1
--B-ADENOMA		0	0	0	0	0	0	0	1	0	0
--B-HAEMANGIOMA		0	0	0	0	0	0	2	0	1	1
--B-LEIOMYOMA		0	0	0	0	0	1	1	0	0	1
--M-HISTIOCYTIC SARCOMA		0	0	0	0	0	0	0	1	2	1
--M-ADENOCARCINOMA		0	0	0	0	0	0	2	0	0	0
--M-SARCOMA - NOS		0	0	0	0	0	1	1	0	0	0

** END OF LIST **

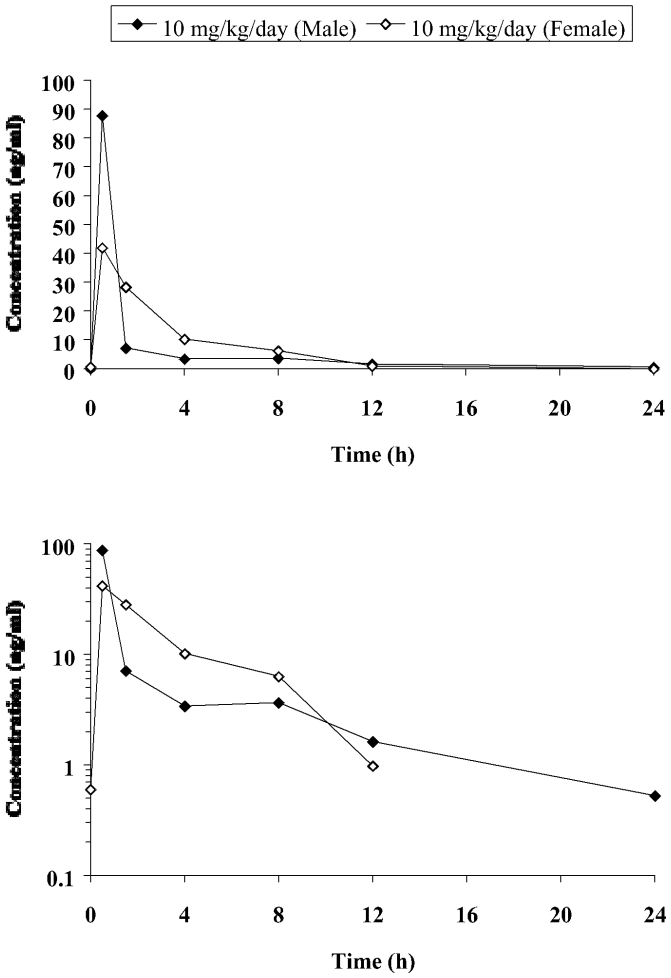
Toxicokinetics:

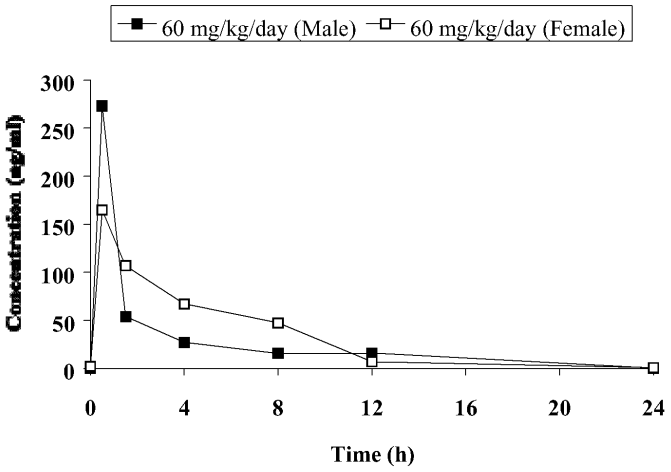
Maximum plasma concentrations were observed at 0.5-1.5 h post-dose in male and female mice. After reaching peak concentrations, plasma concentrations declined in a multiphase manner with an apparent terminal half-life of approximately 2 to 7 h. The individual plasma concentrations of ZD4522 varied greatly at each sampling time-point (coefficient of variation range 5-173%), indicating high inter-animal variability.

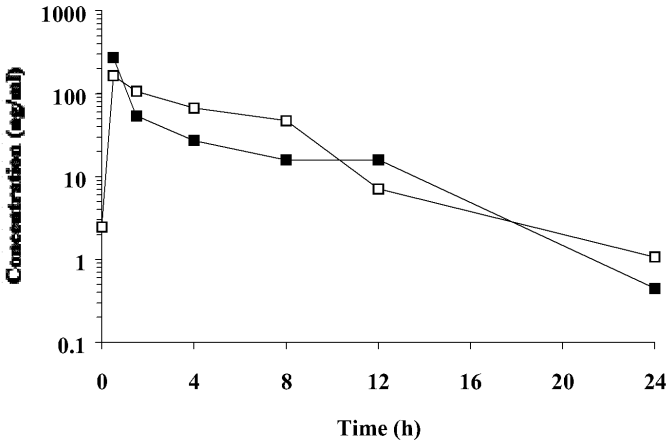
Plasma concentrations of ZD4522 increased with increasing dose. Overall, the increase in extent of systemic exposure to ZD4522 was slightly greater than dose-proportional. Therefore, the pharmacokinetics of ZD4522 appeared to be non-linear with respect to dose over the dose range 10 to 200 mg/kg/day.

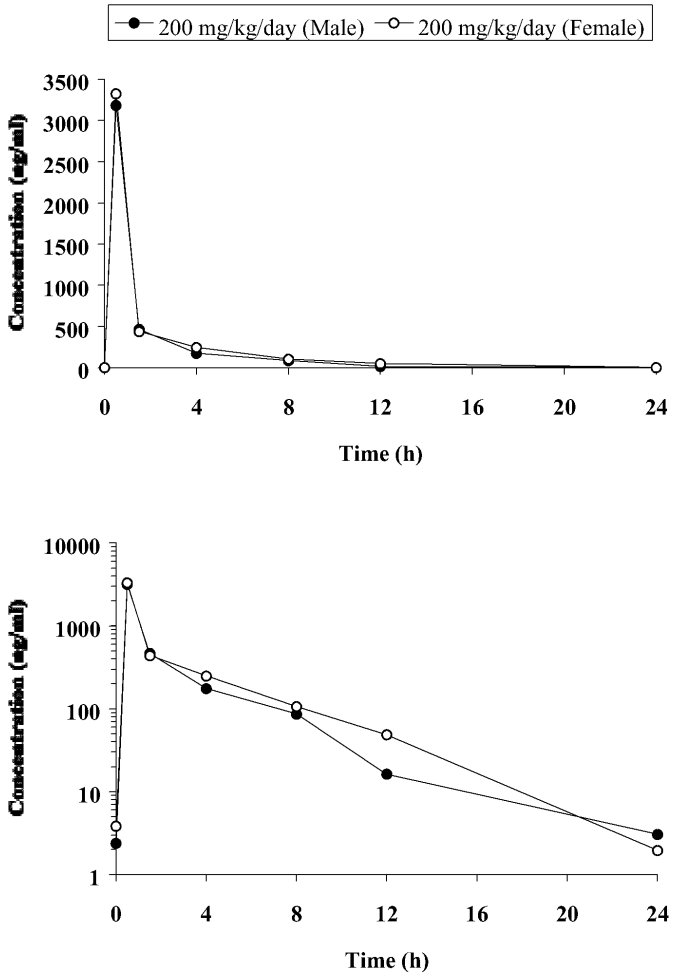
The extent of systemic exposure of male mice to ZD4522 was similar to that of female mice indicating no apparent sex-related difference in systemic exposure.

	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


10 mg/kg/day (Male)
10 mg/kg/day (Female)
Concentration (ng/ml)
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Time (h)
Concentration (ng/ml)
100
10
1
0.1
0
4
8
12
16
20
24
Time (h)


60 mg/kg/day (Male)
60 mg/kg/day (Female)
Concentration (ng/ml)
300
250
200
150
100
50
0
0
4
8
12
16
20
24
Time (h)


Concentration (ng/ml)
1000
100
10
1
0.1
0
4
8
12
16
20
24
Time (h)


200 mg/kg/day (Male)
200 mg/kg/day (Female)
Concentration (ng/ml)
3500
3000
2500
2000
1500
1000
500
0
0
4
8
12
16
20
24
Time (h)
Concentration (ng/ml)
10000
1000
100
10
1
0
4
8
12
16
20
24
Time (h)

Summary of individual study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model:

The test species appears to be appropriate, since mice is a common used species for carcinogenicity study in other statins. The test doses appeared to be adequate. The originally proposed high dose of 400 mg/kg/day was poorly tolerated. Therefore, 200 mg/kg appeared to be a reasonable high dose.

Evaluation of tumor findings:

Oral dosing for 2 years at 60 and 200 mg/kg/day resulted in a number of non-neoplastic changes in the liver, stomach, thyroid and kidney. A no-effect dose for these changes was established at 10 mg/kg/day.

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, and 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

Study title: 104 Week Oral (Gavage Administration) Oncogenicity Study in the Rats

Key study findings: Crestor tested positive in females in the 2-year rat carcinogenicity study. Higher incidence of pancreatic islet cell adenoma/carcinoma were observed in females at the high dose of 80 mg/kg.

Study number: (b) (4) Study Number 88/232. Sponsor Reference Number TCP/2852
Volume #, and page #: Electronic submission, file name: tcr2852.pdf
Conducting laboratory and location: (b) (4)
(b) (4)
Date of study initiation: May 1998
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity:

(b) (4) lot number	Sponsors Analytical Reference Number	Quantity supplied (g)	Purity (%)	Date of receipt at (b) (4)
2	00518I98	(b) (4)	96.86	1 April 1998
4	00518I98		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 rats was initiated in April, 1998. Six eCAC meetings and a number of T-con had been held before the final report was submitted and no concurrence had been reached.

Study Type: 2-year bioassay
Species/strain: Sprague Dawley rats of the Crl:(IGS)CD BR strain from (b) (4)

Number/sex/group:

Group number	Group description	Dose level (mg/kg/day)#	Animals/group Male	Female
1	Control 1	0	50	50
2	Low	2	50	50
3	Intermediate I	20	50	50
4	Intermediate II	60	50	50
5	High	80	50	50
6	Control 2	0	50	50

a correction factor was used to convert salt to base

Age and weight at start of study: aged 6 weeks old and weighed 147.7 to 227.8 g (males) and 127.3 to 181.8 g (females).

Animal housing: rats 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, 2, 20, 60, 80, and 0 mg/kg

Basis of dose selection:

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.

Further dose range finding study was recommended by FDA. The first study with a single dose level of 160 mg/kg failed to established MTD. In the second study with doses of 80, 160, 240, and 320 mg/kg, significant number of mortality occurred at ≥ 160 mg/kg. 2/24 males died or were killed in extremis at 80 mg/kg, indicating that 80 mg/kg was probably an acceptable high dose for the 2-year study, though the exposure at 80 mg/kg in this study was generally 2 times the values in the 2-year study.

Restriction paradigm for dietary restriction studies:
Rats had access *ad libitum* to SQC Rat and Mouse Maintenance Diet No 1, Expanded (b) (4) 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: no.

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

Statistical methods:
Body weight gains and food consumption variables 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. In all cases, this showed no evidence of heterogeneity ($p\geq0.01$).

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 105).

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.

Male and female data were analyzed separately.

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 (Peto R et al, 1980), 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 104 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 at 6, 12, 18 and 24 months in 20 animal/sex in both control groups and the high dose group.

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

Clinical chemistry: at sacrifice. AST, ALT, ALP, Na, K, Ca, P, Cl, total protein, albumin, globulin, A/G, total cholesterol, glucose, urea, total bilirubin, creatinine were examined.

Organ weights: at sacrifice.

Gross pathology: at sacrifice.

Histopathology: all tissues listed in the table.

(b) (4) study number 88/232. Sponsor reference number TCR/2852.
Tissues taken for histopathological evaluation

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

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

c see clinical pathology section d preserved with the head *in situ* f female only

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

Toxicokinetics: on day 1, and during weeks 5 and 53 (pre-dose and at 0.5, 1.5, 4, 8, 12 and 24 hours after dosing).

Results:

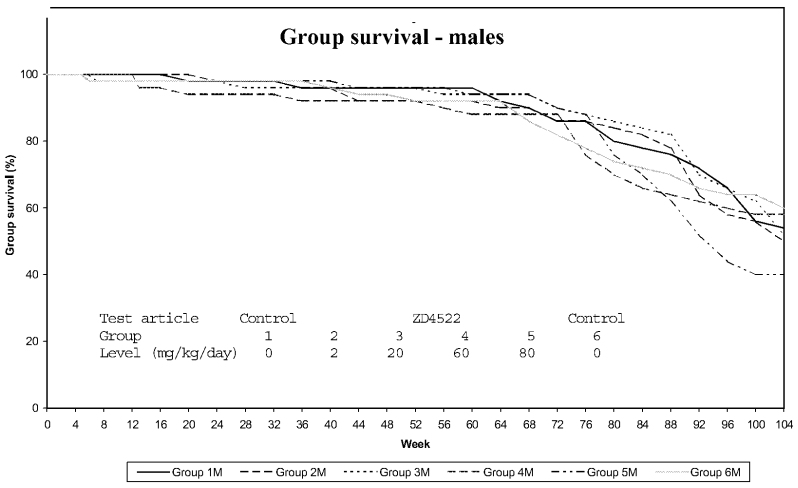
Mortality:

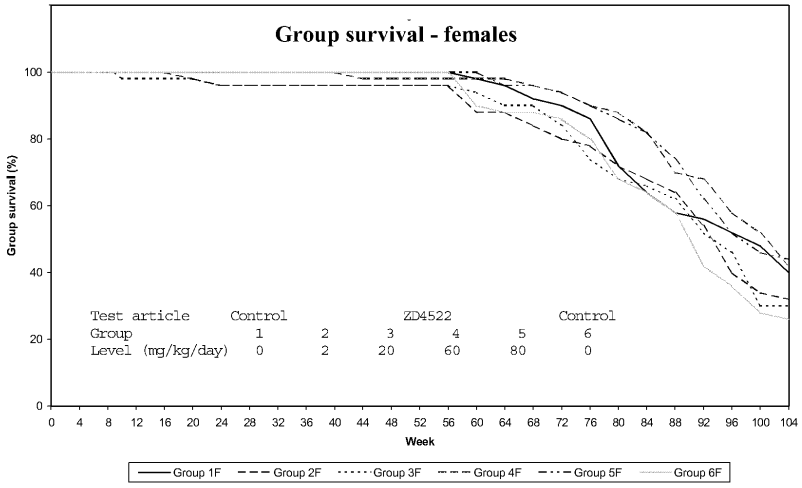
Generally the mortality was comparable between controls and treated groups during the 52 week treatment. There was no significant dose response in mortality (P> 0.05).

The majority of the deaths were due to tumors. The most common cause of mortality in females was mammary, pituitary, and skin/subcutis tumors and in males skin/subcutis, pituitary, and haemolymphoreticular tumors.

Survival at terminal kill

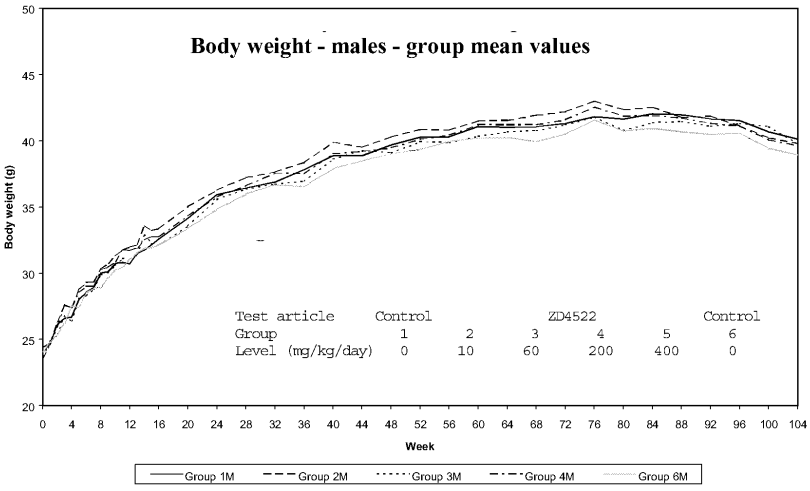
Group number	Dose levels (mg/kg/day)	Number of Animals/sex	Survival (%) Male	Female
1	0	50	27 (54)	20 (40)
2	2	50	25 (50)	16 (32)
3	20	50	26 (52)	15 (30)
4	60	50	29 (58)	21 (42)
5	80	50	20 (40)	22 (44)
6	0	50	30 (60)	13 (26)



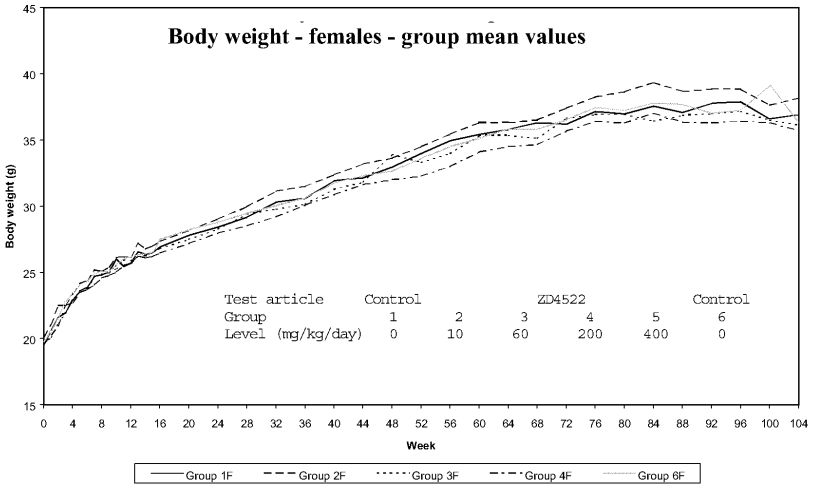


Clinical signs: No treatment related clinical signs were noted at ≤ 200 mg/kg/day.

