3.2.9. 52-Week Oral Toxicity Study of Telmisartan in Dogs (Study #66R, Report #U94-2105) Vol. 42-44

This GLP study was conducted by[ ] between January 25, 1993 and February 6, 1994.

Male and female beagle dogs were approximately 9 to 10 months of age and weighed 9.1-11.8 kg (males) or 8.4-11.9 kg (females) at the start of the study. The test substance (batches 8230231, 8330441) was weighed separately for each animal each day based on the individual body weight and administered as a suspension in 0.5% Natrosol® 250HX (hydroxyethylcellulose) at a volume of 10 ml/kg body weight. The control animals received the same quantity of 0.5% Natrosol® 250HX. Telmisartan was given each day in the morning, using a stomach tube, for 52 weeks, 7 days a week at doses of 5, 50 or 500 mg/kg. Each group consisted of 4 male and 4 female dogs. The animals were housed in groups in kennels. The doses were selected on the basis of a 4 week toxicity study in which individual alterations of the gastro intestinal mucosa were observed at 40 or more mg/kg/day and a 13 week toxicity study in which marginal alterations of the stomach mucosa were observed in a few animals that received 50 mg/kg/day. Other changes in these subchronic dog studies were decreased hematological parameters and hypertrophy and hyperplasia of the juxtaglomerular apparatus at 10 or more mg/kg/day.

Observations and Measurements

Clinical Observations: at least twice daily on working days (once on non-working days).
Water Consumption: daily.
Body Weight and Food Consumption: weekly.
Blood Pressure (from the femoral artery of hind leg): weeks -1 (prestudy), 12, 25 and 51 at 0 and 2 hr after administration.
Heart Rate and ECG: weeks -1 (prestudy), 12, 25 and 51 at 0, 2 and 5 hr after administration.
Ophthalmoscopic Examination: week -2 and during study weeks 13, 26 and 52.
Hematology and Clinical Chemistry: weeks -1, 13, 26, 40 and 52 of the study.
Urinalysis: weeks -2, 13, 26, 39, 51 (naturally voided urine in the morning for these five intervals), and 53 (obtained at necropsy by puncturing the urinary bladder).
Feces Examined for Occult Blood: weeks 14, 25/26, 39 and 51 of the study.
Plasma Renin and Aldosterone levels: week 52 (day and time of collection not given).
Plasma Telmisartan Levels: study days 1 and 361 (at 0, 1, 2, 4, 7, 15 and 24 hr postdose), 193 (at 0, 1, 2, 4, and 7 hr postdose), and 319 (at 0, 1, 2 4, 7 and 24 hr postdose).
Gross Pathology: a complete necropsy was performed on all animals, and all macroscopic changes were recorded.
Histopathology and Organ Weights: the following organs or tissues were collected from all animals on study (Table 3.2.9.1). Of the organs listed below both eyes were fixed in Davidson solution; all other tissues were fixed in 10% neutral buffered formalin. Representative sections of all tissues collected at necropsy from all animals were processed.

TABLE 3.2.9.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenals*
Aorta
Bone marrow
Brain*
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with optic nerves
Femur
Gall bladder
Heart*
Ileum
Jejunum
Kidneys*
Liver*
Lungs*
Lymph nodes -jejunalis
-popliteus
-cervicalis
Mammary glands
Ovaries
Pancreas
Parotids
Pituitary*
Prostate
Rectum
Submandibular salivary glands
Sublingual salivary glands
Sciatic nerve, peripheral
Skeletal muscle
Skin
Spinal cord (neck, chest, lumbar)
Spleen*
Stomach - cardia
- fundus
- pylorus
Testes
Thymus
Thyroid*/parathyroid glands
Tongue
Trachea
Urinary bladder
Uterus

*organ weighed

Results

One high dose female was killed in extremis at the end of the 14th week of treatment, after presenting with apathy, pallor, hypothermia and hemorrhagic diarrhea. This animal, on treatment day 97, prior to killing, showed no food intake and vomiting. It also showed elevated levels of total bilirubin, total protein, glucose, urea nitrogen and creatinine compared to controls. Death of this animal was attributed to esophageal lesions caused by mechanical irritation from the gavage apparatus, resulting in a debilitated condition. During the first week, all males and two females from the high dose group vomited at least once. In subsequent weeks, vomiting was observed in all high dose animals sporadically and in an irregular manner. The feces of all high dose animals were discolored white from day 1 of administration until study termination, suggesting unabsorbed test substance. There were no variations in body weight gain in males that could be attributed to drug treatment (Fig. 3.2.9.1, top panel). However, one dog in each of the 50 mg/kg/day and 500 mg/kg/day groups showed decreased weight gain over the entire study period or from the first week of the study until week 35, respectively. In the case of females, both the mid and high dose group animals displayed a body weight loss (mean) for the entire study period and it was dose-dependent (Fig. 3.2.9.1, lower panel). However, females of the mid dose group regained their initial body weights by the end of the 52 week treatment period (Table 3.2.9.2).

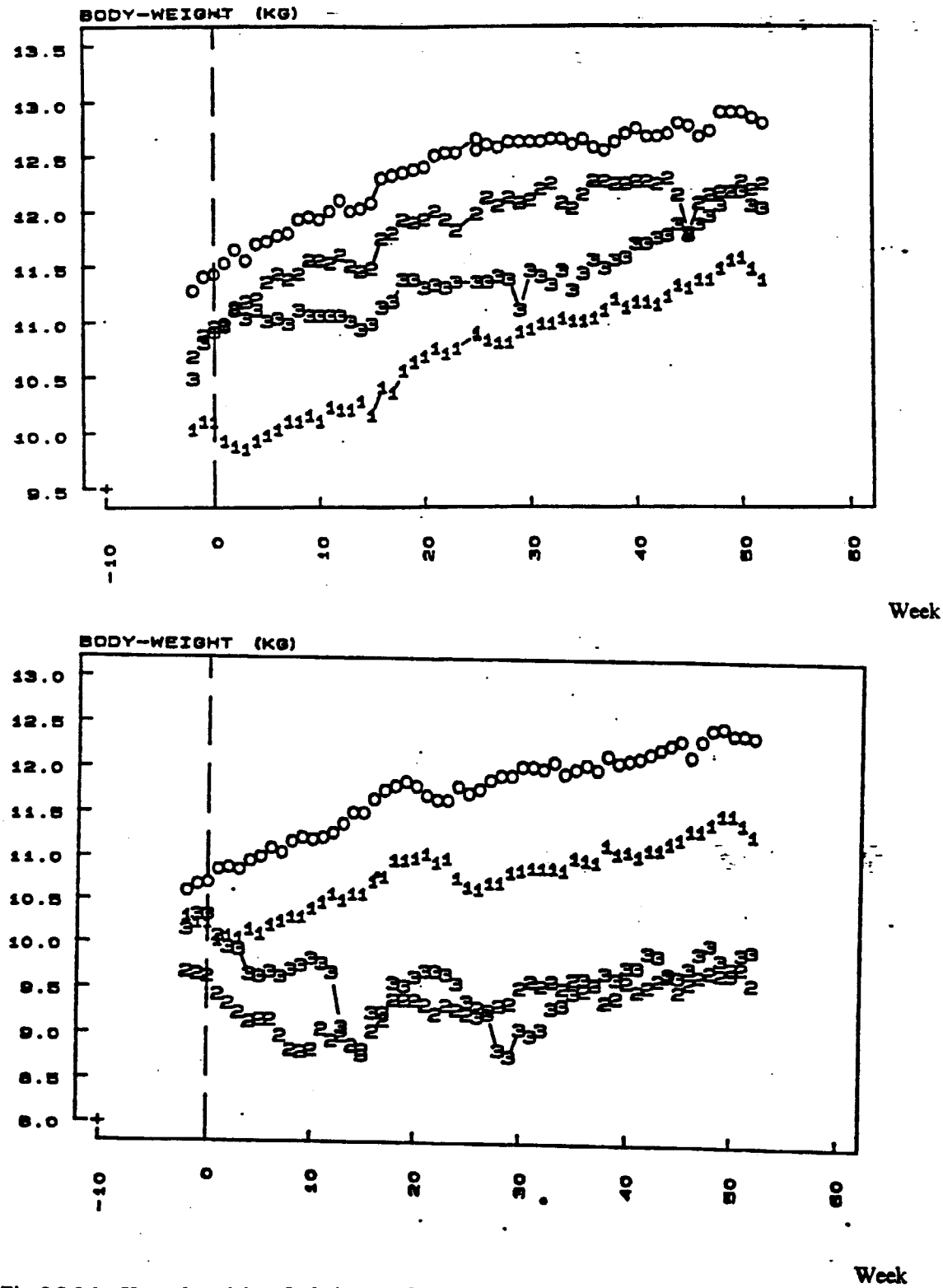


Fig. 3.2.9.1.: 52-week toxicity of telmisartan. Group mean body weight changes in male (top) and female (bottom) dogs. 0: Control, 1: 5 mg/kg/day, 2: 50 mg/kg/day, 3: 500 mg/kg/day.

TABLE 3.2.9.2
MEAN BODY WEIGHT GAINS[1] FOR VARIOUS STUDY WEEKS

Week		1		4		13		26		39		52	
Dose mg/kg/d		diff[1]	%	diff	%	diff	%	diff	%	diff	%	diff	%
Contl	M	0.1	0.89	0.3	2.43	0.6	5.05	1.2	10.29	1.3	11.19	1.4	12.05
	F	0.2	1.44	0.3	2.29	0.7	6.41	1.1	10.13	1.4	2.67	1.7	15.66
5	M	-0.2	-1.68	-0.2*	-1.68	0.1	1.08	0.7	7.21	1.0	10.15	1.3	12.73
	F	-0.2	-2.01	-0.1	-0.70	0.3	3.10	0.4	4.65	0.9	9.02	1.1	11.06
50	M	0.0	0.18	0.2	2.24	0.5	4.82	1.1	10.29	1.3	1.37	1.3	11.41
	F	-0.2	-2.22	-0.5	-5.23	-0.6*	-6.54	-0.3*	-3.56	-0.2*	-2.40	0.0*	-0.30
500	M	0.1	0.50	0.2	1.88	0.1	0.75	0.5	3.92	0.7	5.92	1.1	10.22
	F	-0.2	-2.46	-0.6	-6.53	-1.2*	-12.14	-1.1*	-2.13	-0.7*	-7.99	-0.3*	-4.86

[1]: Mean body weight gain is expressed as weight differences (kg) from initial weight (week -1)
*: Values significantly different ($p < 0.05$) from control group

No significant differences in food intake were observed for males except for one mid dose and one high dose animal. In the case of females, 3 of 4 mid dose and all high dose animals showed decreased food intake for most of the study. No differences in water consumption were noted.

Significant decreases in systolic and diastolic blood pressure, lasting 24 hr, were observed in all groups treated with telmisartan throughout the dosing period (Table 3.2.9.3). The degree of blood pressure reduction was constant during the administration period. The lack of dose-dependency and the absence of further decrease of b.p. after dosing demonstrate that maximum effects lasting over 24 hr were already achieved at the lowest dose of 5 mg/kg. No changes in heart rate or ECGs were observed during the study period.

TABLE 3.2.9.3
EFFECT OF TELMISARTAN ON BLOOD PRESSURE IN 52-WEEK ORAL TOXICITY STUDY IN DOGS (GROUP MEAN VALUES).
Results are expressed as changes in systolic/diastolic b.p. (% change from prestudy week values)

Dose (mg/kg/day)	WEEK OF ADMINISTRATION		
	12	25	51
Control	+ 13.3/ + 11.2	+ 0.8/ - 2.1	+ 8.6/ - 0.1
5	- 15.3/ - 33.1	- 23.7/ - 39.5	- 15.8/ - 33.6
50	- 26.5/ - 44.7	- 23.8/ - 38.2	- 19.7/ - 38.9
500	- 23.1/ - 42.0	- 27.4/ - 42.4	- 30.6/ - 55.8

Opthalmoscopic examination revealed dilated retinal blood vessels in the fundic area in animals receiving 50 and 500 mg/kg/day. This change is attributed to local or systemic vasodilation caused by the administration of telmisartan (the result of angiotensin II receptor antagonism).

Slight but significant decreases in erythrocyte parameters (RBC, hemoglobin, hematocrit) were observed in females receiving 50 mg/kg/day and both males and females receiving 500 mg/kg/day at all times of measurement. This decrease was also seen in males at 50 mg/kg/day

and in both males and females at 5 mg/kg/day during weeks 13 and/or 26 of treatment. White blood cell count was statistically low in male animals receiving 50 and 500 mg/kg/day (dose-independent) relative to control after 13 weeks of treatment. Platelet counts were statistically higher in high dose females when compared with control (Table 3.2.9.4). There were no bone marrow changes.

TABLE 3.2.9.4
EFFECT OF TELMISARTAN ON HEMATOLOGY PARAMETERS IN 52-WEEK ORAL TOXICITY STUDY IN DOGS

Sex		Male				Female			
Dose (mg/kg/day)		Ctl	5	50	500	Ctl	5	50	500
RBC ($x10^6/mm^3$)	w -1	6.83	6.23	6.65	6.20	6.79	7.16	7.05	6.83
	w 13	6.48	5.31§	4.88§	5.01§	6.29	5.73	4.79§	5.16§
	w 26	7.02	5.96*	5.97*	5.23§	6.64	6.08	5.08§	5.23§
	w 40	7.12	6.25	6.76	5.22§	6.68	6.09	5.41§	4.81§
	w 52	7.39	6.43	6.95	5.26§	6.87	6.19	5.40*	5.38§
Hemoglobin (g/100 ml)	w -1	16.4	15.0	15.8	14.7	16.1	17.1	16.6	16.2
	w 13	15.6	13.2§	12.0§	12.4§	15.6	14.0*	11.8§	12.6§
	w 26	16.9	14.7*	14.5*	12.9§	16.2	14.9	12.3§	12.5§
	w 40	16.9	15.5	16.7	12.8*	16.3	15.1	13.1§	11.5§
	w 52	17.4	15.5	16.9	13.0§	16.7	15.1	13.2*	12.6*
Hematocrit (vol. %)	w -1	49.3	45.8	46.8	44.0	48.3	51.5	50.0	47.8
	w 13	46.8	40.3§	36.5§	37.3§	46.5	41.8*	35.8§	38.0§
	w 26	51.0	44.8*	44.0*	39.3§	48.3	45.0	37.0§	38.7§
	w 40	50.5	47.0	50.8	39.3*	48.8	45.5	39.5§	34.3§
	w 52	52.3	48.3	51.5	39.5*	49.5	45.3	40.3*	39.0*
WBC ($1000/mm^3$)	w -1	8.95	11.02	7.55	8.85	8.00	8.55	7.97	9.65
	w 13	10.00	10.20	7.47*	7.42*	Not reported			
	w 26	10.65	9.67	6.92§	8.02*				
	w 40	11.77	10.02	6.75§	7.40§	7.30	8.02	8.55	10.20*
	w 52	9.47	8.85	6.95§	7.67*	Not reported			
Thrombocytes ($1000/mm^3$)	w -1	269	257	235	281	222	244	262	265
	w 13	265	303	297	353	252	360*	359*	324*
	w 26	273	270	261	355	255	332	320	413§
	w 40	329	314	303	410	295	332	374	445*
	w 52	300	307	286	401	271	370	347	476*

Significant when compared with control: *: $p < 0.05$; §: < 0.01

Statistically significant increases in blood urea nitrogen and creatinine levels were noted for mid and high dose animals from week 13 to week 52 of the study. Dose dependency was seen only in females for both parameters. Low dose animals showed a slight increase in urea nitrogen but not creatinine (Table 3.2.9.5). Magnesium increased in both sexes at all dose levels, however, the data were significant only at 50 and 500 mg/kg/day.

TABLE 3.2.9.5
EFFECT OF TELMISARTAN ON CLINICAL CHEMISTRY PARAMETERS IN 52-WEEK ORAL TOXICITY STUDY IN DOGS

Sex		Male				Female			
Dose (mg/kg/day)		Ctl	5	50	500	Ctl	5	50	500
Urea nitrogen (mmol/l)	w -1	3.99	4.33	4.86	4.27	4.83	4.78	3.82[§]	4.65
	w 13	5.29	8.53[§]	15.51[§]	9.64[§]	5.59	8.20	13.26[§]	11.89[*]
	w 26	4.76	7.86[*]	18.82[§]	10.41[§]	5.07	7.31	11.32	14.75[*]
	w 40	4.29	7.29[*]	19.94[§]	9.20[§]	4.70	9.80	14.75[*]	16.61[*]
	w 52	4.56	7.13	24.02[§]	12.29[§]	4.46	8.53	11.71[*]	15.35[§]
Creatinine (µmol/l)	w -1	73.6	69.4	68.8	69.3	77.2	80.4	74.2	72.3
	w 13	75.1	76.6	95.4[§]	88.9[*]	78.3	75.4	103.3[§]	108.9[§]
	w 26	72.6	74.7	103.5[§]	87.2	74.1	73.4	87.4	122.3[*]
	w 40	73.5	74.4	122.3[§]	83.6	79.3	79.8	124.4	117.8
	w 52	75.1	77.5	135.9[§]	108.3[§]	82.3	77.3	94.5	104.2
Magnesium (µmol/l)	w -1	720	739	754	775	779	769	781	800
	w 13	734	828	1052[§]	905[§]	800	844	1213[§]	1045[*]
	w 26	764	875	1119[§]	967[§]	791	884	1128[§]	1086[§]
	w 40	773	836	1110[§]	941[§]	786	935	1134[*]	1062
	w 52	787	882	1200[§]	1061[§]	812	976	1183[*]	1083

Significant when compared with control: [*]: $p < 0.05$; [§]: < 0.01

No significant changes in plasma renin activity were observed although there was a tendency to higher values in male animals receiving 5 mg/kg/day. Most of the data points in plasma aldosterone assays were below the detection limit of the radioimmunoassay.

Urinalyses showed a decrease in pH values from normal 7.3 (females) and 7.8 (males) to 5.8 (females) and 5.5 (males). However, the decrease was not dose-dependent and was significant only in mid dose group animals. A few animals dosed at 50 (males) and 500 (females) mg/kg/day showed slightly positive findings of glucose in the urine obtained at necropsy. The significance of these findings is not clear. Three male and 4 female animals dosed at 500 mg/kg/day and one female dosed at 50 mg/kg/day tested, at different time points of the study, positive for occult blood in feces, which is reflective of transient gastrointestinal mucosal alterations.

At the 52 week sacrifice, mean relative heart weights for all treated male groups were 13-25% lower than concurrent control (absolute decreases in the 5 mg/kg treated males only). Absolute and relative kidney weights for male groups receiving 50 and 500 mg/kg/day were (24-60%) higher than control. The absolute and relative mean spleen weights of females receiving 50 and 500 mg/kg/day and males receiving 500 mg/kg/day were significantly lower (49-58% lower) than control. A decrease (relative to concurrent control) in both absolute and relative pituitary weights was noted for all treated groups of males (20-25%) and females (11-20%). However, the data was statistically significant only for males dosed at 5 and 50 mg/kg/day (see Table 3.2.9.6). There was no evidence of dose-dependency for any of these organ weight effects.

