2.16. Plasma Levels of Olmesartan After Repeated Oral Dose Administration of Olmesartan Medoxomil to Animals and Humans

See section 3.1 (Toxicology) for details of the mouse, rat and dog studies.

Animal species (strain)	Study	Route	Interval	Sex	Dose mg/kg/d	C_{max} µg/ml	Tmax h	AUC_{0-24} µg.h/ml	T½ h	Ref. Sec #
Mouse (C57BL/6)	Oral[1] 4-week	Gavage[2]	Week 4	M	100	2.58		7.06		3.3.2
				F		6.63		28.72		
				M	250	2.13		8.00		
				F		5.00		44.75		
				M	500	2.38		19.65		
				F		7.60		48.58		
				M	1000	3.71		14.71		
				F		12.26		68.52		
Mouse (C57BL/6, P53(+/-))	Oral 26-week	Gavage[2]	Week 26	M	100	0.72				3.3.2
				F		1.02				
				M	300	1.47				
				F		1.93				
				M	1000	3.23				
				F		6.63				
Mouse (HRAS2)	Oral[1] 26-wk	Diet	Week 26	M	1000	2.00[3]				3.3.3
				F		2.70[3]				
Rat (Wistar)	Oral[1,5] 21-day	Stomach tube[4]	Day 21	M	5	5.7[6]	1	25.0[6]	3.4	2.4
Rat (F344)	Oral[1] 6-month	Stomach tube[2]	Day 85	M	30	1.15		9.88		3.2.1
				F		0.79		3.44		
				M	100	1.39		6.57		
				F		1.36		5.61		
				M	300	1.93		9.97		
				F		2.89		13.45		
				M	1000	4.16		29.13		
				F		4.21		29.64		
			Day 176	M	30	1.36		5.61		3.2.1
				F		1.43		6.41		
				M	100	1.75		7.60		
				F		1.44		7.38		
				M	300	2.99		10.27		
				F		4.02		20.55		
				M	1000	5.07		31.15		
				F		3.55		31.49		

Animal species (strain)	Study	Route	Interval	Sex	Dose mg/kg/d	C_{max} µg/ml	Tmax h	AUC_{0-24} µg.h/ml	T½ h	Ref. Sec #
Dog (beagle)	Oral[1] 3-month	Capsule	Day 28	M	125	3.21	8.0	24.66		3.2.3
				F		1.18	5.0	12.99		
				M	250	2.09	3.3	12.54		
				F		2.05	3.7	18.29		
				M	500	2.26	2.0	17.01		
				F		2.61	4.0	16.46		
			Day 91	M	125	1.83	4.7	14.20		
				F		1.49	1.0	7.13		
				M	250	2.48	2.7	13.72		
				F		3.36	6.0	30.61		
				M	500	2.94	3.0	17.35		
				F		3.67	4.0	31.97		
	Oral[1] 12-month	Capsule	week25	M	10	0.17	3.3	0.82		3.2.4
				F		0.10	5.0	1.08		
				M	40	0.50	5.3	5.40		
				F		0.46	2.5	2.64		
				M	160	1.60	6.0	15.41		
				F		1.82	3.3	14.87		
			Week52	M	10	0.11	2.5	0.61		
				F		0.11	2.5	0.66		
				M	40	0.56	5.0	5.68		
				F		0.42	3.3	3.68		
				M	160	1.28	3.3	8.64		
				F		1.03	3.3	7.26		
Human[7]	Tablet 10 days	SS	Day 10	M	20 mg	0.51	1.7	2.95	14.9	Study #866-102
					40	0.74	1.9	4.37	14.5	
					80	1.38	1.8	9.38	14.1	

1: not fasted
2: in 0.5% CMC
3: mean of two time points, 1 AM and 5 PM
4: solution in DMA and PEG
5: ^{14}C form
6: unit, µg equivalent instead of µg, total radioactivity
7: healthy volunteers

3. TOXICOLOGY

3.1. *Acute Toxicity Studies*

3.1.1. Acute Oral Toxicity in Mice (Report #TR 138-178) Vol. 7

This GLP study was conducted by the Laboratory Animal Science and Toxicology Laboratories, Sankyo Co. Ltd., Fukuroi, Shizuoka 437, Japan, between January 21 and February 4, 1992.

Three groups, each consisting of five male (19-21 g) and five female (16-17 g) SPF RFVL 5-week-old mice, were given olmesartan medoxomil (lot #4) as a 10% suspension in 0.5% sodium carboxymethylcellulose (CMC) by gavage. Volumes of 0.05, 0.1, or 0.2 ml per 10 g body weight were given, corresponding to doses of 500, 1000, and 2000 mg/kg, respectively. Animals were fasted for 24 hr and fed soon after the test substance administration.

Mice were observed at 1, 10, and 30 minutes, at 1, 3, and 5 hours after administration on the first day, and more than once a day for 14 days thereafter. Body weights were measured before administration and on days 3, 7, 10, and 14 after administration. On the final day, all surviving animals were anesthetized with ether and exsanguinated, and an autopsy was performed; organ weight determinations and histopathology examinations were not done as there were no gross abnormalities detected.

No deaths occurred in any treatment group. Thus, the LD_{50} value for mice of either sex is greater than 2000 mg/kg. There were no treatment-related clinical signs, effects on body weights, or macroscopic findings at necropsy.

A single dose oral toxicity study was also conducted in Crj:CD-1 (ICR) mice to compare the profile in this strain with the RFVL mice (report #TR 142-026, nonGLP study, study dates: February 16 to May 17, 1995). Olmesartan medoxomil (lot No. NH001C3) was suspended in 0.5% CMC and administered at doses of 500, 1000, or 2000 mg/kg (5/sex/group) by gastric intubation. There were no deaths and no treatment-related clinical signs. The results were identical to those obtained from the single oral dose toxicity study in RFVL mice (TR 138-178).

3.1.2. Acute Oral Toxicity in Rats (Report #TR 138-175) Vol. 7

This GLP study was conducted by the Laboratory Animal Science and Toxicology Laboratories, Sankyo Co. Ltd., Fukuroi, Shizuoka 437, Japan, between January 14 and January 28, 1992.

Three groups, each consisting of five male (116-129 g) and five female (98-107 g) SPF F344 7-week-old rats, were given olmesartan medoxomil (lot #4) as a 10% suspension in 0.5% CMC by gavage. Volumes of 0.5, 1, or 2 ml per 100 g body weight were given, corresponding to doses of 500, 1000, and 2000 mg/kg, respectively. Animals were fasted for 24 hr and fed soon after the test substance administration.

Rats were examined at 1, 10, and 30 minutes, at 1, 3, and 5 hours after administration on the first day, and more than once a day for 14 days thereafter. Body weights were determined before administration and on days 3, 7, 10, and 14 after administration. On the final day, all surviving rats were anesthetized with ether and exsanguinated, and an autopsy was performed; organ weight determinations and histopathology examinations and histopathology were not done as there were no gross abnormalities detected.

No deaths occurred in any treatment group. Thus, the LD_{50} value for rats of either sex is greater than 2000 mg/kg. There were no changes in the general condition of the animals, or in their normal body weight gain, throughout the 14-day observation period. No abnormalities were observed in the gross examinations made at autopsy.

3.1.3. Acute Oral Toxicity in Dogs (Report #TR 139-097) Vol. 7

This GLP study was conducted by the Laboratory Animal Science and Toxicology Laboratories, Sankyo Co. Ltd., Fukuroi, Shizuoka 437, Japan, between May 25 and June 8, 1992.

Two 12-month-old beagle dogs (one male 9.5 kg, one female 8.6 kg) were used in this study. Each dog was given olmesartan medoxomil (Lot #5) orally, in a gelatin capsule, at a dose of 1500 mg/kg. The dogs were observed closely four times a day on the day of administration, and then once daily for 14 days. Body weights were measured on days 1, 7, and 14 after drug administration. Food intake was measured daily. Blood sampling was done on two occasions before drug administration and on days 1, 7, and 14 after administration; effects on hematological and blood chemistry parameters were evaluated. No gross or histopathologic examinations were made.

No changes in the general condition of the dogs were noted during the post-administration period. Body weights remained unaltered, and the dogs ate all food offered during the 14-day period. Hematology and blood chemistry results showed no changes or trends indicative of drug toxicity.

3.2. *Subchronic and Chronic Toxicity Studies*

3.2.1. Six-Month Oral Toxicity Study in Rats (Report #TR 142-086, Toxicokinetics #TRK 141-013) Vol. 12

This GLP study was conducted by the Laboratory Animal Science and Toxicology Laboratories, Sankyo Co. Ltd., Fukuroi, Shizuoka 437, Japan, between May 24, 1994 and February 9, 1996. (Dates of dosing and necropsy not provided.)

Male and female albino rats (F344 [redacted] were approximately 7 weeks old and weighed 135-172 g (males) or 105-129 g (females) at the start of the study. Olmesartan medoxomil (batch #NH004C1) was given at doses of 30, 100, 300 or 1000 mg/kg/day (15/sex/group) each day for 6 months (by stomach tube) as a suspension in 0.5% CMC at a volume of 1.5 ml/kg body weight in the 30 mg/kg group and 5 ml/kg body weight in the other groups. The control animals (15/sex/group) received the vehicle (5 ml/kg body weight). Five additional satellite animals/sex per group were used for toxicokinetic study. Animals were housed individually. The doses were selected on the basis of a 3 month oral administration study (same rat strain and same mode of administration) in which the highest dose (300 mg/kg/day) was associated with a progressive nephropathy in one of 10 males.