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

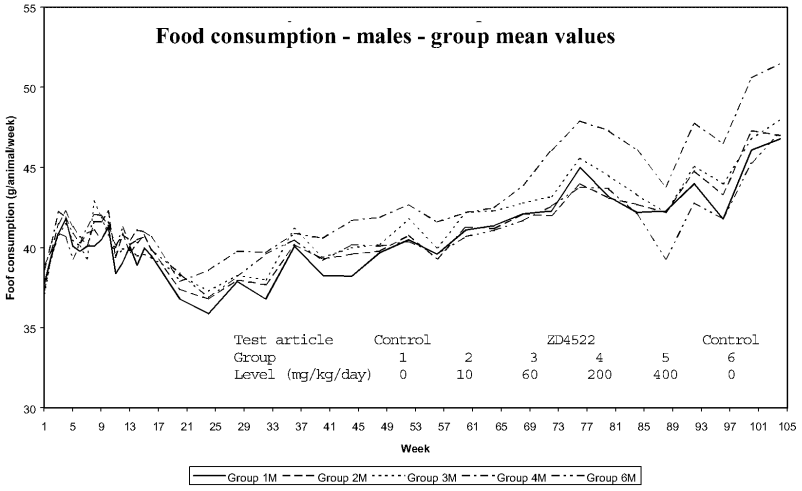


All Group 5 terminated beginning of week 3; data not presented

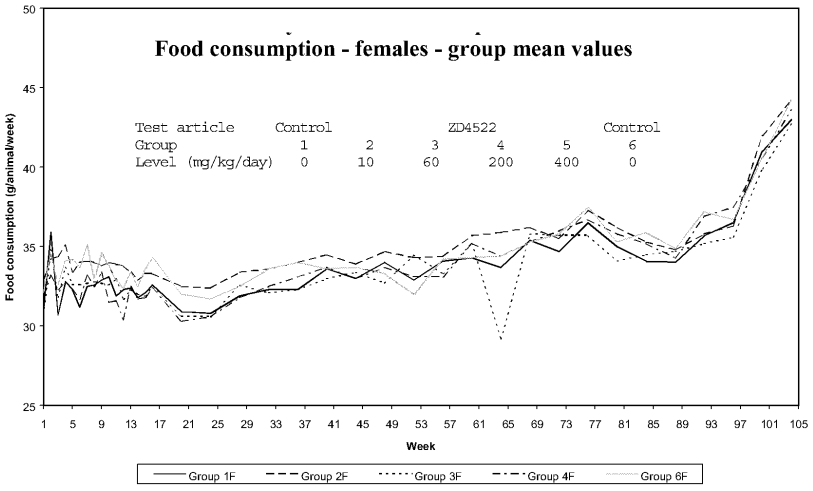


All Group 5 terminated beginning of week 3; data not presented

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

Ophthalmoscopy: no treatment related changes.

Hematology: no treatment related changes in red and white blood cell counts.

Clinical chemistry: no treatment related changes.

Organ weights: no data provided.

Gross pathology:

Treatment-related increase in the incidence of macroscopic findings were observed in the stomach and liver.

In the stomach there was an increased incidence of thickening (primarily involving the cardia) and a minor increase in the incidence of raised foci in the forestomach of males and females dosed 80 mg/kg/day. The incidence of thick forestomach was also increased in females dosed at 60 mg/kg/day.

In the liver, an increased incidence in pale foci and pallor was recorded in males dosed at 80 mg/kg/day. The incidence of pale foci was also increased in males dosed at 60 mg/kg/day. These macroscopic observations generally correlated with findings seen microscopically. Macroscopic findings in the treated females were generally comparable with the controls.

Histopathology:

Non-neoplastic:

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

There were dose-related findings in the liver and stomach.

In the liver, the main treatment-related change was an increase in the level of focal and diffuse hepatocellular alterations in males and females dosed at 20, 60 and 80 mg/kg/day. The predominant liver changes were an increase in basophilic and eosinophilic foci, together with a minor increase in focal and diffuse hepatocyte vacuolation. Basophilic foci were characterized by variable-sized foci of hepatocytes with either diffuse or focal areas of basophilic-staining cytoplasm. Similarly, eosinophilic foci comprised groups of hepatocytes with pale eosinophilic-staining cytoplasm and varying levels of coarse vacuolation, characteristic of glycogen. Diffuse hepatocyte basophilia was also recorded for some males dosed at 20, 60 and 80 mg/kg/day and minor hepatocyte hypertrophy in males dosed at 80 mg/kg/day and in females dosed at 60 and 80 mg/kg/day. There was also a decrease in the incidence of higher grade (slight to moderate) bile duct proliferation in the liver of males dosed at 60 and 80 mg/kg/day and females dosed at 80 mg/kg/day. Findings in the liver of animals dosed at 2 mg/kg/day were comparable with the controls and the overall level of the liver changes was generally less in the treated females than in the males.

In the forestomach, there was an increase in the level of hyperkeratosis, squamous cell hyperplasia and erosion/ulceration, together with a minor inflammatory cell infiltration of the submucosa, in males and females dosed at 60 and 80 mg/kg/day and in males dosed at 20 mg/kg/day. Findings in the forestomach of males dosed at 2 mg/kg/day and females dosed at 2 and 20 mg/kg/day were comparable with the controls.

(b) (4) study number 88/232. Sponsor reference number TCR/2852.
Incidence of salient microscopic findings

Tissue and finding	Group: / Level: (mg/kg/day)	1M 0	2M 2	3M 20	4M 60	5M 80	6M 0	1F 0	2F 2	3F 20	4F 60	5F 80	6F 0
Liver	No. Exam:	50	50	50	50	50	50	50	50	50	50	50	50
hepatocyte hypertrophy	Grade -	50	49	49	49	44	50	49	49	50	42	42	49
	1	0	0	1	1	3	0	1	1	0	6	4	1
	2	0	1	0	0	3	0	0	0	0	2	4	0
hepatocyte basophilia	Grade -	50	48	43	38	30	47	50	48	47	47	47	48
	1	0	0	6	6	10	0	0	2	0	0	0	0
	2	0	1	1	5	8	2	0	0	1	2	3	1
	3	0	0	0	1	0	1	0	0	2	0	0	1
	4	0	1	0	0	0	0	0	0	0	1	0	0
	5	0	0	0	0	2	0	0	0	0	0	0	0
basophilic focus	Grade -	34	31	10	6	5	34	16	21	9	1	1	16
	1	14	19	8	10	7	15	18	18	13	4	5	21
	2	2	0	13	14	10	1	10	9	15	9	11	11
	3	0	0	14	12	13	0	6	2	10	16	13	2
	4	0	0	5	6	14	0	0	0	3	18	16	0
	5	0	0	0	2	1	0	0	0	0	2	4	0
eosinophilic focus	Grade -	32	34	19	10	13	38	43	43	46	31	33	41
	1	16	15	18	11	14	10	6	7	3	14	14	8
	2	2	1	10	23	11	2	1	0	1	2	2	1
	3	0	0	3	6	8	0	0	0	0	2	0	0
	4	0	0	0	0	4	0	0	0	0	1	1	0
bile duct hyperplasia	Grade -	18	10	15	27	31	24	29	37	40	39	38	29
	1	22	28	28	22	18	16	17	7	7	8	12	16
	2	7	10	7	1	1	8	3	6	2	3	0	5
	3	3	2	0	0	0	2	1	0	1	0	0	0
Stomach	No. Exam:	50	50	50	50	50	50	50	50	50	50	50	50
hyperkeratosis	Grade -	47	48	40	32	15	48	44	45	45	27	25	44
	1	3	1	5	8	12	1	4	3	5	12	8	4
	2	0	1	5	10	13	1	2	1	0	8	9	1
	3	0	0	0	0	10	0	0	1	0	3	8	1
squamous cell hyperplasia	Grade -	49	48	38	30	17	49	48	48	49	32	24	47
	1	0	0	6	9	9	0	0	1	0	7	14	1
	2	0	2	3	9	12	0	2	1	0	8	7	1
	3	1	0	3	2	11	1	0	0	1	2	4	1
	4	0	0	0	0	1	0	0	0	0	1	1	0
erosion/ulcer – forestomach	Grade -	50	49	47	44	39	50	49	50	49	45	45	48
	1	0	0	0	3	6	0	0	0	0	3	1	0
	2	0	0	1	2	1	0	0	0	1	1	2	0
	3	0	1	1	1	3	0	1	0	0	0	2	2
	4	0	0	1	0	0	0	0	0	0	1	0	0
	5	0	0	0	0	1	0	0	0	0	0	0	0
inflammatory cell infiltration – forestomach													
	1	0	2	7	9	18	1	1	0	1	8	11	2
	2	0	0	0	1	3	0	2	1	0	0	0	0
	3	0	0	0	0	1	0	0	0	0	0	0	0
Uterus	No. Exam:	-	-	-	-	-	-	50	50	50	50	50	50
B-polyp		-	-	-	-	-	-	5	6	0	8	12	6

Key: Grade "-" = finding not present, 1 = minimal, 2 = slight, 3 = moderate, 4 = moderately severe, 5 = severe

(b) (4) study number 88/232. Sponsor study number TCR/2852.
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	2	20	60	80	0

(b) (4)

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STUDY NUMBER: 88232

							--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---					
TABLE INCLUDES:												
SEX=ALL;GROUP=ALL;WEEKS=ALL	SEX:	----------MALE----------					----------FEMALE----------					
DEATH=ALL;FIND=P;SUBSET=T												
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
** TOP OF LIST **													
ABDOMINAL CAVITY	NUMBER EXAMINED:	0	0	0	1	0	2	0	2	1	1	0	2
--FAT NECROSIS		0	0	0	0	0	0	0	1	0	0	0	0
ADRENAL	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--ADRENAL CONGESTION/HAEMORRHAGE		1	0	1	2	1	3	1	0	0	0	0	4
--CONGESTION		0	0	0	0	0	1	0	1	0	1	0	1
--INFLAMMATORY CELL FOCI		0	0	0	1	0	1	0	0	0	0	0	0
--CORTICOMEDULLARY PIGMENT		0	1	2	2	0	2	2	3	1	1	4	1
--HAEMOPOIESIS		0	0	0	0	1	0	1	1	1	1	0	2
--MINERALISATION		0	1	0	0	0	0	0	1	0	0	0	0
--CORTICAL VACUOLATION		0	0	0	0	0	0	1	0	0	0	0	0
--HAEMATOCYST		0	0	0	0	0	0	1	4	3	3	5	3
--HAEMANGIECTASIS		4	9	6	4	5	5	39	44	41	43	45	44
--FIBROSIS		0	0	0	1	0	1	1	0	0	0	0	0
--CORTICAL NECROSIS		1	1	0	1	0	0	0	0	0	0	0	0
--CORTICAL ATROPHY		0	0	0	0	0	0	1	1	0	3	0	0
--CORTICAL HYPERTROPHY		3	1	3	0	4	1	1	2	3	3	2	2
--CORTICAL ALTERED CELL FOCI		33	26	28	31	32	28	30	25	36	25	24	24
--MEDULLARY HYPERPLASIA - FOCAL		7	13	13	8	9	14	11	2	6	5	8	10
--SUBCAPSULAR CELL HYPERPLASIA		0	0	0	0	0	0	0	1	0	0	0	0
BLOOD	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	49	50	50	50
--POLYCHROMASIA		0	0	0	0	0	0	0	0	0	0	1	0
BONE	NUMBER EXAMINED:	1	0	0	1	1	0	0	0	0	0	0	0
--EXOSTOSIS		0	0	0	0	1	0	0	0	0	0	0	0
BRAIN	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--COMPRESSION		10	9	11	8	4	5	21	20	15	16	18	19
--HAEMORRHAGE		1	0	1	1	0	0	3	1	2	2	0	4
--VACUOLATION		1	0	0	0	0	0	0	0	0	0	0	0
--ENCEPHALOPATHY		0	1	0	0	0	0	0	0	0	0	1	0
--ENCEPHALITIS		0	0	0	1	0	0	0	0	0	0	0	0
--INFARCT		0	0	0	0	0	0	0	0	0	0	0	1
CAECUM	NUMBER EXAMINED:	44	43	44	42	45	45	48	46	50	46	47	45
--BARBITURATE LYSIS		1	1	0	0	1	1	1	1	3	0	3	1
--ARTERITIS		2	1	0	0	0	0	1	0	1	1	0	1
--GRANULOMA		0	2	0	0	0	0	0	0	0	0	0	0
--CAECITIS		0	1	0	0	2	1	0	1	0	0	0	1
--EROSION/ULCER		0	1	0	0	0	0	0	1	0	0	0	0
--LYMPHOID HYPERPLASIA		0	0	0	2	2	0	2	0	0	0	0	0
COLON	NUMBER EXAMINED:	48	49	50	48	48	48	50	48	50	48	49	48
--LYMPHOID HYPERPLASIA		2	4	2	3	0	2	6	4	1	6	6	2
--NEMATODE		0	1	0	0	0	3	0	3	0	0	0	1
--DISTENSION		1	0	1	1	4	0	0	0	1	0	0	0
--BARBITURATE LYSIS		0	0	0	0	0	0	1	0	0	0	0	1
CONNECTIVE TISS	NUMBER EXAMINED:	2	1	0	0	1	0	1	0	0	0	1	0
--BARBITURATE LYSIS		0	0	0	0	0	0	1	0	0	0	0	0
--FAT DEPOT		1	0	0	0	0	0	0	0	0	0	0	0

Test article	Control	ZD4522				Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	2	20	60	80	0

(b) (4)