TABLE 3.2.9.6
TELMISARTAN: GROUP MEAN ABSOLUTE AND RELATIVE ORGAN WEIGHTS (GM) FOR DOGS KILLED AFTER 52 WEEKS OF TREATMENT

Organ		Absolute and relative (normalized to brain weight) organ weights in groups							
		Control		5 mg/kg/day		50 mg/kg/day		500 mg/kg/day	
		M	F	M	F	M	F	M	F
Heart, g	abs wt.	115.4	96.8	87.6*	82.4	98.0	83.8	101.1	88.4
	Rel wt.	1.44	1.18	1.07*	0.99*	1.09*	1.08	1.26*	1.13
Kidney, g	abs wt.	50.6	43.2	50.3	44.3	80.9*	40.2	62.6	45.2
	Rel wt.	0.63	0.53	0.62	0.53	0.90*	0.52	0.78*	0.58
Spleen, g	abs wt.	55.3	57.2	37.1	49.3	46.3	26.9*	28.0*	24.1*
	Rel wt.	0.69	0.69	0.45	0.59	0.52	0.35*	0.35*	0.31*
Pituitary, mg	abs wt.	88.3	83.8	66.8*	66.9	70.5*	73.8	66.3*	74.2
	Rel wt.	1.10	1.02	0.82*	0.81*	0.79*	0.95	0.83	0.95

Significant when compared with control: *: $p < 0.05$

Treatment-related macroscopic findings were largely confined to high dose animals and included ulcers of the gastric or duodenal mucosa, associated with enlarged regional lymph nodes or adhesive processes in some animals. Treatment-related histopathological organ changes were observed in the kidneys, stomach and duodenum. Chronic ulcers were observed in the stomach or the duodenum of two males and one female receiving the high dose. Another high dose female had gastric submucosal inflammation. The GIT of the remaining 3 high dose dogs did not show histopathological changes. In the kidneys of all treated dogs, the juxtaglomerular apparatus was distinctly hyperplastic. Dilation of the loop of Henle and distal tubules was observed in animals of all drug-treated groups, but was most pronounced in 50 mg/kg/day males (more so than in high dose males). Bilateral proximal tubular atrophy was observed in some animals of both sexes given 50 or 500 mg/kg/day. This indicates tubular injury or ischemic changes as a result of drug treatment. The increased cytoplasmic translucence of the proximal tubular epithelial cells in females at all dose levels and in high dose males suggests functional changes. Two high dose males showed slight and multifocal hypertrophy of tubular epithelial cells. The amount of brown pigment (lipofuscin) deposition in the tubular epithelia was higher in the high dose group animals than in the other treated groups (for detail see Table 3.2.9.7).

TABLE 3.2.9.7A
TELMISARTAN: HISTOLOGICAL RENAL CHANGES IN MALE DOGS AFTER 52 WEEKS OF TREATMENT

Dose[1]/		Juxtaglomerular app.		Tubules						Interst.
Animal #		Hyperplasia	dil vas aff[2]	Dilation[3]	Transln[4]	Lipofus[5]	Fatty[6]	Atrophy[7]	Casts	infiltn[8]
Contl.	1	-	-	-	-	++	+	-	-	-
	2	-	-	-	-	++	-	-	-	-
	3	-	-	-	-	+	+	-	-	-
	4	-	-	-	-	+	+	-	-	-
5	1	++	+	+	-	+	+	-	-	-
	2	++	-	++	-	+	+	+[9]	-	-
	3	++	+	+	-	+	++	+[9]	-	-
	4	++	+	++	-	+	++	-	-	-
50	1	++	++	++	-	+	-	++	-	+[9]
	2	++	+	+++	-	++	-	++	-	++
	3	++	+	+++	-	++	+	++	-	+
	4	+	++	++	-	+	+	-	-	+
500	1	+	++	+	+++	+++	+	-	-	-
	2	+	++	-	+	+	+	+	+	-
	3	++	++	+	+	++	+	+	+	-
	4	++	++	+	++	++++	++	-	-	+

For footnote see Table 3.2.9.7B

TABLE 3.2.9.7B
TELMISARTAN: HISTOLOGICAL RENAL CHANGES IN FEMALE DOGS AFTER 52 WEEKS OF TREATMENT

Dose[1]/		Juxtaglomerular app.		Tubules						Interst.
Animal #		Hyperplasia	dil vas aff[2]	Dilation[3]	Transln[4]	Lipofus[5]	Fatty[6]	Atrophy[7]	Casts	infiltn[8]
Contl.	1	-	-	-	-	+	+	-	-	-
	2	-	-	-	-	+	++	-	-	-
	3	-	-	-	-	-	+++	-	-	-
	4	-	-	-	-	+	+++	-	-	-
5	1	+	+	+	-	+	+	-	-	-
	2	++	+	-	+	-	+	-	-	+
	3	++	+	-	+	+	++	-	-	+[9]
	4	++	+	-	+	++	++	-	-	-
50	1	+	+	-	+	+	-	+	-	+[9]
	2	+	+++	++	-	+	++	-	-	-
	3	++	+	++	+	++	+	+	-	+[9]
	4	++	++	-	+	++	++	-	-	-
500	1	++	+++	++	+	++++	-	-	-	+[9]
	2	++	++	-	++	+++	+	++	-	-
	3	++	++	++	-	+	+++	++	++++	-
	4	++	+++	+	++	++	++	+++	-	-

[1]: mg/kg/day; [2]: dilation of vas afferens; [3]: dilation of loop of Henle, distal tubules; [4]: cytoplasm of proximal convoluted tubule translucent indicating clear cell change; [5]: lipofuscin; [6]: fatty change of tubular epithelial cells; [7]: atrophy of proximal tubules; [8]: interstitial mononuclear cell infiltration; [9]: unilateral

Toxicokinetic investigations showed that Cmax occurred very late (2-15 hr) in comparison to its time of occurrence in rat and man. Cmax and AUC values were higher in females than in males at dose levels of 50 and 500 mg/kg/day. There was no difference in concentrations measured on day 1 and day 193 (concentrations were slightly lower on days 319 and 361 when a different batch was used) suggesting no accumulation of the drug between day 1 and 193 (and between day 319 and 361) (Table 3.2.9.8). Excretion of white discolored feces in high dose animals suggested presence of unabsorbed drug. At 5 mg/kg/day (a dose at which a number of adverse effects were noted), mean (combined for all intervals of study) Cmax and $AUC_{0\text{-}24hr}$ were respectively, 131 (range 71 to 240) ng/ml and 1878 (range 1324 to 2809) ng.h/ml for males and 202 (range 111 to 325) ng/ml and 2472 (range 1158 to 4291) ng.h/ml for females. A dose of 160 mg telmisartan for humans (protocol #502.201, sex not identified) resulted in mean Cmax of 2900 ng/ml (range 530 to 6000 ng/ml) and mean $AUC_{0\text{-}24hr}$ of 5400 ng.h/ml (range 1000 to 8500 ng.h/ml).

TABLE 3.2.9.8

PHARMACOKINETIC PARAMETERS OF TELMISARTAN IN DOGS DURING THE 52-WEEK TOXICITY STUDY (N = 4)

Sampling period	Dose mg/kg/day	Cmax (ng/ml)		$AUC_{0\text{-}24hr}$ (ng.h/ml)	
		Males	Females	Males	Females
Day 1	5	160.3	227.8	1811	2084
	50	3079.0	7574.3	45809	83420
	500	36360.0	43197.5	488524	605628
Day 193	5	158.5	205.9	2082	2593
	50	1737.0	3008.5	23667	39421
	500	21019.8	35593.3*	240767	387343*
Day 319	5	119.5	169.9	1866	2359
	50	1777.0	1729.5	21307	26461
	500	11561.8	31046.7*	134396	352200*
Day 361	5	118.7	227.7	1947	3454
	50	1804.3	4336.3	24777	47399
	500	17080.3	23340.0*	177545	250918*

*: n = 3

In summary, oral administration of telmisartan to dogs at 5, 50 or 500 mg/kg/day fot 52 weeks resulted in marked and persistent reduction in blood pressure. Decreased heart weight, possibly resulting from afterload reduction (as a result of angiotensin II antagonism) was observed in all treated groups. This and blood pressure reduction showed no dose dependency, suggesting maximum effects were reached at 5 mg/kg/day. A dose-dependent loss in body weight for the study period was observed for females that received 50 and 500 mg/kg/day. The principal findings in this study consist of morphological and clinical laboratory evidence of ulcers of the gastric or duodenal mucosa at 500 but not 50 mg/kg/day. (In 4- and 13-week toxicity studies in dogs, gastrointestinal ulceration was observed at 40 or 50 mg/kg/day.) Also observed in the one year study were reduced erythrocytic indices (at 50 and 500 mg/kg/day) and evidence of altered renal function (at all dose levels). Microscopic examination revealed hyperplasia/hypertrophy of the juxtaglomerular apparatus in all treated groups, which may have triggered higher plasma urea, creatinine and magnesium concentrations. A no toxic effect level was not achieved in this study.

3.3. *Carcinogenicity Studies*

3.3.1. 13-Week Oral Range-Finding Toxicity Study of Telmisartan in Mice (Report #U94-2024, Study #9384 TCS) Vol. 40-41

This GLP study was conducted at [redacted] between November 12, 1992 and February 16, 1993. It was conducted to aid in the selection of dosages for an oncogenicity study in this species.

Male and female Swiss CD-1 mice [redacted] were approximately 6 weeks of age and weighed 24-28 g (males) or 21-24 g (females) at the start of the study. Telmisartan (batch 8230151) was administered orally by dietary admixture (20% lactose trituration) *ad libitum*, for 13 weeks at doses of 30, 100, 300 or 1000 mg/kg. Control animals received the untreated diet *ad libitum*. Each group consisted of 10 male and 10 female mice. The animals were housed individually in polycarbonate cages.

Observations and Measurements

All animals were observed at least twice daily (once during weekends and holidays) for mortality and drug effects. The body weights were recorded a week before treatment, on day 1 of treatment, then weekly throughout the treatment period. The water intake per animal per day was calculated using the amount of water given and left in each bottle. The quantity of food consumed by each animal was recorded for each week throughout the treatment period. Food intake per animal per day was calculated using the amount of food supplied and that remaining in the feeder. The achieved intake of test substance in mg/kg/day was calculated on a weekly basis during the 13 weeks of treatment for each sex and each treated group, based on the body weight and mean food consumption and the nominal concentrations in the diet.

$$D = C \times FC/BW$$

where, D= achieved dosage, mg/kg/day; C= nominal concentration, ppm; FC= mean food consumption (gm/animal/day); BW= mean body weight (gm).

No specific stability study was performed for test article since diets were prepared every week. Concentration and homogeneity was tested by sampling the dietary mixture in weeks 1, 4, 8 and 12. Blood samples were withdrawn from the retro-orbital sinus of the overnight fasted surviving animals under anesthesia in week 13 for hematology and clinical blood chemistry examinations. For toxicokinetics study, blood samples were collected in week 2 (satellite animals) and in week 14 (main study animals) at 8 a.m. and 4 p.m. (n=4/sex/group/sample time and each animal sampled only once). Urinalysis was not performed. The satellite animals were sacrificed after sampling in week 2 without further investigation. All main study animals were subjected to a detailed necropsy that included weighing of selected organs (Table 3.3.1.1). Macroscopical lesions and all tissues collected from high dose and control animals were examined histopathologically. Gross lesions, stomach and kidneys were examined from animals in the remaining drug-treated groups.

TABLE 3.3.1.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenals*
Aorta
Brain*
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with
Harderian glands
Femoral bone
Gall bladder
Heart*
Ileum
Jejunum
Kidneys*
Lacrimal glands
Liver*
Lungs* with bronchi
Lymph nodes -
mandibular,
-mesenteric
Mammary glands
Ovaries*
Pancreas
Pituitary ¶
Prostate*
Rectum
Salivary gland
Sciatic nerve
Seminal vesicles
Skeletal muscle ♦
Skin
Spinal cord
Spleen*
Sternum with
bone marrow
Stomach with
forestomach
Testes* and
epididymides
Thymus*
Thyroids* with
parathyroids
Tongue
Trachea
Urinary bladder
Uterus- horns and
cervix

*Organ weighed (paired organs were weighed separately, except adrenals and thyroids which were weighed together), ¶: weighed after 24 hr fixation, ♦: saved for future examination

Results

The homogeneity of dietary mixtures in the range of concentration 90-6000 ppm was satisfactory. The consumed doses of telmisartan administered in the diet were in close correspondence to the targeted doses in weeks 1, 4, 8 and 12, except for females targeted to receive 100 mg/kg/day. In week 1, the latter group achieved a mean dose of only 28 mg/kg/day. The mean doses achieved over the 13 weeks of treatment ranged from 72 to 115% of the intended daily doses (Table 3.3.1.2).

TABLE 3.3.1.2
13-WEEK ORAL DOSE RANGE-FINDING STUDY IN MICE: ACHIEVED DOSES (MEAN VALUES)

	Sex	Intended Daily dose (mg/kg/day)			
		30	100	300	1000
Achieved daily dose (mg/kg/day)	Male	28.2	95.8	292.6	998.4
	Female	29.1	95.3	288.1	990.7

There were no clinical signs attributed to the treatment. A total of 11 mice died or were sacrificed for humane reasons during the study (Table 3.3.1.3). All these deaths occurred either immediately or within a few days after blood sampling and were considered by the sponsor to be unrelated to treatment with telmisartan. The slight to moderate hepatocellular necrosis noted in 3 of these animals was considered by the sponsor to be of a spontaneous nature.

TABLE 3.3.1.3
13-WEEK ORAL DOSE RANGE-FINDING STUDY IN MICE: MORTALITY

Dose (mg/kg/day)	# of deaths M	F	Study Wk	Day	Ante-mortem/post-mortem findings
30	0	1	13	91	Found dead. Signs of poor physical condition were noted just before death. Moderate multifocal hepatocellular necrosis noted post-mortem.
100	1	2	12	89	All three found dead. No *ante-mortem* clinical signs were noted. No relevant histopathological findings were noted in these animals.
300	1		13	91	No *ante-mortem* clinical signs were noted; thin and hemorrhagic gastric mucosa noted at necropsy.
	1	1	12	89	Male died after blood sampling. No *ante-mortem* clinical signs and no relevant histopathological findings for both these animals.
1000	1		13	93	Found dead. Signs of poor physical condition were noted just before death. Noted reddish colored mucosa of stomach, moderate multifocal hepatocellular necrosis.
	1	1	12	89	Dead; no *ante-mortem* clinical signs were noted.
		1	12	90	Found dead. Signs of poor physical condition noted. before death, reddish colored gastric mucosa, slight multifocal hepatocellular necrosis in the liver (in both females).

The overall mean body weight gains of all treated male groups (20 to 21% gain) were lower than that of control (34% gain), though no dosage relationship was apparent (Fig. 3.3.1.1 top panel). The difference was noticeable from week 3 onwards, and was statistically significant ($p < 0.05$ to 0.01) from week 4 or 5 for all treated groups except the high dose group where it was statistically significant from week 10. In contrast, the mean body weight gains of the females from all treated groups were similar to that of control throughout the treatment period (Fig. 3.3.1.1 bottom panel). The mean food consumptions were not affected by treatment. The mean water consumptions were slightly higher in females than in males of all treated groups, when compared to the respective control groups. Thus, for the treatment period, the mean water consumption for males given 30, 100, 300 and 1000 mg/kg/day was 10%, 7%, 17% and 18% higher, and for females was 4%, 7%, 10% and 7% higher, respectively, than the control.

Red blood cell indices (RBC, hemoglobin, mean corpuscular volume, packed cell volume) decreased 10 to 20% in all drug treated groups relative to control. A slightly lower (-12% compared to control) platelet count was noted in the males given 300 or more mg/kg/day. In week 13, a moderate dose-related increase in blood urea nitrogen was observed in males (1.6- to 2.6-fold) and females (2- to 2.4-fold) at all dose levels compared to controls. This was associated with a non dose-dependent increase in creatinine levels in the males (19% relative to control, $p < 0.05$) given 300 or more mg/kg/day and in females at all dose levels (11 to 22% relative to control, $p < 0.05$ except at 1000 mg/kg/day). Serum potassium increased in all treated groups but significantly only in high dose females.

There were no significant changes in the weights of organs of treated animals compared to those of control. Macroscopic examinations did not show any treatment-related differences in surviving animals. Reddish/purplish areas in the glandular mucosa of one male and one female in the high dose group, that died before term (see Table 3.3.1.2), according to the sponsor, occur spontaneously in untreated laboratory mice.

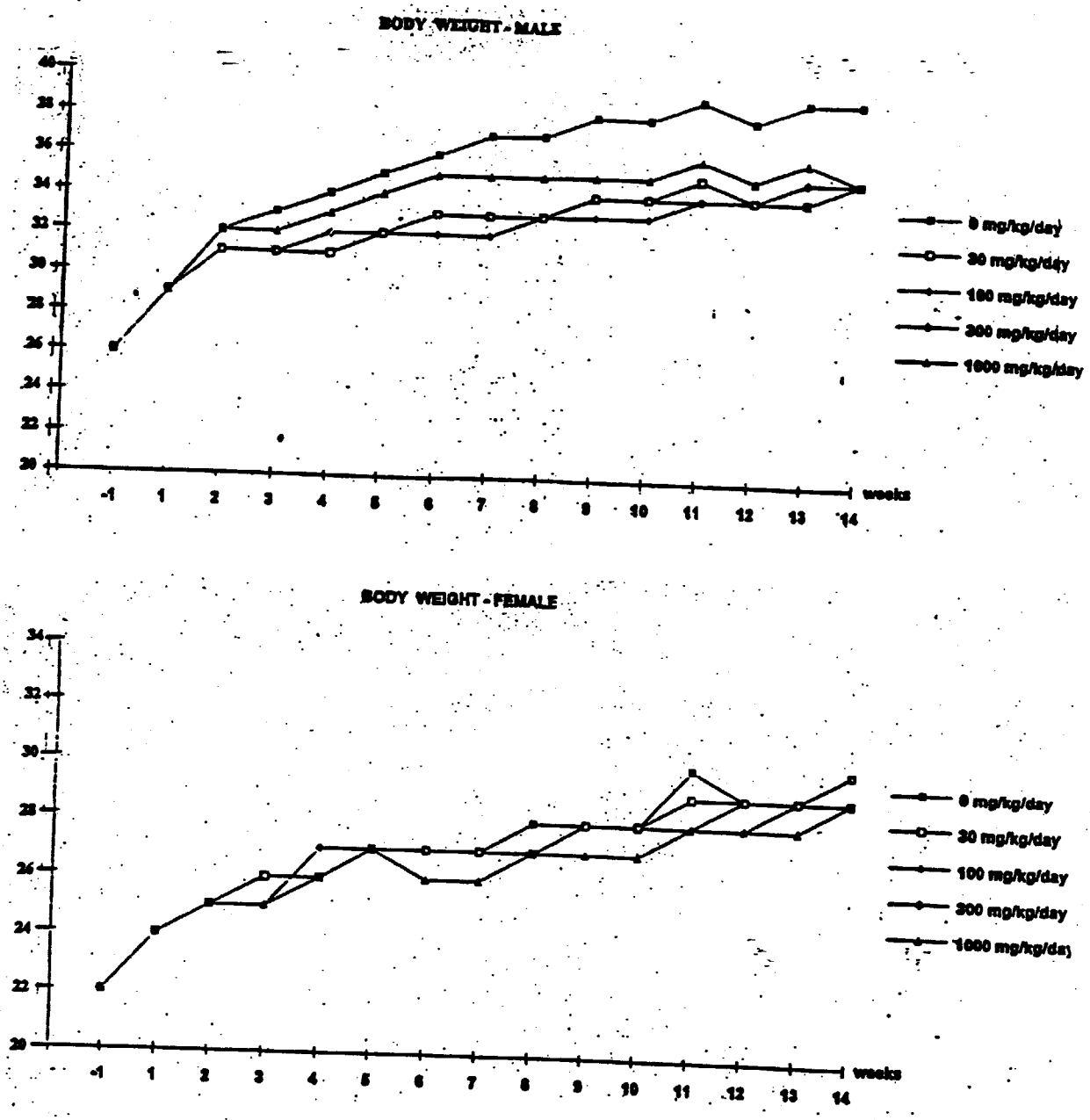


Fig. 3.3.1.1.: 13-week toxicity study of telmisartan in mice. Group mean body weight (grams, on Y-axis) *versus* treatment period (in weeks, X-axis) in male (upper panel) and female (lower panel) mice.