Observations and Measurements

All animals were observed more than once daily. Body weight and food consumption were recorded a week before treatment and then at weekly intervals. Water consumption and urine volume were measured in 5 males and 5 females from each group before the start of dosing and on days 24, 86 and 177 of the treatment. Urinalysis was done for 5 males and 5 females from each group before the start of dosing and on treatment days 27, 90 and 181. Ophthalmic examination was conducted on all animals before the start of dosing and 5 males and 5 females from control and high dosage groups on day 182. Blood samples were drawn from all surviving animals under ether anesthesia at the end of the dosing period for hematology and clinical chemistry examinations. For toxicokinetics study, blood samples were collected from satellite animals at 2, 6 and 24 hr after dosing on days 1, 85 and 176. All main study animals including those that died during the study were subjected to a detailed necropsy that included weighing of organs in all dose groups, and histopathological examination of selected organs/tissues from the control and the 1000 mg/kg/day groups, and from the organs whose weights were measured in the other groups (Table 3.2.1.1). Additionally, kidney sections from control and high dose groups (3/sex/gp) were preserved to determine juxtaglomerular cell granule indices (JGIs).

Results

One male rat in the high dose group had irregular respiration and abnormal respiratory noise on day 115 of dosing and died approximately 1 hr later. Based on the pathological findings in the lungs of this animal, death was considered to be due to a dosing error. Additionally, one high dose male in the satellite group died on day 72 of the dosing period from mis-gavage. There were no treatment-related clinical signs in the surviving animals. Males given 100 or 300 mg/kg/day

TABLE 3.2.1.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Aorta	Liver*	Spinal cord (cervical to lumbar)
Adrenals*	Lungs*	Spleen*
Bone marrow (femur, sternum)	Mammary gland (♀ only)	Stomach
Brain*	Mesenteric lymph node	Submaxillary gland
Cecum	Ovaries*	Submandibular lymph node
Colon	Pancreas	Testes*
Duodenum	Pituitary *	Tongue
Epididymides	Perpetual gland	Trachea
Esophagus	Prostate (ventral)*	Thymus*
Eyeball (left)[1]	Rectum	Thyroid with parathyroid*
Harderian gland	Renal lymph node	Urinary bladder
Heart*	Sciatic nerve	Uterus*
Ileum	Seminal vesicles*	Vagina
Jejunum	Skeletal muscle (thigh)	
Kidneys*	Skin	

*: Organ weighed
[1]: not collected from dead animals

gained less weight (4.2 to 7.3%) than control in all weeks of measurement, whereas in the high dose group, the differences were less pronounced and reached statistical significance only on days 14 and 21 (5.5 and 5.1%, respectively) (Table 3.2.1.2 and Fig. 3.2.1.1). Females given 300 mg/kg/day gained significantly less weight (4.6 to 6.7%) relative to control in all weeks of measurement except at termination of the study (day 182) (Table 3.2.1.2 and Fig. 3.2.1.1).

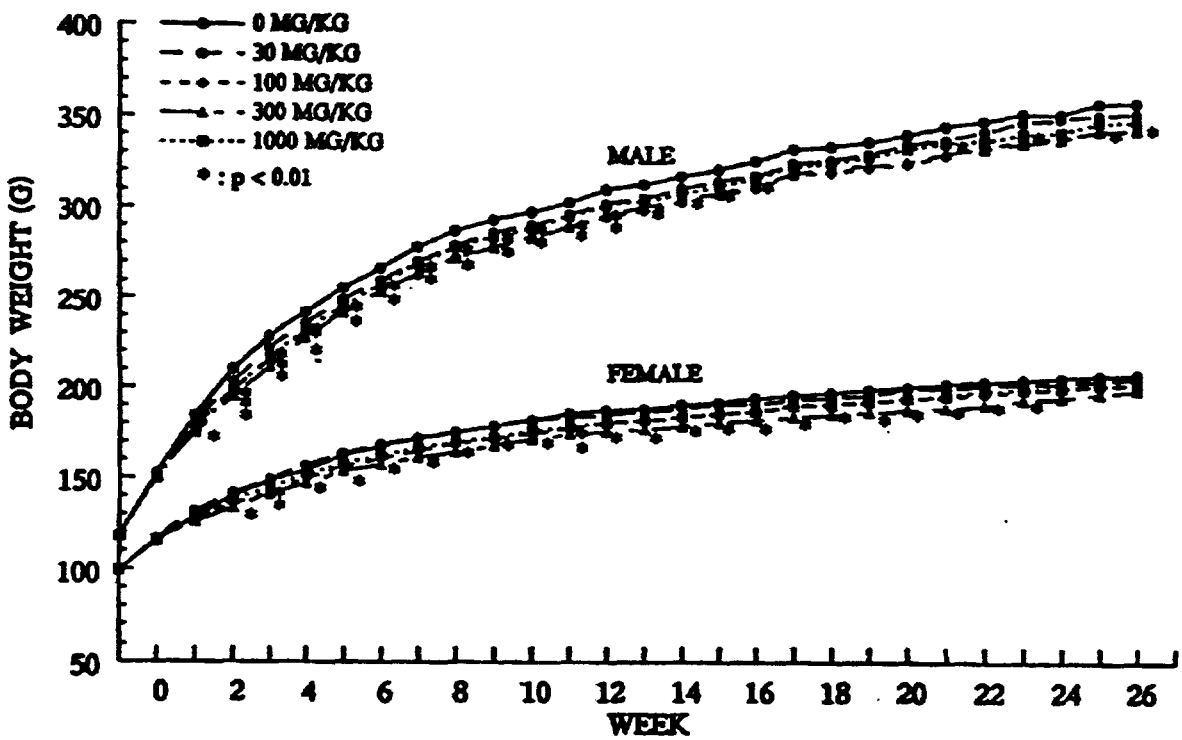

Fig. 3.2.1.1.: Six month toxicity study of olmesartan medoxomil in rats. Group mean body weights.

TABLE 3.2.1.2
6 MONTH TOXICITY STUDY IN RATS[¶]: GROUP MEAN BODY WEIGHTS

Study day	Parameter	Dosage (mg/kg/day)									
		Male					Female				
		Control	30	100	300	1000	Control	30	100	300	1000
0	B.wt., g	152.5	150.9	151.4	150.6	149.9	115.1	116.9	116.7	115.7	116.1
	% diff[@]										
14	B.wt., g	209.9	203.2	198.7*	194.9*	198.3*	139.9	141.5	135.5	133.5*	137.5
	% diff		-3.2	-5.3	-7.2	-5.5		+1.1	-3.1	-4.6	-1.7
21	B.wt., g	228.2	221.9	215.5*	211.5*	216.6*	148.5	149.5	141.2*	141.0*	144.1
	% diff		-2.3	-5.6	-7.3	-5.1		+0.7	-5.0	-5.0	-3.0
42	B.wt., g	267.1	260.5	254.1*	253.1*	258.2	167.5	168.9	160.7	157.4*	162.6
	% diff		-2.5	-4.9	-5.2	-3.3		+0.8	-4.0	-6.0	-3.0
56	B.wt., g	287.5	279.3	272.8*	272.7*	278.5	175.5	175.9	169.3	164.5*	170.1
	% diff		-2.9	-5.1	-5.2	-3.1		+0.2	-3.5	-6.3	-3.1
70	B.wt., g	297.8	290.5	284.0*	283.1*	288.8	182.5	181.7	174.6	171.5*	176.5
	% diff		-2.5	-4.6	-4.9	-3.0		-0.4	-4.3	-6.0	-3.0
84	B.wt., g	310.1	302.5	295.2*	296.2*	301.5	187.8	185.4	180.9	175.7*	180.7
	% diff		-2.5	-4.8	-4.5	-2.8		-1.3	-3.7	-6.4	-3.8
112	B.wt., g	326.1	318.0	311.2*	312.9§	316.4	194.6	191.6	187.6	182.5*	187.1
	% diff		-2.5	-4.6	-4.0	-3.0		-1.5	-3.6	-6.2	-3.9
147	B.wt., g	345.9	338.3	329.9*	330.9§	336.8	203.1	200.5	195.9	189.5*	196.5
	% diff		-2.2	-4.6	-4.3	-2.6		-1.3	-3.5	-6.7	-3.2
161	B.wt., g	353.0	348.2	338.0§	336.5*	341.4	205.6	203.1	199.7	194.1*	200.3
	% diff		-1.4	-4.3	-4.7	-3.3		-1.2	-2.9	-5.6	-2.6
182	B.wt., g	359.1	353.3	344.1*	344.2§	348.6	208.7	206.3	202.9	199.8	203.0
	% diff		-1.6	-4.2	-4.2	-2.9		-1.1	-2.8	-4.3	-2.7

[@]: Per cent (%) difference from control body weight
*: $p < 0.01$ when compared to control
§: $p < 0.05$ when compared to control using one way ANOVA and Dunnett's method (done by the reviewer)
[¶]: n=15/sex/gp on all days of measurement except for the high dose group (14/sex/group from days 147 to 182)

Mean weekly food consumption was slightly but significantly reduced relative to control group consumption for males given 300 (6.8 to 8.5%) or 1000 (5.3 to 8.5%) mg/kg/day on days 7 to 21. For females, the values were significantly lower than control in the 100 mg/kg/day group on day 14 (7.6%) and in the 300 mg/kg/day group on days14, 42, 105 and 119 to 133 (6.7 to 10.7%). The values for the other drug-treated groups were either higher than or similar to control. A tendency toward increased water intake was observed in males given 100 or more mg/kg/day. For high dose males, the values were significantly higher than control on all days of measurement (24 to 34%). For high dose females, the increase in water consumption was not significant.

Urinalysis showed a tendency toward a decrease in urinary protein in males at 100 or more mg/kg/day and females at 30 or more mg/kg/day. A statistically significant, non dose-dependent decrease in specific gravity (1.6 to 2%) and osmotic pressure (21 to 28%) was noted in the 24 hr urine collected from males given 100 or more mg/kg/day. Red blood cell indices (RBC, hemoglobin, and hematocrit) decreased (3 to 14%) significantly and dose-dependently in all dose groups. However, other parameters that classify anemia, such as mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) increased dose-dependently in all treated female groups. For males, the values were significant at 300 or more mg/kg/day (high dose group only in case of MCHC). A dose-dependent increase in platelet

counts (9-11%) was noted in females given 300 and 1000 mg/kg/day and males given 1000 mg/kg/day. Prothrombin time decreased marginally (2%) but significantly in high dose males only. Males given 300 or 1000 mg/kg/day showed significant changes in differential count of leukocytes. Percentage of neutrophils was higher than control (66% and 77% higher) whereas percentage of lymphocytes was lower than control (12 and 13% lower) in these two groups (Table 3.2.1.3).