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STUDY NUMBER: 88232

		--- 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-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
DUODENUM	NUMBER EXAMINED:	50	50	46	46	47	49	50	49	50	50	49	47
--ADRENAL CONGESTION/HAEMORRHAGE		1	0	0	0	1	0	0	0	0	1	0	0
--EROSION/ULCER		0	0	0	0	0	0	0	0	0	1	0	1
--HYPERPLASIA - AVILLOUS		0	0	0	0	0	0	0	0	1	0	0	0
EAR	NUMBER EXAMINED:	1	2	1	0	1	0	3	1	1	1	1	2
--CHONDROPATHY/CHONDRITIS		1	0	0	0	0	0	2	1	1	1	1	0
--DERMATITIS		0	0	1	0	1	0	0	0	0	0	0	0
--ABSCESS		0	0	0	0	0	0	0	0	0	0	0	1
EPIDIDYMIS	NUMBER EXAMINED:	50	50	50	50	50	50	0	0	0	0	0	0
--BARBITURATE LYSIS		0	0	0	1	0	0	0	0	0	0	0	0
--TUBULAR VACUOLATION		2	0	0	0	0	0	0	0	0	0	0	0
--SPERMATOCOELE		2	0	0	0	0	0	0	0	0	0	0	0
--OLIGOSPERMIA		5	8	5	5	7	4	0	0	0	0	0	0
--CELLULAR DEBRIS		0	1	1	1	0	0	0	0	0	0	0	0
--ARTERITIS		1	0	0	0	0	0	0	0	0	0	0	0
--EPIDIDYMITIS		0	1	0	0	0	0	0	0	0	0	0	0
--SPERM GRANULOMA		0	0	0	0	0	1	0	0	0	0	0	0
EYE	NUMBER EXAMINED:	49	49	48	47	47	50	50	49	50	50	49	47
--LENTICULAR DEGENERATION		0	1	0	0	0	1	0	0	0	0	1	0
--RETINAL ATROPHY		0	0	0	0	0	0	1	0	0	0	1	1
--BLEPHARITIS		0	0	0	0	0	0	0	0	0	0	0	1
--KERATITIS		0	0	0	1	0	0	0	0	0	0	0	0
--PHTHISIS BULBI		0	0	0	0	0	0	1	0	0	0	2	0
FEMUR + MARROW	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--MARROW FAT		17	11	15	11	10	11	5	7	7	9	6	8
--HAEMANGIECTASIS		0	1	1	0	1	0	0	0	0	0	0	0
--ARTHROPATHY		2	1	1	0	0	0	0	1	0	0	0	1
--FIBROSIS		0	0	0	1	1	0	0	0	0	0	0	0
--CHONDROPATHY		0	1	0	0	0	0	0	0	0	0	0	0
--ARTHRITIS		0	1	0	0	0	0	0	0	0	0	0	0
--MARROW HYPERPLASIA		4	13	7	9	7	11	13	10	22	10	15	12
--ENOSTOSIS		0	0	0	0	0	0	1	0	0	0	0	1
FOOT/LEG	NUMBER EXAMINED:	6	8	6	7	8	8	5	5	6	2	4	2
--CYST		0	0	0	0	0	0	0	1	0	0	0	0
--PODODERMATITIS		1	2	1	4	5	5	4	3	5	0	4	1
--DERMATITIS		0	0	1	0	0	0	0	0	0	1	0	1
--CELLULITIS		0	0	2	2	1	2	0	1	0	0	0	0
--FIBROSIS		0	0	0	0	1	0	0	0	0	0	1	0
--ARTHRITIS		3	4	3	3	2	3	0	0	1	1	0	0
--PARONYCHIA		0	0	1	0	0	0	0	0	0	0	0	0
--ABSCESS		1	0	0	0	0	0	0	0	0	0	0	0
--LYMPHOCYTIC DERMATITIS		0	1	0	0	0	0	0	0	0	0	0	0
HARDERIAN GLAND	NUMBER EXAMINED:	49	49	49	50	50	50	50	50	50	50	50	50
--ADRENAL CONGESTION/HAEMORRHAGE		1	2	1	0	1	2	0	0	0	1	2	0
--INFLAMMATORY CELL FOCI/ADENITIS		28	27	29	28	24	29	21	23	18	22	29	27
--PIGMENT		4	5	6	8	4	5	1	1	1	3	1	0
--HYPERPLASIA		8	11	9	10	11	10	7	2	4	4	6	9

(b) (4) study number 88/232. Sponsor study number TCR/2852.
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	2	20	60	80	0

(b) (4)

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STUDY NUMBER: 88232

						--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---						
TABLE INCLUDES:												
SEX=ALL;GROUP=ALL;WEEKS=ALL	SEX:	----------MALE----------					----------FEMALE----------					
DEATH=ALL;FIND=P;SUBSET=T												
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
HEART	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--DEGENERATION/FIBROSIS		26	32	23	25	32	27	15	13	18	17	12	15
--CHAMBER DISTENSION		1	0	1	2	1	2	0	0	0	2	0	0
--HAEMORRHAGE		1	1	0	0	0	0	0	0	0	0	0	0
--MINERALISATION		0	0	0	0	0	0	0	0	0	0	0	1
--ARTERITIS		0	0	1	0	0	1	0	0	0	0	0	0
--EMBOLUS		0	0	0	1	0	0	0	0	0	0	0	0
--CARDIOMYOPATHY		0	0	0	0	0	0	0	0	0	0	0	1
--ATRIAL THROMBUS		0	0	0	0	1	0	0	0	1	0	0	0
--VALVULAR ENDOCARDITIS		0	0	0	0	0	0	0	0	1	0	0	0
--CARTILAGINOUS METAPLASIA		0	0	2	1	0	2	0	0	1	1	1	0
ILEUM	NUMBER EXAMINED:	46	49	46	47	47	47	49	46	50	49	48	49
--BARBITURATE LYSIS		0	0	0	0	2	0	0	1	1	0	0	0
--NEMATODE		0	0	0	0	0	0	0	0	0	0	0	1
--DISTENSION		1	0	1	3	3	0	0	0	1	0	1	0
--LYMPHOID HYPERPLASIA		1	0	0	1	0	0	0	0	1	2	1	0
JEJUNUM	NUMBER EXAMINED:	47	48	44	48	47	47	50	49	49	49	47	48
--AGONAL CONGESTION/HAEMORRHAGE		0	0	0	0	0	0	0	0	0	1	0	0
--BARBITURATE LYSIS		0	0	0	1	0	0	0	0	0	0	0	1
--DISTENSION		1	3	0	4	3	0	1	1	0	1	1	0
--ENTERITIS		0	0	0	0	1	0	0	0	0	0	0	0
--FIBROSIS		0	0	0	0	0	0	0	0	1	0	0	0
--LYMPHOID HYPERPLASIA		2	0	1	0	1	1	0	0	0	1	0	0
KIDNEY	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--AGONAL CONGESTION/HAEMORRHAGE		3	2	2	1	2	2	0	0	1	0	0	0
--INFLAMMATORY CELL FOCI		2	1	0	3	1	2	0	0	3	0	0	1
--PIGMENT		1	1	3	1	1	2	11	9	12	5	12	10
--TUBULAR LYSIS		0	0	0	0	0	0	0	1	0	0	0	0
--CORTICAL MINERALISATION		3	0	1	2	2	2	2	0	1	0	0	2
--CORTICOMEDULLARY MINERALISATION		0	0	0	0	1	0	1	2	0	0	2	1
--PELVIC MINERALISATION		11	12	14	4	6	8	42	37	40	32	29	44
--PAPILLARY MINERALISATION		4	2	0	3	3	3	8	10	6	6	6	7
--HYDRONEPHROSIS		2	4	5	2	3	2	4	7	8	1	8	6
--CYST		1	4	3	3	1	2	1	0	1	1	1	0
--CYSTIC TUBULES		0	0	0	0	0	1	0	0	0	0	0	1
--HYALINE DROPLETS		4	2	3	2	4	3	2	1	1	3	3	1
--TUBULAR VACUOLATION		0	0	0	0	0	0	0	1	0	0	0	0
--CASTS		2	4	1	4	6	4	2	5	4	6	4	1
--ARTERITIS		1	0	0	0	0	1	0	0	0	0	0	0
--SEPTIC EMBOLUS		0	0	0	1	0	0	0	0	0	0	0	0
--INTERSTITIAL NEPHRITIS		1	1	0	1	0	0	0	1	0	0	0	1
--PYELONEPHRITIS		0	0	0	0	0	0	0	0	0	1	0	1
--PYELITIS		16	5	11	12	11	5	10	7	8	8	10	6
--PAPILLITIS		0	1	0	0	1	0	0	0	0	0	0	1
--CHRONIC NEPHROPATHY		34	37	32	35	21	31	31	20	28	25	28	23
--TUBULAR NEPHROPATHY		0	0	0	0	1	0	0	0	0	0	0	0
--CHRONIC CONTRACTED KIDNEY		0	0	0	0	0	1	0	0	0	0	0	0
--TUBULAR DILATION		0	0	1	1	2	2	2	0	1	0	0	0
--CORTICAL SCAR		2	0	3	3	1	3	0	0	1	0	1	0

** CONTINUED ON NEXT PAGE **

Test article	Control	ZD4522				Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	2	20	60	80	0

(b) (4)

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STUDY NUMBER: 88232

		--- 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-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
** FROM PREVIOUS PAGE **													
KIDNEY	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--PAPILLARY NECROSIS		0	0	0	0	1	1	0	0	0	0	0	0
--INFARCT		0	0	0	1	0	0	0	0	0	0	0	0
--OSSEOUS METAPLASIA		0	0	0	0	0	0	0	0	1	0	0	0
--TUBULAR CELL HYPERPLASIA		0	3	4	3	2	2	0	1	2	0	0	0
--POLYPOID UROTHELIAL HYPERPLASIA		4	4	7	5	1	2	16	7	6	8	8	14
LACRIMAL GLAND	NUMBER EXAMINED:	0	0	0	0	1	0	1	3	0	0	0	2
--HARDERIAN GLAND ALTERATION		0	0	0	0	1	0	0	0	0	0	0	0
LIVER	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--AGONAL CONGESTION/HAEMORRHAGE		12	5	5	7	6	7	8	10	6	7	1	6
--INFLAMMATORY CELL FOCI		43	45	45	43	42	45	41	35	41	41	35	42
--INFLAMMATORY CELL INFILTRATION		0	0	0	1	0	0	0	0	0	0	0	0
--PIGMENTED HISTIOCYTES		0	1	1	0	0	1	2	1	2	1	1	1
--HAEMOPOIESIS		1	1	1	4	2	5	5	7	5	4	4	7
--VACUOLATED AREA		0	2	1	0	0	3	0	3	0	0	0	1
--BILIARY CYST		1	0	0	0	1	0	0	0	0	1	0	3	0
--GLYCOGEN VACUOLATION		5	3	2	5	4	2	3	3	5	4	4	3
--HEPATOCYTE VACUOLATION		30	19	38	39	41	18	29	20	25	37	37	27
--FOCAL HEPATOCYTE VACUOLATION		5	3	17	31	27	4	3	4	3	5	14	3
--TELANGIECTASIS		3	2	3	6	2	6	11	6	7	8	12	8
--MICROCYSTIC DEGENERATION		6	6	6	4	7	5	1	0	0	0	0	2
--CAPSULAR FIBROSIS/ADHESION		0	0	0	0	0	1	0	1	0	0	0	0
--FOCAL NECROSIS		3	2	4	1	3	4	1	3	5	3	4	2
--CENTRILOBULAR NECROSIS		0	0	0	1	1	1	0	0	1	0	0	1
** CONTINUED ON NEXT PAGE **													
** FROM PREVIOUS PAGE **													
LIVER	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--LOBAR NECROSIS		1	0	0	0	0	0	0	0	0	0	0	0
--FIBROSIS		1	0	0	0	0	0	1	1	0	1	1	3
--HEPATOCYTE HYPERTROPHY		0	1	1	1	6	0	1	1	0	8	8	1
--HEPATOCYTE BASOPHILIA		0	2	7	12	20	3	0	2	3	3	3	2
--BASOPHILIC FOCUS		16	19	40	44	45	16	34	29	41	49	49	34
--EOSINOPHILIC FOCUS		18	16	31	40	37	12	7	7	4	19	17	9
--BILE DUCT HYPERPLASIA		32	40	35	23	19	26	21	13	10	11	12	21
--OVAL CELL HYPERPLASIA		0	0	0	0	0	1	0	0	1	0	1	0
LUNG	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--AGONAL CONGESTION/HAEMORRHAGE		12	8	10	13	8	13	3	8	4	6	5	7
--INFLAMMATORY CELL FOCI		8	11	6	11	7	8	6	12	10	7	10	7
--FOAMY HISTIOCYTES		30	17	23	24	24	25	32	26	29	25	28	20
--HAEMORRHAGE		0	1	0	0	0	1	0	0	0	0	0	0
--GRANULOMA		1	0	0	0	0	1	0	0	0	0	0	0
--PIGMENTED HISTIOCYTES		3	3	0	6	6	4	3	3	3	4	1	3
--THROMBUS		0	0	1	0	0	0	0	0	0	0	0	0
--EMBOLUS		0	1	0	0	0	0	0	0	0	0	0	0
--FIBROSIS		0	0	0	0	0	1	0	0	0	0	0	0
--PLEURAL FIBROSIS/ADHESION		1	1	2	0	0	1	0	0	0	0	1	0
--PNEUMONITIS		2	1	3	3	1	5	2	1	0	1	0	0
--OSSEOUS METAPLASIA		3	3	2	3	2	2	1	2	1	1	2	0
--BRONCHIOLO-ALVEOLAR HYPERPLASIA		5	4	2	0	3	1	0	1	0	0	2	1

Test article	Control	ZD4522				Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	2	20	60	80	0

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STUDY NUMBER: 88232

		--- 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-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
LYMPH NODE	NUMBER EXAMINED:	2	1	2	0	3	0	0	0	1	0	1	0
--AGONAL CONGESTION/HAEMORRHAGE		0	0	1	0	0	0	0	0	0	0	1	0
--CONGESTION		0	0	0	0	1	0	0	0	0	0	0	0
--LYMPHANGIECTASIS		0	1	0	0	2	0	0	0	0	0	0	0
MAMMARY GLAND	NUMBER EXAMINED:	0	1	0	1	1	0	50	50	50	49	49	50
--HYPERPLASIA - CYSTIC		0	0	0	0	0	0	31	29	25	23	26	32
--HYPERPLASIA - ACINAR		0	0	0	0	0	0	13	16	16	22	18	13
MANDIBULAR LN	NUMBER EXAMINED:	49	49	50	49	50	50	50	48	49	50	50	48
--AGONAL CONGESTION/HAEMORRHAGE		11	7	14	12	11	10	11	6	6	3	7	10
--PIGMENT		0	0	0	0	0	1	0	0	0	0	0	0
--LYMPHANGIECTASIS		4	3	2	2	0	0	2	1	3	1	1	2
--LYMPHADENITIS		0	2	0	0	1	1	0	0	0	0	0	0
--ATROPHY		0	0	0	0	0	1	0	0	0	0	0	0
--LYMPHOID HYPERPLASIA		10	18	15	21	15	16	21	19	15	20	19	14
MESENTERIC LN	NUMBER EXAMINED:	50	50	48	50	50	49	50	50	50	50	50	50
--AGONAL CONGESTION/HAEMORRHAGE		1	0	1	0	2	0	0	0	0	0	2	0
--CONGESTION		1	0	1	1	1	0	0	0	0	0	0	0
--HAEMOPOIESIS		0	0	0	0	0	1	0	0	1	0	0	0
--LYMPHANGIECTASIS		0	1	1	0	1	1	1	1	0	0	0	0
--MINERALISATION		0	0	1	0	0	0	0	0	0	0	0	0
--ATROPHY		1	0	1	0	1	0	0	1	0	0	2	1
--GRANULOMA		0	0	0	0	0	1	0	0	0	0	1	0
--ANGIOMATOUS HYPERPLASIA		3	2	0	1	4	4	3	0	1	1	3	1

** CONTINUED ON NEXT PAGE **

MESENTERIC LN	NUMBER EXAMINED:	50	50	48	50	50	49	50	50	50	50	50	50
--LYMPHOID HYPERPLASIA		0	0	0	1	0	0	0	0	0	1	0	0
MUSCLE	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--INFLAMMATORY CELL FOCI		0	1	0	0	2	0	0	0	0	1	0	1
--MYOPATHY		0	0	1	0	1	2	0	1	0	0	1	0
--ATROPHY		11	10	5	4	3	7	0	1	0	2	0	0
NASAL CAVITY	NUMBER EXAMINED:	0	0	0	0	1	0	0	0	0	0	0	0
--PHARYNGITIS		0	0	0	0	1	0	0	0	0	0	0	0
OESOPHAGUS	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--ABSCESS		0	0	0	0	1	0	0	0	0	0	0	0
--OESOPHAGITIS		0	1	0	0	0	0	0	0	0	0	0	0
OPTIC NERVE	NUMBER EXAMINED:	50	50	48	50	50	50	50	49	50	50	50	50
--NEUROPATHY		0	0	0	0	0	0	1	0	0	0	3	0
OVARY	NUMBER EXAMINED:	0	0	0	0	0	0	50	50	50	50	50	50
--AGONAL CONGESTION/HAEMORRHAGE		0	0	0	0	0	0	1	1	0	1	0	0
--CYST		0	0	0	0	0	0	11	13	18	22	16	10
--ACYCLIC - FOLLICULAR		0	0	0	0	0	0	25	20	19	15	22	27
--ACYCLIC - LUTEAL		0	0	0	0	0	0	0	0	1	0	0	0
--ATROPHY		0	0	0	0	0	0	7	6	1	2	3	0
--SEX CORD STROMAL HYPERPLASIA		0	0	0	0	0	0	14	14	13	18	13	11

Test article	Control	ZD4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	2	20	60	80	0