Regarding microscopic pathology, a dose-related minimal to marked hyperplasia of the juxtaglomerular cells was noted in the kidneys of all treated animals. A focal or multifocal, minimal to moderate hepatocellular necrosis was noted in one female given 30 mg/kg/day, and 1 male and 3 females given 1000 mg/kg/day. Again, this finding was considered spontaneous by the sponsor on taking into account the nature of hepatocellular necrosis.

Plasma concentrations of telmisartan increased with the dose in both genders at both time points but lacked dose-proportionality. At both time points, slightly higher plasma concentrations were observed in females than males. Variabilities were high in all dose groups. The estimated

$AUC_{0\text{-}24h}$ values (obtained by multiplying the means of the two time points, 8 and 16 hr, male and female, by 24) were 11.8, 41, 119.8 and 355.2 µg.h/ml for the 30, 100, 300 and 1000 mg/kg/day group, respectively. A dose of 120 mg telmisartan for humans (protocol #502.124) resulted in $AUC_{0\text{-}24hr}$ of 2.04 (male) and 2.38 (female) µg.h/ml.

In summary, administration of telmisartan to mice for 13 weeks at dosages of 30, 100, 300 and 1000 mg/kg/day resulted in 11 deaths, none of which were, according to the sponsor, related to treatment. The mean body weight gains over the 13 week study period were 14% lower for all treated male groups than for the male control group. There were no significant effects on body weight gain for treated females. There were no apparent effects on organ weights, and no drug-related macroscopic or microscopic findings. Based on the above, it can be concluded that the maximum tolerated dose (MTD) was not attained or identified in the female mice. However, the high dose (1000 mg/kg/day) resulted in a mean AUC value 160-fold greater than that attained at a clinical dose of 120 mg tested in healthy human volunteers.

3.3.2. 104-Week Oral Carcinogenicity Study of Telmisartan in Mice (Report #U96-2371, Study #10371 TCS) Vol. 52-60.

This GLP study was conducted at[, between June 22, 1993 and June 23, 1995. The aim of the study was to assess the oncogenic effects of telmisartan during its repeated daily oral administration to CD-1 mice for 104 weeks.

Male and female Swiss CD-1 mice[ ] were approximately 6 weeks of age and weighed 29.1-30.4 g (males) or 22.3-23.0 g (females) at the start of the study. Telmisartan (batch #30520, 31124, 40728, supplied as a 20% trituration in lactose) was administered orally by dietary admixture *ad libitum*, for up to 105 weeks for the males, and up to 100 weeks for the females at doses of 10, 100 or 1000 mg/kg. Control animals received the untreated diet *ad libitum*. Each group consisted of 50 male and 50 female mice. Half of each group were kept in one room, the other half in a second room. Satellite animals (8/sex/group) for toxicokinetics were kept in one of the rooms. Allocation of animals to various groups is shown in Table 3.3.2.1. Sentinel animals were kept in the same environment (10/sex/study room). Before beginning of the study and every 6 months thereafter, 2 male and 2 female sentinel animals per study room were sacrificed to check bacterial, virus and mycoplasm contamination. All animals were housed individually in polycarbonate cages.

TABLE 3.3.2.1
CARCINOGENICITY STUDY IN MICE: DOSAGE GROUPS (MG/KG/DAY)

Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
0		0		0		10		100		1000	
(untreated diet)		(untreated diet)		(lactose/diet)		(drug/diet)		(drug/diet)		(drug/diet)	
m	f	m	f	m	f	m	f	m	f	m	f
50	50	50	50	50	50	50	50	50	50	50	50
Satellite animals for toxicokinetics (week 52)						8	8	8	8	8	8

Observations and Measurements

All animals were observed at least twice daily (once during weekends and holidays) for mortality and drug effects. After 6 months into study, all animals were palpated every 2 weeks to record date of onset and changes in palpable masses.

The body weights were recorded a week before treatment, on day 1 of treatment, at weekly intervals for the first 13 weeks of treatment and every 4 weeks after that. The water intake was checked by visual inspection. The quantity of food consumed by each animal was recorded for each week for the first 13 weeks of treatment and then every 4 weeks until the end of the study. Food intake per animal per day was calculated using the amount of food supplied and that remaining in the feeder. Diets were prepared weekly up to 14 weeks and monthly thereafter. Diets were analyzed for stability and homogeneity in weeks 1, 5 and every 3 months until the end of the study. The achieved intake of test substance in mg/kg/day was calculated on a weekly basis during the first 13 weeks of treatment, then every 4 weeks until the end of the study for

each sex and each treated group using mean body weight and food consumption and the nominal concentrations of test substance in the diet.

$$D = C \times FC/BW$$

where, D= achieved dosage, mg/kg/day; C= nominal concentration, ppm; FC= mean food consumption (gm/animal/day); BW= mean body weight (gm).

Blood samples were withdrawn from the retro-orbital sinus of the overnight fasted surviving animals under anesthesia in week 98/99 for females and in week 105 for males and in any moribund animals sacrificed during the study when possible for hematological examination (clinical blood chemistry parameters not studied). For toxicokinetics study, blood samples were collected on day 360 (8 satellite animals per sex per drug-treated group) and at the end of the study (main study animals, day 702 in males, day 693 in females) at 8:00 a.m. and 4 p.m. (n=8 (first 4 and last 4 surviving animals)/sex/group/time point and each animal sampled only once). Urinalysis was not performed. The satellite animals were sacrificed after blood sampling without further investigation. All surviving main study animals were subjected to a detailed necropsy (animals fasted 18 hr before killing) that included weighing of selected organs from the first 10 surviving animals per group (Table 3.3.2.2). Histopathological examination was performed on all masses, macroscopic lesions and tissues listed below in animals of all groups killed at term or dying during the study. Electron microscopic examinations of kidney and liver were performed on the first 3 surviving males and females in each group. Tumorigenicity for drug-treated groups was assessed by comparing number of neoplasms of a specific histomorphological type and designation (benign or malignant) by organ and by group to the control 1 group using the Peto test (1-tailed) and by trend analysis (Armitage test, 2-tailed).

TABLE 3.3.2.2
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

- Adrenals*
- Aorta
- Brain* (including medulla/pons, cerebellum and cerebral cortex)
- Cecum
- Colon
- Duodenum
- Epididymides
- Esophagus
- Eyes with Harderian glands
- Femoral bone
- Gall bladder
- Harderian glands
- Heart
- Ileum
- Jejunum
- Kidneys*
- Liver*
- Lungs* with bronchi
- Lymph nodes
  - mandibular,
  - mesenteric
- Mammary glands
- Ovaries*
- Pancreas
- Pituitary
- Prostate
- Rectum
- Salivary gland
- Sciatic nerve
- Seminal vesicles
- Skeletal muscle
- Skin
- Spinal cord
- Spleen
- Sternum with bone marrow
- Stomach
- Testes* and epididymides
- Thymus
- Thyroids with parathyroids
- Tongue
- Trachea
- Urinary bladder
- Uterus- horns and cervix
- Vagina

*Organ weighed (paired organs were weighed separately, except adrenals which were weighed together)

Results

The consumed doses of telmisartan administered in the diet were in close correspondence to the targeted doses (Table 3.4.2.3). The concentration of drug in the diet generally increased over the course of the study.

TABLE 3.3.2.3
104-WEEK CARCINOGENICITY STUDY IN MICE: ACHIEVED DOSES (MEAN VALUES) AND CONCENTRATION IN THE DIET

	Sex	Intended Daily dose (mg/kg/day)		
		10	100	1000
Achieved daily dose (mg/kg/day)	Male	9.8	98.5	992.7
	Female	9.8	98.6	976.4
Conc. in the diet, low and high, ppm (% of the diet)	Male	41.42 – 74.13 (0.004 - 0.0074%)[a]	352.1 – 723.2 (0.035 – 0.072%)	4143 – 6770 (0.41 – 0.68%)
	Female	34.28 – 61.42 (0.003 – 0.0061%)	342.8 – 601.8 (0.034 – 0.06%)	3286 – 6000 (0.33 – 0.6%)

[a]: However, in week 5, the concentration of drug in the diet was 0.5, 0.24 and 2.32%, respectively, at 10, 100 and 1000 mg/kg/day, and in week 10 it was 0.27% at 100 mg/kg/day.

The survival rates in combined control males were about 50% and in combined control females about 46% for the study period. These values are similar to the testing laboratory's historical control data for this mouse strain (57% for males, 42% for females in week 104). The survival rates of the animals of both sexes from the three treated groups were similar to those of the combined controls. Males were sacrificed as scheduled starting in week 105. Females were sacrificed in weeks 98 to 100 due to mortality ≥50% in the untreated control groups (Table 3.3.2.4.). The factors contributing to death or premature sacrifice were similar in control and treated animals. The most frequent factors contributing to the death or premature sacrifice of control and treated males were: hepatocellular carcinoma, malignant lymphoma and myeloid leukemia; while for control and treated females they were: endometrial sarcoma and malignant lymphoma.

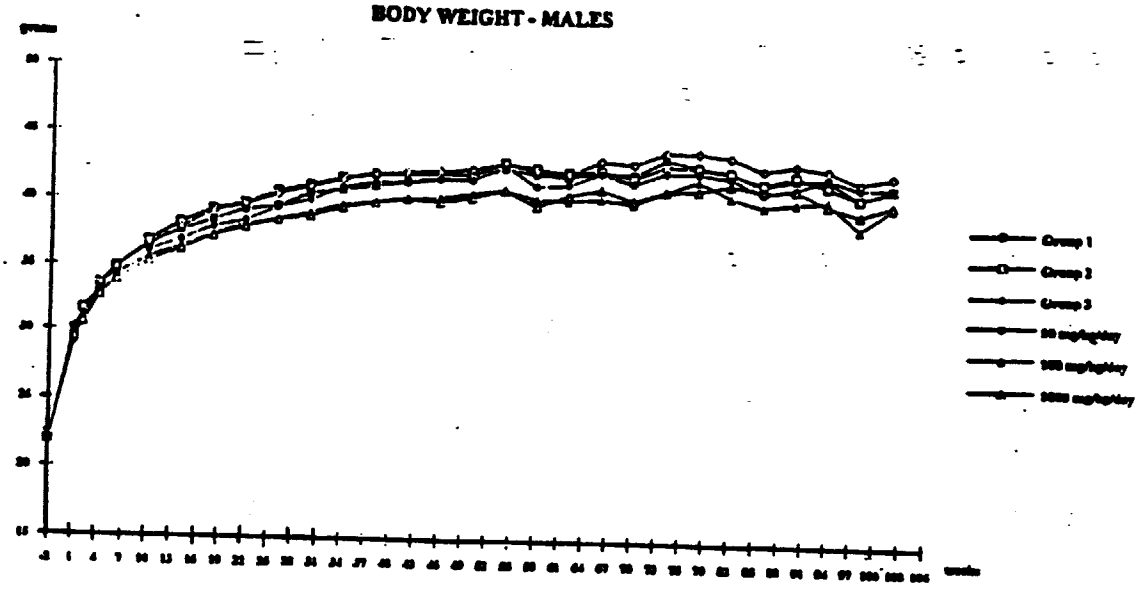
TABLE 3.3.2.4

CARCINOGENICITY STUDY IN MICE: NUMBERS OF DEATHS/MORIBUND SACRIFICES [% SURVIVAL]

Weeks	Dose level (mg/kg/day)											
	0		0		0		10		100		1000	
	Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
	Diet Control		Diet Control		Lactose Control		Low Dose		Mid Dose		High Dose	
	m	f	m	f	m	f	m	f	m	f	m	f
1-52[a]	4 [92]	3 [94]	4 [92]	2 [96]	0 [100]	3 [94]	1 [98]	0 [100]	4 [92]	8 [84]	3 [94]	1 [98]
1-60	5 [90]	5 [90]	5 [90]	6 [88]	2 [96]	5 [90]	1 [98]	1 [98]	7 [86]	9 [82]	3 [94]	2 [96]
1-72	8 [84]	12 [76]	7 [86]	6 [88]	3 [94]	8 [84]	3 [94]	2 [96]	10 [80]	17 [66]	5 [90]	4 [92]
1-84	13 [72]	18 [64]	12 [76]	10 [80]	5 [90]	18 [64]	6 [88]	11 [78]	15 [70]	21 [58]	12 [76]	14 [72]
1- 105 M 1- 100 F	25 [50]	30 [40]	26 [46]	28 [44]	22 [56]	24 [52]	22 [56]	22 [56]	29 [42]	24 [52]	22 [56]	22 [56]
mean survival*	92	85	91	90	98	86	98	92	90	81	93	91
# found dead	13	13	19	17	18	12	12	6	20	13	16	7
# killed prematurely	12	17	8	11	4	12	10	16	9	11	6	15
Total loss	25	30	27	28	22	44	22	22	29	24	22	22

*: mean time (weeks) to death or sacrifice

No drug-related clinical signs were noted. The total number of palpable swellings and the number of animals bearing them were no higher in treated groups than in control groups. The overall mean body weight gains of animals receiving 100 and 1000 mg/kg/day were slightly lower than those of the controls, though no dosage relationship could be seen (Fig. 3.4.2.1). At the end of the treatment period, males receiving 100 and 1000 mg/kg/day had mean body weight gains 3% below control ($p > 0.05$), while females receiving 100 and 1000 mg/kg/day were 6% below control ($p < 0.05$) and 4% below control ($p > 0.05$), respectively (Table 3.3.2.5). Considering that these decreases are slight and not dose-related, they are not regarded as toxicologically important. The food and water consumption of the animals of both sexes in the three control groups and three treated groups were similar.



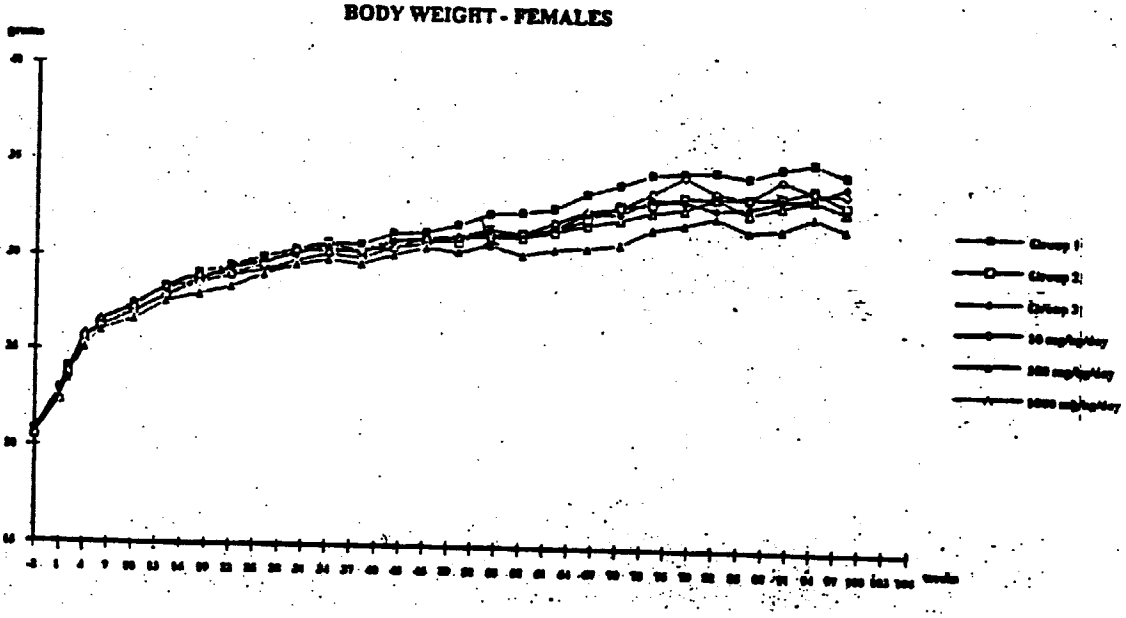


Fig. 3.3.2.1.: 104-week carcinogenicity study of telmisartan in mice. Group mean body weight (grams, on Y-axis) *versus* treatment period (in weeks, X-axis) in male (upper panel) and female (lower panel) mice.

TABLE 3.3.2.5

CARCINOGENICITY STUDY IN MICE: MEAN BODY WEIGHTS§

	Dose level (mg/kg/day)						
		Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
	Week	0 untreated diet	0 untreated diet	0 lactose/diet	10 drug/diet	100 drug/diet	1000 drug/diet
Males	1	29.5	30.0	29.1	30.4	30.3	29.5
	13	37.2	37.6	36.7	37.5	36.2	35.8
	26	39.5	40.6	39.4	40.4	38.7	38.4
	54	42.6	43.0	42.8	43.0	41.0	41.0
	78	42.9	42.8	42.4	43.9	41.9	41.1
	102	41.4	41.5	41.6	42.4	40.1	40.3
Females	1	23.0	22.5	22.9	22.4	22.3*	22.4*
	13	27.9	27.6	27.9	27.6	27.4	28.0
	26	30.0	29.7	29.8	29.2	29.0	29.6
	54	32.4	31.6	31.6	31.3	30.8*	31.2
	78	34.7	33.4	33.2	34.5	32.0*	32.8
	98	34.7	33.1	34.1	33.7	31.9*	32.8

§: Mean body weights in grams

*: Statistically significant ($p<0.05$) compared to group 1 (control)

**: Statistically significant ($p<0.01$) compared to group 1 (control)

Significantly reduced RBC, hematocrit, packed cell volume and hemoglobin were noted in males given 10 mg/kg and in animals of both sexes given 100 or 1000 mg/kg when compared with compared with group 1 (control). Differences exceeded 10% at the high dose in males and at the mid and high dose in females and were, therefore, considered clinically and toxicologically meaningful. The decreased red cell indices with a trend to decreased cell volume were consistent with normocytic normochromic anemia. Platelet count was mildly increased in both sexes (males: +28%; females: +17%) at the high dose. The total and differential white cell count in all treated groups was similar to controls (Table 3.3.2.6).