TABLE 3.2.1.3
STATISTICALLY SIGNIFICANT CHANGES IN HEMATOLOGY PARAMETERS IN RATS TREATED ORALLY WITH OLMESARTAN MEDOXOMIL FOR 6 MONTHS
(Percent change from control values)

Parameter	Dose (mg/kg/day)							
	Male				Female			
	30	100	300	1000	30	100	300	1000
RBC	↓(3)	↓(8)	↓(11))	↓(12)	↓(9)	↓(11)	↓(14)	↓(13)
Hemoglobin	↓(3)	↓(6)	↓(8)	↓(9)	↓(6)	↓(7)	↓(9)	↓(8)
Hematocrit		↓(7)	↓(10)	↓(12)	↓(9)	↓(11)	↓(13)	↓(13)
MCH			↑(4)	↑(4)	↑(4)	↑(5)	↑(6)	↑(6)
Mean corpuscular vol								↑(1)
MCHC				↑(3)	↑(3)	↑(4)	↑(5)	↑(6)
Platelet		↑(11)					↑(9)	↑(10)
Percentage of neutrophils			↑(66)	↑(77)				
Percentage of lymphocyte			↓(12)	↓(13)				
Absolute neutrophil ct			↑(65)					
Prothrombin time				↓(2)				

Drug-related biochemical changes were most pronounced in the 300 and 1000 mg/kg/day male groups. Significant dose-related decreases in transaminases (AST, ALT) were observed in all treated male groups (22 to 30%). Urea nitrogen was increased significantly and dose-dependently in both male (32 to 60%) and female (18 to 24%) groups at 100 or more mg/kg/day in both 3 and 6 months toxicity studies. However, creatinine was increased only in the high dose male group. Total protein and sodium decreased modestly but significantly in males receiving 300 or more mg/kg/day. Serum potassium and chloride were increased in males receiving 100 (300 in case of chloride) or more mg/kg/day (Table 3.2.1.4).

At the 6 month sacrifice, the mean absolute and relative heart weights in all treated groups were significantly reduced (8 to 14%) relative to control. High mean absolute and relative weights of kidneys were observed for males given 100 or more mg/kg/day (9 to 16% greater than control) and for females given 1000 mg/kg/day (7 to 8% higher than control). High relative weights of kidneys were also observed for other treated female groups (5 to 8% greater than control). Absolute and relative adrenal weights were significantly increased in high dose males (14 and 17% greater than control) sacrificed at the end of 6 months treatment. The mean absolute lung weight in high dose males, and the absolute thymus weight in high dose females, were decreased relative to control (6% and 18%, respectively, Table 3.2.1.5).

TABLE 3.2.1.4
STATISTICALLY SIGNIFICANT CHANGES IN CLINICAL CHEMISTRY PARAMETERS IN RATS TREATED ORALLY WITH OLMESARTAN MEDOXOMIL FOR 6 MONTHS
(Percent change from control values)

Parameter	Dose (mg/kg/day)							
	Male				Female			
	30	100	300	1000	30	100	300	1000
Asp aminotransferase	↓ (22)	↓ (22)	↓ (23)	↓ (25)				
Alanine aminotransferase	↓ (27)	↓ (30)	↓ (28)	↓ (30)				
Urea nitrogen		↑ (32)	↑ (53)	↑ (60)		↑ (18)	↑ (21)	↑ (24)
Creatinine				↑ (10)				
Total protein	↓ (2)		↓ (4)	↓ (3)				↑ (1)
Potassium		↑ (8)	↑ (15)	↑ (15)				
Sodium		↓ (1)	↓ (1)	↓ (1)				
Chloride			↑ (1)	↑ (1)				

TABLE 3.2.1.5
6 MONTH TOXICITY STUDY IN RATS: TREATMENT-RELATED ABSOLUTE (G) AND RELATIVE[1] (%) ORGAN WEIGHTS

Organ	Dosage (mg/kg/day)								
	Control	30		100		300		1000	
	Wt.	Wt.	Δ%[§]	Wt.	Δ%[§]	Wt.	Δ%[§]	Wt.	Δ%[§]
Males (BW in g)[¶]	359.1	353.3		344.1*	-4.2	344.2		348.6	
Heart (g)	0.94	0.84*	-10.6	0.81*	-13.8	0.81*	-13.8	0.82*	-13.0
% relative (g)	0.26	0.24*	-7.7	0.24*	-7.7	0.23*	-11.5	0.23*	-11.5
Kidneys[2] (g)	1.07			1.21*	+13.1	1.24*	+15.9	1.24*	+15.9
% relative (g)	0.32			0.35*	+9.4	0.36*	+12.5	0.36	+12.5
Adrenal[2] (mg)	20.38							23.22*	+13.9
% relative (mg)	5.70							6.67*	+17.0
Lung (g)	1.01							0.95*	-5.9
% relative (g)									
Females (BW in g)[¶]	208.7	206.3		202.9		199.8		203.0	
Heart (g)	0.64	0.58*	-9.4	0.57*	-10.9	0.55*	-14.1	0.56*	-12.5
% relative (g)	0.31	0.28*	-9.7	0.28*	-9.7	0.27*	-12.9	0.27*	-12.9
Kidneys[2] (g)	0.74	0.79*	+6.8					0.79*	+6.8
% relative (g)	0.36	0.38*	+5.6	0.38*	+5.6	0.39*	+8.3	0.39*	+8.3
Thymus (g)	0.11							0.09*	-18.2

¶: mean body weight at terminal sacrifice; [1]: % relative to body weight; [2]: right and left, combined weight
*: statistically significant ($p \leq 0.01$) compared to control group
§: % increase or decrease compared to control group

The high dose male that died on dosing day 115 had mottles in the lung and foamy content in the trachea. There were no other treatment-related macroscopic findings at necropsy. Several treatment-related *microscopic findings* were observed in the kidney and spleen. The males were affected to a greater extent than the females, as no degeneration or regeneration of tubular epithelium and no dilatation of the tubules was observed in the treated female groups (Table 3.2.1.6). These changes were observed in approximately 30% of the males treated with 300 or more mg OM/kg/day. Thickening of arterial wall from interlobular artery to afferent arteriole

was observed with greater frequency in all groups of OM-treated females and in males given 100 or more mg OM/kg/day. The JGI was statistically significantly increased for both males and females in the 30, 100 and 300 mg/kg/day groups; values were increased for both sexes of the 1000 mg/kg/day group but not significantly ($p > 0.05$). None of the animals in the control groups showed kidney pathology. In the spleen, increased hemosiderin deposition was observed in high dose males (Table 3.2.1.6). No histomorphological correlate of the decreased heart weight was noted.

TABLE 3.2.1.6
INCIDENCE OF TREATMENT-RELATED PATHOLOGICAL FINDINGS IN RATS TREATED ORALLY WITH OLMESARTAN MEDOXOMIL FOR 6 MONTHS

Parameter	Dose (mg/kg/day)									
	Male					Female				
	0	30	100	300	1000	0	30	100	300	1000
No. of Animals Examined	15	15	15	15	14	15	15	15	15	15
Kidney										
Thickening of arterial wall	0	0	5	15	14	0	4	13	15	15
Degeneration with necrosis of tubular epithelium	0	0	1	0	1	0	0	0	0	0
Regeneration of tubular epithelium with thickening of basement membrane	0	0	0	4	4	0	0	0	0	0
Dilatation of tubular lumen	0	0	1	0	0	0	0	0	0	0
Hyaline cast	0	0	0	0	1	0	0	0	0	0
Regeneration of tubular epithelium	0	0	1	0	0	0	0	0	0	0
Spleen										
Hemosiderin deposition	0	0	0	0	8	0	0	0	0	0

The plasma concentration of olmesartan increased with increasing dose but was not dose proportional. The levels were higher at 2 hr than at 6 hr after administration of the drug and, at 24 hr, were not detectable or very low in the 30 and 100 mg/kg/day groups. AUC values suggest no accumulation of the drug on repeated dosing. Further, there were no significant gender differences (Table 3.2.1.7).

TABLE 3.2.1.7
MEAN AUC (µg.hr/ml) AND CMAX (µg/ml) VALUES FOR OLMESARTAN IN RATS TREATED ORALLY WITH OLMESARTAN MEDOXOMIL FOR 6 MONTHS

Dose	Day 1		Day 85		Day 176	
(mg/kg/day)	AUC_{0-24}	C_{max}	AUC_{0-24}	C_{max}	AUC_{0-24}	C_{max}
Male						
30	3.61	0.72	9.88	1.15	5.61	1.36
100	8.50	1.51	6.57	1.39	7.60	1.75
300	14.77	1.77	9.97	1.93	10.27	2.99
1000	23.58	2.40	29.13	4.16	31.15	5.07
Female						
30	4.29	0.79	3.44	0.79	6.41	1.43
100	6.76	1.09	5.61	1.36	7.38	1.44
300	12.12	1.50	13.45	2.89	20.55	4.02
1000	28.42	2.33	29.64	4.21	31.49	3.55

3.2.2. Escalating Oral Doses in Dogs (Study #91-0099, Report #TR 138-186) Vol. 7

This **nonGLP** study was conducted by the Laboratory Animal Science and Toxicology Laboratories, Sankyo Co. Ltd., Fukuroi, Shizuoka 437, Japan, between November 18 and 22, 1991.

Two beagle dogs (one 12-month male, 8.6 kg; one 14-month female, 8.5 kg) were used in this study. Doses of olmesartan medoxomil (lot #4) were given as follows: 50 mg/kg on day 1, 150 mg/kg on day 2, 500 mg/kg on day 3, and 1500 mg/kg on day 4. The drug was given in gelatin capsules. Observations of clinical signs and general condition of the dogs were done twice daily during the dosing period. Body weights were recorded on days 2 and 4, and food consumption was measured daily. Urine collections were made on days 1 and 3, and a fecal occult blood test was performed daily. Hematology and blood chemistry examinations were done on blood samples collected daily during the 4-day administration period. Twenty-four hours after the final dose was given, the dogs were euthanized, a full autopsy performed, 15 selected organs weighed, and histopathology examination done on 34 organs/tissues.