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STUDY NUMBER: 88232

		--- 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-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
PANCREAS	NUMBER EXAMINED:	50	50	49	50	49	50	50	49	50	50	50	50
--AGONAL CONGESTION/HAEMORRHAGE		2	0	1	0	0	1	1	1	0	0	0	0
--INFLAMMATORY CELL FOCI		1	3	1	0	0	3	4	5	7	0	2	1
--ARTERITIS		1	0	0	0	0	2	0	1	0	0	0	0
--DEGRANULATION		0	1	1	0	1	0	0	0	0	0	0	0
--ACINAR CELL VACUOLATION		0	0	0	0	0	0	0	0	1	0	0	0
--OEDEMA		1	1	1	0	0	1	0	1	0	0	0	1
--ISLET FIBROSIS		15	12	16	14	10	11	0	2	3	3	1	1
--GRANULOMA		0	0	0	0	0	0	0	1	0	0	0	0
--FAT INFILTRATION		2	1	0	0	1	1	0	0	0	0	0	1
--FATTY ATROPHY		2	0	0	1	0	1	0	0	0	2	2	1
--LOBULAR ATROPHY		17	16	19	18	20	19	14	12	7	11	8	11
--ACINAR CELL HYPERTROPHY		7	6	13	14	10	10	6	9	8	9	7	5
--ACINAR CELL HYPERPLASIA		4	6	2	6	7	1	1	0	0	1	3	0
--ISLET CELL HYPERPLASIA		3	1	2	2	1	2	2	0	1	0	0	3
PARATHYROID	NUMBER EXAMINED:	50	48	48	48	50	47	50	46	48	49	44	48
--HYPERPLASIA - FOCAL		2	7	5	3	5	5	1	3	1	0	2	0
PAROTID GLAND	NUMBER EXAMINED:	49	48	50	49	50	50	50	47	48	50	49	48
--INFLAMMATORY CELL FOCI		5	3	4	2	2	3	0	1	2	2	0	0
--MINERALISATION		1	0	1	0	0	1	0	3	1	2	0	4
--LOBULAR ATROPHY		6	0	1	6	2	2	4	0	2	5	2	1
PITUITARY	NUMBER EXAMINED:	50	50	49	50	50	50	50	49	50	49	50	50
--AGONAL CONGESTION/HAEMORRHAGE		0	0	1	0	1	0	0	2	1	1	0	2
PITUITARY	NUMBER EXAMINED:	50	50	49	50	50	50	50	49	50	49	50	50
--CYST		1	0	1	3	0	1	0	0	0	0	0	1
--CYSTIC CLEFT		1	0	0	1	0	0	0	0	0	0	0	0
--HAEMANGIECTASIS		0	1	0	0	0	0	1	0	1	0	1	0
--TUBULAR REMNANTS		0	0	0	0	0	0	1	0	0	0	0	0
--HYPERPLASIA - DIFFUSE		0	0	0	0	0	0	3	0	3	1	3	1
--HYPERPLASIA - FOCAL		12	10	10	13	14	12	10	7	16	17	14	8
PREPUT/CLIT GL	NUMBER EXAMINED:	0	0	0	0	0	0	2	0	1	0	0	0
--DUCT ECTASIA		0	0	0	0	0	0	2	0	0	0	0	0
--CYST		0	0	0	0	0	0	0	0	1	0	0	0
PROSTATE	NUMBER EXAMINED:	50	50	50	50	50	50	0	0	0	0	0	0
--BARBITURATE LYSIS		1	0	0	0	1	0	0	0	0	0	0	0
--INFLAMMATORY CELL FOCI		3	3	3	6	0	2	0	0	0	0	0	0
--COAGULATING GLAND DISTENSION		0	0	0	0	1	0	0	0	0	0	0	0
--COAGULATING GLAND ADENITIS		0	1	2	0	0	0	0	0	0	0	0	0
--PROSTATITIS		25	19	27	20	23	21	0	0	0	0	0	0
--ATROPHY		0	1	1	0	0	0	0	0	0	0	0	0
--ACINAR CELL HYPERPLASIA		1	1	1	1	2	2	0	0	0	0	0	0
RECTUM	NUMBER EXAMINED:	48	50	46	47	48	48	50	49	50	49	49	48
--NEMATODE		6	8	0	0	0	4	2	4	0	0	0	4
--PERIANAL DERMATITIS		1	1	1	0	1	0	0	0	0	2	0	0
--EROSION/ULCER		0	0	0	0	0	0	0	0	0	1	0	0
--PROCTITIS		0	0	0	0	0	0	0	0	0	1	0	0

** CONTINUED ON NEXT PAGE **

(b) (4) study number 88/232. Sponsor study number TCR/2852.
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	2	20	60	80	0

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STUDY NUMBER: 88232

						--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---						
TABLE INCLUDES:												
SEX=ALL;GROUP=ALL;WEEKS=ALL	SEX:	----------MALE----------						----------FEMALE----------				
DEATH=ALL;FIND=P;SUBSET=T												
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
** FROM PREVIOUS PAGE **													
RECTUM	NUMBER EXAMINED:	48	50	46	47	48	48	50	49	50	49	49	48
--PERIANAL ABSCESS		0	1	0	0	0	0	0	0	0	0	0	0
SALIVARY GLAND	NUMBER EXAMINED:	50	49	50	49	50	50	50	48	49	50	50	48
--ACINAL CONGESTION/HAEMORRHAGE		1	0	0	0	1	0	0	0	0	0	0	0
--INFLAMMATORY CELL FOCI		0	1	0	1	0	0	0	0	0	0	0	0
--OEDEMA		0	1	0	0	2	0	1	1	1	0	0	1
--CYST		0	0	1	0	0	0	0	0	0	0	0	0
--LOBULAR ATROPHY		0	1	0	0	0	0	0	1	0	0	0	0
SCIATIC NERVE	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--VASCULAR MINERALISATION		0	0	0	0	0	1	0	0	0	0	0	0
--NEUROPATHY		29	30	34	25	31	24	13	16	15	19	19	15
SEMINAL VESICLE	NUMBER EXAMINED:	50	50	49	50	47	50	0	0	0	0	0	0
--DISTENSION		3	2	1	1	3	2	0	0	0	0	0	0
--VESICULITIS		0	2	1	0	1	0	0	0	0	0	0	0
--ATROPHY		3	2	5	2	1	1	0	0	0	0	0	0
--CONTRACTION		0	0	3	1	0	0	0	0	0	0	0	0
SKIN + SUBCUTIS	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--FAT DEPOT		1	0	0	0	0	0	3	1	2	3	4	2
--ADNEXAL ATROPHY		1	0	0	2	0	0	8	1	3	6	2	2
--SQUAMOUS CYST		1	0	0	2	0	0	0	1	0	0	0	0
--ACANTHOSIS		3	0	3	4	2	0	7	6	14	7	7	7
--HAEMORRHAGE		0	0	0	0	0	0	0	0	1	0	0	0
SKIN + SUBCUTIS	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--DERMATITIS		4	9	5	5	9	9	4	8	4	2	1	6
--LYMPHOCYTIC DERMATITIS		0	1	0	0	0	0	1	0	0	0	0	0
--CELLULITIS		0	0	0	0	0	0	0	0	1	0	0	0
--PYOGRANULOMA		0	0	0	0	0	0	0	1	0	0	0	0
--ABSCESS		1	0	1	1	1	2	0	0	0	0	0	1
--FIBROSIS		0	0	0	0	0	1	0	0	0	0	0	0
--FIBROSIS: SUBCUTIS		0	0	0	0	0	0	1	0	0	0	1	0
SPINAL CORD	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--HAEMORRHAGE		0	1	0	0	0	1	0	0	1	0	0	0
--MYELOPATHY		0	1	0	0	0	0	0	0	0	0	0	0
--COMPRESSION		0	1	0	0	0	0	0	0	0	0	0	0
SPLEEN	NUMBER EXAMINED:	50	50	49	50	50	50	50	50	50	50	50	49
--BARBITURATE LYSIS		0	0	0	0	0	0	0	0	0	0	0	1
--PIGMENT		19	27	30	27	35	27	45	43	45	49	49	42
--CYST		0	0	1	0	0	0	0	0	0	0	0	0
--CAPSULAR FIBROSIS		1	2	2	0	0	0	0	0	0	0	1	0
--HAEMATOMA		0	0	0	0	0	0	0	0	0	0	1	0
--NECROSIS		1	0	0	0	0	0	0	0	1	0	0	0
--HAEMOPOIESIS		13	7	18	16	18	15	21	25	30	27	23	23
--ATROPHY		0	0	0	0	0	0	0	0	0	0	1	0
--LYMPHOID ATROPHY		1	1	1	1	1	2	0	0	1	0	0	0
--LYMPHOID HYPERPLASIA		0	2	2	0	0	0	1	0	0	0	0	0

(b) (4) **study number 88/232. Sponsor study number TCR/2852.**
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	2	20	60	80	0

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STUDY NUMBER: 88232

		--- NUMBER-OF-ANIMALS-AFFECTED ---											
TABLE INCLUDES: SEX=ALL;GROUP=ALL;WEEKS=ALL DEATH=ALL;FIND=P;SUBSET=T	SEX:	----------MALE----------						----------FEMALE----------					
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
STERNUM + MARROW	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--MARROW FAT		7	2	6	5	5	2	6	2	5	6	11	6
--HAEMANGIECTASIS		0	1	0	0	0	0	0	0	0	0	0	0
--DEFORMITY		1	0	0	0	0	0	1	0	0	0	1	1
--MARROW HYPERPLASIA		10	14	8	12	6	12	7	7	13	11	6	7
--ENOSTOSIS		0	0	0	0	0	0	1	0	0	0	0	0
STOMACH	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--AGONAL CONGESTION/HAEMORRHAGE		2	1	2	1	1	1	0	3	0	0	0	0
--INFLAMMATORY CELL INFILTRATION - FORESTOMACH SUBMUCOSA		0	2	7	10	22	1	3	1	1	8	11	2
--CYSTIC GLANDS		18	19	13	20	19	22	28	25	29	26	25	23
--SQUAMOUS CYST		2	1	0	0	0	0	1	1	0	0	1	1
--MINERALISATION		1	0	0	0	0	0	0	0	0	0	0	1
--FORESTOMACH: LYMPHOCYTIC GASTRITIS		0	1	0	0	0	0	1	0	0	0	0	0
--GASTRITIS		2	1	0	1	1	1	0	0	0	1	0	0
--EROSION/ULCER - FORESTOMACH		0	1	3	6	11	0	1	0	1	5	5	2
--EROSION/ULCER - GLANDULAR STOMACH		3	2	0	0	1	3	0	2	0	2	4	0
--HYPERKERATOSIS		3	2	10	18	35	2	6	5	5	23	25	6
--SQUAMOUS CELL HYPERPLASIA		1	2	12	20	33	1	2	2	1	18	26	3
--BASAL CELL HYPERPLASIA		0	0	0	0	0	0	0	0	1	0	0	0
TAIL	NUMBER EXAMINED:	9	15	19	11	10	12	14	8	10	12	10	7
--FRACTURE/DISLOCATION		1	0	0	0	0	0	0	0	1	0	0	0
--DERMATITIS/FOLLICULITIS		9	13	18	11	10	9	14	6	10	10	10	6
--HYPERKERATOSIS		0	1	0	0	0	0	0	1	0	0	0	0
--LYMPHOCYTIC DERMATITIS		0	1	0	0	0	0	0	0	0	0	0	0
TAIL	NUMBER EXAMINED:	9	15	19	11	10	12	14	8	10	12	10	7
--OSTEOMYELITIS		0	0	0	0	0	0	0	1	0	0	0	0
TESTIS	NUMBER EXAMINED:	50	50	50	50	50	50	0	0	0	0	0	0
--AGONAL CONGESTION/HAEMORRHAGE		3	1	2	0	0	3	0	0	0	0	0	0
--ARTERITIS		1	1	1	1	3	1	0	0	0	0	0	0
--VASCULAR MINERALISATION		1	0	1	0	0	0	0	0	0	0	0	0
--TUBULAR MINERALISATION		2	6	1	2	4	2	0	0	0	0	0	0
--TUBULAR DILATION		0	0	1	0	0	0	0	0	0	0	0	0
--TUBULAR ATROPHY		11	9	6	11	13	8	0	0	0	0	0	0
--SPERM GRANULOMA		0	1	0	1	0	0	0	0	0	0	0	0
--INTERSTITTIAL CELL HYPERPLASIA - DIFFUSE		0	0	0	1	1	0	0	0	0	0	0	0
--INTERSTITTIAL CELL HYPERPLASIA - FOCAL		2	4	1	2	1	0	0	0	0	0	0	0
THORACIC CAVITY	NUMBER EXAMINED:	0	1	0	0	0	1	1	0	0	0	1	0
--FIBROSIS/ADHESION		0	0	0	0	0	0	0	0	0	0	1	0
--FIBROSIS		0	0	0	0	0	0	1	0	0	0	0	0
THYMUS	NUMBER EXAMINED:	49	47	46	50	47	44	47	48	49	48	48	49
--AGONAL CONGESTION/HAEMORRHAGE		1	2	0	2	0	1	0	2	2	0	0	3
--ECTOPIC THYROID		0	0	0	1	0	0	0	0	1	0	0	1
--ATROPHY		39	40	41	43	35	35	40	36	35	35	39	36
--MEDULLARY HYPERPLASIA		0	0	0	0	1	0	1	1	0	0	0	0
--EPITHELIAL HYPERPLASIA		0	0	0	0	0	1	0	0	0	0	0	0
--LYMPHOID HYPERPLASIA		0	0	0	0	0	0	0	0	0	1	0	0
--CYST/TUBULAR HYPERPLASIA		10	7	8	3	4	6	21	24	19	23	22	18

(b) (4) **study number 88/232. Sponsor study number TCR/2852.**
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	2	20	60	80	0

(b) (4)

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STUDY NUMBER: 88232

						--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---							
TABLE INCLUDES:													
SEX=ALL;GROUP=ALL;WEEKS=ALL	SEX:	----------MALE----------						----------FEMALE----------					
DEATH=ALL;FIND=P;SUBSET=T													
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
THYROID	NUMBER EXAMINED:	50	50	48	48	48	48	50	49	48	50	49	49
--AGONAL CONGESTION/HAEMORRHAGE		0	1	0	1	1	0	0	0	0	0	0	0
--CYST		5	4	7	6	3	2	7	4	7	7	5	8
--CYSTIC FOLLICLES		2	1	1	0	1	0	0	0	1	1	1	0
--FOLLICULAR CELL HYPERTROPHY		4	3	1	2	7	3	1	1	4	6	3	1
--FOLLICULAR CELL HYPERPLASIA - CYSTIC		1	0	4	2	0	3	0	0	1	1	2	0
--C-CELL HYPERPLASIA		21	16	9	14	19	12	28	21	27	23	23	21
--FOLLICULAR DISTENSION		0	0	0	0	0	0	0	0	0	0	0	1
TONGUE	NUMBER EXAMINED:	49	49	50	49	50	50	50	48	49	50	50	49
--ARTERITIS		0	0	0	0	0	1	0	0	1	1	0	0
--GLOSSITIS		0	1	0	0	0	0	1	0	0	0	0	0
--MYOSITIS		0	0	0	0	0	0	0	1	0	0	0	0
TRACHEA	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--TRACHEITIS		0	1	0	0	0	0	0	0	0	0	0	0
URETER	NUMBER EXAMINED:	0	0	0	0	0	1	0	0	0	0	0	0
--DISTENSION		0	0	0	0	0	1	0	0	0	0	0	0
URINARY BLADDER	NUMBER EXAMINED:	50	50	50	50	48	50	50	50	50	50	50	50
--BARBITURATE LYSIS		0	0	0	0	1	0	0	0	0	0	0	0
--INFLAMMATORY CELL FOCI		1	2	4	2	1	4	2	3	2	2	0	1
--DISTENSION		2	3	6	3	3	6	4	1	5	1	3	2
--ARTERITIS		0	1	0	0	0	0	0	0	0	0	0	0
--CONGESTION/HAEMORRHAGE		0	1	1	0	1	0	0	0	0	0	1	0
URINARY BLADDER	NUMBER EXAMINED:	50	50	50	50	48	50	50	50	50	50	50	50
--CYSTITIS		0	2	2	0	1	0	0	0	0	1	0	2
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	0	50	50	50	50	50	50
--AGONAL CONGESTION/HAEMORRHAGE		0	0	0	0	0	0	0	2	1	0	1	1
--BARBITURATE LYSIS		0	0	0	0	0	0	1	0	0	0	0	0
--CYSTIC GLANDS		0	0	0	0	0	0	15	20	15	14	12	20
--DISTENSION		0	0	0	0	0	0	3	0	1	1	0	0
--ATROPHY		0	0	0	0	0	0	4	3	0	2	2	1
--CERVICAL HYPERTROPHY		0	0	0	0	0	0	0	0	2	1	1	1
--SQUAMOUS CELL METAPLASIA		0	0	0	0	0	0	11	7	8	6	6	10
--GRANULAR CELL HYPERPLASIA		0	0	0	0	0	0	1	5	1	2	5	2
VAGINA	NUMBER EXAMINED:	0	0	0	0	0	0	50	50	50	50	50	50
--CYST		0	0	0	0	0	0	0	0	1	0	0	0
--MUCIFICATION		0	0	0	0	0	0	19	19	28	21	19	21
--VAGINITIS		0	0	0	0	0	0	0	0	0	1	0	0
** END OF LIST **													

Neoplastic:

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.