TABLE 3.3.2.6
CARCINOGENICITY STUDY IN MICE: HEMATOLOGICAL PARAMETERS. GROUP MEAN VALUES
(Numbers in parentheses represent % difference from control group 1)

Parameter	Group 1 0 untreated diet	Group 2 0 untreated diet	Group 3 0 lactose/ diet	Group 4 10 drug/diet	Group 5 100 drug/diet	Group 6 1000 drug/diet
Males						
RBC, 10^6/mm^3	9.3	9.3	9.3	8.7 (-7)	8.6 (-8)	7.8** (-16)
Hemoglobin, g/dl	14.3	14.2	14.1	13.0** (-9)	13.0* (-9)	11.3** (-21)
Hematocrit, l/l	0.44	0.43	0.44	0.40* (-9)	0.40 (-9)	0.35** (-20)
MCV, fl	47.3	46.6	47.0	46.2	46.8	44.6** (-6)
MCH, pg	15.4	15.3	15.2	15.0	15.1	14.5** (-6)
MCHC, g/dl	32.6	32.8	32.4	32.6	32.4	32.4
Platelets, g/l	1436	1394	1326	1423	1418	1772* (+28)
Females						
RBC, 10^6/mm^3	8.8	8.5	8.5	8.4 (-4)	7.2** (-17)	6.7** (-24)
Hemoglobin, g/dl	14.1	13.3	13.5	13.2 (-6)	11.1** (-21)	10.2** (-28)
Hematocrit, l/l	0.43	0.41	0.41	0.40 (-7)	0.34** (-21)	0.31** (-28)
MCV, fl	48.6	48.1	48.3	47.9	47.4* (-2)	46.9** (-3)
MCH, pg	16.1	15.7	16.0	15.8	15.5* (-4)	15.6* (-3)
MCHC, g/dl	33.1	32.6	33.0	33.1	32.8	33.1
Platelets, g/l	923	892	935	930	842	1114* (+17)

Compared to control 1 group: * Statistically significant ($p<0.05$); ** Statistically significant ($p<0.01$)

The mean absolute and relative liver weights of males and relative liver weight of females given 1000 mg/kg/day were significantly lower than control 1 values but not control 3 values (lactose diet). Absolute and relative kidney and relative adrenal weights of females given 100 or 1000 mg/kg/day were higher than control 1 values (Table 3.3.2.7).

TABLE 3.3.2.7
CARCINOGENICITY STUDY IN MICE: TREATMENT-RELATED ORGAN WEIGHTS

Organ	Dose level (mg/kg/day)											
	0 Group 1		0 Group 2		0 Group 3		10 Group 4		100 Group 5		1000 Group 6	
	m	f	m	f	m	f	m	f	m	f	m	f
Kidneys												
Absolute (g)	0.82	0.51	0.83	0.48	0.80	0.49	0.81	0.51	0.82	0.55	0.79	0.56
Relative/BW	2.22	1.63	2.25	1.62	2.18	1.66	2.13	1.67	2.31	1.94**	2.20	1.90*
Liver												
Absolute (g)	1.75	1.52	1.64	1.32	2.03	1.67	1.63	1.42	1.46	1.31	1.89**	1.73
Relative/BW	4.73	4.93	4.42	4.43	5.37	5.41	4.26	4.57	4.11	4.66	5.29**	5.86**
Adrenals												
Absolute (mg)	8	13	9	13	8	13	9*	13	9	15	8	15
Relative/BW	21	40	24	44	21	44	24	42	25*	51**	23	50*

Compared to control 1 group (Dunn's test): *: Statistically significant ($p<0.05$); **: Statistically significant ($p<0.01$)

Gross Pathology findings were related to the commonly occurring geriatric changes in aged mice and were of comparatively similar incidence in both control and treated animals and showed no indication of treatment or dose relationship. The masses found in organs and tissues were equally distributed in control and treated animals and showed no indication of treatment or dose relationship either in size or multiplicity.

Non-neoplastic histopathology considered to be related to treatment was seen in the kidneys and was characterized by slight to marked hypertrophy/hyperplasia of JG cells together with higher incidence of renal tubular dilatation in females receiving 10 mg/kg/day and animals of both sexes given 100 or more mg/kg/day. Also, a trend to slightly higher incidence of chronic tubulointerstitial nephritis was noted in mid and high dose males (Table 3.3.2.8). No microscopical correlates for increased liver and adrenal weights were observed. Spontaneously-occurring atrial thromboses and myocardial degeneration and fibrosis, which according to the sponsor, are common age-related changes particularly in males of this mouse strain, occurred at a lower incidence in all drug-treated groups than in controls. The main non-neoplastic findings are summarized in Table 3.3.2.8.

TABLE 3.3.2.8
CARCINOGENICITY STUDY IN MICE: INCIDENCE OF THE MAIN NON-NEOPLASTIC HISTOPATHOLOGICAL FINDINGS

Organ / Finding	0 Group 1		0 Group 2		0 Group 3		10 Group 4		100 Group 5		1000 Group 6	
	m	f	m	f	m	f	m	f	m	f	m	f
# of animals in the study	50	50	50	50	50	50	50	50	50	50	50	50
Kidney # examined	49	50	48	49	49	49	50	50	49	50	47	50
JG hypertrophy/hyperplasia	0	0	0	0	0	0	0	34	35	35	45	39
Tubular dilatation	3	8	5	6	4	6	3	25	10	23	14	31
Chronic tubulointerstitial nephritis	3	9	6	1	7	5	7	13	12	5	11	5
Heart # examined	49	50	50	50	50	50	50	50	50	50	50	50
Atrial thrombosis	4	0	4	1	7	1	2	0	1	0	0	0
Myocardial degeneration/fibrosis	18	3	9	0	11	0	3	1	4	0	0	0

Regarding *neoplastic* findings, no drug-induced effects on number of tumor-bearing animals, number of animals bearing benign tumors, number of animals bearing malignant tumors or number of animals bearing multiple tumors were apparent in either sex of mice that were killed or died during the treatment period, or killed at term (Table 3.3.2.9). Further, there was no evidence of decrease in the latency of tumor appearance in telmisartan-treated animals. The sponsor performed Peto trend tests and assigned 0.05 (for rare tumors) and 0.01 (for common tumors) as critical p-values for significance. Their statistical analyses did not show any positive trend.

TABLE 3.3.2.9
CARCINOGENICITY STUDY IN MICE: SUMMARY OF NEOPLASTIC FINDINGS*

Dosage (mg/kg/day) Group	0 Group 1		0 Group 2		0 Group 3		10 Group 4		100 Group 5		1000 Group 6	
Sex	m	f	m	f	m	f	m	f	m	f	m	f
# animals in the study	50	50	50	50	50	50	50	50	50	50	50	50
No. tumor-bearing animals	27	33	29	29	31	21	31	28	27	24	29	26
(% incidence)	(54)	(66)	(58)	(58)	(62)	(42)	(62)	(56)	(54)	(48)	(58)	(52)
Benign	12	14	14	11	16	8	18	11	14	10	17	12
Malignant	11	17	14	14	10	9	9	13	9	10	10	13
No. with multiple tumors	8	9	6	9	7	7	8	8	9	6	7	4
(% incidence)	(16)	(18)	(12)	(18)	(14)	(14)	(16)	(16)	(18)	(12)	(14)	(8)
No. primary tumors	40	44	37	40	38	29	41	37	39	31	37	31
Benign	23	23	19	20	23	14	26	18	24	17	24	14
Malignant	17	21	18	20	15	15	15	19	15	14	13	17

*: primary tumors

Incidence of neoplastic findings (primary tumors) by histomorphological type, organ/tissue and system is shown in Table 3.3.2.10 which follows on the next 3 pages.

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TABLE 3.3.2.12
CARCINOGENICITY STUDY IN MICE: INCIDENCE OF PRIMARY NEOPLASMS

Histopathological finding / ORGAN SYSTEM / Organ/Tissue / Neoplasm	TD	Dose level (mg/kg/day)											
		0 Group 1 Diet Control		0 Group 2 Diet Control		0 Group 3 Lactose Control		10 Group 4 Low Dose		100 Group 5 Mid Dose		1000 Group 6 High Dose	
		m 50	f* 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50
DIGESTIVE SYSTEM													
Salivary glands*		0	0	0	0	0	0	0	0	0	0	0	1
Adenocarcinoma	MA	0	0	0	0	0	0	0	0	0	0	0	1
Cecum		41	40	36	37	36	39	41	46	36	38	40	47
Mucinous carcinoma	MA	0	0	0	0	0	0	0	1	0	0	0	0
ENDOCRINE SYSTEM													
Pituitary		48	49	43	46	48	48	48	45	47	48	48	50
Adenoma (small cell)	BE	0	0	0	0	1	0	0	0	0	0	0	0
Adenoma (acidophil cell)	BE	0	1	0	0	0	0	0	0	0	1	0	0
Thyroid gland		50	50	46	49	47	49	49	49	46	50	48	50
Follicular cell adenoma	BE	0	0	1	1	0	0	0	1	0	0	0	0
Adrenal gland		50	50	47	48	48	50	48	50	49	50	48	49
Spindle cell tumor (benign)	BE	0	0	0	0	0	0	0	1	0	1	0	0
Spindle cell tumor (malignant)	MA	0	0	0	1	0	0	0	0	0	0	0	0
HEMATOPOIETIC/LYMPHOID SYSTEM													
Generalized tumors		50	50	50	50	50	50	50	50	50	50	50	50
Lymphoma (lymphoblastic)	MA	1	2	0	0	0	1	1	1	0	3	4	1
Lymphoma (heterogeneous)	MA	1	6	1	2	1	2	1	4	2	1	0	5
Lymphoma (lymphocytic)	MA	0	2	0	0	0	1	0	0	0	0	0	0
Myeloblastic leukemia	MA	0	0	1	1	0	0	0	1	0	0	0	0
Granulocytic leukemia	MA	3	2	3	1	3	1	4	2	3	2	0	0
Mesenteric lymph node		42	44	42	42	44	43	45	46	38	42	43	49
Hemangiosarcoma	MA	0	0	0	0	0	0	0	0	1	0	0	1
Spleen		49	50	46	49	48	49	49	50	48	50	50	50
Hemangioma	BE	1	0	0	0	1	0	0	0	0	0	0	0
Hemangiosarcoma	MA	0	0	0	0	1	0	0	0	0	0	1	1
Histiocytic sarcoma	MA	0	0	0	0	0	1	0	0	0	0	0	0
Thymus		35	47	35	42	36	44	41	45	36	43	41	46
Thymoma, benign	BE	0	3	0	2	0	2	0	1	0	2	0	1
Thymoma, malignant	MA	0	0	0	2	0	0	1	0	0	0	0	1
HEPATOPANCREATIC SYSTEM													
Liver		50	50	48	48	49	49	50	50	50	48	50	50
Hepatocellular adenoma	BE	7	4	7	5	10	0	7	2	9	1	8	0
Hepatocellular carcinoma	MA	1	0	4	1	5	0	2	1	1	0	3	0
Hemangioma	BE	0	0	2	1	1	0	1	0	2	0	2	1
Hemangiosarcoma	MA	1	0	1	0	0	1	0	0	1	0	2	1

TD: Tumor designation (BE = benign; MA = malignant)
Note: No statistically significant increases or decreases in tumor frequency compared to controls
The numbers in each row against an organ/tissue indicates the number of animals examined unless marked by an asterisk (*).
*: Number of animals with macroscopic findings (histopathological investigation conducted only for these animals)

TABLE 3.3.2.12 (continued)
CARCINOGENICITY STUDY IN MICE: INCIDENCE OF PRIMARY NEOPLASMS

Histopathological finding		Dose level (mg/kg/day)											
ORGAN SYSTEM	TD	0		0		0		10		100		1000	
Organ/Tissue		Group 1		Group 2		Group 3		Group 4		Group 5		Group 6	
Neoplasm		Diet Control		Diet Control		Lactose Control		Low Dose		Mid Dose		High Dose	
		m	f	m	f	m	f	m	f	m	f	m	f
		50	50	50	50	50	50	50	50	50	50	50	50
HEPATOPANCREATIC SYSTEM (CONT.)													
Pancreas		49	50	48	47	48	47	49	49	47	50	49	49
Islet cell carcinoma	MA	1	0	0	0	0	0	0	0	0	0	0	0
INTEGUMENTARY SYSTEM													
Skin		50	50	47	49	49	50	49	50	49	50	50	49
Malign. Fibrous histiocytoma	MA	1	0	1	0	0	0	1	1	1	1	0	0
Basal cell carcinoma	MA	0	0	0	0	0	0	0	0	0	0	0	1
Squamous cell carcinoma	MA	0	0	0	0	0	1	0	0	0	0	0	0
Mammary gland			50		49		50		50		50		49
Adenoma	BE		0		1		0		0		1		0
Adenocarcinoma	MA		1		0		2		0		2		1
Adenoacanthoma	MA		0		0		0		0		1		0
Harderian gland		48	48	46	48	49	50	49	49	49	50	50	49
Adenoma	BE	3	2	2	1	2	2	2	1	2	2	2	0
MUSCULOSKELETAL SYSTEM													
Femur		50	49	46	48	47	50	49	49	49	50	50	48
Osteosarcoma	MA	0	1	0	0	0	0	0	0	0	0	0	0
Rib*		0	1	0	0	0	0	0	0	0	1	0	0
Chondrosarcoma	MA	0	0	0	0	0	0	0	0	0	1	0	0
Cranium*		0	0	1	0	0	0	0	1	0	0	0	0
Osteoma	BE	0	0	0	0	0	0	0	1	0	0	0	0
RESPIRATORY SYSTEM													
Lungs		50	49	50	50	50	50	50	50	50	50	50	50
Bronchiolar adenoma	BE	2	0	0	1	1	1	1	3	2	0	1	1
Alveolar adenoma	BE	2	1	1	0	2	0	3	0	1	1	2	1
Bronchiolar/alveolar adenoma	BE	5	4	2	2	4	3	7	4	6	2	6	6
Bronchiolar/alveolar carcinoma	MA	4	2	4	3	5	0	2	0	4	1	0	0
URINARY SYSTEM													
Kidney		49	50	48	49	49	49	50	50	49	50	47	50
Adenoma	BE	1	0	3	0	0	0	2	0	2	0	3	0
Tubular carcinoma	MA	1	0	0	0	0	0	0	0	0	0	0	0
Urinary bladder		50	45	41	43	46	44	45	46	48	44	49	49
Carcinoma in situ	MA	0	0	0	0	0	0	0	0	1	0	0	0

TD: Tumor designation (BE = benign; MA = malignant)
Note: No statistically significant increases or decreases in tumor frequency compared to controls
The numbers in each row against an organ/tissue indicates the number of animals examined unless marked by an asterisk (*).
*: Number of animals with macroscopic findings (histopathological investigation conducted only for these animals)

TABLE 3.3.2.12 (continued)
CARCINOGENICITY STUDY IN MICE: INCIDENCE OF PRIMARY NEOPLASMS

Histopathological finding / ORGAN SYSTEM / Organ/Tissue / Neoplasm	TD	Dose level (mg/kg/day)											
		0 Group 1 Diet Control		0 Group 2 Diet Control		0 Group 3 Lactose Control		10 Group 4 Low Dose		100 Group 5 Mid Dose		1000 Group 6 High Dose	
		m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50
REPRODUCTIVE SYSTEM													
Testes		50		46		49		49		49		50	
Leydig (interstitial) cell tumor	BE	0		1		1		3		0		0	
Epididymides		50		46		48		49		49		49	
Fibroleiomyoma	BE			1		0		0		0		0	
Malign. fibrous histiocytoma	MA	0		0		0		1		0		0	
Seminal vesicles		50		47		50		49		48		50	
Anaplastic carcinoma	MA	1		1		0		0		0		0	
Ovary			49		47		46		50		50		49
Granulosa-theca cell tumor	BE		1		0		0		1		0		0
Thecoma	BE		1		1		2		0		2		1
Luteoma	BE		1		0		0		0		0		0
Cystadenoma	BE		0		0		0		0		1		0
Papillary Cystadenoma	BE		0		1		0		0		0		0
Tubular adenoma	BE		0		0		0		1		0		0
Sex cord stromal tumor (undiff:)	BE		0		0		0		1		0		1
Uterus			49		48		49		50		49		50
Endometrial polyp	BE		0		1		1		0		2		1
Leiomyoma	BE		1		0		2		0		2		0
Leiomyofibroma	BE		1		0		0		0		0		1
Hemangioma	BE		2		1		1		0		0		0
Angiomyoma	BE		0		1		0		0		0		0
Granular cell tumor	BE		1		0		0		0		0		0
Endometrial carcinoma	MA		0		2		0		0		2		0
Malignant fibrous histiocytoma	MA		0		1		0		0		0		0
Squamous cell carcinoma	MA		1		0		0		0		0		0
Endometrial sarcoma	MA		1		3		4		3		1		1
Histiocytic sarcoma	MA		1		0		0		1		1		0
Leiomyosarcoma	MA		1		2		0		1		0		1
Vagina			46		46		46		48		48		48
Leiomyofibroma	BE		0		0		0		1		0		0
BODY CAVITIES													
Abdominal Cavity*		1	1	1	0	0	1	3	1	0	0	1	0
Histiocytic sarcoma	MA	1	0	1	0	0	1	1	1	0	0	1	0
Liposarcoma	MA	0	0	0	0	0	0	1	0	0	0	0	0
Fibrosarcoma	MA	0	1	0	0	0	0	0	0	0	0	0	0
Adipose tissue*		0	2	0	2	0	1	0	1	0	1	0	1
Hemangioma	BE	0	0	0	1	0	0	0	0	0	0	0	0

TD: Tumor designation (BE = benign; MA = malignant)
Note: No statistically significant increases or decreases in tumor frequency compared to controls
The numbers in each row against an organ/tissue indicates the number of animals examined unless marked by an asterisk (*).
*: Number of animals with macroscopic findings (histopathological investigation conducted only for these animals)

Toxicokinetics: In treated animals, plasma concentrations of telmisartan increased with the administered dose in non-proportional fashion over the dose range studied. Male mice exhibited lower plasma concentrations of test substance than female mice. Plasma concentrations measured at 8 a.m. were comparable to those measured at 4 p.m. No evidence of accumulation was noted on repeated dosing. The mean $AUC_{0\text{-}24h}$ value was estimated by regarding the mean of the two measurements, C_{mean} (8 hr and 16 hr postdose) as the AUC_{mean} and then multiplying this value by 24 (Table 3.3.2.13). Since a dose of 120 mg telmisartan for humans (protocol #502.124) resulted in $AUC_{0\text{-}24hr}$ of 2.04 (male) and 2.38 (female) µg.h/ml, the systemic exposure at the high dose of 1000 mg/kg/day in mouse (late study AUCs) exceeded the human therapeutic AUC value by a factor of approximately 218 (males) or 319 (females).