Results

The male dog showed no changes in general condition, apart from the appearance of some white material in the feces on days 3 and 4 (500 mg/kg and 1500 mg/kg, respectively). In the female, in addition to the appearance of white material in the feces on days 3 and 4, there was vomiting of a white substance on day 4 (1500 mg/kg) immediately following administration; there were no other changes in the dog's general condition. Body weights in both dogs were unchanged, but the female ate less than the food offered throughout the pre-dosing and the dosing period. Urinalysis, fecal occult blood testing, hematology, and blood chemistry examinations showed no abnormalities. Autopsy was unremarkable, organ weights were normal (compared with historical control values), and no histologic changes were found that were attributed to drug administration.

The white substance observed in the feces after administration of 500 mg/kg or more was analyzed. Rf values on [redacted] and retention times on [redacted] revealed the substance to be unchanged olmesartan. This indicates that, at this dose level, part of administered olmesartan may be unabsorbed and excreted unchanged. Therefore 500 mg/kg was chosen as the appropriate maximum dose for longer-term toxicology studies in the dog.

3.2.3. Three-Month Oral Toxicity Study in Dogs (Study #93-0009, Report #TR 140-178 and Toxicokinetics #TR 141-031) Vol. 8 and 9

This GLP study was conducted by the Laboratory Animal Science and Toxicology Laboratories, Sankyo Co. Ltd., Fukuroi, Shizuoka 437, Japan. Dosing was initiated on January 26, 1993.

Three groups, each consisting of three male (8.5 to 12.2 kg) and three female (9.3 to 12.3 kg) 9- to 16-month-old beagles, were given olmesartan medoxomil (lot #NH001C2) daily in gelatin capsules at doses of 125, 250 or 500 mg/kg. An additional group of equal size was given empty capsules and served as control. All animals were housed individually in aluminum cages with full access to food and water. The doses were selected on the basis of a 14-day oral administration study in which one of 4 dogs receiving 500 mg/kg/day lost weight (weight at termination of treatment 7% below pre- test weight; no effect on food consumption). Another dog from this dosage group showed a significant decrease in food intake during the second half of the treatment period but did not lose weight. Treatment had no effect on hematology or blood chemistry parameters and there were no treatment-related macroscopic findings at necropsy.

Observations and Measurements

Animals were observed closely twice each day of treatment, 4 and 24 hours (next day) after drug administration. Body weights were measured on day 3 and then weekly during the period of drug administration, and food intake was measured daily. Water consumption and urine volume were measured over 24 hours on two occasions (weeks 7 and 12). Urinalysis was done on urine collected on days 42 and 77 of drug administration in all dogs. It was also conducted on day 28 in a high dose male that was sacrificed moribund on day 34 of the study. Feces collected for 24 hr were tested for occult blood on day 77 of drug administration (all dogs). Electrocardiography, blood pressure determinations, ophthalmology examinations and electroretinography were done for all animals at weeks 11/12 of the dosing period. Blood samples were taken (from jugular vein) prior to feeding, pretest and before drug administration on dosing days 13, 27, 55, 83 and 90 for hematology and blood chemistry examinations. To examine hepatic function, a bromsulphalein excretion (BSP) test was done on all dogs on day 84. To examine renal function, a phenolsulfonphthalein excretion (PSP) test was done on all dogs on day 86. For toxicokinetics study, blood samples were collected from all surviving animals prior to administration and 1, 2, 4, 6, 8, and 24 hours after administration on days 1, 28 and 91. At the end of the study, all of the surviving dogs were autopsied, 15 organs weighed and 34 tissues/organs evaluated histomorphologically (Table 3.2.3.1).

Results

One male dog given 500 mg/kg became moribund, and was sacrificed on day 34. This dog was depressed from day 27 onward and vomited blood and lost its righting reflex on day 34. One control male was diagnosed as having exocrine pancreas dysfunction on day 7, and was excluded from the study. Among surviving dogs, vomiting and loose stools were observed in all groups including the control. Feces containing whitish material, which was considered unabsorbed test substance, was noted in all high dose females, and occasionally in other treated animals. There were no significant differences in blood pressure, ECG or heart rates between the control and

treated groups. Also, no significant changes were noted on ophthalmologic examination or electroretinograms.

TABLE 3.2.3.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Aorta	Ileum	Sciatic nerve
Adrenals*	Jejunum	Skeletal muscle (thigh)
Bone marrow (femur, sternum)	Kidneys*	Spinal cord (cervical)
Brain*	Lacrimal gland (left)	Spleen*
Cecum	Liver*	Stomach
Colon	Lungs*	Submandibular glands
Duodenum	Mesenteric lymph node	Testes*
Epididymides*	Ovaries*	Thymus*
Eyeball (left)	Pancreas	Thyroid with parathyroid*
Gall bladder	Pituitary *	Urinary bladder
Harderian gland	Prostate*	Uterus*
Heart*	Rectum	

*Organ weighed

There were no significant differences in body weights between the treated and control groups. Occasionally, some individual dogs in each treatment group showed decreases in body weight more than the maximum change in the corresponding control group. Food consumption was normal throughout, except in the high dose male that was sacrificed on day 34. Water consumption and urine volumes were unaffected by treatment. Urinalysis results were unremarkable, except for the occurrence of occult blood and casts in the 28-day urine of the high dose male dog sacrificed on day 34. Fecal occult blood tests were negative throughout the study period.

The high dose male sacrificed on day 34 had a depressed white cell count, and an elevated red cell count, along with elevated hemoglobin, hematocrit and fibrinogen just prior to sacrifice. At last blood sampling (day 27), its BUN and creatinine were, respectively, 948% and 858% above pretest level and 15 and 10 times the mean concurrent control level. Although all treated groups (both male and female) had mean BUNs above pretest levels, and although differences from control were significant toward the end of the study in mid and high dose female groups ($p < 0.05$), with the exception of the high dose male group, none of these values were at least twice as high as the concurrent control mean. Serum potassium was 11% higher than control in the high dose female group on dosing day 90 ($p < 0.01$). BSP and PSP test results were unaffected by treatment. None of these tests were done on the high dose male sacrificed moribund on day 34.

TABLE 3.2.3.2
CHANGES IN CLINICAL CHEMISTRY PARAMETERS IN DOGS
TREATED ORALLY WITH OLMESARTAN MEDOXOMIL FOR 3 MONTHS
(Mean percent change from pretreatment values)

Parameter		Dose (mg/kg/day)					
		Male			Female		
		125	250	500	125	250	500
Urea nitrogen	d 13	↑ 12*	↑ 25	↑ 29	↑ 3	↑ 29	↑ 52
	d 27	↑ 31	↑ 27	↑ 403	↑ 26	↑ 34	↑ 52
	d 55	↑ 12	↑ 20	↑ 18[a]	↑ 28	↑ 49*	↑ 35
	d 83	↑ 16	↑ 37	↑ 27[a]	↑ 41	↑ 89	↑ 65[§]
	d 90	↑ 14	↑ 25	↑ 27[a]	↑ 14	↑ 65	↑ 43*
Potassium	d 90	↓ 1	↓ 3	↑ 8	NC	NC	↑ 11*

n = 3 unless otherwise specified
[a]: One dog was sacrificed on day 34, n = 2
*: significant at 1% level compared with control
[§]: significant at 5% level compared with control
NC: no change

Organ weight analyses revealed significantly ($p < 0.05$) decreased mean absolute but not relative heart weights in males at doses of 125 (21%), 250 (21%) and 500 (24%) mg/kg/day relative to the concurrent control group. The individual heart weights were reported as falling within the historical control range.

Histopathologic changes were observed in kidneys, heart, skeletal muscle, liver, spleen, stomach, thymus, bone marrow, pancreas, testes, oral cavity and tongue in the high dose male dog which was sacrificed in a moribund condition on day 34. The changes consisted of moderate juxtaglomerular cell hyperplasia and increase in number of juxtaglomerular cell granules, severe dilatation of tubules and regeneration of epithelium in the kidney, mild intramural coronary and skeletal muscle arteritis and necrosis of muscle fiber. There was mild congestion and atrophy of liver cells, mild congestion of the spleen, severe necrosis of mucosa of the stomach fundus, and hemorrhagic ulceration of mucosa and submucosa at the fundus, in the oral mucous membranes and on the tongue. Mild atrophy of the thymus, mild decrease in hematopoietic cells, moderate atrophy of the exocrine gland of the pancreas, mild degeneration of seminiferous epithelium and mild hemosiderin deposition in the spleen were also observed. The cause of death in this animal was considered to be renal failure. Changes suggestive of renal damage (mild dilatation of renal tubules, and mild to moderate tubular regeneration) were also observed in the animals that survived to the end of the study, indicating that the kidney was a target organ for toxicity (Table 3.2.3.3). Regeneration of tubular epithelium suggests that tubular damage occurred in advance of it. The findings were considered to be related to treatment with the test substance. Microscopic changes in other organs were considered to be incidental and unrelated to treatment with the test substance.

TABLE 3.2.3.3
INCIDENCE OF TREATMENT-RELATED RENAL FINDINGS IN DOGS TREATED ORALLY WITH OLMESARTAN MEDOXOMIL FOR 3 MONTHS

Parameter	Dose (mg/kg/day)							
	Male				Female			
	0[a]	125	250	500	0	30	100	300
No. of Animals Examined	**2**	**3**	**3**	**2 + 1[b]**	**3**	**3**	**3**	**3**
Juxtaglomerular cell hyperplasia	0	3	3	2 + 1	0	3	3	3
Increase in Juxtaglomerular granules	0	2	3	1 + 1	0	1	3	3
Dilatation of tubules	0	0	2	0 + 1	0	1	1	1
Regeneration of tubular epithelium	0	1	2	2 + 1	0	0	0	1

a: one animal was excluded from the study due to the incidental development of pancreatic dysfunction.
b: one animal was sacrificed *in extremis* on day 14.