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 ≥ 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.

(b) (4) **study number 88/232. Sponsor reference number TCR/2852. Overall incidence of neoplasia**

Test article	Control	ZD4522			Control
Group	1	2	3	4	5	6
Level (mg/kg/day)	0	2	20	60	80	0

(b) (4)

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DRAFT STUDY NUMBER: 88232

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

--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---

SEX:	MALE						FEMALE					
GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
NEOPLASM CLASSIFICATION SUMMARY NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
TOTAL PRIMARY NEOPLASMS	88	85	84	61	71	86	127	119	122	132	123	124
ANIMALS WITH ONE OR MORE	44	39	45	37	41	39	50	45	48	47	49	49
PERCENT WITH ONE OR MORE	88%	78%	90%	74%	82%	78%	100%	90%	96%	94%	98%	98%
TOTAL BENIGN NEOPLASMS	74	68	69	57	55	70	110	104	99	115	109	104
ANIMALS WITH ONE OR MORE	39	36	40	34	34	34	45	44	43	43	46	48
PERCENT WITH ONE OR MORE	78%	72%	80%	68%	68%	68%	90%	88%	86%	86%	92%	96%
TOTAL MALIGNANT NEOPLASMS	14	17	15	4	16	16	17	15	23	17	14	20
ANIMALS WITH ONE OR MORE	13	13	15	4	16	15	15	11	18	14	11	16
PERCENT WITH ONE OR MORE	26%	26%	30%	8%	32%	30%	30%	22%	36%	28%	22%	32%
TOTAL METASTATIC NEOPLASMS	3	18	8	3	6	6	17	6	6	3	6	3
ANIMALS WITH ONE OR MORE	1	4	3	2	1	3	3	1	4	2	3	1
PERCENT WITH ONE OR MORE	2%	8%	6%	4%	2%	6%	6%	2%	8%	4%	6%	2%
TOTAL LOCALLY INVASIVE NEOPLASMS	1	0	1	0	0	0	2	1	3	1	0	2
ANIMALS WITH ONE OR MORE	1	0	1	0	0	0	2	1	2	1	0	2
PERCENT WITH ONE OR MORE	2%	0%	2%	0%	0%	0%	4%	2%	4%	2%	0%	4%

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(b) (4) **study number 88/232. Sponsor reference number TCR/2852. Background incidence of uterine stromal polyps and pancreas islet cell tumours**

Female rat: Crl CD BR – Sprague Dawley (IGS), 104wk carcinogenicity studies

	Year study end:	1996	1997	1997	1996	1998
	Actual study duration:	104	108	126	105	107
Tissue and finding	Study identifier:	62	64	65	66	110
Uterus	Number examined:	120	60	100	100	120
B-polyp		5	8	3	5	7
M-stromal sarcoma		0	0	0	1	0
Pancreas	Number examined:	120	60	100	100	120
B-islet cell adenoma		1	4	2	1	0
M-islet cell carcinoma		1	0	0	1	0

(b) (4) **study number 88/232. Sponsor study number TCR/2852.**
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	2	20	60	80	0

(b) (4)

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STUDY NUMBER: 88232

		--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---											
TABLE INCLUDES:													
SEX=ALL;GROUP=ALL;WEEKS=ALL	SEX:	----------MALE----------						----------FEMALE----------					
DEATH=ALL;FIND=B,M;SUBSET=ALL													
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
** TOP OF LIST **													
ABDOMINAL CAVITY	NUMBER EXAMINED:	0	0	0	1	0	2	0	2	1	1	0	2
--B-LIPOMA		0	0	0	0	0	0	0	0	0	0	0	1
--M-RHABDOMYOSARCOMA		0	0	0	1	0	0	0	0	0	0	0	0
--M-SARCOMA - NOS		0	0	0	0	0	0	0	0	0	0	1	0
--M-MALIGNANT SCHWANNOMA		0	0	0	0	0	0	0	0	0	0	0	1
ADRENAL	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--B-BENIGN PHAEOCHROMOCYTOMA		9	6	7	6	7	9	4	4	3	2	2	4
--B-CORTICAL ADENOMA		1	1	1	0	0	0	0	0	2	1	0	0
--M-CORTICAL CARCINOMA		0	0	0	0	0	0	0	0	0	1	0	0
--M-MALIGNANT PHAEOCHROMOCYTOMA		0	2	2	0	0	1	0	0	1	0	0	0
BRAIN	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--B-BENIGN GRANULAR CELL MENINGIOMA		0	0	0	0	0	0	1	0	0	0	0	0
--M-MALIGNANT ASTROCYTOMA		2	1	1	0	0	1	0	0	0	0	0	0
--M-MALIGNANT GLIOMA - NOS		0	1	0	0	0	0	0	0	0	0	0	0
CONNECTIVE TISS	NUMBER EXAMINED:	2	1	0	0	1	0	1	0	0	0	1	0
--M-HISTIOCYTIC SARCOMA		1	1	0	0	1	0	0	0	0	0	0	0
CRANIAL CAVITY	NUMBER EXAMINED:	0	0	1	0	0	1	0	0	1	0	0	0
--M-HAEMANGIOSARCOMA		0	0	0	0	0	1	0	0	0	0	0	0
EAR	NUMBER EXAMINED:	1	2	1	0	1	0	3	1	1	1	1	2
--B-NEUROFIBROMA		0	1	0	0	0	0	1	0	0	0	0	0
EPIDIDYMIS	NUMBER EXAMINED:	50	50	50	50	50	50	0	0	0	0	0	0
--M-SARCOMA - NOS		0	0	0	0	0	1	0	0	0	0	0	0
FOOT/LEG	NUMBER EXAMINED:	6	8	6	7	8	8	5	5	6	2	4	2
--M-FIBROSARCOMA		0	1	0	0	0	0	0	0	0	0	0	0
HAEM/LYMPH/RETIC	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--M-GRANULOCYTIC LEUKAEMIA		1	0	1	0	1	0	0	0	0	0	0	0
--M-HISTIOCYTIC SARCOMA		1	0	0	0	0	0	0	0	0	0	0	0
--M-MALIGNANT LYMPHOMA		2	1	1	0	2	2	1	0	1	0	3	0
HEART	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--B-BENIGN ENDOCARDIAL SCHWANNOMA		0	0	0	0	0	1	0	0	0	0	1	0
KIDNEY	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--B-TUBULAR CELL ADENOMA		0	0	1	0	0	0	0	0	0	0	0	0
--M-NEPHROBLASTOMA		0	0	0	0	0	0	0	0	1	0	0	0
LIVER	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--B-HEPATOCELLULAR ADENOMA		0	0	0	1	1	1	0	1	0	1	1	1
--B-CHOLANGIOMA		0	0	0	1	0	0	0	0	0	0	0	0
--M-HEPATOCELLULAR CARCINOMA		0	0	1	0	0	0	0	0	0	1	0	0
--M-HAEMANGIOSARCOMA		0	0	0	0	0	0	0	0	1	0	0	0
LUNG	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--B-BRONCHIOLO-ALVEOLAR ADENOMA		1	0	0	0	1	0	0	0	0	1	0	1

** CONTINUED ON NEXT PAGE **

(b) (4) study number 88/232. Sponsor study number TCR/2852.
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	2	20	60	80	0

(b) (4)

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STUDY NUMBER: 88232

TABLE INCLUDES:
SEX=ALL;GROUP=ALL;WEEKS=ALL
DEATH=ALL;FIND=B,M;SUBSET=ALL

		--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---											
	SEX:	----------MALE----------						----------FEMALE----------					
	GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	-1-	-2-	-3-	-4-	-5-	-6-
ORGAN AND FINDING DESCRIPTION	NUMBER:	50	50	50	50	50	50	50	50	50	50	50	50
** FROM PREVIOUS PAGE **													
LUNG	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--M-BRONCHIOLO-ALVEOLAR CARCINOMA		0	0	1	0	0	0	0	0	0	0	0	0
MAMMARY GLAND	NUMBER EXAMINED:	0	1	0	1	1	0	50	50	50	49	49	50
--B-FIBROADENOMA		0	0	0	1	0	0	31	28	32	25	27	28
--B-ADENOMA		0	0	0	0	0	0	6	1	3	2	4	3
--M-ADENOCARCINOMA		0	0	0	0	1	0	8	7	11	6	5	11
MESENTERIC LN	NUMBER EXAMINED:	50	50	48	50	50	49	50	50	50	50	50	50
--B-LYMPHANGIOMA		0	1	0	0	0	0	1	0	0	0	0	0
--B-HAEMANGIOMA		1	0	1	0	1	4	0	0	1	0	0	0
--M-HAEMANGIOSARCOMA		0	1	0	0	0	0	0	0	0	0	0	0
ORAL CAVITY	NUMBER EXAMINED:	0	1	0	0	0	0	0	0	0	0	0	0
--B-BENIGN ODONTOGENIC TUMOUR		0	1	0	0	0	0	0	0	0	0	0	0
OVARY	NUMBER EXAMINED:	0	0	0	0	0	0	50	50	50	50	50	50
--B-BENIGN MIXED SEX CORD STROMAL TUMOUR		0	0	0	0	0	0	0	1	0	1	0	0
--B-BENIGN THECOMA		0	0	0	0	0	0	0	0	0	0	0	1
PANCREAS	NUMBER EXAMINED:	50	50	49	50	49	50	50	49	50	50	50	50
--B-ISLET CELL ADENOMA		2	1	4	2	4	2	0	0	1	2	1	0
--B-ACINAR CELL ADENOMA		1	1	1	1	0	0	0	0	0	0	1	0
--B-ACINAR-ISLET CELL ADENOMA		0	0	2	0	0	0	0	0	0	0	0	0
--M-ACINAR CELL ADENOCARCINOMA		0	0	0	0	0	0	0	1	0	0	0	0
--M-ISLET CELL CARCINOMA		0	0	0	0	2	2	1	0	1	1	2	0
PARATHYROID	NUMBER EXAMINED:	50	48	48	48	50	47	50	46	48	49	44	48
--B-ADENOMA		1	0	1	0	0	0	0	0	0	0	0	0
PAROTID GLAND	NUMBER EXAMINED:	49	48	50	49	50	50	50	47	48	50	49	48
--B-ADENOMA		0	0	0	0	0	0	0	0	0	0	0	1
PITUITARY	NUMBER EXAMINED:	50	50	49	50	50	50	50	49	50	49	50	50
--B-ADENOMA		28	22	23	18	20	23	34	37	27	28	32	36
--M-CARCINOMA		0	0	1	0	0	0	2	1	2	1	0	2
PROSTATE	NUMBER EXAMINED:	50	50	50	50	50	50	0	0	0	0	0	0
--B-ADENOMA		0	0	0	0	1	0	0	0	0	0	0	0
--M-ADENOCARCINOMA		0	1	0	0	0	1	0	0	0	0	0	0
SKIN + SUBCUTIS	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--B-BENIGN BASAL CELL TUMOUR		0	2	0	0	0	0	0	0	0	0	0	0
--B-FIBROMA		3	3	5	0	3	4	0	4	1	4	1	1
--B-LIPOMA		0	1	1	3	1	0	0	0	1	0	1	1
--B-BENIGN HAIR FOLLICLE TUMOUR		0	0	3	2	2	4	0	0	0	0	0	0
--B-SQUAMOUS CELL PAPILLOMA		1	0	0	0	0	1	0	0	0	0	0	2
--B-DERMAL FIBROMA		8	3	3	3	5	3	0	0	0	1	0	0
--B-SEBACEOUS CELL ADENOMA		1	2	0	0	0	1	0	0	0	0	0	0
--M-SARCOMA		0	2	1	0	1	2	1	0	0	1	0	0
--M-FIBROSARCOMA		4	1	0	2	2	2	0	0	0	0	0	0
--M-SQUAMOUS CELL CARCINOMA		0	0	1	0	2	0	0	0	0	0	0	0
--M-HISTIOCYTIC SARCOMA		0	1	1	1	0	0	2	2	0	2	2	1

(b) (4) study number 88/232. Sponsor study number TCR/2852.
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	2	20	60	80	0

(b) (4)

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STUDY NUMBER: 88232

						--- N U M B E R - O F - A N I M A L S - A F F E C T E D ---							
TABLE INCLUDES:													
SEX=ALL;GROUP=ALL;WEEKS=ALL						SEX:	----------MALE----------					----------FEMALE----------	
DEATH=ALL;FIND=B,M;SUBSET=ALL													
						GROUP:	-1-	-2-	-3-	-4-	-5-	-6-	
ORGAN AND FINDING DESCRIPTION						NUMBER:	50	50	50	50	50	50	
SPINAL CORD	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--M-MALIGNANT OLIGODENDROGLIOMA		1	0	0	0	0	0	0	0	0	0	0	0
SPLEEN	NUMBER EXAMINED:	50	50	49	50	50	50	50	50	50	50	50	49
--M-SARCOMA - NOS		0	0	1	0	1	1	0	0	0	0	0	0
--M-HAEMANGIOSARCOMA		0	1	0	0	0	1	0	0	0	0	0	0
STOMACH	NUMBER EXAMINED:	50	50	50	50	50	50	50	50	50	50	50	50
--M-ADENOCARCINOMA		0	0	0	0	1	0	0	0	0	0	0	0
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	0	1	0	0	0	0	0	0
TAIL	NUMBER EXAMINED:	9	15	19	11	10	12	14	8	10	12	10	7
--B-SQUAMOUS CELL PAPILLOMA		0	0	0	0	1	2	0	0	0	0	0	0
--B-HAEMANGIOMA		0	0	0	0	1	0	0	0	0	0	0	0
--B-FIBROMA		0	0	0	0	0	0	0	0	0	1	0	0
--M-SQUAMOUS CELL CARCINOMA		0	0	1	0	0	0	0	0	0	0	0	0
TESTIS	NUMBER EXAMINED:	50	50	50	50	50	50	0	0	0	0	0	0
--B-BENIGN INTERSTITIAL CELL TUMOUR		0	5	3	2	0	2	0	0	0	0	0	0
THORACIC CAVITY	NUMBER EXAMINED:	0	1	0	0	0	1	1	0	0	0	1	0
--M-MALIGNANT ENDOCRINOID TUMOUR		0	1	0	0	0	0	0	0	0	0	0	0
THYMUS	NUMBER EXAMINED:	49	47	46	50	47	44	47	48	49	48	48	49
--B-BENIGN THYMOMA		1	0	0	0	0	1	0	1	1	0	1	1
--M-MALIGNANT THYMOMA		0	0	1	0	0	0	0	0	0	0	0	0
THYROID	NUMBER EXAMINED:	50	50	48	48	48	48	50	49	48	50	49	49
--B-C-CELL ADENOMA		9	10	11	11	6	5	8	6	7	5	4	1
--B-FOLLICULAR CELL ADENOMA		1	0	1	2	0	0	1	2	1	0	0	0
--M-C-CELL CARCINOMA		1	0	0	0	2	0	0	0	0	0	0	1
--M-FOLLICULAR CELL CARCINOMA		0	1	1	0	0	0	0	0	0	0	0	0
TONGUE	NUMBER EXAMINED:	49	49	50	49	50	50	50	48	49	50	50	49
--M-SQUAMOUS CELL CARCINOMA		1	0	0	0	0	0	0	0	0	1	0	0
UTERUS	NUMBER EXAMINED:	0	0	0	0	0	0	50	50	50	50	50	50
--B-STROMAL POLYP		0	0	0	0	0	0	5	6	0	8	12	6
--B-BENIGN GRANULAR CELL TUMOUR		0	0	0	0	0	0	2	1	1	1	1	0
--B-ADENOMA		0	0	0	0	0	0	0	0	0	2	0	0
--B-HAEMANGIOMA		0	0	0	0	0	0	0	1	0	0	0	0
--M-STROMAL SARCOMA		0	0	0	0	0	0	0	0	0	0	1	0
--M-ADENOCARCINOMA		0	0	0	0	0	0	0	0	0	0	1	0
VAGINA	NUMBER EXAMINED:	0	0	0	0	0	0	50	50	50	50	50	50
--B-BENIGN GRANULAR CELL TUMOUR		0	0	0	0	0	0	0	1	0	0	0	0
--M-SQUAMOUS CELL CARCINOMA		0	0	0	0	0	0	0	1	1	0	0	0
--M-STROMAL SARCOMA		0	0	0	0	0	0	0	0	0	1	0	0

** END OF LIST **

Toxicokinetics:

Maximum plasma concentrations were observed at 0.5-1.5 h post dose in male and female rats. After reaching peak concentrations, plasma concentrations declined in a multiphasic manner with an apparent terminal half-life of 3-11 h. The extent of systemic exposure of male rats was not consistently different to that of female rats, indicating no apparent sex-related difference in systemic exposure. Plasma concentrations of ZD4522 increased with increasing dose. Overall, the increase in extent of systemic exposure to ZD4522 was greater than dose-proportional. Therefore, the pharmacokinetics of ZD4522 appeared to be non-linear with respect to dose over the dose range 2 to 80 mg/kg/day.