TABLE 3.3.2.13
CARCINOGENICITY STUDY IN MICE: TOXICOKINETICS ($AUC_{0\text{-}24}$ µg.h/ml)

Dose (mg/kg/day)	Males		Females	
	Week 52	Week 101	Week 52	Week 99
10	3.91	3.87	6.39	6.39
100	3.52	6.67	78.97	57.39
1000	547.20	445.70	663.10	759.10

In summary, in the 104-week mouse carcinogenicity study, dietary administration of telmisartan at dose levels up to 1000 mg/kg/day elicited no clinical signs of toxicity. The survival rates for all treated groups were similar to the combined control survival rate. The overall mean body weight gain of high dose animals was slightly lower ($p > 0.05$) than the control body weight gain. Mild to moderate anemia was observed ($p < 0.05$) in mid and high dose group animals. At terminal sacrifice, the mean absolute and relative liver weights of males and relative liver weight of females given 1000 mg/kg/day were significantly lower than liver weights of control 1 but not control 3 (lactose diet) groups. Absolute and relative kidney and relative adrenal weights were higher in females given 100 or 1000 mg/kg/day than in control 1 females. Drug-related histopathology was limited to slight to marked renal hypertrophy/hyperplasia, together with a higher incidence of renal tubular dilatation, in females of all drug-treated groups. Also, a trend to slightly higher incidence of chronic tubulointerstitial nephritis was noted in mid and high dose males. There were no neoplastic findings considered to be related to treatment. Toxicokinetics performed during this study revealed a dosage-related exposure of the animals to telmisartan. Based on the mean AUC values, the systemic exposure at the high dose of 1000 mg/kg/day in the mouse exceeds the human AUC (at a clinical dose of 120 mg) by a factor of more than 200. Additionally, based on the mortality data in the dose range-finding study, it may be concluded that 1000 mg/kg/day, the highest dosage used in this study, is or is close to a maximum tolerated dose (MTD).

3.3.3. 13-Week Oral Range-Finding Toxicity Study of Telmisartan in Rats (Report #U93-2069, Study #44R) Vol. 36-41

This GLP study was conducted by [redacted] between September 09, 1992 and December 08, 1992. It was conducted to aid in the selection of dosages for an oncogenicity study in this species.

Male and female rats [redacted] were approximately 28 days old and weighed 68.7-98.5 g (males) or 59.9-79.4 g (females) at the start of the study. Telmisartan (batch 8230151) was administered orally by dietary admixture (20% lactose trituration), *ad libitum*, for 13 weeks at doses of 10, 30, 100 or 300 mg/kg/day. Control animals received the untreated diet *ad libitum*. Each group consisted of 10 male and 10 female mice. Satellite animals (5/sex/group) were used for toxicokinetic study. The animals were housed individually.

Observations and Measurements

All animals were observed at least twice daily (once during weekends and holidays) for mortality and drug effects. The body weights were recorded a week before treatment and then weekly throughout the treatment period. The water intake per animal per day was calculated using the amount of water given and left in each bottle. The quantity of food consumed by each animal was recorded for each week throughout the treatment period. Food intake per animal per day was calculated using the amount of food supplied and that remaining in the feeder. The achieved intake of test substance in mg/kg/day was calculated on a weekly basis during the 13 weeks of treatment for each sex and each treated group, based on the body weight and mean food consumption and the nominal concentrations in the diet. Diets were prepared weekly for every dose group.

Systolic blood pressure and heart rate were measured indirectly 1 hr after the end of the dark phase in weeks 7 and 12 in 3 males and 3 females per group.

Blood samples were withdrawn from the retrobulbar venous plexus under halothane anesthesia in week 13 for hematology and clinical blood chemistry examinations (animals not fasted). Urinalysis was performed in week 13 on samples collected in metabolism cages. The test for occult blood in feces was made in weeks 7 and 8. For toxicokinetics study, blood samples were collected from satellite animals in weeks 2, 7 and 13 at 8:00 a.m. and 4 p.m. (n=5/sex/group/interval and same animals used for all intervals). The satellite animals were sacrificed after final sampling without further investigation. All main study animals were subjected to a detailed necropsy that included weighing of selected organs (Table 3.3.3.1). All organs and tissues listed in the following table and obtained from control and high dose group animals were microscopically examined. Macroscopical lesions and target organs (heart, liver, spleen, kidney, adrenal gland, stomach, duodenum and thymus) were histopathologically evaluated in animals given 10, 30 and 100 mg/kg/day.

TABLE 3.3.3.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Accessory glands
Adrenals*
Aorta
Brain*
Bone marrow
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes with
optic nerve
Femur
Gall bladder
Heart*
Ileum
Jejunum
Kidneys*
Lacrimal glands
Liver*
Lungs*
Lymph node
-neck region
-mesenteric
Mammary glands
Ovaries*
Pancreas
Parotids
Pituitary*
Prostate*
Rectum
Salivary gland
- mandibular,
-mesenteric
Sciatic nerve,
peripheral
Seminal vesicles
Skeletal muscle
Skin
Spinal cord
Spleen*
Sternum
Stomach
Testes*
Thymus*
Thyroids* /
parathyroids
Tongue
Trachea
Urinary bladder
Uterus
Vagina

*Organ weighed

Results

The achieved doses of telmisartan over the 13 weeks of treatment were, an average, close to the targeted doses (Table 3.3.3.2).

TABLE 3.3.3.2
13-WEEK CARCINOGENICITY STUDY IN RATS: ACHIEVED DOSES (MEAN VALUES)

	Sex	Intended Daily dose (mg/kg/day)			
		10	30	100	300
Achieved daily dose, mg/kg/day (%)[1]	Male	9.93 (99.3)	29.65 (98.8)	99.60 (99.6)	296.83 (98.9)
	Female	9.89 (98.9)	29.51 (98.4)	98.76 (98.8)	296.47 (98.8)

[1]: % of targeted dose (given in parentheses)

There were no deaths. The only clinical sign observed was rough hair coat in high dose group animals during weeks 1 and 2 of drug administration. Mean body weights of treated male groups were significantly lower than control starting from week 1. The reduction in body weight gain was attributed to decreased food intake, especially in the two highest dosage groups, for most of the treatment period. At the end of the 13 week treatment period, mean body weights of treated males were 15 to 20% lower than control weight (weight gain 24-32% lower than control), with maximum difference achieved at 300 mg/kg/day (Table 3.3.3.3, Fig. 3.3.3.1). In female rats, reduced body weight gain and food consumption, relative to control animals, was consistently observed (beginning with the first week) in groups given 100 or more mg/kg/day (Table 3.3.3.4). At study termination, the mean body weight of the high dose female group was 10% lower than control weight. The overall body weight gains of females receiving 30, 100 and 300 mg/kg/day

were, respectively, 87, 79 and 77% ($p < 0.05$ for all groups) of control group weight gain (Table 3.3.3.4, , Fig. 3.3.3.2).

TABLE 3.3.3.3

13-WEEK MTD STUDY IN RATS: BODY WEIGHT (BW), FOOD CONSUMPTION (FC) AND FC:BW RATIOS IN MALE RATS

		Dosage (mg/kg/day)									
		0		10		30		100		300	
Wk		grams	ratio§	grams	ratio	grams	ratio	grams	ratio	grams	ratio
-1	BW	198.4		193.0		192.5		198.3		192.8	
	FC	172.2	0.87	166.1	0.86	168.6	0.88	169.2	0.85	163.4	0.85
1	BW	248.6		231.4*		227.8*		231.6		221.0*	
	FC	175.2	0.70	169.8	0.73	167.9	0.74	155.0*	0.67	146.2*	0.66
2	BW	292.4		265.7*		257.8*		264.2*		250.7*	
	FC	187.3	0.64	183.9	0.69	173.7*	0.67	164.8*	0.62	152.1*	0.61
3	BW	322.3		295.0*		280.9*		287.7*		277.6*	
	FC	193.0	0.60	182.9	0.62	176.9*	0.63	168.5*	0.59	165.2*	0.60
9	BW	454.2		394.0*		372.9*		383.2*		372.7*	
	FC	186.1	0.41	172.0*	0.40	166.6*	0.45	163.9*	0.43	157.3*	0.42
13	BW	485.3		410.7*		393.1*		402.4*		387.5*	
	FC	177.2	0.36	157.8*	0.38	152.6*	0.39	157.9*	0.37	139.7*	0.36
13	BW %¶	-		-15%		-19		-17		-20	
1-13	BWG♦	287		218*		201*		204*		195*	
1-13	BWG%⊕			-24%*		-30*		-29*		-32*	

§ Ratio of food consumed (grams) per gram body weight

¶ Difference in body weight from control at termination (%)

⊕ Overall (1-13 weeks) BWG relative to control (%)

* Significantly different from control ($p \leq 0.05$)

♦ Absolute BWG (body weight gain) in grams

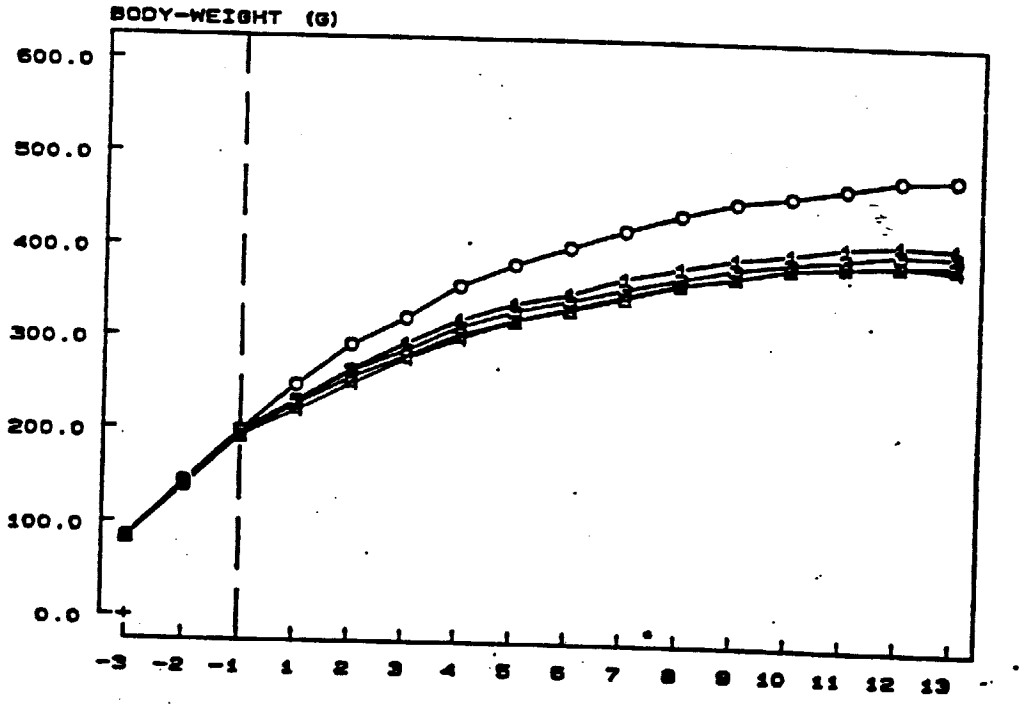

Fig. 3.3.3.1.: 13-week toxicity study of telmisartan in male rats. Group mean body weight (grams, on Y-axis) *versus* treatment period (in weeks, X-axis). 0: Control 1, 1: telmisartan 10 mg/kg/day, 2: telmisartan 30 mg/kg/day, 3: telmisartan 100 mg/kg/day, 4: telmisartan 300 mg/kg/day

TABLE 3.3.3.4

13-WEEK MTD STUDY IN RATS: BODY WEIGHT (BW), FOOD CONSUMPTION (FC) AND FC:BW RATIOS IN FEMALE RATS

		Dosage (mg/kg/day)									
		0		10		30		100		300	
Wk		grams	ratio§	grams	ratio	grams	ratio	grams	ratio	grams	ratio
-1	BW	140.0		143.4		140.8		143.3		140.3	
	FCN	133.5	0.97	130.7	0.91	130.5	0.93	131.1	0.91	127.3	0.91
1	BW	158.9		162.4		154.2		155.6		148.9	
	FCN	126.1	0.79	127.5	0.79	119.2	0.77	113.0*	0.73	102.9*	0.66
2	BW	174.8		177.5		168.8		168.8		156.5*	
	FCN	121.6	0.70	133.1	0.75	123.0	0.73	112.3	0.67	98.4*	0.63
3	BW	190.1		192.9		179.9		180.0		174.4*	
	FCN	137.6	0.72	130.8	0.68	125.4*	0.70	119.5*	0.66	117.5*	0.67
9	BW	241.3		240.9		227.6		220.2*		220.2*	
	FCN	138.8	0.58	131.9	0.55	130.6	0.57	113.2*	0.51	120.4*	0.55
13	BW	249.6		248.6		237.0		230.7		225.5*	
	FCN	123.2	0.49	118.6	0.48	111.2*	0.47	109.1*	0.47	102.6*	0.45
13	BW %¶	-		-0.4		-5		-8		-10	
1-13	BWG ♦	110		105		96*		87*		85*	
1-13	BWG%⊕	100		-5%		-13*		-21*		-23*	

§ Ratio of food consumed (grams) per gram body weight

¶ Difference in body weight from control at termination (%)

⊕ Overall (1-13 weeks) BWG relative to control (%)

* Significantly different from control ($p \leq 0.05$)

♦ Absolute BWG (body weight gain) in grams

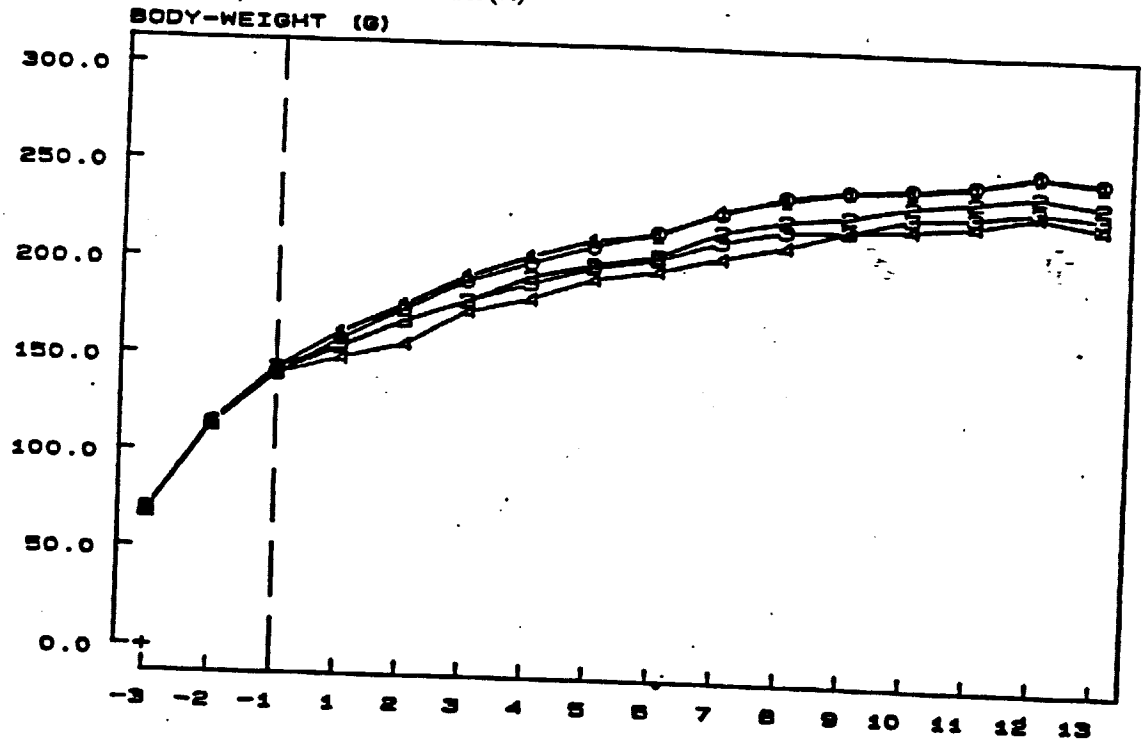

Fig. 3.3.3.2: 13-week toxicity study of telmisartan in female rats. Group mean body weight (grams, on Y-axis) *versus* treatment period (in weeks, X-axis). 0: Control 1, 1: telmisartan 10 mg/kg/day, 2: telmisartan 30 mg/kg/day, 3: telmisartan 100 mg/kg/day, 4: telmisartan 300 mg/kg/day

Mean systolic blood pressure was lower than control for all treated groups. The reductions relative to control were 25, 35, 33 and 47 mm Hg, respectively, for animals receiving telmisartan at 10, 30, 100 and 300 mg/kg/day in week 7. No further reductions were observed in week 12. In all treated groups, heart rate was increased relative to control animals but increase was statistically significant only in groups receiving 100 and 300 mg/kg/day. In these two groups, the mean heart rates were increased in week 7 by 49 and 78 beats per minute and in week 12 by 51 and 57 beats per minute, respectively. Water consumed over the course of the study was significantly greater than control for all treated male groups (18, 50, 56 and 43%, respectively, at 10, 30, 100 or 300 mg/kg/day) and for female group receiving 100 mg/kg/day (19%). The remaining treated female groups showed a very slight, insignificant elevation in water consumption.

Red blood cell indices (RBC, hemoglobin, hematocrit) decreased 4 to 20% ($p < 0.05$) in all drug treated groups relative to control (Table 3.3.3.5). In week 13, a moderate increase in blood urea nitrogen and creatinine (relative to control) was observed in males and females at all dose levels. Total bilirubin and cholesterol were increased (relative to control) in males at 30 or more mg/kg/day and in females at 100 or more mg/kg/day. Reduced glycerol and total protein (relative to control) were noted in males and females at all doses. Serum potassium, magnesium, calcium and chloride increased in all treated groups (Table 3.3.3.5).

TABLE 3.3.3.5
13-WEEK MTD STUDY IN RATS: CLINICAL LABORATORY VALUES IN WEEK 13

		Dosage (mg/kg/day)									
	units	0		10		30		100		300	
		m	f	m	f	m	f	m	f	m	f
Hematology											
RBC	$10^6/mm^3$	7.94	7.53	7.60*	6.96*	7.18*	6.70*	6.61*	6.42*	6.30*	6.34*
Hb	g/100 ml	15.8	15.2	15.2*	14.2*	14.7*	13.7*	13.9*	12.9*	13.2*	13.2*
HCT	vol. %	47.3	45.5	45.5*	42.6*	44.4*	41.3*	41.5*	38.9*	39.1*	39.8*
Clin. chem.											
BUN	mmol/l	7.4	8.8	12.2*	13.5*	20.0*	15.2*	22.7*	21.6*	25.1*	20.7*
Creatinine	µmol/l	45.4	45.3	48.8	45.7	53.9*	48.8	56.0*	52.6*	63.5*	51.4*
TBILI	µmol/l	0.9	1.0	0.8	0.9	1.2	1.1	1.4*	1.3	2.9*	2.1*
Glycerol	mmol/l	4.09	2.80	2.95*	1.83*	1.72*	1.85*	1.54*	1.44*	1.24*	1.16*
CHOL	mmol/l	1.75	1.68	1.61	1.73	2.00*	1.86	2.19*	1.99	2.12*	2.00
TPROT	g/l	65.7	62.5	60.9*	58.7*	59.1*	57.5*	58.0*	57.2*	57.3*	58.6*
K	mmol/l	4.2	4.1	5.1*	4.8*	5.9*	4.6	6.2*	5.6*	6.1*	5.1*
Mg	µmol/l	705	792	758	799	859*	910*	917*	1000*	1033*	950*
Ca	mmol/l	2.78	2.67	2.74	2.6	2.67*	2.62	2.62*	2.62	2.63*	2.56*
Cl	mmol/l	100.0	101.4	100.8	102.8	102.0*	103.0	103.3*	103.5*	102.9*	103.5*

*: Significantly different from control ($p \leq 0.05$)
Chol: cholesterol, Tbili: total bilirubin, Tprot: total protein

Urinalyses and investigation of feces for occult blood revealed no significant differences between treated and control groups. At the week 14 sacrifice, the mean relative and absolute heart weights in all treated groups and the mean relative and absolute liver weights in males receiving 100 or more mg/kg/day and females receiving 300 mg/kg/day were reduced relative to control. High mean relative (to body weight) and not absolute weights of kidneys were observed

for females given 30 or more mg/kg/day. Additionally, the mean relative spleen weights in high dose males and females given 100 or more mg/kg/day, and the mean relative adrenal weights in males given 30 or more mg/kg/day, were increased relative to control (Table 3.3.3.6).