Toxicokinetic measurements showed an absence of dose-dependency and gender differences for area-under-the-curve (AUC) and maximum drug concentration (C_{max}) values. Peak blood concentration level was reached between 2 and 8 hours after administration. A high individual variability and small sample size precludes any statistical interpretation of the data. AUC and C_{max} values of olmesartan were not measurably changed after repeated administration, suggesting that there is no drug accumulation (Table 3.2.3.4). Further, plotting the pathological findings in the kidney against the AUC or Cmax did not reveal any relationship, suggesting that the toxicological findings were not related to the magnitude of systemic exposure.

TABLE 3.2.3.4
PHARMACOKINETIC PARAMETERS (VALUES ARE GIVEN AS MEAN ± SD) OF OLMESARTAN ON DAY 1, DAY 28 AND DAY 91 IN DOGS TREATED ORALLY WITH OLMESARTAN MEDOXOMIL FOR 3 MONTHS

Sex	Dose (mg/kg)	N	Day 1			Day 28			Day 91		
			$AUC_{(0-24)}$ (µg.hr/ml)	Tmax (hr)	Cmax (µg/ml)	$AUC_{(0-24)}$ (µg.hr/ml)	Tmax (hr)	Cmax (µg/ml)	$AUC_{(0-24)}$ (µg.hr/ml)	Tmax (hr)	Cmax (µg/ml)
M	125	3	18.89 ± 7.969	3.7 ±2.52	1.65 ± 0.746	24.66 ± 9.803	8.0 ±4.00	3.21 ± 1.703	14.20 ± 3.244	4.7 ±3.06	1.83 ± 0.497
	250	3	13.96 ± 5.884	3.3 ±2.31	2.04 ± 0.775	12.54 ± 4.853	3.3 ±1.15	2.09 ± 0.649	13.72 ± 3.579	2.7 ±1.15	2.48 ± 0.639
	500	3	26.34 ± 10.572	5.3 ±3.06	2.75 ± 0.090	17.01 ± 6.418	2.0 ±0.00	2.26 ± 0.393	17.35#) ± 10.239	3.0#) ±1.41	2.94#) ± 1.089
F	125	3	9.89 ± 9.290	5.0 ±6.08	1.05 ± 0.649	12.99 ± 11.572	5.0 ±6.08	1.18 ± 0.748	7.13 ± 5.870	1.0 ±0.00	1.49 ± 0.361
	250	3	43.66 ± 6.449	10.7 ±2.31	3.66 ± 0.285	18.29 ± 11.252	3.7 ±2.52	2.05 ± 0.425	30.61 ± 17.668	6.0 ±5.29	3.36 ± 1.603
	500	3	32.09 ± 3.067	5.3 ±3.06	3.79 ± 1.211	16.46 ± 0.742	4.0 ±2.00	2.61 ± 0.400	31.97 ± 6.385	4.0 ±3.46	3.67 ± 0.911

#) n=2

3.2.4. Twelve-Month Oral Toxicity Study in Dogs (Report #TR 142-128, Study #94-0043 and Toxicokinetics #TRK 142-004) Vol. 12, 13 and 17

This GLP study was conducted by Laboratory Animal Science and Toxicology Laboratories, Sankyo Co. Ltd., Fukuroi, Shizuoka, Japan, between April 19, 1994 and July 8, 1996 (dates of dosing and necropsy are not given). Assay of blood concentration of olmesartan (active metabolite) was performed by [redacted]

Four groups, each consisting of four male and four female 9- to 17-month-old beagles weighing 7.7 to 12.1 kg, were given olmesartan medoxomil (Lot #NH005C1) daily in gelatin capsules at doses of 0, 10, 40 or 140 mg/kg. Animals were housed individually in stainless steel cages with *ad libitum* access to food and water. The doses were selected based on two 3-month studies (section 3.2.3) in which renal toxicity was observed at 125 or more mg/kg/day.

Observations and Measurements

Clinical observations: twice each day of treatment, 4 and 24 hours after drug administration.
Body weights: once a week for 3 weeks before initiation of dosing, weekly for the first 13 weeks of the treatment period, and every 4 weeks thereafter.
Food intake: measured individually daily and calculated weekly.
Water consumption: daily, 1 week before initiation of dosing and in treatment weeks 5, 13, 24, 37 and 50.
Urine volume: 1 week before initiation of dosing and in treatment weeks 5, 13, 24, 37 and 50.
Urinalysis was done on urine (24 hr collection) collected 2 weeks before treatment and in treatment weeks 5, 13, 24, 37 and 50.
Feces, collected for 24 hours, were tested for occult blood in weeks -1 (prestudy), 5, 24 and 50.
Electrocardiography, blood pressure determinations, ophthalmology examinations and electroretinography were done in weeks -3/-2 (prestudy), 28 (b.p.), 47 (ERG), 48 (ophthalmology) and 49 (ECG and b.p.).

Blood samples were taken pretest (weeks -1, -2, and -3) and before drug administration in weeks 3, 6, 9, 12, 24, 36, 48 and 52. Full hematology and blood chemistry examinations were done. To examine hepatic function, a bromsulphalein (BSP) excretion test was done on all dogs in weeks -2, 25 and 50. To examine renal function, a phenolsulfonaphthalein (PSP) excretion test was done on all dogs in weeks -3, 13, 26, 39 and 51. Blood samples for toxicokinetic studies (plasma levels of the active metabolite, olmesartan) were taken at 1, 4, 8 and 24 hr after dosing on day 1, and in weeks 25 and 52.

At the end of the study, all dogs were examined macroscopically for abnormalities of various organs and tissues. A number of organs were weighed. Microscopic examination was performed on all tissues listed below from all dogs (Table 3.2.4.1). Kidneys were examined by electron microscopy.

TABLE 3.2.4.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenals*	Kidneys*	Skin (abdominal)
Aorta	Lacrimal gland (left)	Spinal cord (cervical)
Bone marrow (sternum, femur)	Liver*	Spleen*
Brain*	Lungs*	Stomach
cecum	Mesenteric lymph node	Testes/Epididymides*
Colon	Ovaries*	Thymus
Duodenum	Pancreas*	Thyroids/Parathyroids*
Esophagus	Pituitary*	Tongue
Eyeball	Prostate*	Trachea
Gall bladder	Rectum	Urinary bladder
Heart*	Submandibular glands	Uterus*
Ileum	Sciatic nerve	Vagina
Jejunum	Skeletal muscle (thigh)	

*: organ weighed

Results

All animals survived to term. Vomitus, loose stool, mucoid stool, lacrimation and salivation were observed in all groups including the control.

Body weights showed no significant differences between the treated and control groups. Two male dogs, one receiving 40 and one receiving 160 mg/kg/day, had, on occasion, showed decreases in body weight greater than the maximum decrease in the corresponding control group. Food and water consumption and urine volumes were unaffected by treatment. Urinalysis results showed moderately to severely positive occult blood in one control female, one male and female given 10 mg/kg/day, one female given 40 mg/kg/day, and 3 females given 160 mg/kg/day. Fecal occult blood tests were negative throughout the study period. Blood pressure readings, results of ophthalmologic examinations, and electroretinography were all unremarkable.

In hematology examinations, the female dogs given 160 mg/kg/day on some occasions showed decreased red cell counts, mean corpuscular hemoglobin, reticulocyte counts, and activated partial thromboplastin time ($p > 0.05$). Blood chemistry evaluations did not show associations with treatment other than an approximately 2-fold increase (relative to concurrent control and baseline) in BUN levels in one high dose female in week 24. There were no significant organ weight differences between the control and treated groups.

There were no drug-related macroscopic findings at necropsy. Hyperplasia of the juxtaglomerular apparatus in high dose animals and an increase in number of juxtaglomerular cell granules in mid and high dose animals are considered to be due to an adaptive response to the action of olmesartan medoxomil on the RAAS. Thus, it may be concluded that oral administration of olmesartan medoxomil to dogs at 160 mg/kg/day for 12 months produced effects that are not of toxicological significance.

In this study, AUC and C_{max} values for olmesartan increased as the dose increased, but in a manner less than proportional to the increase in dose. AUC and C_{max} values were not measurably

changed after repeated administration (i.e. at weeks 25 and 52), suggesting that there is no olmesartan accumulation at these dose levels (Table 3.2.4.2). Also, there were no apparent differences between the sexes. In healthy male volunteers, 10 daily oral doses of 40 mg olmesartan medoxomil achieved a mean olmesartan Cmax and $AUC_{216-240}$ of 0.733 µg/ml and 4.366µg.h/ml, respectively (study #866-102). Thus, at 160 mg/kg, the dose that produced effects that are not of toxicological significance in the dog study, systemic exposure to olmesartan in males (1.60 µg/ml and 8.64 µg.h/ml, respectively) was 2.2 times higher than human exposure levels on the basis of Cmax and 2 times higher on the basis of AUC.

TABLE 3.2.4.2
MEAN PHARMACOKINETIC VALUES FOR OLMESARTAN ON DAY 1 AND IN WEEKS 25 AND 52 FOR DOGS TREATED ORALLY WITH OLMESARTAN MEDOXOMIL FOR 12 MONTHS

Sex	Dose (mg/kg)	n	Day 1			week 25			week 52		
			$AUC_{(0-24)}$ (µg.hr/ml)	Tmax (hour)	Cmax (µg/ml)	$AUC_{(0-24)}$ (µg.hr/ml)	Tmax (hour)	Cmax (µg/ml)	$AUC_{(0-24)}$ (µg.hr/ml)	Tmax (hour)	Cmax (µg/ml)
Male	10	4	1.02	3.5	0.17	0.82	3.3	0.17	0.61	2.5	0.11
	40	4	5.00	4.3	0.48	5.40	5.3	0.50	5.68	5.0	0.56
	160	4	12.15	3.3	1.46	15.41	6.0	1.60	8.64	3.3	1.28
Female	10	4	1.40	4.0	0.18	1.08	5.0	0.10	0.66	2.5	0.11
	40	4	2.02	3.3	0.32	2.64	2.5	0.46	3.68	3.3	0.42
	160	4	11.16	3.3	1.19	14.87	3.3	1.82	7.26	3.3	1.03

3. 3. ***Carcinogenicity Studies***

3.3.1. 24-Month Oral Carcinogenicity Study of Olmesartan Medoxomil in Rats (Study #97-0022, Report #TR 146-570, #TRC 144-026 (Toxicokinetics) Vol. 20-22

This GLP study was conducted by the Medicinal Safety Research Laboratories at Sankyo Co., Ltd., Horikoshi, Fukuroi, Shizuoka-ken, Japan, between April 24, 1997 and April 28, 1999. Dosing was initiated between April 24 and 29, 1997. Animals were necropsied between April 22 and 28, 1999. This study was conducted to assess the carcinogenic effects of olmesartan medoxomil during its repeated dietary administration to rats for 24 months.