In general, the systemic exposure of male and female rats after repeated dosing (month 1 and year 1) were very variable. Thus, the time difference can not be evaluated.

Mean pharmacokinetic parameters at one year

Parameter	Dose level							
	2 mg/kg/day		20 mg/kg/day		60 mg/kg/day		80 mg/kg/day	
	Male	Female	Male	Female	Male	Female	Male	Female
C_{max} (ng/ml)	16.1	34.6	284	312	1052	1757	1976	2990
T_{max} (h)	0.5	1.5	0.5	0.5	0.5	0.5	0.5	0.5
$AUC_{(0-t)}$ (ng.h/ml)	59.6	88.5	659	565	2021	2968	3903	4636

Great variations in exposure were observed at 80 mg/kg group. Compared with the AUC at 80 mg human dose, not enough safety margin can be reached. However, based on FDA tentatively approved dose of 10 mg, safety margin reaches 100-fold.

Table 10 D4522 KPR009. Individual and mean plasma concentrations (ng/ml) of ZD4522 in male and female rats following repeated oral (gavage) administration of ZD4522 at 80 mg/kg/day: Day 1

	Male Rats				Female Rats			
Nominal Sampling Time (h)	Rat Number	Concentration (ng/ml)	Mean	SD	Rat Number	Concentration (ng/ml)	Mean	SD
Pre-dose	201	BLQ	BLQ	-	501	BLQ	BLQ	-
	202	BLQ			502	BLQ		
	203	BLQ			503	BLQ		
0.5	204	2168[R2]	944	1060	504	822[R2]	4407	4088
	205	355[R2]			505	3541[R2]		
	206	309			506	8859[R2]		
1.5	207	1123[R2]	655	407	507	1128[R1]	823	287
	208	389			508	784[R2]		
	209	452			509	558[R2]		
4	210	161	247	130	510	142	132	15.2
	211	397[R2]			511	114		
	212	184			512	139		
8	213	63.0	183	171	513	51.0	93.0	58.3
	214	378[R2]			514	160		
	215	107			515	68.4		
12	216	21.2	19.8	3.08	516	41.9	30.4	20.3
	217	22.0			517	42.3[R1]		
	218	16.3			518	6.95		
24	219	5.16	1.72	2.98	519	BLQ	2.56	4.43
	220	BLQ			520	7.67		
	221	BLQ			521	BLQ		

BLQ = Below the limit of quantification of the assay (b) (4), taken as zero for calculation of summary statistics

R-Repeat
1 – Instrument failure/failure to extract
2 – Appropriate dilution

Table 11 D4522 KPR009. Individual and mean plasma concentrations (ng/ml) of ZD4522 in male and female rats following repeated oral (gavage) administration of ZD4522 at 80 mg/kg/day: Month 1

	Male Rats				Female Rats			
Nominal Sampling Time (h)	Rat Number	Concentration (ng/ml)	Mean	SD	Rat Number	Concentration (ng/ml)	Mean	SD
Pre-dose	201	5.64	17.5	10.6	501	BLQ	23.6	40.9
	202	26.1			502	70.8		
	203	20.8			503	BLQ		
0.5	204	16379[R]	7975	7512	504	970	828	284
	205	5631[R]			505	1012		
	206	1914			506	501		
1.5	207	222	250	28.4	507	63.5	146	71.8
	208	249			508	194		
	209	279			509	181		
4	210	47.0	161	105	510	92.5	45.8	40.4
	211	255			511	21.4		
	212	180			512	23.7		
8	213	1372[R]	570	695	513	27.0	86.5	72.7
	214	203			514	168		
	215	135			515	64.9		
12	216	89.8	71.9	25.6	516	29.1	50.0	33.8
	217	83.5			517	89.0		
	218	42.6			518	31.8		
24	219	6.64	5.67	5.25	519	BLQ	3.99	3.49
	220	BLQ			520	6.48		
	221	10.4			521	5.50		

BLQ = Below the limit of quantification of the assay (b) (4) taken as zero for calculation of summary statistics

R-Repeat (Appropriate dilution)

Table 12 D4522 KPR009. Individual and mean plasma concentrations (ng/ml) of ZD4522 in male and female rats following repeated oral (gavage) administration of ZD4522 at 80 mg/kg/day: Year 1

	Male Rats				Female Rats			
Nominal Sampling Time (h)	Rat Number	Concentration (ng/ml)	Mean	SD	Rat Number	Concentration (ng/ml)	Mean	SD
Pre-dose	201	8.44	27.9	17.4	501	8.44	7.29	1.64
	202	42.0			502	8.02		
	203	33.4			503	5.41		
0.5	204	1772[R]	1976	177	504	6067[R]	2990	2782
	205	2094[R]			505	2252[R]		
	206	2062[R]			506	652		
1.5	207	191	300	275	507	260	626	524
	208	613			508	1226[R]		
	209	95.2			509	392		
4	210	384	200	165	510	674[R]	264	356
	211	154			511	76.8		
	212	62.9			512	40.3		
8	214	373[R]	145	198	513	36.0	58.2	20.9
	215	19.7			514	77.6		
	216	41.3			515	61.0		
12	217	68.9	72.3	41.1	516	16.4	18.5	3.28
	218	33.1			517	22.3		
	219	115			518	16.9		
24	220	15.6	13.5	5.42	519	8.17	9.72	1.35
	221	17.5			520	10.4		
	222	7.32			521	10.6		

R-Repeat (Appropriate dilution)

Table 16 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

Summary of individual study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model:

The test species appears to be appropriate, since rat is a common used species for carcinogenicity study in other statins. The test doses appeared to be adequate based on the AUC values. The exposure at 80 mg/kg provides about 100X safety margin over the FDA tentatively approved human dose of 10 mg/day. Based on MTD, the high dose of 80 mg/kg may be adequate based on the results of the second 13-week study, while mortality was observed at doses ≥ 80 mg/kg.

Evaluation of tumor findings:

Oral dosing for 2 years at 20, 60 and 80 mg/kg/day resulted in a number of non-neoplastic changes in the liver and stomach. A no-effect dose for these changes was established at 2 mg/kg/day.

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 ≥ 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.

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

Study title: ZD4522: 91-DAY DOSE RANGE FINDING STUDY IN RATS (TKR/3081)

NOTE: This study was intended to determine MTD and to support the dose selections for the 2-year carcinogenicity study in rats.

Study No.: 88/288
Amendment #, Vol #, and Page #: SN134 Page 1
Conducting laboratory and location: (b) (4)
Date of study initiation: September 1999
GLP compliance: Yes
QA report: Yes

Methods: Dose range-finding study for 2-year carcinogenicity (completed by May 2000)
Dosing:

- Species/strain: Rats, Crl:CD(SD)IGSBR, from (b) (4)
- #/sex/group or time point:

Group	Dose (mg/kg)	[illegible]	[illegible]
Control	0	20	20
S4522	160	20	20

- Weight: male: 176.7-224.8 g, female: 149.7-185.3 g
- Age: 6 weeks
- Route: oral gavage, 10 ml/kg
- Diet: SQC Rat and Mouse Maintenance Diet No. 1

Drug: Lot number: ADM03516E98
Vehicle: 5% (w/v) aqueous Gum Arabic

Observations and times:

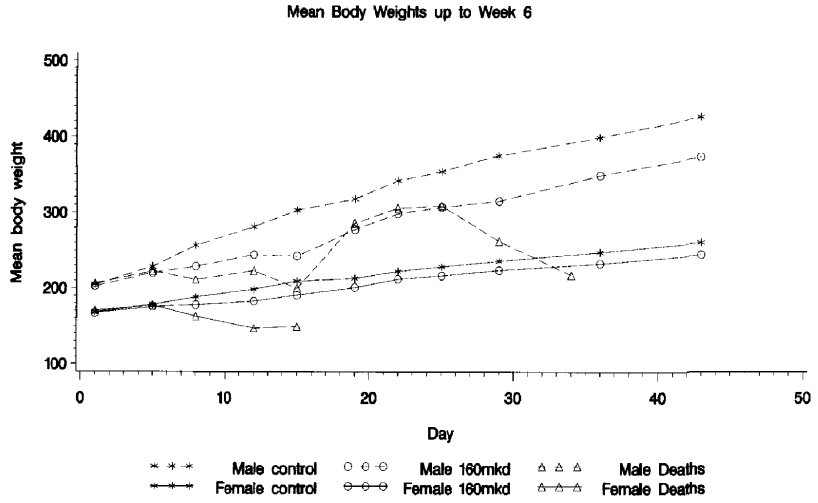
Endpoints	Time of observation
Clinical signs	Daily
Body weights	Predose, 1st day of dose, twice weekly for the first 4 weeks, weekly thereafter
Food consumption	Weekly
Ophthalmoscopy	No data
Hematology	No data
Clinical biochemistry	No data
Urinalysis	No data
Gross pathology	At sacrifice
Organ weight	At sacrifice
Histopathology	At sacrifice
Toxicokinetics	No data

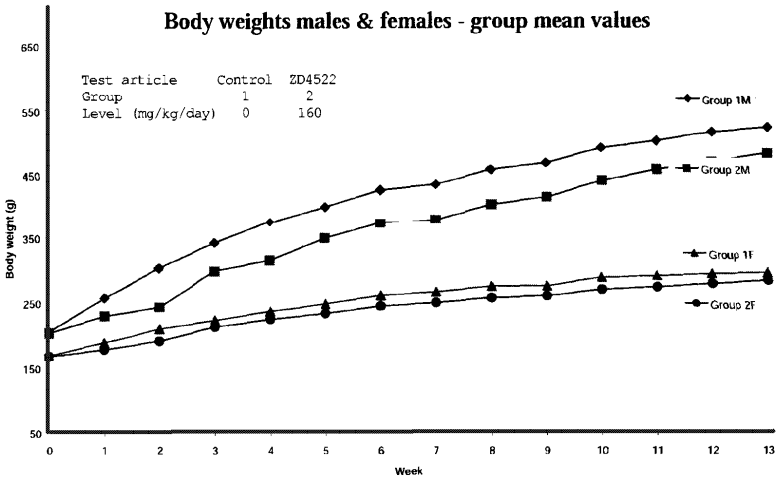
RESULTS:

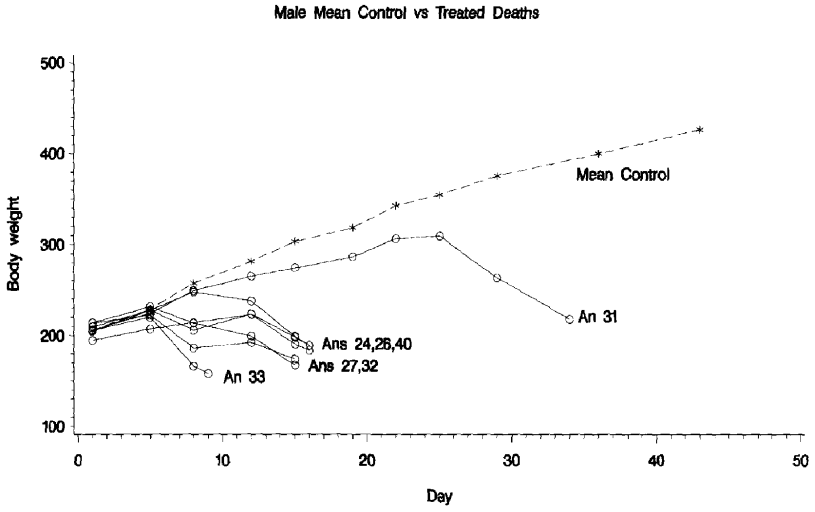
- Mortality: 7/20 males and 3/20 females were terminated early at week 2 (1M and 1F), week 3 (5M and 2F), and week 5 (1M), due to poor condition and/or body weight loss. No other deaths occurred thereafter.

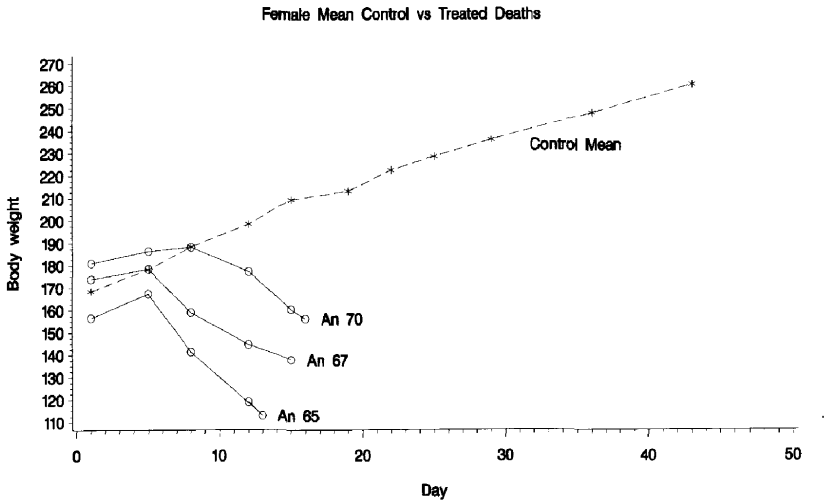
- Clinical signs:
  Early terminated animals: hunched, thin, sluggish, pale, cold, and having thinning fur
  Other treated animals: hair loss/thinning fur, salivation and paddling after dosing

- Body weight:
  7/20 males and 3/20 females showed different growth pattern than the rest of animals. These animals exhibited weight loss from the second week of dosing (-6% to –23% for males and –14% to –28% for females). Other rats appeared to grow normally.




Body weights males & females - group mean values
Test article Control ZD4522
Group 1 2
Level (mg/kg/day) 0 160
Group 1M
Group 2M
Group 1F
Group 2F
Body weight (g)
Week


Male Mean Control vs Treated Deaths
Body weight
Day
Mean Control
An 31
Ans 24,26,40
Ans 27,32
An 33



Body weight gains - group mean values and statistical analysis

Test article Control ZD4522
Group 1 2
Level (mg/kg/day) 0 160

Week of study		Mean body weight gains (g) for Group: 1M	2M	Statistics
Start to 4	Mean	170.2	114.0***	W
	SD	19.24	45.71	
Start to 13	Mean	317.6	281.1*	S
	SD	32.71	51.55	
5 to 8	Mean	58.6	54.0	ST
	SD	9.39	21.18	
9 to 13	Mean	54.4	67.0**	S
	SD	10.75	11.21	
		1F	2F	Statistics
Start to 4	Mean	67.8	57.3*	S
	SD	11.14	13.50	
Start to 13	Mean	126.8	115.9	S
	SD	15.00	19.01	
5 to 8	Mean	26.6	23.9	S
	SD	7.57	10.70	
9 to 13	Mean	20.1	22.9	S
	SD	4.46	4.87	

* P<0.05 W = Wilcoxon rank sum test
** P<0.01 S = two-sample t-test
*** P<0.001 T = log-transformed data

Body weight loss - decedents

Test article Control ZD4522
Group 1 2
Level (mg/kg/day) 0 160

Animal Number	Day Terminated	Initial body weight (g)	Peak Body Weight (g)	Termination body weight (g)	Decrease from initial body weight (%)	Decrease from peak body weight (%)	Difference between termination body weight and control group mean (%)
24M	16	194.1	222.8	183.1	-6	-18	-43
26M	16	204.4	231.1	188.7	-8	-19	-48
27M	15	213.8	227.3	227.3	-22	-26	-48
31M	34	205.1	308.8	217.4	+6	-30	-49
32M	15	213.2	221.8	173.7	-18	-28	-45
33M	9	205.4	219.5	157.6	-23	-28	-44
40M	16	209.0	246.7	188.8	-10	-23	-46
65F	13	156.4	167.2	112.8	-28	-33	-43
67F	15	173.8	178.4	129.2	-26	-28	-38
70F	16	180.9	188.1	156.1	-14	-17	-25

- Food consumption:
  Group mean food consumption was reduced up to 28% in treated animals during weeks 1 to 4 as compared to controls. The survivors began to return to levels comparable to control from week 3 onwards.

- Organ weight:
  Liver weight in treated females increased 10% compared to controls.