TABLE 3.3.3.6
13-WEEK MTD STUDY IN RATS: ORGAN WEIGHTS

Organ		Dosage (mg/kg/day) 0		10		30		100		300	
		m	f	m	f	m	f	m	f	m	f
Body Wt.	grams	493.8	262.8	412.9*	256.4	391.7*	240.1*	405.5*	234.3*	387.6*	225.6*
Heart	abs. (g)§	1.40	0.95	1.05*	0.73*	0.95*	0.72*	0.95*	0.72*	0.97*	0.73*
	relative ¶	0.28	0.36	0.26*	0.29*	0.24*	0.30*	0.23*	0.31*	0.25	0.32*
Liver	abs. (g)	21.23	11.25	17.56*	10.04*	16.20*	10.04*	15.95*	9.39*	13.90*	8.61*
	relative	4.30	4.29	4.25	3.91*	4.13	4.19	3.93*	4.02	3.60*	3.83*
Kidneys	abs. (g)	3.29	2.27	3.07	2.40	2.81*	2.28	2.90*	2.43	2.68*	2.25
	relative	0.67	0.87	0.74*	0.94	0.72*	0.95*	0.71	1.04*	0.70	1.00*
Spleen	abs. (g)	0.88	0.59	0.77	0.60	0.73*	0.61	0.83	0.62	0.88	0.61
	relative	0.18	0.23	0.19	0.24	0.18	0.26	0.20	0.26*	0.23*	0.27*
Adrenals	abs. (mg)	72.7	93.1	63.0*	88.3	71.6	83.9*	76.5	80.1*	73.3	84.0*
	relative	14.7	35.7	15.2	34.7	18.3*	35.1	18.9*	34.3	19.0*	37.3

*: Significantly different from controls ($p \leq 0.05$) §: Absolute weight in grams/mg
¶: Relative weight in grams or milligrams per 100 grams body weight

Macroscopic examinations showed focal discolorations or erosions of the gastric mucosa in all treated groups. As in previous studies with rats, the principal drug-induced microscopical findings observed at all doses were confined to gastric mucosa and kidneys. Gastric mucosal ulcers, erosions, and/or submucosal inflammation, were found in 0, 9, 7 and 9 of 10 males and 1, 3, 5 and 5 of 10 females in the 10, 30, 100 and 300 mg/kg groups (Table 3.3.3.7). Erosions and

TABLE 3.3.3.7
13-WEEK STUDY IN RAT: INCIDENCE OF GASTRIC INJURY OBSERVED MICROSCOPICALLY

Histopathological Findings	Dose (mg/kg/day) 0		10		30		100		300	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	10	10	10	10	10	10	10	10	10	10
No Mucosal Injury	10	10	10	9	1	7	3	5	1	5
Inflammation/fibrosis only*	0	0	0	0	6	3	1	2	6	3
Erosion (with or without inflam)	0	0	0	1	0	0	2	2	2	0
Ulcer (with or w/o erosion, inflam.)	0	0	0	0	3	0	4	1	1	2
Total with Mucosal Injury	0	0	0	1	9	3	7	5	9	5

* Note: Submucosal/mucosal inflammation graded as slight (+) was observed in controls and drug-treated animals and was not considered indicative of gastric mucosal injury. Only changes graded as mild (++) or greater in severity are shown in the table.

ulcers were generally small and localized. Presence of mixed inflammatory cells and fibrosis in the mucosa and submucosa suggested that most erosive and ulcerative lesions occurred at

variable time points after the start of drug administration, with subsequent healing. Males were more sensitive than females and tended to have a higher incidence and severity of gastric lesions.

A dose-related minimal to moderate hypertrophy/hyperplasia of JGA was noted for all treated groups. The effect was more pronounced in males than in females (Table 3.3.3.8). No evidence of drug-related renal tubular injury was observed histopathologically. Incidence and severity of basophilic tubules, which represent a spontaneous or drug-induced degenerative change or a regenerative response to injury, were similar in all groups including control (Table 3.3.3.8). Other drug-related findings, observed in both sexes at 300 mg/kg/day, were an increase in slight to mild extramedullary hematopoiesis of the spleen and a decrease in size of centrilobular hepatocytes with increased basophilia. Slight diffuse bilateral hypertrophy of the zona fasciculata of the adrenal was noted in a few high dose males. No histomorphological correlate for the decreased heart weight was noted.

TABLE 3.3.3.8
13-WEEK STUDY IN RAT: HISTOPATHOLOGICAL FINDINGS IN THE KIDNEY

Histopathological Findings	Dose (mg/kg/day)									
	0		10		30		100		300	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	10	10	10	10	10	10	10	10	10	10
No significant findings in tubules	2	0	3	0	0	0	0	0	0	0
Basophilic tubules										
Minimal	8	9	7	7	10	10	10	10	9	10
Mild	0	1	0	3	0	0	0	0	1	0
No significant JGA changes	10	10	0	0	0	0	0	0	0	0
Increased granules (hyperplasia)	0	0	10	10	10	10	10	10	10	10
Increased vacuolation	0	0	4	0	7	0	10	1	10	10
JGA Hypertrophy										
Minimal	0	0	8	10	1	10	0	1	0	0
Mild	0	0	2	0	9	0	10	9	3	5
Moderate	0	0	0	0	0	0	0	0	7	5

The plasma concentration of telmisartan increased with increasing dose and was more than dose proportional (at both time points) at doses of 30 or more mg/kg/day. The levels were higher in the morning (8 a.m.) than in the afternoon (4 p.m.). High individual variability was present at all doses. There were no significant gender differences. Though no statistically significant effects of repeated dosing were noted, the concentrations tended to be slightly higher in week 13 than in week 2 (Table 3.3.3.9).

TABLE 3.3.3.9

13-WEEK MTD STUDY IN RATS: PLASMA CONCENTRATIONS (μG/ML) IN WEEKS 2, 7 AND 13

Dosage (mg/kg/day)									
Week	Time	10		30		100		300	
		m	f	m	f	m	f	m	f
2	8 a.m.	1.00	0.66	1.06	0.62	4.89	2.55	24.95	27.28
	4 p.m.	0.36	0.26	0.41	0.26	2.51	3.22	4.58	11.19
7	8 a.m.	0.27	0.32	1.26	0.67	8.90	7.12	27.71	44.93
	4 p.m.	0.16	0.13	0.38	0.30	3.85	2.27	7.84	28.69
13	8 a.m.	0.43	0.45	2.47	1.90	7.89	9.33	37.26	58.38
	4 p.m.	0.24	0.18	1.24	1.02	2.77	4.34	19.92	10.74
OVERALL	8 a.m.	0.57	0.47	1.60	1.06	7.23	6.33	29.98	43.53
	4 p.m.	0.253	0.19	0.68	0.53	3.04	3.28	10.78	16.87

In summary, telmisartan was given to rats as a dietary admixture at dosages of 10, 30, 100 and 300 mg/kg/day for 13 weeks. There were no deaths and no demonstrable clinical signs. The mean body weight gains for treated male groups over the 13 week treatment period were 24 to 32% lower than concurrent control gain. For treated female groups receiving doses of 30 or more mg/kg/day, the reduction in mean body weight gain relative to concurrent control (for the 13 week treatment period) was between 13 and 23%. Red blood cell indices decreased 4 to 20% in all drug-treated groups relative to control. Moderate increases in blood urea nitrogen (1.5- to 3-fold relative to control) and creatinine (up to 1.4-fold) were observed in both sexes at all dose levels. Significant organ weight findings included decreased absolute and relative heart weights in all treated groups, and decreased absolute and relative liver weights in males receiving 100 or more mg/kg/day and in females receiving 300 mg/kg/day. The principal drug-related histopathological findings (occurred at all doses) were gastric mucosal ulcers, erosions and/or inflammation and JGA hypertrophy and hyperplasia of the kidney. Based on the above findings, the sponsor concluded that the maximum tolerated dose for the carcinogenicity study would be 100 mg/kg/day for both sexes. Doses higher than 100 mg/kg/day, administered for more than a year, might be expected to result in death due to gastric mucosal ulceration.

3.3.4. 104-Week Oral Carcinogenicity Study of Telmisartan in Rats (Report #U97-2275, Study #86R) Vol. 67-81

This GLP study was conducted by , between June 08, 1993 and June 05, 1995 (dosing period). Animals were necropsied on June 22, 1995. This study was conducted to assess the oncogenic effects of telmisartan during its repeated daily oral administration to rats for 104 weeks.

Male and female rats , were approximately 28 days old and weighed 62-96 g (males) or 53-93 g (females) at the start of the study (pretest, week -2). The animals received a measured weekly food ration in granular form with or without the admixed test substance. Drug-diet admixtures were made weekly for each dose group during the first 12 weeks. From week 13 until the end of the study, admixtures were prepared at 4 week intervals. Food admixtures were analyzed for drug concentration and homogeneity in weeks 4, 9, 23, 34, 49, 60, 76 and 93. Amount given was based on quantity consumed during pretest period (1 week) and during the previous measurement period (especially the first 12 weeks of the study). Both vehicle control groups received food/1.5% lactose. The control 1 group was supplied diet/vehicle *ad libitum*. Diet/vehicle supplied to the second control group (control 2) was restricted to the amount of diet consumed by the high dose group. Groups of 50 male and 50 female rats were given telmisartan (batch 8350071) as a 20% drug/lactose trituration in diet at doses of 3, 15 and 100 mg/kg/day for 104 weeks. To reduce potential palatability problems, animals of the 15 and 100 mg/kg/day groups received 3 mg/kg/day of telmisartan in week 1 and 15 mg/kg/day in week 2. The dose for high dose animals was further escalated to 50 mg/kg in week 3 and 100 mg/kg in week 4. Five additional satellite animals per sex per drug-treated group were used for toxicokinetic study. Twelve untreated male and female sentinel animals were used for bacteriological testing. The animals were housed individually.

Observations and Measurements

All animals were observed at least twice daily (once during weekends and holidays) for mortality and drug effects. Body weight and food and water consumption were recorded a week before treatment and then at weekly intervals for the first 12 weeks, at 4 week intervals thereafter and before necropsy.

Systolic blood pressure and heart rate were measured indirectly, 1 hr after the end of the dark phase in weeks 13, 26, 51, 78 and 102, in 3 males and 3 females of each telmisartan-treated group and in the *ad libitum* diet control (group 1). Blood samples were withdrawn from the retrobulbar venous plexus of all surviving animals (under halothane anesthesia in weeks 102 to 105), and from most of the animals sacrificed intercurrently (in weeks 44 to 102) for clinical laboratory tests (hematology and clinical chemistry for survivors, only hematology for others; animals not fasted). A test for occult blood in feces was made in week 67. Since the results were positive in 2 animals, all animals were retested in weeks 69-70 and 100. For toxicokinetics study, blood samples were collected from satellite animals in weeks 14, 26, 53 and 103 at 8 a.m., and 2 (week 14) or 3 (weeks 26, 53 and 103) days later at 4 p.m. (n=5/sex/group/interval and same animals used at all sampling times). The satellite animals were sacrificed after final sampling

without further investigation. All main study animals were subjected to a detailed necropsy that included weighing and histopathological examination of selected organs/tissues (Table 3.3.4.1).

TABLE 3.3.4.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Accessory sex glands
Adrenals
Aorta
Brain* (cerebrum, cerebellum)
Bone marrow
Cecum
Colon
Duodenum
Ear
Epididymides
Esophagus
Eyes with optic nerve
Femur
Gall bladder
Heart*
Ileum
Jejunum
Kidneys*
Knee
Lacrimal glands (exorbital, harderian)
Liver*
Lungs*
Lymph node
-mandibular
-mesenteric
Macroscopic changes
Mammary glands
Nose
Ovaries with oviducts
Pancreas
Parotids
Pituitary
Prostate
Rectum
Salivary gland
-Submandibular
-sublingual
Sciatic nerve, -peripheral
Seminal vesicles
Skeletal muscle
Skin
Spinal cord
Spleen*
Sternum
Stomach
Testes
Thymus
Thyroids / parathyroids
Tongue
Trachea
Urinary bladder
Uterus (horns, body and cervix)
Vagina

*Organ weighed

Results

The achieved doses of telmisartan over the 93 week measurement period were, on average, close to the targeted 3, 15 and 100 mg/kg/day levels: 2.82, 14.6 and 96.1 mg/kg/day, respectively, in the males, and 2.86, 15.3 and 105.2 mg/kg/day, respectively, in the females (Table 3.3.4.2).

TABLE 3.3.4.2
104-WEEK CARCINOGENICITY STUDY IN RATS: ACHIEVED DOSES

Targeted dose (mg/kg/day)	3	15	100
achieved: males (mg/kg/day)	3.02	15.0	99.7
% of targeted dose	100.60	100.0	99.7
achieved: females (mg/kg/day)	3.01	15.1	100.0
% of targeted dose	100.50	100.5	100.0

A total of 123 animals (43 males, 80 females) died or were sacrificed during the 104 week treatment period. Survival exceeded 60% in all groups with no significant differences between drug treated and control groups. Drug treatment had no effect on mean survival time, survival rate or cause of death (Table 3.3.4.3).

TABLE 3.3.4.3
104-WEEK CARCINOGENICITY STUDY IN RATS: SURVIVAL[¶]

Week/incidence	Dose level (mg/kg/day)									
	0 (Control 1)		0 (Control 2)		3		15		100	
	Group G 0		Group G 4		Group G 1		Group G 2		Group G 3	
	m	f	m	f	m	f	m	f	m	f
Survival										
1	50	50	50	50	50	50	50	50	50	50
%	100	100	100	100	100	100	100	100	100	100
52	50	49	50	50	49	50	48	50	48	50
%	100	98	100	100	98	100	96	100	96	100
60	50	49	49	50	49	50	48	50	48	49
%	100	98	98	100	98	100	96	100	96	98
72	49	49	49	49	49	47	48	48	47	47
%	98	98	98	98	98	94	96	96	94	94
84	47	48	49	47	48	44	46	43	47	45
%	94	96	98	94	96	88	92	86	94	90
102	40	37	45	32	44	36	39	33	42	33
%	80	74	90	64	88	72	78	66	84	66
103-107[§]	39-38	37	44	32	44	36	39	33	42	33-32
%	78-76	74	88	64	88	72	78	66	84	66-64
Nonsurvivals										
No. sacrificed	9	12	3	14	5	10	9	15	4	17
No. found dead	3	1	3	4	1	4	2	2	4	1
Total loss (%)	12 (24)	13 (26)	6 (12)	18 (36)	6 (12)	14 (28)	11 (22)	17 (34)	8 (16)	18 (36)
Pathology state of nonsurvivors										
Non-neoplastic	5	2	2	5	1	4	1	3	3	3
Benign neoplasm	3	5	1	9	2	8	6	9	1	10
Malign neoplasm	4	6	3	4	3	2	4	5	4	5
Survival time										
mean (weeks)	102.5	98.0	101.7	96.9	97.3	96.0	96.0	94.7	97.7	97.9
range (weeks)	72-107	51-107	59-107	52-107	50-107	64-107	12-107	65-107	50-107	55-107

¶: Number of animals surviving and % survival in weeks 1 to 107
§: Period of terminal sacrifice (one decedent each in the control 1 male and high dose female groups)

A significant decrease in systolic blood pressure was noted in all drug treated groups relative to the *ad libitum* control 1 group. Maximum decreases of 27, 41 and 37% (mean of both sexes) were observed in the 3, 15 and 100 mg/kg/day groups, respectively, in week 26. In weeks 13 to 78, the decrease in blood pressure showed no consistent change over time. However, the smallest differences from control (none of which were statistically significant) were seen in week 102 (-12, +2 and -6.5%, respectively, in the 3, 15 and 100 mg/kg/day groups).

There were no drug-related clinical signs. The total number of palpable nodules/masses, both transient or persistent, were equally distributed in control and substance-treated groups (Table 3.3.4.4).

TABLE 3.4.4.4

104-WEEK CARCINOGENICITY STUDY IN RATS: FREQUENCY OF CLINICALLY OBSERVED NODULES AND MASSES. TIME OF APPEARANCE AND HISTOPATHOLOGICAL DESIGNATION (TUMOR/NON-TUMOR)§

	Weeks of observation	Study groups (mg/kg)									
		0 (Contr. 1)		0 (Contr. 2)		3		15		100	
		T	NN	T	NN	T	NN	T	NN	T	NN
Males	1- 12										
	13- 24										
	25- 32										
	33- 40										
	41- 48			1						1	
	49- 56	1				1					
	57- 64	1		2		1					
	65- 72	1				1				1	
	73- 80	1						3			
	81- 88			1				1			
	89- 96			2	3	1				1	
	97-105	7		3	2	5		2		2	
	Total	*11*	*0*	*9*	*5*	*9*	*0*	*6*	*0*	*5*	*0*
Females	1- 12										
	13- 24										
	25- 32		1								
	33- 40									1	
	41- 48			1							
	49- 56	2		2		2				1	
	57- 64			1		1					
	65- 72	1			2	2		1			
	73- 80	1				2		2	1	2	
	81- 88	5		2				4		2	
	89- 96	4		2	2	2	1	4		4	
	97-105	4	2	4		1		3	3	7	1
	Total	*17*	*3*	*12*	*4*	*10*	*1*	*14*	*4*	*17*	*1*

T histopathologically confirmed tumor

NN non-neoplastic nodules and masses

§ excludes transitory nodules

Mean body weight of *ad libitum* fed control 1 males exceeded that of control 2 males (diet restricted to the amount consumed by the high dose group) to a significant degree (>10%) during most of the study. In order to detect body weight changes not due to changes in food intake, mean body weights of drug-treated groups were compared to that of the control 2 group. Low dose males showed a trend to slightly lower body weights relative to control 2 males over the course of the study. However, the decrement never exceeded 5% and at termination, weights of low dose males were ~5% higher than those of control 2 males. Body weights of 15 and 100 mg/kg/day males were significantly lower (4 to 13% and 7 to 15%, respectively) than those of control 2 males over most of the study period (Fig. 3.3.4.1). At termination of the study, differences were less pronounced, with mean weights of mid dose and high dose males about 7 and 9% lower, respectively, than that of control 2 males (see Table 3.3.4.5).