Male and female rats (F344/DuCrj [redacted]) were approximately 6 weeks old and weighed 117-138 g (males) or 90-105 g (females) at the time dosing was initiated. The animals were housed individually and received the powdered feed with or without the admixed test substance *ad libitum*. For each treatment group, the body weight and food intake were estimated so as to calculate the mixing concentrations of olmesartan medoxomil required to produce the specified dose levels. The test samples were prepared once every one or two weeks. The homogeneity of the prepared test substance sample in the diet was verified using [redacted] at the beginning of dosing and once every 3 months thereafter. Groups of 50 male and 50 female rats were given olmesartan medoxomil (OM) admixed with the diet at doses of 200, 600 or 2000 mg/kg/day for 24 months. Additional groups of OM-treated rats (200, 600 or 2000 mg/kg/day), each composed of 10 rats per sex, were used for toxicokinetic study and 15 untreated males and females were used for bacteriological testing. The doses administered in this study were approved by the CAC (see attachment #1).

Observations and Measurements

All animals were observed for clinical signs daily throughout the study. Palpation to examine for nodule formation was conducted, on days 545, 609, 685, 726 in males, and on days 540, 604, 680, 721 in females. Body weight and food consumption were recorded on the day when dosing was started and then at weekly intervals for the first 13 weeks and at 4 week intervals thereafter. Blood pressure was measured (indirectly) in weeks 27, 55, 79 and 102, in 4 males and 4 females of each group.

Urinalysis parameters (pH, protein, ketone body, glucose, occult blood, bilirubin and urobilinogen) were determined using test paper for 20 rats/sex in the control and the high dose groups 5 times (weeks 2, 25, 52, 78 and 103) during the dosing period. Hematology parameters were determined for all surviving rats at the end of the study. Clinical chemistry parameters were not studied. For toxicokinetics study, blood samples were collected from the caudal vein of (unanesthetized) satellite animals (5 males and 5 females/group) in weeks 3, 13, 26 and 39 at 9 a.m. and 4:30 p.m (same animals at each sampling time).

Moribund rats were weighed and anesthetized to collect as much blood as possible and then autopsied to examine their organs and tissues macroscopically. Dead rats were weighed and autopsied, and their organs and tissues were observed macroscopically. At the end of the 24 month dosing period, all surviving main study animals were anesthetized to collect blood from

the abdominal aorta and were autopsied to examine their organs and tissues macroscopically. Selected organs were removed (from all rats) and weighed (Table 3.3.1.1). Histopathological examination was conducted on all organs and tissues from all animals in the control and the high dose groups and for any animal (any group) that died or was moribund sacrificed. Histopathological examination of organs/tissues in the remaining low and mid dose group animals was limited to the liver, kidney, adrenal, uterus and GI tract

TABLE 3.3.1.1.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

Adrenals*	Liver*	Skeletal muscle (rt. rectus muscle of thigh)
Aorta	Lungs*	Skin
Brain*	Lymph node	Spinal cord
Bone & bone marrow (tibia and rt. Femur)	-rt. submandibular	Spleen*
Cecum	-mesenteric	Stomach
Colon	- left renal	Testes*
Duodenum	Mammary glands (♀)	Thymus
Epididymides	Ovaries*	Thyroids including parathyroids
Esophagus	Pancreas	Tongue
Eyeballs	Pituitary*	Trachea
Harderian glands	Preputial gland	Urinary bladder
Heart*	Prostate	Uterus*
Ileum	Rectum	Vagina
Jejunum	Salivary gland	
Kidneys*	Sciatic nerve,	
	Seminal vesicles	

*Organ weighed

Results

The mean intake of olmesartan medoxomil was, on average, close to the targeted dose levels for each group throughout the dosing period (Table 3.3.1.2).

TABLE 3.3.1.2
24-MONTH CARCINOGENICITY STUDY IN RATS: ACHIEVED DOSES

Targeted dose (mg/kg/day)	200	600	2000
achieved: males (mg/kg/day)	197.6	598.6	2012.5
% of targeted dose	98.8	99.8	100.6
achieved: females (mg/kg/day)	198.5	599.8	2032.9
% of targeted dose	99.3	100.0	101.6

There were no drug-related clinical signs. Periodic palpation, which was initiated during week 78 of the dosing period, revealed intra-abdominal or subcutaneous nodules in both control and treated groups. Epilation and corneal opacities occurred in both the control and treated groups. Reduced spontaneous activity, paleness, reduced body temperature and reduced stool were observed in animals that died or were moribund sacrificed.

A total of 83 animals (40 males, 43 females) died or were sacrificed during the 24 month treatment period. Survival for the high dose group was 80% for males and 84% for females and

did not differ significantly from the concurrent control (Table 3.3.1.3). Drug treatment had no effect on mean survival time, survival rate or cause of death. The main cause of moribund sacrifice or death was large granular lymphocytic leukemia and pituitary tumors in both males and females. No increase over the control incidence of moribund sacrifices or deaths due to tumors or toxicity was noted for olmesartan medoxomil-treated groups. The number of rats with leukemia was comparable between the treated and control groups. Thus, administration of test substance did not induce early development of spontaneous neoplastic lesions in this rat strain.

TABLE 3.3.1.3
24-MONTH CARCINOGENICITY STUDY IN RATS: MORTALITY

Week/incidence	Dose level (mg/kg/day)							
	0 (Control)		1		2		3	
	0		200		600		2000	
	m	f	m	f	m	f	m	f
No of animals	50	50¶	50	50	50	50	50	50
Mortality								
1-36						1		
37-40								
41-44							1	
45-56								
57-60	1							
61-68								
69-72				1		1		1
73-76	1			1				1
77-80		1	1	1		1		
81-84		1			1		1	
85-88	2	1	3		1	1	1	
89-92	2	1		2	2	1	4	1
93-96	1		3	1	2		1	1
97-100	3	2	1	1	2	2	2	1
101-104	2	6		4	1	3		2
105						1		1
No. found dead	3	2	3	2	3	3	2	3
No. moribund	9	10	6	9	6	8	8	5
Total loss	12	12	9	11	9	11	10	8
Total loss (%)	24	26	18	22	18	22	20	16

¶: One animal was excluded after 14 months into the study due to input of wrong information on the animal into the general toxicity system

Decreased blood pressure, attributable to the pharmacological action of the drug, was not proportional to dose or duration of the dosing period. Males in the 200 and 600 mg/kg/day groups and females receiving 200 or more mg/kg/day had significantly lower mean blood pressure during week 27 (first measurement) relative to the control group. Significantly decreased values were also observed during week 55 for males receiving 200 mg/kg/day and females receiving 200 and 600 mg/kg/day. At the other measurement times, either there was no difference or higher blood pressure values were found in the treated groups relative to concurrent control or baseline values.

TABLE 3.3.1.4
24-MONTH CARCINOGENICITY STUDY IN RATS: EFFECT ON BLOOD PRESSURE IN MALE RATS

(mmHg)

(mg/kg)		Day 189 SBP	Day 189 MBP	Day 189 DBP	Day 385 SBP	Day 385 MBP	Day 385 DBP	Day 552 SBP	Day 552 MBP	Day 552 DBP	Day 713 or 714 SBP	Day 713 or 714 MBP	Day 713 or 714 DBP
0	N	4	4	4	4	4	4	4	4	4	4	4	4
	Mean	139.0	112.5	99.8	145.8	114.5	98.8	155.3	123.0	106.8	153.5	117.3	99.0
	S.D.	11.1	7.6	7.7	15.1	16.1	17.8	9.9	11.3	14.8	10.5	12.2	13.2
200	N	4	4	4	4	4	4	3	3	3	4	4	4
	Mean	104.5*	80.3*	68.0*	112.0*	82.5*	68.0*	126.7*	96.3*	81.7	157.3	122.0	104.8
	S.D.	4.1	5.7	7.1	8.7	6.5	7.6	15.6	11.8	11.2	10.4	7.1	5.4
600	N	3	3	3	3	3	3	4	4	4	4	4	4
	Mean	104.3*	82.3*	71.0*	122.0	97.3	85.0	146.0	111.5	94.0	155.0	117.8	99.0
	S.D.	2.1	3.5	5.0	16.5	12.5	12.2	12.6	16.4	20.0	18.3	10.4	9.2
2000	N	2	2	2	4	4	4	4	4	4	4	4	4
	Mean	126.5	101.5	89.5	119.0	92.3	79.0	147.5	108.8	89.0	174.5	142.5	127.0
	S.D.	33.2	29.0	27.6	21.4	18.9	18.0	21.2	21.2	23.4	15.8	19.1	22.1

SBP, Systolic blood pressure; MBP, Mean blood pressure; DBP, Diastolic blood pressure
*, Significant at 1% level compared with control
#, Significant at 5% level compared with control

TABLE 3.3.1.5
24-MONTH CARCINOGENICITY STUDY IN RATS: EFFECT ON BLOOD PRESSURE IN FEMALE RATS

(mmHg)