- Histopathology:
  Animals terminated at first 5 weeks:
  Most preterminal terminations were moribund sacrifice and tissues from most of these animals are available for analysis.
  Macroscopic finding includes thick cardia of the stomach in most decedents.
  Histopathological findings include changes in stomach, liver, kidney, duodenum, and spleen. Generally, these findings were infrequent, of a minor nature and consistent with the usual pattern of findings in animals of this strain and age.

  Animals sacrificed on day 91:
  Histopathological findings were similar to the early terminated animals (i.e. slight to minimal in severity). The only finding observed to be of moderate severity was hepatocyte basophilia. There were no histopathologic findings suggested that target organ toxicity would have lead to premature deaths.

	Males		Females	
	Control	S-4522	Control	S-4522
Incidence of selected microscopic findings in decedents				
No. examined	0	7	0	3
Stomach				
Squamous cell hyperplasia	0	7	0	3
Liver				
Hepatocyte basophilia –diffuse	0	7	0	3
Single cell necrosis	0	5	0	3
Cytomegaly/karyomegaly	0	2	0	2
Increased mitoses	0	4	0	3
Kupffer cell pigment	0	0	0	2
Kidney				
Tubular cell degeneration/regeneration	0	6	0	2
Incidence of selected microscopic findings in terminal killed animals				
No. examined	20	13	20	17
Stomach				
Squamous cell hyperplasia	0	3	0	6
Liver				
Hepatocyte basophilia –periportal	0	12	0	7
Basophilic focus	0	11	0	13
Clear cell/eosinophilic focus	0	7	0	2
Single cell necrosis	0	1	0	0
Cytomegaly/karyomegaly	0	11	0	7
Increased mitoses	0	4	0	3
Kupffer cell pigment	0	2	0	4
Oval cell hyperplasia	0	5	0	10

Summary and Conclusions

The rats were dosed with S4522 at 160 mg/kg for 91 days (high dose in the 2-year carcinogenicity study is 80 mg/kg/day).

7/20 males and 3/20 females were sacrificed at first five weeks due to poor condition and/or body weight reduction. Histopathological changes in these early terminated rats occurred in stomach, liver and kidney. Generally, these findings were infrequent, of a minor nature and consistent with the usual pattern of findings in animals of this strain and age.

Rest of the rats survived the 91-day treatment and appeared to be normal. Histopathological findings were similar to those observed in the early terminated rats.

Based on the results of this 91-day dose range-finding study, and the completed 2-year carcinogenicity study, the Reviewer have not been convinced that 160 mg/kg reached TMD.

Study Title: 13 WEEK ORAL DOSE RANGE FINDING STUDY IN RATS (TKR/3309)

NOTE: This study was intended to determine MTD and to support the dose selections for the 2-year carcinogenicity study in rats.

Study No.: 88/365
Amendment #, Vol #, and Page #: Electronic submission, file name: tkr3309f.pdf and kpr076.pdf
Date of submission: October 22, 2001
Conducting laboratory and location: (b) (4)
Date of study initiation: March 2001
GLP compliance: Yes
QA report: Yes

Methods: Dose range-finding study for 2-year carcinogenicity (completed by May 2000)
Dosing:

- Species/strain: Rats, Crl:CD(SD)IGSBR, from (b) (4)
- #/sex/group or time point:

Group number	Group description	Dose level (mg/kg/day)	Animals/group Main study		Satellites	
			Male	Female	Male	Female
1	control	0	15	15		
2	low	80	15	15	9	9
3	intermediate I	160	15	15	9	9
4	intermediate II	240	15	15	9	9
5	high	320	15	15	9	9

- Weight: male: 155.9-208.0 g, female: 133.6-166.7 g
- Age: 6 weeks
- Route: oral gavage, 10 ml/kg
- Diet: SQC Rat and Mouse Maintenance Diet No. 1

Drug: Lot number: ADM80802D01
Vehicle: 5% (w/v) aqueous Gum Arabic

Observations and times:
Clinical signs: daily.

Body weights: predose, 1st day of dose, twice weekly for the first 4 weeks, weekly thereafter.

Food consumption: daily.

Ophthalmoscopy: no data provided.

Hematology: at sacrifice. Haemoglobin concentration, red blood cell count, packed cell volume reticulocytes, mean cell volume, mean cell haemoglobin, mean cell haemoglobin concentration, haemoglobin distribution width, red cell distribution width, platelet count, platelet crit, mean platelet volume, platelet distribution width, total and differential white cell count, prothrombin time, activated partial thromboplastin time were measured.

Clinical chemistry: at sacrifice. AST, ALT, ALP, Na, K, Ca, P, Cl, total protein, albumin, globulin, A/G, total cholesterol, glucose, urea, total bilirubin, creatinine were measured.

Organ weights: at sacrifice.

Gross pathology: at sacrifice.

Histopathology: at sacrifice.

Toxicokinetics: at day 1, 29, and 92.

(b) (4) study number 88/365. Sponsor reference number TKR/3309.
Organs for histopathology

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

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

c see clinical pathology section d preserved with the head *in situ* f female only

† organ weighed š organ examined histopathologically

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

RESULTS:

- Mortality:
  Treatment-related death or kill in extremis were noted at doses ≥ 160 mg/kg in both sexes within the first 7 days of dosing. The remaining animals in ≥ 240 mg/kg groups were terminated during Week 2.

(b) (4) study number 88/365. Sponsor reference number TKR/3309.
Summary of premature mortalities at end of week 2

Group	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
(mg/kg/day)	0	80	160	240	320	0	80	160	240	320
Main test animals										
FD	0/15	0/15	2/15	2/15	3/15	0/15	0/15	0/15	0/15	3/15
KIE	0/15	0/15	6/15	8/15	8/15	0/15	0/15	6/15	7/15	8/15
Total Deaths	0/15	0/15	8/15	10/15**	11/15*	0/15	0/15	6/15	7/15**	11/15**
Satellite animals										
FD	-	0/9	3/9	#6/9	3/9	-	0/9	2/9	3/9	2/9
KIE	-	0/9	3/9	1/9	1/9	-	0/9	1/9	2/9	3/9
Total Deaths	-	0/9	6/9	7/9**	4/9*	-	0/9	3/9	5/9**	5/9**

* all remaining group 5 male animals sent to necropsy on Day 9 # 1 animal died awaiting necropsy
** all remaining animals in these groups sent to necropsy on Day 12
FD Found dead
KIE Killed in extremis (signs including, extremely thin, severely hunched, laboured breathing, lethargic, only moving when provoked, excessive bodyweight loss and very poor food consumption)

At the end of 13 weeks of treatment, 2/24 males at 80 mg/kg died or were killed in extremis.

(b) (4) study number 88/365. Sponsor reference number TKR/3309.
Summary of premature mortalities at end of week 13

Group	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
(mg/kg/day)	0	80	160	240	320	0	80	160	240	320
Main test animals										
FD	0/15	1/15	2/15	2/15	3/15	0/15	0/15	1/15	0/15	3/15
KIE	0/15	1/15	10/15	8/15	8/15	0/15	0/15	9/15	7/15	8/15
Total Deaths	0/15	2/15	12/15	10/15**	11/15*	0/15	0/15	10/15	7/15**	11/15**
Satellite animals										
FD	-	0/9	3/9	#6/9	3/9	-	0/9	3/9	3/9	2/9
KIE	-	0/9	5/9	1/9	1/9	-	0/9	2/9	2/9	3/9
Total Deaths	-	0/9	8/9	7/9**	4/9*	-	0/9	5/9	5/9**	5/9**

* all remaining group 5 male animals sent to necropsy on Day 9 # 1 animal died awaiting necropsy
** all remaining animals in these groups sent to necropsy on Day 12
FD Found dead
KIE Killed in extremis (signs including, extremely thin, severely hunched, laboured breathing, lethargic, only moving when provoked, excessive bodyweight loss and very poor food consumption)

Treatment-related macroscopic and microscopic findings were observed in a number of tissues, but with no specific finding considered to be primarily associated with cause of death.

- Clinical signs:
  Salivation and paddling of the forelimbs, thinning fur, hair loss, sores/lesions, shedding/peeling skin, ocular discharge, thinness and being hunched were seen post dosing in animals at ≥ 160 mg/kg. Abnormal gait was observed in animals at 320 mg/kg/day from day 6 of the study.

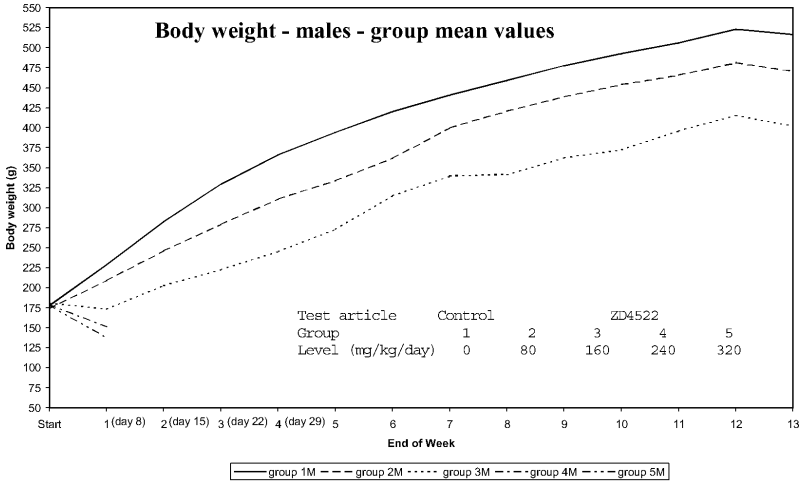
  Several animals at 80 mg/kg/day were noted as having thinning fur, as was one control animal. One male in the 80 mg/kg/day group (animal number 20) was sent to necropsy due to poor condition in week 7 after being described as very thin and hunched, pale, uncoordinated and as having clear discharge from both eyes and soft yellow faeces.

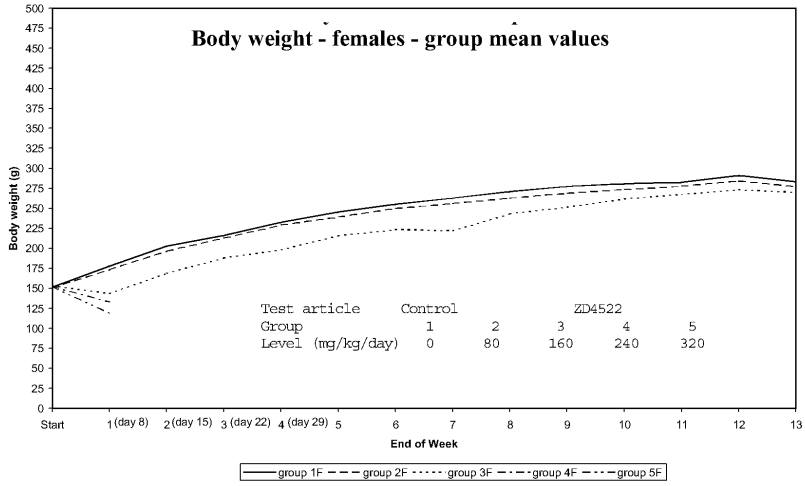
- Body weight:
  Body weight loss was observed at ≥ 160 mg/kg during first week of dosing. Animals at 320 mg/kg/day lost 20% to 30% of their starting weight and animals at 240 mg/kg/day lost 10% to 20% of their starting body weight.

  Animals at 160 mg/kg lost body weight during the first week and then increased throughout the study. Compared to controls, the body weights in males were 80% and

78% of controls on week 2 and 13, and were 85% and 95% of controls in females on week 2 and 13.

Body weight in animals at 80 mg/kg/day increased throughout the study in both sexes. In the males, body weights were 87% and 91% of controls on week 2 and 13. While body weight gain was reduced by 30% during the first three weeks of the study. No effect was noted in females.





(b) (4) study number 88/365. Sponsor reference number TKR/3309.
Body weight gains - group mean values and statistical analysis

Test article	Control	ZD4522			
Group	1	2	3	4	5
Level (mg/kg/day)	0	80	160	240	320

Week of study		Mean body weight gains (g) for Group: 1M	2M	3M	4M	5M	Statistics
Start to 3	Mean	151.9	105.4***	44.2***	.	.	A
	SD	17.88	40.42	28.90	.	.	
Start to 6	Mean	242.4	188.4*	134.4**	.	.	A
	SD	29.12	67.19	23.23	.	.	
Start to 13	Mean	338.8	297.1*	221.4***	.	.	A
	SD	38.85	40.63	53.51	.	.	
3 to 6	Mean	90.6	81.5	71.2	.	.	A
	SD	14.90	28.97	30.99	.	.	
6 to 13	Mean	96.4	92.9	87.0	.	.	A
	SD	15.97	17.69	31.33	.	.	
		1F	2F	3F	4F	5F	Statistics
Start to 3	Mean	64.3	61.9	33.8***	.	.	A
	SD	12.53	9.95	21.85	.	.	
Start to 6	Mean	103.7	99.1	70.9**	.	.	A
	SD	16.23	13.01	28.75	.	.	
Start to 13	Mean	131.7	126.4	118.3	.	.	A
	SD	22.27	17.68	11.87	.	.	
3 to 6	Mean	39.4	37.2	34.0	.	.	A
	SD	6.55	6.76	8.59	.	.	
6 to 13	Mean	28.0	27.3	36.6	.	.	A
	SD	8.64	9.02	6.41	.	.	

* P<0.05
** P<0.01
*** P<0.001

A ANOVA, regression and Dunnett's

- Food consumption:
  Food consumption at 240 mg/kg/day was reduced in week 1 by 57% in males and 45% in females when compared to control values. At 320 mg/kg/day, group mean food consumption was reduced by 72% in males and 57% in females during week 1.

  Dosing at 160 mg/kg/day resulted in a reduction in food consumption of 35% in males ($p<0.001$) and 17% in females ($p<0.01$) during the first six weeks. During weeks 7-13, food consumption in males remained reduced by 12% when compared to controls ($p<0.01$) whereas in females food consumption returned to values comparable to those of controls.

Group mean food consumption was reduced by 16% in males at 80 mg/kg/day during the first six weeks of the study when compared to controls ($p<0.001$). During weeks 7-13, however, food consumption in this group was not significantly different to controls. No effect on food consumption was seen in females at this dose.

(b) (4)study number 88/365. Sponsor reference number TKR/3309.
Food consumption over selected intervals - group mean values and statistical analysis

Test article	Control	ZD4522			
Group	1	2	3	4	5
Level (mg/kg/day)	0	80	160	240	320

Week of study		Mean food consumption (g/animal/week) for Group: 1M	2M	3M	4M	5M	Statistics
1 to 3	Mean	190.6	157.1*	98.5***	.	.	A2
	SD	7.28	5.48	26.69	.	.	
1 to 6	Mean	193.1	162.9***	126.4***	.	.	A2
	SD	5.35	4.48	18.53	.	.	
1 to 13	Mean	191.4	171.5**	148.8***	.	.	A2
	SD	4.69	4.58	15.27	.	.	
4 to 6	Mean	195.5	168.6	139.3	.	.	DR* J1
	SD	3.46	4.90	44.83	.	.	
7 to 13	Mean	189.9	178.9	168.0**	.	.	A2
	SD	4.17	7.58	12.45	.	.	
		1F	2F	3F	4F	5F	Statistics
1 to 3	Mean	131.6	129.1	90.4**	.	.	A2
	SD	3.87	2.80	20.76	.	.	
1 to 6	Mean	133.0	132.3	110.5**	.	.	A2
	SD	4.30	1.68	5.56	.	.	
1 to 13	Mean	131.7	131.0	120.3	.	.	DR* A2
	SD	2.87	1.64	5.31	.	.	
4 to 6	Mean	134.3	135.6	130.5	.	.	J1
	SD	5.20	0.62	12.87	.	.	
7 to 13	Mean	130.7	129.8	128.6	.	.	A2
	SD	1.80	1.59	7.09	.	.	

* P<0.05
** P<0.01
*** P<0.001
DR significant dose response test

A2 two-way ANOVA, regression and Dunnett's
J1 Terpstra-Jonckheere test

- Hematology: no apparent treatment related change.

- Clinical chemistry:
  Statistically significant increases of ALT, AST and ALP were observed in both 80 and 160 mg/kg groups.