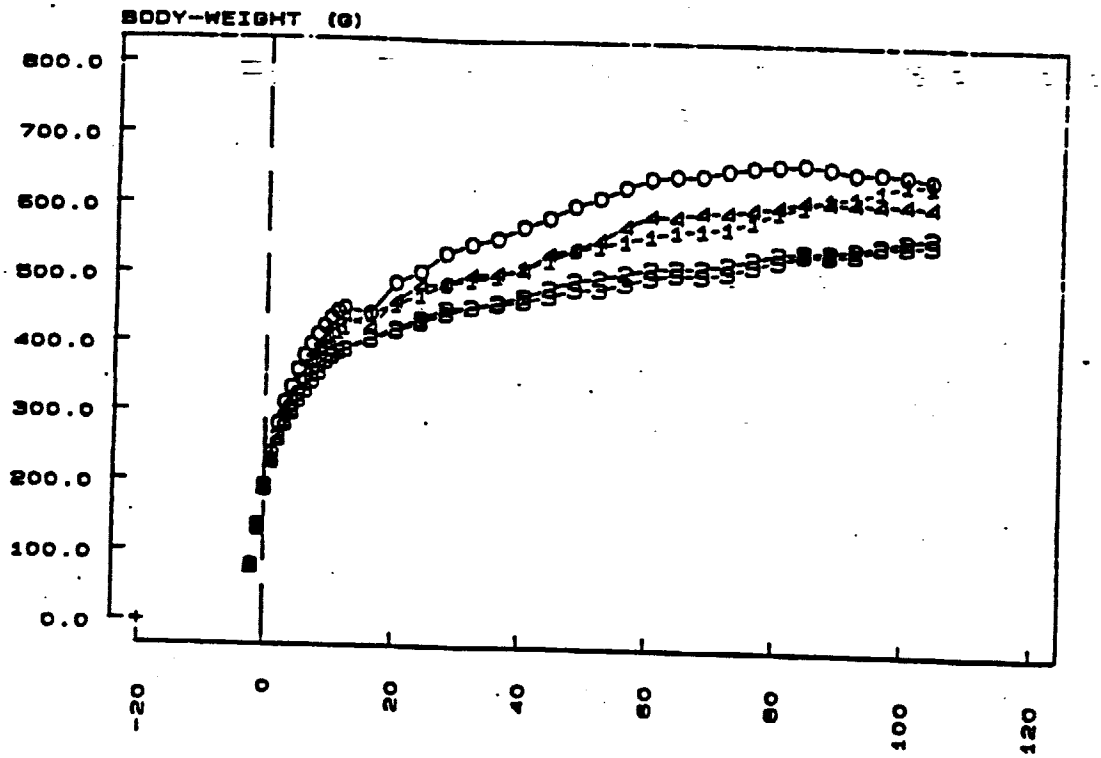

Fig. 3.3.4.1.: 104-week carcinogenicity study of telmisartan in male rats. Group mean body weight (grams, on Y-axis) *versus* treatment period (in weeks, X-axis). 0: Control 1, 1: telmisartan 3 mg/kg/day, 2: telmisartan 15 mg/kg/day, 3: telmisartan 100 mg/kg/day, 4: control 2.

TABLE 3.3.4.5

104 WEEK CARCINOGENICITY STUDY: GROUP MEAN BODY WEIGHT DIFFERENCES IN MALE RATS

Study week		Dosage (mg/kg/day)				
		Control 2[1]	Control 1	3	15	100
6	B.wt., g	353.6	379.2	361.1	339.8	328.4
	% diff[§]		+7.2	+2.1	-3.9	-7.1
	%BWG[#]		+13.4*	+3.2	-11.2	-15.4*
12	B.wt	437.1	449.7	421.3	389.8	388.4
	% diff		+2.9	-3.6	-10.8	-11.1
	%BWG		+3.7	-7.2	-20.8*	-19.7*
36	B.wt	502.6	551.8	497.6	460.3	456.8
	% diff		+9.8	-1.0	-8.4	-9.1
	%BWG		+14.6*	-2.3	-14.9*	-14.7*
60	B.wt	587.9	642.2	558.8	512.2	498.9
	% diff		+9.2	-5.0	-12.9	-15.1
	%BWG		+12.8*	-7.8	-20.0*	-22.3*
84	B.wt	614.4	665.8	606.9	541.7	536.8
	% diff		+8.4	-1.2	-11.8	-12.6
	%BWG		+11.3*	-2.4	-18.0*	-18.2*
104	B.wt	609.5	647.2	640.9	565.9	554.4
	% diff		+6.2	+5.2	-7.2	-9.1
	%BWG		+8.4	+6.9	-11.2	-12.9

[1]: Reference group = control 2; *: $p < 0.01$ when compared to control 2.
[§]: Per cent (%) difference from control 2 body weight
[#]: Per cent (%) increase from initial weight (week –1) relative to control 2

As in males, mean body weight of the female *ad libitum* fed control 1 group was significantly higher than that of the control 2 group (up to ~7% higher). Mean body weight of low dose animals was comparable to that of the food restricted control 2 group except at the terminal week when the mean weight was 4% higher. Females given 15 or 100 mg/kg/day gained less weight than control 2 females during the first 12 study weeks (body weight ~7 and 5% lower, respectively, at week 12). Thereafter, differences were less pronounced; from week 60 to study termination, mean body weight gain approximated or exceeded that of the control 2 group. At termination of the study, mean body weights of treated groups were 2.7 to 5.6% higher than that of the control 2 group (Fig 3.3.4.2 and Table 3.3.4.6).

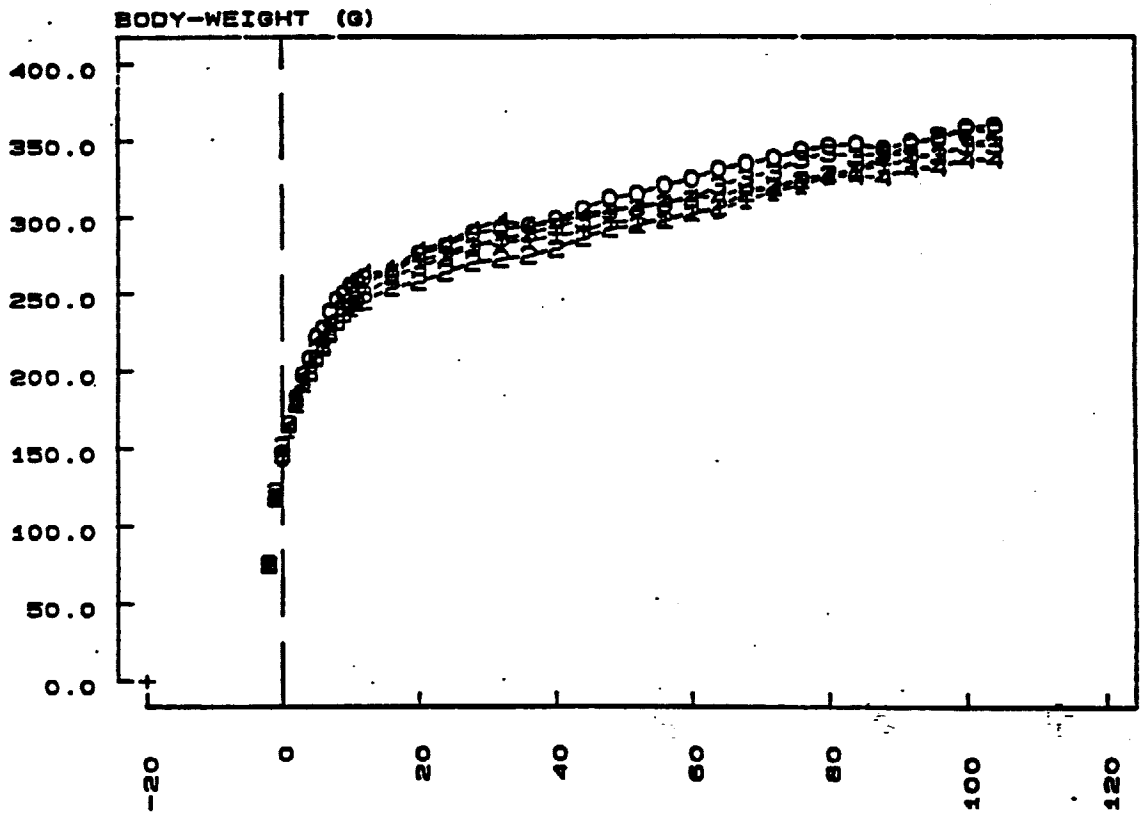

Fig. 3.3.4.2.: 104-week carcinogenicity study of telmisartan in female rats. Group mean body weight (grams, on Y-axis) *versus* treatment period (in weeks, X-axis). 0: Control 1, 1: telmisartan 3 mg/kg/day, 2: telmisartan 15 mg/kg/day, 3: telmisartan 100 mg/kg/day, 4: control 2.

TABLE 3.3.4.5

104 WEEK CARCINOGENICITY STUDY: GROUP MEAN BODY WEIGHT DIFFERENCES IN FEMALE RATS

Study week		Dosage (mg/kg/day)				
		Control 2[1]	Control 1	3	15	100
6	B.wt., g	222.5	227.4	220.6	216.5	213.8
	% diff[f]		+2.2	-0.85	-2.7	-3.9
	%BWG[#]		+10.9	+2.5	-6.1	-16.6
12	B.wt	263.2	260.2	254.9	244.6	249.2
	% diff		-1.1	-3.2	-7.1	-5.3
	%BWG		+0.3	-3.9	-14.8*	-15.4*
36	B.wt	294.2	293.9	284.5	274.6	288.9
	% diff		-0.1	-3.3	-6.7	-1.8
	%BWG		+2.0	-4.0	-12.4*	-6.2
60	B.wt	312.8	324.6	303.3	302.0	311.4
	% diff		+3.8	-3.0	-3.5	-0.5
	%BWG		+9.3	-3.4	-5.7	-3.1
84	B.wt	326.2	347.7	329.9	330.6	339.4
	% diff		+6.6	+1.1	+1.3	+4.1
	%BWG		+14.1	+4.5	+3.1	+5.3
104	B.wt	337.4	359.6	351.5	356.2	346.5
	% diff		+6.6	+4.2	+5.6	+2.7
	%BWG		+13.2	+9.5	+10.6	+3.4

[1]: Reference group = control 2
[f]: Per cent (%) difference from control 2 body weight
[#]: Per cent (%) increase from initial weight (week –1) relative to control 2
*: $p < 0.01$ when compared to control 2

Mean weekly food consumption was slightly reduced (5 to 8% relative to *ad libitum* control 1 group and not dose-dependent) in all treated male groups during the period of study. Mean food consumption calculated as a ratio of grams consumed per 100 g body weight was slightly but significantly increased in the 15 and 100 mg/kg/day male groups over the entire study period, demonstrating that reduced food intake alone did not account for reduced body weight. An initial and terminal increase of this ratio was apparent in the 3 mg/kg/day male group. In females, no consistent and toxicologically relevant change in food consumption/body weight ratio was noted. The mean weekly water consumption was dose-dependently increased in all treated male groups, with increases of 29 and 40% (both $p < 0.01$) in mid and high dose males, respectively, relative to consumption in the control 2 group for the entire treatment period. The maximum increases were 50% and 64% in the 15 and 100 mg/kg/day treated male groups, respectively, during weeks 37 to 60. All drug-treated female groups showed a dose-related increase in water intake (between 12 and 22%) relative to intake in the control 2 group during the first 6 months of the study. Thereafter, water consumption decreased and remained 10 to 15% below control levels.

Red blood cell indices (RBC, hemoglobin, hematocrit) decreased ≥10 % in high dose males and 5% or less in mid dose males relative to control 2 group (Table 3.3.4.7). Other parameters that classify anemia, such as MCH, MCHC and MCV, showed no consistent and dose-dependent changes in any of the treated groups. Thus, the sponsor classifies the slight anemia observed in males as normocytic and normochromic. Significant but non-dose-dependent reductions in thrombocyte counts (about 9-12%) were noted in all treated male groups. Treated females showed no statistically significant changes compared to the control 2 group.

TABLE 3.3.4.7
104 WEEK CARCINOGENICITY STUDY IN RATS: HEMATOLOGY. GROUP MEAN VALUES AND % DIFFERENCE FROM CONTROL 2 GROUP

Parameter	Sex	Dose (mg/kg/day)						
		0 (Control 1)	0 (Control 2)	3	15	Δ%	100	Δ%
Hemoglobin (g/100 ml)	m	16.9**	16.0	16.4	15.2**	(-5.0)	14.4**	(-10)
	f	15.4	14.9	14.8	14.9		14.3	
RBC (10^6/mm³)	m	8.52*	8.05	8.33	7.66*	(-4.8)	7.24**	(-10)
	f	7.36	6.99	7.04	7.14		6.96	
Hematocrit (Vol.%)	m	48.5	46.6	48.4	45.1	(-3.2)	41.5**	(-11)
	f	43.0	42.1	41.0	41.7		40.3	
MCH (pg)	m	19.9	19.9	19.7	20.0		19.9	
	f	21.0	21.6	21.1	20.9		20.5	
MCHC (g/100 ml)	m	34.9	34.4	33.9*	33.8**		34.6	
	f	35.8	35.4	36.2	35.9		35.4	
MCV (µm³)	m	57.1	58.0	58.2	59.2*		57.4	
	f	58.5*	60.8	58.4*	58.4*		57.9**	
Thrombocytes (1000/mm³)	m	808	792	724**	694**		700**	
	f	726	713	722	708		711	

* and ** significantly different from control 2 group ($p < 0.05$ and < 0.01, respectively)
Δ% per cent change compared to control 2 group

Drug-related biochemical changes were most pronounced in mid and high dose males. Significant but not dose-related increases in blood urea nitrogen (128 and 138% in males, and 29 and 71% in females) and creatinine (significant only in males, 25%) relative to control 2 animals were observed in mid and high dose groups. Total bilirubin was increased in both high dose male (94%) and female (93%) rats compared to control 2 animals. Also observed were higher values of alkaline phosphatase in all treated male groups (27, 37 and 47% at 3, 15 and 100 mg/kg/day, respectively), and LAP in all treated groups (males: 15-21%, females: 9-13%) compared to the control 2 group (Table 3.3.4.8). Since neither of these enzyme values attained levels as high as 1.5 times control, the sponsor considers them not to be toxicologically important. Decreased cholesterol (maximum difference from control 2 group 20%) was noted in males ($p < 0.05$) and females ($p > 0.05$). Among electrolytes, serum potassium and calcium were increased (12 to 35% in males and 3 to 19% in females) in all treated groups compared to the control 2 group (see Table 3.3.4.8).

TABLE 3.3.4.8

104 WEEK CARCINOGENICITY STUDY IN RATS: CLINICAL CHEMISTRY. GROUP MEAN VALUES AND % DIFFERENCE FROM CONTROL 2 GROUP (GIVEN IN PARENTHESES)

Parameter	Sex	Dose (mg/kg/day)									
		0 (Control 1)		0 (Control 2)	3		15		100	
Total bilirubin	m	1.7	(6.3)	1.6	1.5	(-6.3)	1.8	(12.5)	3.1**	(93.8)
(µmol//l)	f	1.7	(21.4)	1.4	1.6	(14.3)	1.7	(21.4)	2.7**	(92.9)
AP	m	164*		137	174**	(27.0)	188**	(37.2)	201**	(46.7)
(U/l)	f	133		132	134	(1.5)	136	(3)	143	(8.33)
LAP	m	18.2		19.8	16.9**	(-14.7)	16.6**	(-16.2)	15.6**	(-21.2)
(U/l)	f	16.6**		18.5	16.2**	(-12.4)	16.8**	(-9.2)	16.1**	(-13.0)
Total cholesterol	m	3.72	(6.9)	3.48	2.82**	(-19.0)	2.94**	(-15.5)	2.78**	(-20.1)
(mmol/l)	f	4.88**	(35.9)	3.59	3.54	(-1.4)	3.23	(-10.0)	2.96	(-17.5)
Total glycerol	m	5.89**	(45.8)	4.04	4.31	(6.7)	3.07*	(-24.0)	2.44**	(-39.6)
(mmol/l)	f	11.46**	(104.6)	5.60	9.26*	(65.4)	7.24	(29.3)	4.13	(-26.3)
BUN	m	9.93*	(21.7)	8.16	9.15	(12.1)	19.43**	(138.1)	18.64**	(128.4)
(mmol/l)	f	9.67**	(16.5)	7.84	8.30	(5.9)	10.10**	(28.8)	13.37**	(70.5)
Creatinine	m	55.2**	(14.0)	48.4	48.1	(0.6)	60.7**	(25.4)	60.5**	(25.0)
(µmol/l)	f	52.3	(2.8)	50.6	47.8	(-5.5)	50.9	(0.6)	51.6	(2.0)
K	m	4.55**	(8.6)	4.19	4.71**	(12.4)	5.68**	(35.6)	5.37**	(28.2)
(mmol/l)	f	3.95**	(-8.8)	4.33	3.83**	(-11.5)	4.46	(3.0)	5.17**	(19.4)
Ca	m	2.71**		2.63	2.66	(1.1)	2.69**	(2.3)	2.64	(0.4)
(mmol/l)	f	2.73**		2.63	2.69*	(2.3)	2.77**	(5.3)	2.82**	(7.2)

* and ** significantly different from control 2 group ($p < 0.05$ and 0.01)

LAP: leucine arylamidase or aminopeptidase

Testing of feces for occult blood was positive for a male and a female rat from the *ad libitum* control group and for one low dose male. Histopathological evaluation showed colonic adenocarcinoma in both control animals, esophageal papilloma in the control male and squamous cell carcinoma of the anorectal junction in the low dose male.

Significant but non dose-related decreases (14-24%) in absolute and relative heart weights relative to the diet restricted control 2 group were noted in males at all doses. Absolute and relative kidney weights were significantly reduced (11-14%) in both sexes at 15 and 100 mg/kg/day (Table 3.3.4.9). Changes in other organ weights were not toxicologically meaningful.