(mg/kg)		Day 185 SBP	Day 185 MBP	Day 185 DBP	Day 381 SBP	Day 381 MBP	Day 381 DBP	Day 553 SBP	Day 553 MBP	Day 553 DBP	Day 710 or 711 SBP	Day 710 or 711 MBP	Day 710 or 711 DBP
0	N	4	4	4	4	4	4	4	4	4	4	4	4
	Mean	138.0	113.0	100.5	131.8	108.0	96.3	144.0	115.0	100.3	163.3	132.3	117.0
	S.D.	11.7	6.2	4.8	11.1	2.4	3.8	9.9	10.1	12.1	24.2	14.2	9.6
200	N	4	4	4	4	4	4	4	4	4	4	4	4
	Mean	110.0#	88.5#	77.8#	104.5#	82.3#	71.3#	141.5	116.5	104.3	194.3	162.3#	146.0#
	S.D.	12.0	12.7	13.4	11.0	9.8	9.2	7.4	8.3	9.4	29.1	19.3	14.8
600	N	4	4	4	4	4	4	4	4	4	4	4	4
	Mean	98.5#	80.3#	71.3#	110.3#	85.8#	73.3#	131.5	101.3	86.0	188.8	154.0	136.8
	S.D.	11.8	12.6	12.6	2.1	6.7	9.6	10.1	14.2	17.1	22.0	21.8	21.6
2000	N	4	4	4	4	4	4	4	4	4	4	4	4
	Mean	104.8#	81.5#	70.3#	102.3#	84.3	75.3	122.5	101.0	90.0	171.0	137.3	120.5
	S.D.	6.2	5.4	6.3	17.1	18.2	15.8	21.4	19.0	18.6	28.9	23.4	21.9

SBP, Systolic blood pressure; MBP, Mean blood pressure; DBP, Diastolic blood pressure
*, Significant at 1% level compared with control
#, Significant at 5% level compared with control

Mean body weights were statistically significantly decreased ($p < 0.05$) in all treated groups relative to the control group, beginning on day 8 of drug administration and continuing through termination of the study (Fig. 3.3.1.1). Decrements were greater than 10% for all treated male groups from day 197 onwards and were maximal (between 14.1 and 17%) on day 449 for all treated male groups. In contrast, body weight decrements, relative to control, were greater than 10% for females only in the high dose group and only from day 533 to termination of the study (Table 3.3.1.6).

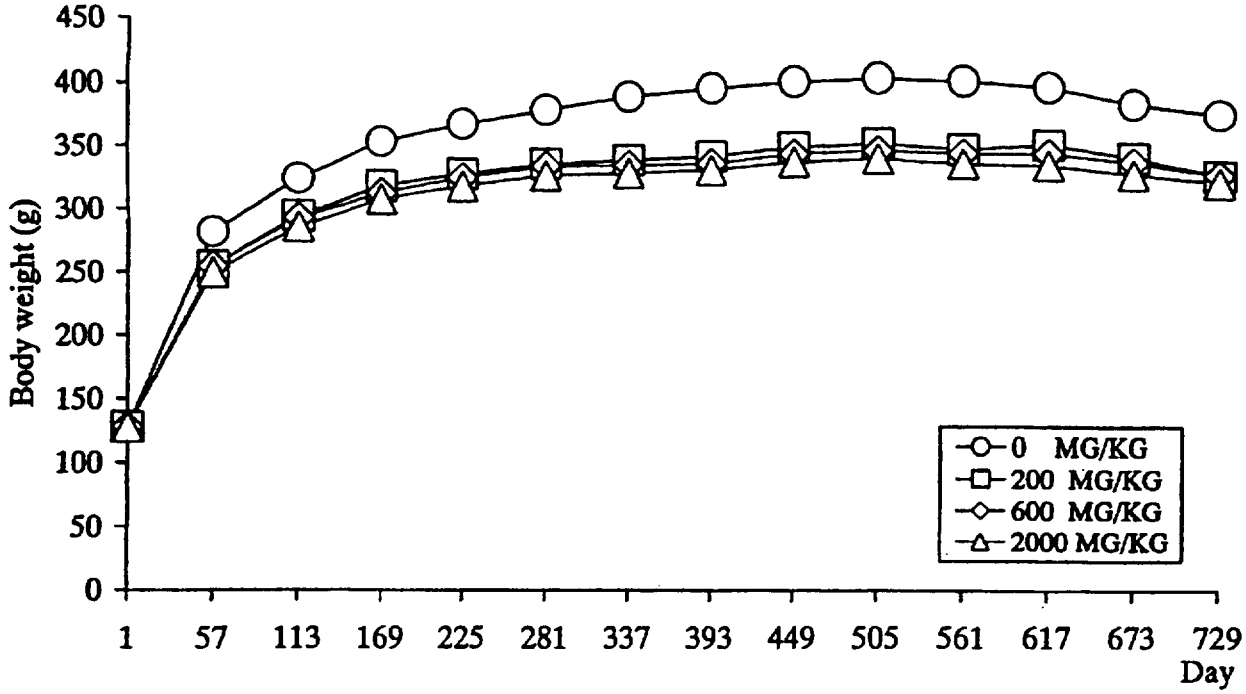

Fig. 3.3.1.1.: Body weight changes in male rats treated with OM in their diet for 24 months

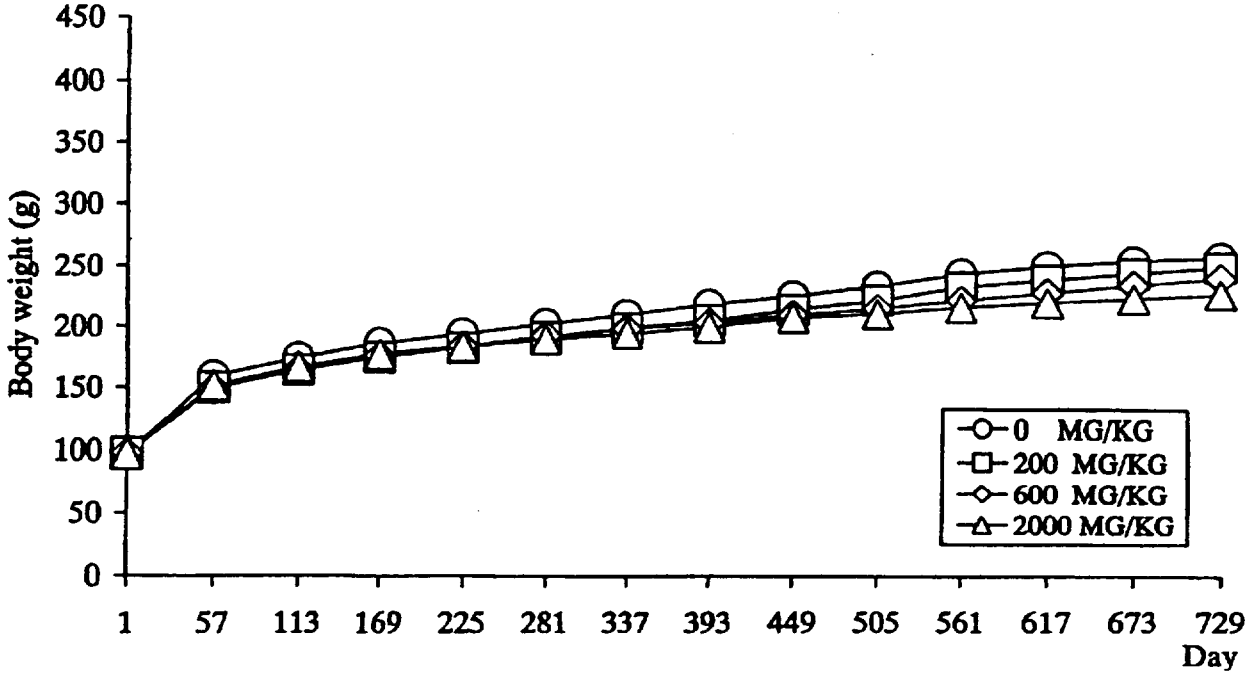

Fig. 3.3.1.2.: Body weight changes in female rats treated with OM in their diet for 24 months

TABLE 3.3.1.6
24 MONTH CARCINOGENICITY STUDY: GROUP MEAN BODY WEIGHTS

Study day		Dosage (mg/kg/day)							
		Male				Female			
		Control	200	600	2000	Control	200	600	2000
8	B.wt., g	160.6	155.5*	156.3*	155.5*	110.6	108.5¶	108.1*	108.4¶
	% diff§		-3.2	-2.7	-3.2		-1.9	-2.3	-1.9
29	B.wt., g	227.6	208.6*	208.7*	206.5*	139.5	133.2*	132.1*	132.4*
	% diff		-8.3	-8.3	-9.3		-4.5	-5.3	-5.0
57	B.wt., g	281.5	254.1*	254.4*	249.6*	159.3	150.1*	149.0*	151.9*
	% diff		-9.7	-9.6	-11.3		-5.8	-6.5	-4.6
85	B.wt., g	308.9*	280.4*	278.3*	272.3*	169.1	159.3*	159.7*	161.3*
	% diff		-9.2	-9.9	-11.9		-5.8	-5.6	-4.6
113	B.wt., g	324.1*	294.7*	293.0*	285.9*	174.6	164.7*	165.1*	167.4*
	% diff		-9.1	-9.6	-11.8		-5.7	-5.4	-4.1
169	B.wt., g	353.1	318.0*	312.5*	307.8*	186.5	175.4*	176.0*	177.9*
	% diff		-9.9	-11.5	-12.8		-6.0	-5.6	-4.6
225	B.wt., g	367.6	328.0*	324.9*	318.3*	194.9	183.4*	185.0*	184.7*
	% diff		-10.8	-11.6	-13.4		-5.9	-5.1	-5.2
281	B.wt., g	379.4	336.4*	334.6*	327.1*	203.2	192.6*	193.7*	190.6*
	% diff		-11.3	-11.8	-13.8		-5.2	-4.7	-6.2
337	B.wt., g	390.1	339.9*	335.6*	329.4*	211.4	200.0*	199.8*	195.6*
	% diff		-12.9	-13.9	-15.6		-5.4	-5.5	-7.5
393	B.wt., g	397.0	343.2*	337.6*	332.4*	220.4	207.1*	205.1*	201.7*
	% diff		-13.6	-14.9	-16.3		-6.0	-6.9	-8.5
449	B.wt., g	408.5	350.7*	345.6*	339.2*	227.9	216.2*	212.0*	209.6*
	% diff		-14.1	-15.4	-17.0		-5.1	-7.0	-8.0
505	B.wt., g	405.8	354.3*	348.8*	342.2*	236.4	224.2*	217.3*	213.0*
	% diff		-12.7	-14.1	-15.7		-5.2	-8.1	-9.9
561	B.wt., g	404.1	349.9*	346.5*	338.5*	247.0	236.1¶	224.8*	218.7*
	% diff		-13.4	-14.3	-16.2		-4.4	-9.0	-11.5
617	B.wt., g	399.6	354.0*	346.8*	337.4*	253.5	242.1¶	231.3*	222.3*
	% diff		-11.4	-13.2	-15.6		-4.5	-8.8	-12.3
673	B.wt., g	386.7	343.8*	340.2*	330.5*	258.2	248.0	238.1*	226.7*
	% diff		-11.1	-12.0	-14.5		-4.0	-7.8	-12.2
729	B.wt., g	378.6	330.0*	330.4*	324.3*	261.5	253.5	244.2*	230.5*
	% diff		-12.8	-12.7	-14.3		-3.1	-6.6	-11.9