(b) (4) study number 88/365. Sponsor reference number TKR/3309.
Clinical chemistry - group mean values and statistical analysis

Occasion: Week 13

Test article	Control	ZD4522			
Group	1	2	3	4	5
Level (mg/kg/day)	0	80	160	240	320

Group/ Sex	AST IU/L	ALT IU/L	ALK PHOS IU/L	Na mmol/L	K mmol/L	Cl mmol/L
1M Mean	87	42	194	143	4.7	101
SD	16	8	45	1	0.3	2
2M Mean	167***	71***	316***	142	4.8	102
SD	38	17	52	1	0.3	2
3M Mean	117	42	252	141*	4.8	101
SD	11	6	70	1	0.1	1
Statistics	A	A	A	A	A	A
1F Mean	90	42	160	144	4.1	103
SD	35	11	42	2	0.5	1
2F Mean	97	59*	201	143*	4.5	103
SD	19	22	81	2	0.5	2
3F Mean	128	57	303***	142**	4.8*	103
SD	59	23	102	1	0.4	2
Statistics	A	A	A	A	A	A

* P<0.05
** P<0.01
*** P<0.001

A ANOVA, regression and Dunnett's

- Organ weight:
  Liver weight in females increased 15% and 22% for 80 and 160 mg/kg groups, respectively.

- Histopathology:
  Animals died or premature terminated:
  Dose related histopathological findings include degenerative, inflammatory or proliferative changes in various epithelial tissues, namely the liver, kidney, gastrointestinal tract, pancreas, skin, skeletal muscle and salivary gland; atrophic changes in lymphohaemopoietic tissues and changes in some endocrine related tissues; namely the adrenal and the female reproductive tract.

Incidence of selected microscopic findings: decedents

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	80	160	240	320	0	80	160	240	320
Liver	No. Examined:	0	2	12	15	14	0	0	10	15	15
hepatocyte basophilia		0	2	12	14	12	0	0	10	12	15
single cell necrosis		0	1	4	9	10	0	0	6	12	12
cytomegaly/karyomegaly		0	1	11	10	9	0	0	8	10	8
increased mitosis		0	1	5	4	6	0	0	3	5	7
hepatocyte vacuolation		0	1	9	12	9	0	0	7	14	13
oval cell hyperplasia		0	1	1	0	0	0	0	2	0	0
Kidney	No. Examined:	0	2	12	15	14	0	0	10	15	15
tubular cell degeneration/regeneration		0	2	11	13	10	0	0	6	5	10
Stomach	No. Examined:	0	2	12	15	15	0	0	10	15	15
hyperkeratosis		0	2	12	14	14	0	0	9	12	15
squamous cell hyperplasia		0	2	10	14	9	0	0	10	9	13
erosion/ulcer: forestomach		0	0	3	5	2	0	0	6	2	1
Duodenum	No. Examined:	0	2	11	14	14	0	0	10	15	15
villous atrophy		0	0	4	6	6	0	0	1	4	6
Jejunum	No. Examined:	0	2	12	14	13	0	0	8	14	14
villous atrophy		0	0	2	6	3	0	0	0	2	4
Ileum	No. Examined:	0	2	11	14	13	0	0	10	15	15
villous atrophy		0	0	3	5	1	0	0	1	3	6
Caecum	No. Examined:	0	1	12	14	13	0	0	10	15	15
caecitis		0	1	8	7	5	0	0	5	7	7
Colon	No. Examined:	0	2	12	14	13	0	0	10	15	15
colitis		0	0	4	4	2	0	0	0	0	3
Pancreas	No. Examined:	0	2	12	15	14	0	0	10	15	15
prominent zymogen granules		0	2	11	12	9	0	0	3	4	5
acinar cell degeneration/vacuolation		0	0	5	3	4	0	0	0	2	1
Skin + Subcutis	No. Examined:	0	2	12	15	15	0	0	10	15	15
acanthosis		0	0	8	9	6	0	0	7	5	11
dermatitis/folliculitis		0	1	2	2	0	0	0	0	1	4
myopathy: panniculus muscle		0	1	5	1	0	0	0	5	3	4
myopathy: abdominal muscle		0	0	0	0	0	0	0	1	0	0
Salivary Gland	No. Examined:	0	2	12	15	15	0	0	10	15	15
ductular cell degeneration/adenitis		0	1	5	9	9	0	0	3	4	5
Thymus	No. Examined:	0	2	12	15	15	0	0	8	15	15
atrophy		0	2	12	15	15	0	0	8	10	14
Spleen	No. Examined:	0	2	12	15	14	0	0	10	15	15
lymphoid atrophy		0	1	10	11	10	0	0	7	7	11
Femur + Marrow	No. Examined:	0	2	12	14	15	0	0	10	15	15
marrow atrophy		0	0	3	7	6	0	0	8	6	11
myopathy		0	1	1	0	0	0	0	0	1	0

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	80	160	240	320	0	80	160	240	320
Sternum + Marrow	No. Examined:	0	2	12	15	15	0	0	10	15	15
marrow atrophy		0	0	6	7	5	0	0	8	8	9
Mandibular Lymph node	No. Examined:	0	2	12	14	15	0	0	10	15	15
atrophy		0	0	6	8	7	0	0	4	4	6
Mesenteric Lymph node	No. Examined:	0	2	12	15	14	0	0	10	15	15
atrophy		0	2	11	11	12	0	0	9	7	10
Adrenal	No. Examined:	0	2	12	15	14	0	0	10	15	15
acute zonal cortical congestion		0	0	3	6	1	0	0	0	4	5
cortical hypertrophy		0	0	3	3	4	0	0	1	1	1
Vagina	No. Examined:	0	0	0	0	0	0	0	10	15	14
dioestrus		0	0	0	0	0	0	0	10	15	14

Animals sacrificed on day 91:

Fewer treatment-related changes were seen at the terminal kill than in the decedents. The main treatment-related changes were in the liver, with changes in the gastrointestinal tract and skin in only a small number of animals.

Incidence of selected microscopic findings: terminal kill

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	80	160	240	320	0	80	160	240	320
Liver	No. examined: :	15	13	3	0	0	15	15	5	0	0
hepatocyte basophilia		0	9	3	0	0	0	7	5	0	0
single cell necrosis		0	1	0	0	0	0	1	1	0	0
cytomegaly/karyomegaly		0	10	3	0	0	0	2	5	0	0
increased mitoses		0	1	0	0	0	0	0	1	0	0
hepatocyte vacuolation		1	2	0	0	0	2	8	5	0	0
basophilic focus		0	9	3	0	0	0	10	2	0	0
eosinophilic focus		0	5	3	0	0	0	0	1	0	0
vacuolated focus		0	6	1	0	0	0	3	3	0	0
oval cell hyperplasia		0	8	3	0	0	0	5	5	0	0
Skin+subcutis	No. examined: :	15	13	3	0	0	15	15	5	0	0
acanthosis		0	0	0	0	0	0	2	0	0	0
dermatitis/folliculitis		0	0	0	0	0	0	0	1	0	0
Stomach	No. examined: :	15	13	3	0	0	15	15	5	0	0
hyperkeratosis		0	1	1	0	0	0	1	0	0	0
Colon	No. examined: :	15	13	3	0	0	15	15	5	0	0
colitis		0	0	1	0	0	0	0	0	0	0

- Toxicokinetics:
  Great inter-animal variability was noted in both sexes, irrespective of the dose level administered or duration of dosing.

  The systemic exposure of male and female rats generally increased in a greater than dose-proportional manner over the dose range studied (80 to 320 mg/kg/day).

No apparent sex-related difference in systemic exposure after single oral administration. After repeated dosing at 80 mg/kg/day, the systemic exposure in male rats appeared to be greater than that in female rats.

There was no apparent accumulation of ZD4522 in male or female rats following once daily dosing for 3 months at 80 mg/kg/day.

		Male Rats		Female Rats	
Dose (mg/kg/day)	Study Timepoint	C_{max} (ng/ml)	$AUC_{(0-24)}$ (ng.h/ml)	C_{max} (ng/ml)	$AUC_{(0-24)}$ (ng.h/ml)
80	Day 1	1900	7530	7060	7130
160	Day 1	11600	50500	42900	52400
240	Day 1	26100	134000	26900	71800
320	Day 1	33500	162000	61300	144000
80	Day 28	12500	17100	6910	4390
80	Month 3	4710	9370	4160	4800

Data was unavailable at higher dose levels due to termination of dosing.

DBIT1172 (AstraZeneca Reference Number D4522 KPR076). Individual and mean (± SD) concentrations of ZD4522 in plasma following single (Day 1) oral administration of ZD4522 to male and female rats at a target dose level of 80 mg/kg/day

Male Rats

Time (h)	Animal Number	Concentration (ng/ml)	Mean (ng/ml)	SD (ng/ml)	CV (%)
Pre-dose	151	BLQ	BLQ	-	-
	152	BLQ			
	153	BLQ			
0.167	154	699	835	338	40.5
	155	587			
	156	1220			
0.333	157	1000	674	285	42.3
	158	475			
	159	547			
0.5	151	2120	1770	578	32.7
	152	2080			
	153	1100			
0.75	154	1490	1170	324	27.7
	155	1170			
	156	843			
1	157	1400	1740	941	54.1
	158	1010			
	159	2800			
1.5	151	990	1900	1750	92.1
	152	3920			
	153	797			
2	154	2120	1190	842	70.8
	155	482			
	156	962			
4	157	258	376	108	28.7
	158	471			
	159	398			
8	151	464	395	62.4	15.8
	152	380			
	153	342			
12	154	126	84.7	50.4	59.5
	155	99.5			
	156	28.5			
24	157	6.78	22.9	26.6	116
	158	8.19			
	159	53.6			

BLQ = Below the limit of quantification of the assay (b) (4)

DBIT1172 (AstraZeneca Reference Number D4522 KPR076). Individual and mean (± SD) concentrations of ZD4522 in plasma following single (Day 1) oral administration of ZD4522 to male and female rats at a target dose level of 80 mg/kg/day (continued)

Female Rats

Time (h)	Animal Number	Concentration (ng/ml)	Mean (ng/ml)	SD (ng/ml)	CV (%)
Pre-dose	187	BLQ	BLQ	-	-
	188	BLQ			
	189	BLQ			
0.167	190	524	460	105	22.8
	191	339			
	192	516			
0.333	193	1440	689	651	94.5
	194	289			
	195	337			
0.5	187	8490	7060	4530	64.2
	188	1990			
	189	10700			
0.75	190	1200	1120	151	13.5
	191	944			
	192	1210			
1	193	4290	2240	1840	82.1
	194	719			
	195	1710			
1.5	187	2370	1610	714	44.3
	188	951			
	189	1520			
2	190	507	398	129	32.4
	191	431			
	192	255			
4	193	533	637	152	23.9
	194	566			
	195	812			
8	187	235	184	52.0	28.3
	188	185			
	189	131			
12	190	27.3	41.8	20.9	50.0
	191	65.7			
	192	32.3			
24	193	15.6	10.1	4.76	47.1
	194	6.84			
	195	7.99			

BLQ = Below the limit of quantification of the assay (b) (4)

DBIT1172 (AstraZeneca Reference Number D4522 KPR076). Individual and mean (± SD) concentrations of ZD4522 in plasma following repeated (Day 28) oral administration of ZD4522 to male and female rats at a target dose level of 80 mg/kg/day

Male Rats

Time (h)	Animal Number	Concentration (ng/ml)	Mean (ng/ml)	SD (ng/ml)	CV (%)
Pre-dose	151	41.7	23.7	15.7	66.2
	152	16.9			
	153	12.5			
0.167	154	1460	1340	740	55.2
	155	542			
	156	2010			
0.333	157	15100	12500	7310	58.5
	158	4210			
	159	18100			
0.5	151	1170	5200	3790	72.9
	152	8690			
	153	5730			
0.75	154	5690	3930	1540	39.2
	155	2840			
	156	3250			
1	157	5920	5660	2570	45.4
	158	2970			
	159	8090			
1.5	151	3640	3000	572	19.1
	152	2820			
	153	2540			
2	154	786	623	160	25.7
	155	466			
	156	617			
4	157	2620	1210	1250	103
	158	228			
	159	779			
8	151	300	756	674	89.2
	152	438			
	153	1530			
12	154	490	196	255	130
	155	53.7			
	156	43.2			
24	157	14.9	24.1	25.6	106
	158	4.38			
	159	53.0			

DBIT1172 (AstraZeneca Reference Number D4522 KPR076). Individual and mean (± SD) concentrations of ZD4522 in plasma following repeated (Day 28) oral administration of ZD4522 to male and female rats at a target dose level of 80 mg/kg/day (continued)

Female Rats

Time (h)	Animal Number	Concentration (ng/ml)	Mean (ng/ml)	SD (ng/ml)	CV (%)
Pre-dose	187	4.72	11.6	9.27	79.9
	188	22.1			
	189	7.83			
0.167	190	186	420	404	96.2
	191	187			
	192	886			
0.333	193	286	610	299	49.0
	194	668			
	195	875			
0.5	187	5360	6910	5390	78.0
	188	2460			
	189	12900			
0.75	190	452	655	204	31.1
	191	652			
	192	860			
1	193	910	649	246	37.9
	194	421			
	195	617			
1.5	187	1120	1020	487	47.7
	188	491			
	189	1450			
2	190	139	214	67.7	31.6
	191	271			
	192	231			
4	193	296	295	71.0	24.1
	194	223			
	195	365			
8	187	149	112	36.0	32.1
	188	111			
	189	77.0			
12	190	36.4	29.4	13.1	44.6
	191	14.3			
	192	37.4			
24	193	2.69	4.67	1.88	40.3
	194	6.43			
	195	4.90			

DBIT1172 (AstraZeneca Reference Number D4522 KPR076). Individual and mean (± SD) concentrations of ZD4522 in plasma following repeated (Month 3) oral administration of ZD4522 to male and female rats at a target dose level of 80 mg/kg/day

Male Rats

Time (h)	Animal Number	Concentration (ng/ml)	Mean (ng/ml)	SD (ng/ml)	CV (%)
Pre-dose	151	1.25	2.36	1.60	67.8
	152	4.20			
	153	1.64			
0.167	154	3510	1810	1480	81.8
	155	1130			
	156	791			
0.333	157	3410	4710	4620	98.1
	158	882			
	159	9840			
0.5	151	2680	2050	1560	76.1
	152	3190			
	153	272			
0.75	154	6930	3160	3260	103
	155	1290			
	156	1260			
1	157	3750	2800	2190	78.2
	158	4360			
	159	291			
1.5	151	1040	654	505	77.2
	152	839			
	153	83.1			
2	154	1750	1490	322	21.6
	155	1130			
	156	1590			
4	157	182	171	55.8	32.6
	158	111			
	159	221			
8	151	163	182	30.1	16.5
	152	167			
	153	217			
12	154	307	255	170	66.7
	155	394			
	156	65.0			
24	157	26.6	90.5	58.7	64.9
	158	103			
	159	142			

DBIT1172 (AstraZeneca Reference Number D4522 KPR076). Individual and mean (± SD) concentrations of ZD4522 in plasma following repeated (Month 3) oral administration of ZD4522 to male and female rats at a target dose level of 80 mg/kg/day (continued)

Female Rats					
Time (h)	Animal Number	Concentration (ng/ml)	Mean (ng/ml)	SD (ng/ml)	CV (%)
Pre-dose	187	2.08	1.42	0.821	57.8
	188	1.68			
	189	BLQ			
0.167	190	751	477	239	50.1
	191	312			
	192	367			
0.333	193	3430	4160	3290	79.1
	194	1300			
	195	7750			
0.5	187	4720	3570	2300	64.4
	188	926			
	189	5070			
0.75	190	637	434	188	43.3
	191	266			
	192	400			
1	193	684	714	43.0	6.02
	194	694			
	195	763			
1.5	187	174	266	129	48.5
	188	357			
	189	BLQ*			
2	190	216	152	74.1	48.8
	191	170			
	192	71.0			
4	193	430	200	199	99.5
	194	81.2			
	195	89.8			
8	187	108	194	141	72.7
	188	357			
	189	117			
12	190	371	139	201	145
	191	14.0			
	192	30.6			
24	193	14.6	15.3	10.4	68.0
	194	5.18			
	195	26.0			

* = Below the limit of quantification of the assay (b) (4); insufficient sample for re-analysis (excluded from calculation of summary statistics)
BLQ = Below the limit of quanitification of the assay (b) (4) taken as LOQ for calculation of summary statistics

Summary and Conclusions

The rats were dosed with S4522 at doses of 80, 160, 240, and 320 mg/kg for 13 weeks. The experiment conditions (animal strain, diet, etc) were the same as the 2-year carcinogenicity study.

320 mg/kg: 15/24 males and 15/24 females died or were killed in extremis within the first 7 days of dosing. The remaining animals were terminated during week 2. Clinical signs including salivation and paddling of the forelimbs, thinning fur, hair loss, sores/lesions, shedding/peeling skin, ocular discharge, thinness and being hunched. Body weight lost 20 – 30% during first week of dosing. Marked decrease in food consumption (57-72%). Histopathological findings including degenerative, inflammatory or proliferative changes in various epithelial tissues, namely the liver,