TABLE 3.3.4.9
104 WEEK CARCINOGENICITY STUDY IN RATS: ABSOLUTE (G) AND RELATIVE (%) ORGAN WEIGHTS

Organ	Dosage (mg/kg/day)								
	Control 1		Control 2	3		15		100	
		Δ%[‡]			Δ%		Δ%		Δ%
Males (BW in g)[†]	638.9	(+4.6)	611.0	650.3*	(+6.4)	567.9*	(-7.1)	558.0*	(-8.7)
Heart (g)	1.74		1.70	1.47*	(-14)	1.29*	(-24)	1.39	(-18)
% Brain weight	0.74		0.73	0.63*	(-14)	0.57*	(-22)	0.60*	(-18)
Kidneys	3.82		3.71	3.72		3.25*	(-12)	3.20*	(-14)
% Brain weight	1.63		1.60	1.60		1.43*	(-11)	1.39*	(-13)
Liver	23.3*	(+17.7)	19.8	22.4*	(+13)	20.0	(+1)	19.4	(-2)
% Brain weight	9.95*	(+16.6)	8.53	9.62*	(+13)	8.77	(+2.8)	8.45	(-0.9)
Females (BW in g)[†]	355.9	(+6.2)	335.2	351.0	(+4.7)	355.4	(+6.0)	347.8	(+3.8)
Heart (g)	1.31		1.24	1.16		1.23		1.24	
% Brain weight	0.63*	(+8.6)	0.58	0.56		0.59		0.59	
Kidneys	2.97*	(+6.8)	2.78	2.76		2.97*	(+7)	2.93	(+5)
% Brain weight	1.42*	(+7.6)	1.32	1.32		1.41*	(+7)	1.40*	(+6)
Liver	15.9*	(+15.2)	13.8	14.9*	(+8)	15.4*	(+12)	14.2	(+2.9)
% Brain weight	7.62*	(+16.9)	6.52	7.13*	(+9)	7.30*	(+12)	6.78	(+4.0)

†: mean body weight at terminal sacrifice
*: statistically significant ($p \leq 0.05$) compared to control 2 group
‡: Δ% increase or decrease compared to control 2 (food-restricted group)

Gross pathology findings included a higher than control incidence of renal cysts in all telmisartan-treated female groups and in the mid and high dose male groups. Incidence of external nodules and masses was similar in drug-treated and control groups. The most frequently observed spontaneous gross pathological findings (testicular enlargement, cysts in the liver and ovary, enlargement and discoloration of the pituitary and enlarged adrenals and uterus) were typical of the rat strain. Of the 123 premature deaths (43 males and 80 females), 54 had benign neoplasms (13 males and 41 females), 40 had malignant neoplasms (18 males and 22 females) and the remaining 29 animals (12 males and 17 females) showed no tumors. No drug-related pattern of mortality was observed for neoplastic or non-neoplastic changes. Non-neoplastic deaths were most often due to pneumonia/rhinitis, generally associated with aspiration of food (1 control 2 female, 1 /sex in each telmisartan-treated group) and uterine ulceration/hemorrhage (1 each in control and high dose groups, 3 in low and 2 in mid dose groups). Advanced chronic progressive glomerulonephropathy (CPG) of the kidney was fatal to three control 1 group males and one control 2 group female.

Non-neoplastic histopathology considered to be related to treatment was seen in the kidneys, gastric mucosa, thymus and lymph nodes. Thickening of intralobular renal arteries, an extension of JGA hypertrophy and hyperplasia, was observed in a dose-dependent manner in animals of both sexes given 15 or more mg/kg/day, and to a lesser extent in low dose animals. Some animals in these groups showed JGA vacuolation. Chronic progressive glomerulonephropathy (CPG), a spontaneously-occurring aging change of laboratory rats characterized by varying degrees of glomerulosclerosis, interstitial mononuclear inflammation and fibrosis and tubular changes of cytoplasmic basophilia, atrophy, cysts, basement membrane thickening, hyaline casts

and tubular epithelial hypertrophy/hyperplasia, was noted in a majority of animals irrespective of treatment group and was more severe in males than in females. Renal tubular cysts were increased in animals given 15 or more mg/kg/day confirming the higher incidence of cysts noted at gross examination (Table 3.3.4.10).

TABLE 3.3.4.10
104 WEEK CARCINOGENICITY STUDY IN RATS: HISTOPATHOLOGICAL FINDINGS IN THE KIDNEY

Frequency of the Main Nonproliferative Changes in the Kidney										
	Dosage (mg/kg/day)									
	Control 1		Control 2		3		15		100	
	m	f	m	f	m	f	m	f	m	f
No. of animals examined	50	50	50	50	50	50	50	50	50	50
Intrarenal artery thickening	0	0	0	0	4↑	7↑	50↑	48↑	48↑	50↑
JGA vacuolation	0	0	0	0	0	3↑	7↑	8↑	18↑	4↑
Chronic progr. glomerulonephropathy	49	49	49	50	49	50	49	49	49	50
mean grade §	3.0	2.6	2.3	2.1	1.8	1.7	2.3	1.9	2.5	2.1
Tubular cysts	10	1	4	8	3	10	30↑	28↑	37↑	33↑
mean grade §	1.9	1.0	3.5	2.0	1.3	2.2	1.5	1.5	1.8	1.8
Renal tubular hypertrophy	31	31	30	29	12*	15*	38	30	43*	39
mean grade §	1.1	1.1	1.1	1.0	1.0	1.0	1.1	1.0	1.1	1.1
Corticomedullary nephrocalcinosis	2	49	0	47	2	48	4	47	8	47

§ Mean grade is average severity (slight = 1, mild = 2, moderate = 3 and severe = 4) in animals with this finding
↑ Frequency/incidence increased. Not subjected to statistical analysis.
* Frequency/incidence decreased. Not subjected to statistical analysis.

The second toxic effect of telmisartan was gastric mucosal injury (manifested as increased incidence of gastric erosions, ulcers and/or submucosal/mucosal inflammation of mild or higher grade) noted in both sexes given 15 or more mg/kg/day. Gastric lesions in control and low dose animals were mainly acute (agonal) in nature, while many of the lesions in mid and high dose animals were subchronic to chronic and signs of healing were present in some animals. Gastric mucosal injury was most pronounced in mid dose males and therefore, not strictly dose-dependent. Incidence was 42 and 26% in males and 18 and 22% in females in the 15 and 100 mg/kg/day groups, respectively, compared to 8 to 16% in male controls and 10 to 12% in female controls. In the 3 mg/kg/day group, a 2 and 8% incidence was noted in males and females, respectively (Table 3.3.4.11).

TABLE 3.3.4.11
104 WEEK CARCINOGENICITY STUDY IN RATS: HISTOPATHOLOGICAL FINDINGS IN THE STOMACH

Frequency of Gastric Mucosal Lesions										
	Dosage (mg/kg/day)									
	Control 1		Control 2		3		15		100	
	m	f	m	f	m	f	m	f	m	f
# animals examined	50	50	50	50	50	50	49	50	50	50
Inflammation (++ or higher grade)*	0	0	1	1	0	0	11δ	2	1	2
Erosion	3	5	6	4	1	4	8δ	6	9δ	5
Ulcer	2	1	3	2	0	1	7δ	3	4	7δ
Ulcer and/or erosion	4	5	7	5	1η	4	13δ	7δ	10δ	9δ
Ulcer and/or erosion and/or inflam.	4	5	8	6	1η	4	21δ	9δ	10δ	11δ
Acute lesions only	4	5	6	4	1η	4	5δ	4	5	5
Subchronic and/or chronic lesions	0	0	2	2	0	0	16δ	5δ	5δ	6δ
Regenerative hyperplasia §	0	0	0	0	0	0	3δ	1δ	8δ	1δ
Total gastric mucosal injury ¶	4	5	8	6	1	4	21δ	9δ	13δ	11δ
% gastric mucosal injury ¶	8	10	16	12	2	8	42δ	18δ	26δ	22δ

* Includes animals with mucosal and / or submucosal inflammation only
§ Hyperplasia and cystic glandular hyperplasia
¶ Mucosal injury includes animals with inflammation (mild or higher grade), erosion, ulcer and/or hyperplasia
δ Frequency/incidence increased. Not subjected to statistical analysis.
η Frequency/incidence decreased. Not subjected to statistical analysis.

Non-neoplastic proliferative changes observed at a lower than control incidence were clear cell foci of the aldosterone-secreting adrenal zona glomerulosa in high dose animals of both sexes and adrenal medullary hyperplasia and pancreatic acinar hyperplasia in mid and high dose males. The decrease of foci in the zona glomerulosa was most likely a pharmacodynamic change since angiotensin II receptor blockade reduces aldosterone production. Decreases in frequency of some other non-neoplastic, non-proliferative changes [hepatic spongiosis (cystic degeneration); pancreatic atrophy; myocardial inflammation/fibrosis; testicular atrophy, decreased spermatogenesis, edema; and peripheral nerve degeneration] which occur spontaneously in aged rats, were noted mainly in males given 15 or 100 mg/kg/day. These changes along with increased incidences of thymic atrophy in high dose males (32/50 *versus* 24/50 and 21/50 for control 1 and control 2, respectively) and cystic ectasia (dilatation) of lymph nodes in mid and high dose males (16/50 and 18/50 *versus* 8/50 and 7/50 for control 1 and control 2, respectively) , may have been, according to the sponsor, entirely or partly due to body weight gain suppression in these groups.

Regarding *neoplastic* findings, no drug-induced effects on number of tumor-bearing animals, number of animals bearing benign tumors, number of animals bearing malignant tumors, or number of animals bearing multiple tumors were apparent in rats (of either sex) that were killed or died during the treatment period, or killed at term (Table 3.3.4.12). Further, telmisartan did not appear to induce a decrease in the latency of tumor appearance relative to control. The sponsor has performed Peto's trend test and assigned 0.05 (for rare tumors) and 0.01 (for common tumors) as critical p-values for significance. FDA statisticians assign 0.025 and 0.005, respectively, as critical p- values for significance in evaluating trend. Both the sponsor's and the FDA's analyses revealed no statistically significant increased trend in the incidence of any

neoplasm that could be attributed to treatment with telmisartan for either sex of rats that were killed or died during the treatment period.

TABLE 3.3.4.12
104 WEEK CARCINOGENICITY STUDY IN RATS: SUMMARY OF NEOPLASTIC FINDINGS*

Dosage (mg/kg/day) Group	Control 1 Group 0		Control 2 Group 4		3 Group 1		15 Group 2		100 Group 3	
Sex	m	f	m	f	m	f	m	f	m	f
# animals examined	50	50	50	50	50	50	50	50	50	50
No. tumor-bearing animals	45	47	43	46	47	45	38	48	42	45
(% incidence)	90	94	86	92	94	90	76	96	84	90
Benign	27[1]	35	37[2]	34	33	32	25[1]	41	30	34
Malignant	4	1	3	1	2	2	3	0	4	3[3]
Benign + Malignant	14[4]	11	3[5]	11	12[4]	11	10[4]	7	8	8
No. with multiple tumors	31	32	27	31	24	32	26	27	21	34
(% incidence)	62	64	54	62	48	64	52	54	42	68
No. primary tumors	102	106	79	105	84	94	80	91	85	108
Benign	83	91	72	92	69	80	66	83	73	96
Malignant	19	15	7	13	15	14	14	8	12	12

*: primary tumors
[1] statistically significant decrease ($p \leq 0.05$) vs. control 2
[2] statistically significant increase ($p \leq 0.05$) vs. control 1
[3] statistically not significant increase ($p > 0.1$) vs. control 1 and control 2
[4] statistically significant increase ($p \leq 0.05$) vs. control 2
[5] statistically significant decrease ($p \leq 0.05$) vs. control 1
Note: designations Benign only, Malignant only and Benign + Malignant are based on % of total tumors

The most common tumors were pituitary adenoma (224 animals), Leydig cell tumor of the testis (88 animals), adrenal pheochromocytoma (80 animals), thymoma (68 animals), thyroid C cell adenoma/carcinoma (59 animals), hemangioma/hemangiosarcoma (57 animals), adrenal cortical cell adenoma/adenocarcinoma (47 animals), mammary fibroadenoma (40 animals) and hepatocellular adenoma/carcinoma (24 animals). Incidence in per cent is shown in table 3.3.4.13. Increased latency (longer time to tumor appearance)[1] was noted for pituitary adenoma in all drug-treated male groups and mammary fibroadenoma in all drug-treated female groups. The increase was statistically significant compared to both control groups and inversely dose-related for pituitary adenoma. For mammary fibroadenoma, the increase was significant compared to control 2 for all dose groups and compared to control 1 for the low and high dose groups. Since the increased latency was not accompanied by decreased incidence of these two tumor types, the results were not considered biologically meaningful.

A statistically significant increase in the incidence of C cell adenoma of the thyroid gland was noted in the high dose female group compared to the diet restricted control group 2 ($p = 0.02$), but not the non-diet restricted control group 1 ($p = 0.298$). Incidence was 14, 6, 12, 12 and 22% in control 1, control 2, 3, 15 and 100 mg/kg/day female groups, respectively. Mean severity grade for this tumor was not increased in high dose females relative to control 2 animals (1.6 *vs*

[1] Information on tumor latency was gained from the analysis according to Peto's method. All tumors were clusterred in 4 categories: first occurrence earlier than week 53, from week 53- week 66, from week 67- week 80, from week 81- week 93, and later than week 91.

2.0) and most tumors were low grade (Table 3.3.4.13) or slightly larger than lesions classified as hyperplasia (diameter ≤5 average thyroid follicles). Incidence and mean grade hyperplasia (considered pre-neoplastic for this tumor type) were not increased. When hyperplasias and tumors tumors were combined, incidence in all groups was similar: 96, 88, 92, 94 and 96% for the control 2, 3, 15 and 100 mg/kg/day groups, respectively. Time-to-tumor (latency) also was not decreased. Thus, the sponsor argues that there was no evidence of progression of lesion (hyperplasia → benign tumor → malignant tumor). Based on these considerations, the statistically significant increase in C cell adenomas in high dose females was not considered biologically meaningful and was most likely an artifact of the criteria used to distinguish hyperplasia from benign neoplasia for this cell type in the rat. The sponsor's argument is further substantiated by the observation of a dose-related decrease in C cell adenoma incidence in males (14%, 8%, 12%, 4% and 2%, respectively, in control 1, control 2, 3, 15 and 100 mg/kg/day groups), the high dose incidence being statistically significantly ($p = 0.0255$) lower than the incidence for control 1 males. There were no C cell carcinomas in females in concurrent control groups, while one each was observed in females receiving 3 and 100 mg/kg/day.

TABLE 3.4.4.13
104 WEEK CARCINOGENICITY STUDY IN RATS. NEOPLASTIC FINDINGS: THYROID C CELLS

Number of Animals with Hyperplastic or Neoplastic Lesions of the Thyroid C Cells												
Histopathological Finding	Historical Controls, %		Dosage (mg/kg/day)									
			Control 1		Control 2		3		15		100	
	M	F	M	F	M	F	M	F	M	F	M	F
#animals examined[II]	250	250	50	50	50	50	50	50	50	50	50	50
C cell hyperplasia	36%	47.6%	37	47	42	44	47	46	40	47	37	43
grade 1	(range:	(range:	28	29	35	35	44	35	31	36	34	33
grade 2	12-64)	20-86)	8	17	6	9	3	9	9	10	2	8
grade 3			1	1	1	0	0	2	0	0	1	2
grade 4			0	0	0	0	0	0	0	1	0	0
Mean grade §			1.3	1.4	1.2	1.2	1.1	1.3	1.2	1.3	1.1	1.3
C cell adenoma	5.2%	11.2%	7	7	4	3	6	6	2	6	1▲	11*
grade 1	(range:	(range:	4	5	2	1	6	5	2	5	1	7
grade 2	2-10)	6-14)	2	1	1	1	0	1	0	0	0	1
grade 3			1	0	1	1	0	0	0	1	0	3
grade 4			0	1	0	0	0	0	0	0	0	0
Mean grade §			1.6	1.6	1.8	2.0	1.0	1.2	1.0	1.3	1.0	1.6
C cell carcinoma	0.4%	0.8%	1	0	0	0	2	1	0	0	1	1
	(0-2)	(0-4)										
# animals with H and/or N			40	48	44	44	48	46	40	47	37	48
% animals with H and/or N			80	96	88	88	96	92	80	94	74	96

II Animals with at least one thyroid gland of pair examined
§ Mean grade calculated based on number of animals having lesion
% based on number of thyroid glands examined. Grading system: slight (grade 1) = 1, mild (grade 2) = 2, moderate (grade 3) = 3, severe (grade 4) = 4
* statistically significant increase ($p < 0.05$) compared to control 2 group
▲ statistically significant decrease ($p \leq 0.05$) compared to control 1 group
H: hyperplasia, N: neoplasia

Summary of tumor incidence is given in Table 3.3.4.14 that follows on the next four pages.

TABLE 3.3.4.14
CARCINOGENICITY STUDY IN RATS: INCIDENCE OF PRIMARY NEOPLASMS

Histopathological finding / ORGAN SYSTEM / Organ/Tissue / Neoplasm	TD	Dose level (mg/kg/day)									
		0 Group 0 *Ad lib* diet		0 Group 4 Restricted diet		3 Group 1 Low Dose		15 Group 2 Mid Dose		100 Group 3 High Dose	
		m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50	m 50	f 50
DIGESTIVE SYSTEM											
Tongue		50	50	50	50	50	50	49	50	50	50
Granular cell tumor	BE	0	1	0	0	0	0	0	0	0	0
Salivary glands		50	50	50	50	50	50	49	50	50	50
Parotid acinar cell adenoma	BE	2	0	2	2	0	0	1	1	1	2
Parotid acinar adenocarcinoma	MA	1	0	0	0	0	0	0	0	0	0
Parotid mixed tumor	BE	0	0	0	1	0	0	0	0	0	0
Sublingual carcinosarcoma	MA	1	0	0	0	0	0	0	0	0	0
Esophagus		50	50	50	49	50	50	48	50	50	50
Papilloma	BE	1	0	0	0	0	0	0	0	0	0
Stomach		50	50	50	50	50	50	49	50	50	50
Adenocarcinoma	MA	0	0	0	0	0	1	0	0	0	0
Duodenum		50	50	50	50	49	50	49	50	50	50
Leiomyoma	BE	0	1	0	0	0	0	0	0	0	0
Jejunum		50	50	50	50	49	49	50	50	50	50
Adenocarcinoma	MA	0	0	0	1	0	0	0	0	0	0
Leiomyosarcoma	MA	0	0	0	1	0	0	0	0	0	0
Colon		50	50	50	50	49	50	50	50	50	50
Adenocarcinoma	MA	1	0	0	0	1	0	0	0	1	0
Leiomyosarcoma	MA	0	0	0	0	1	0	0	0	0	0
Rectum		49	50	49	49	50	50	48	50	48	48
Squamous cell carcinoma	MA	0	1	0	0	0	0	0	0	0	0
Adenocarcinoma	MA	0	0	0	0	0	0	0	0	1	0
ENDOCRINE SYSTEM											
Pituitary		50	50	49	49	50	50	49	50	50	49
Adenoma	BE	10	38	12	40	10	38	6	33	9	28①
Carcinoma	MA	0	0	0	1	0	0	0	0	0	1
Thyroid gland		50	50	49	50	50	50	50	50	49	50
Follicular cell adenoma	BE	1	1	2	0	4	0	1	2	2	1
Follicular cell carcinoma	MA	1	0	0	2	1	1	1	0	0	0
C cell adenoma	BE	7	7	4	3	6	6	2	6	1②	11③
C cell carcinoma	MA	1	0	0	0	2	1	0	0	1	1
Parathyroid		49	48	48	50	50	50	49	49	49	48
Adenoma	BE	1	1	1	2	2	0	2	1	4	1
Adrenal gland		50	50	50	50	50	50	50	50	50	50
Cortical adenoma	BE	4	3	4	3	2	5	4	3	5	5
Cortical adenocarcinoma	MA	2	0	0	0	1	2	1	0	2	1
Pheochromocytoma (benign)	BE	5	11	4	12	2	7	0	12	4	19
Pheochromocytoma (malignant)	MA	1	1	0	0	1	1	0	0	3	0

① Statistically significant decrease (p=0.0098, 0.0328) compared to both control groups
② Statistically significant decrease (p=0.0255) compared to contol 1 group
③ Statistically significant increase (p=0.02) compared to control 2 group

TD (Tumor designation)
BE Benign
MA Malignant

The numbers in each row against an organ/tissue indicate the number of animals examined.