§: Per cent (%) difference from control body weight
¶: $p < 0.05$ when compared to control
*: $p < 0.01$ when compared to control

Food intake was statistically significantly decreased in all treated groups beginning on day 9 of the study. The decrease continued for an extended duration of dosing especially for low dose groups (day 729 for males and day 506 for females). A statistically significantly increased food intake was observed in mid and high dose groups toward the end of the study (Table 3.3.1.7).

TABLE 3.3.1.7
24 MONTH CARCINOGENICITY STUDY: GROUP MEAN FOOD INTAKE

Sex	Dosage mg/kg/day	Days of Dosing	
		Lower food intake*	Higher food intake*
Male	200	9 to 179, 226, 310, 534, 729	None
	600	9 to 93, 142, 170, 310	590, 618
	2000	9 to 65, 310	422 to 506, 590, 618, 702
Female	200	9 to 114, 170, 226, 254, 310, 366, 394, 450, 506	None
	600	9 to 58	702
	2000	9 to 37	65 to 86, 114, 142, 226, 366, 422, 534, 590, 674, 702

* $p < 0.05$

There were no remarkable differences in urinalysis between the control group and the high dose group except for a non-significant tendency toward lower protein levels ($p > 0.05$) in high dose males. Changes in hematological parameters were not remarkable as they occurred in one sex or were not dose-related. The incidence of leukemia ("measured as mature leukemia cell and blast leukemia cell") in animals autopsied during or at the end of the administration period was not significantly increased in any of the treated groups compared to the control group.

In males, statistically significant increases in absolute and relative adrenal weights at 200, 600 and 2000 mg/kg/day (108, 45 and 22% absolute, 147, 64 and 43% relative) and thyroid weights at 600 (14% absolute, 32% relative) and 2000 (47% absolute, 73% relative) mg/kg/day relative to the control group were noted. Significantly decreased absolute (24%) and relative (12%) liver weights were observed in the high dose male group (Table 3.3.1.8). In the females, absolute and relative kidney weights in the 200 (9% absolute, 12% relative) and 600 (6% absolute, 14% relative) mg/kg/day groups were higher than the control, as were left adrenal weights (15% absolute, 25% relative) in the 600 mg/kg/day group. Significantly lower than control ($p < 0.01$) absolute liver weight (12%) was observed in the high dose female group.

TABLE 3.3.1.8
24 MONTH CARCINOGENICITY STUDY: GROUP MEAN ORGAN WEIGHTS IN MALE RATS

	Males							
	Control		200 mg/kg		600 mg/kg		2000 mg/kg	
	A	R	A	R	A	R	A	R
Thyroid (mg)	22.09	5.85	24.64	7.44†	25.22†	7.69†	32.54†	10.14†
Adrenal (mg)								
Right	24.88	6.59	74.29†	23.49†	40.80†	12.15†	30.94†	9.61†
Left	27.33	7.23	32.42†	9.88†	34.32†	10.44†	32.79†	10.16†
Liver (g)	12.104	3.196	10.450†	3.169	10.057†	3.040	9.179†	2.828†

A = absolute; R= % of body weight; †$p < 0.01$

Macroscopic drug-related pathology included renal cysts in all treated male groups and rough surface kidney in all treated male groups and the low dose female group. Increased incidence of renal and mesenteric lymph node enlargements and testicular atrophy were found in the high dose male group. Mottled lung and adrenals, and uterine nodule were most pronounced in high dose females. A significantly increased number of females in mid and high dose groups showed dilated esophagus. These findings are summarized in Table 3.3.1.9.

TABLE 3.3.1.9
INCIDENCE OF GROSS PATHOLOGICAL FINDINGS IN ALL RATS

	Dosage (mg/kg/day)							
	0		200		600		2000	
	M	F	M	F	M	F	M	F
No. Examined	50	50	50	49	50	50	50	50
Macroscopic Findings								
Liver, hepatodiaphragmatic nodule	7	9	8	17	4	7	8	14
Mottle	5	10	3	5	6	11	4	11
Esophagus, dilatation	0	0	2	1	0	6*	1	15§
Pituitary, mottled	13	8	4	9	5	8	8	11
Adrenal, mottled	2	0	3	4	2	4	1	5*
Thyroid, enlargement	0	0	0	0	0	0	2	0
Mottled	1	4	2	1	3	0	4	0
Nodule	5	0	2	3	3	1	2	4
Kidney, cyst	0	2	7§	2	9§	2	6*	0
discoloration	0	0	0	4	2	1	3	0
rough surface	2	0	24§	6*	23§	4	41§	3
Lung, mottled	4	3	2	3	2	5	2	10*
Submandibular lymph node, enlargement	0	1	1	0	0	0	1	0
Mesenteric lymph node, enlargement	0	0	1	1	0	1	5*	2
Renal lymph node, enlargement	1	1	5	2	0	0	7*	1
Mammarygland nodule		5		5		7		7
Testis, atrophy	15		23		19		26*	
Uterus, cyst		6		5		5		9
nodule		2		6		3		8*

*: Significantly different from control, $p < 0.05$
§: Significantly different from control, $p < 0.01$

Non-neoplastic histopathology considered to be related to treatment consisted of an increased incidence of chronic nephropathy and kidney cysts in all treated male groups, an increased incidence of thickening of the arterial wall of the kidney in all treated groups, and an increase in tubular cell hyperplasia of the kidney in all high dose groups (Table 3.3.1.10 and 3.3.1.11). Thickening of the arterial walls in the kidneys probably reflected hypertrophy/hypercellularity of the JGA. The latter change is consistent with OM's antagonism of the angiotensin II receptors in the kidney. Similar findings were observed in a 6 month rat study. According to the sponsor, the tubular cell hyperplasia most likely developed in association with a chronic nephropathy. In non-target organs (examination generally limited to rats in control and 2000 mg/kg/day groups), increased incidences of esophagectasis (females), foreign body bronchopneumonia (males and females), exudative inflammation of the eye (male), increased foci of cytoplasmic vacuolation in the adrenal glands (females) and periarteritis in the testis (males) were noted in high dose group. (NOAELs were not established as these tissues were not routinely examined in the low and mid

dosage groups.) On the other hand, incidence of cardiomyopathy and myocardial fibrosis were significantly decreased ($p < 0.01$) in high dose males and females, respectively, compared to concurrent controls (Table 3.3.1.10).

Additionally, the effect of OM (2000 mg/kg/day only) on intestinal epithelium was examined in two male rats (week 58) and two female rats (week 57) for cell proliferation, aberrant crypt foci and esterase activity. No abnormal findings were noted either in the control (4 female rats) or in the treated animals. However, the extent of exposure of intestinal mucosal epithelial cells to OM was not confirmed as the concentration of the test substance in intestinal contents was not determined in the study.

TABLE 3.3.1.10
INCIDENCE OF HISTOPATHOLOGICAL FINDINGS IN ALL RATS (SCHEDULED AND UNSCHEDULED DEATHS)

Non-neoplastic Microscopic Findings	Dosage (mg/kg/day)							
	0		200		600		2000	
	M	F	M	F	M	F	M	F
No of animals in the study	**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
No. of unscheduled deaths	**12**	**12**	**9**	**11**	**9**	**11**	**10**	**8**
No. of scheduled deaths	**38**	**37**	**41**	**39**	**41**	**39**	**40**	**42**
Kidney, thickening of arterial wall	0	0	50**	47**	50**	48**	50**	49**
Kidney, chronic nephropathy	21	6	45**	10	46**	10	47**	11
Kidney, cyst	0	2	8**	4	7**	3	6*	2
Kidney, tubular cell hyperplasia	0	0	14**	1	13**	3	19**	5*
Esophagus, esophagectasis	0	0	**0/9**	**0/11**	**0/9**	**0/11**	2	15**
Lung, foreign body bronchopneumonia	1	0	**0/9**	**0/11**	**0/9**	**0/11**	8*	15**
Eye, swelling of lens fiber	4	1	-	**1/11**	**0/9**	-	10*	4
Eye, exudative inflammation	3	5	-	**1/11**	**1/9**	-	11*	4
Testis, periarteritis	0		**0/9**		**0/9**		6*	
Adrenal, focus of cytoplasmic vacuolation	5	2	4	5	5	25	5	3
focal hypertrophy of cortex	6	6	5	14*	5	12	7	12

*: significantly different from control, $p < 0.05$
**: significantly different from control, $p < 0.01$
- : organ not examined for this group
0: finding absent
Note the shaded cells containing bold numbers show the incidence of the finding in animals that died or were moribund sacrificed, the only animals in the 200 and 600 mg/kg/day groups for which the subject tissue was microscopically examined..

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 3.3.1.12). The sponsor used Fisher's

direct probability test with significance levels set at 5% for all comparisons. On the other hand, the FDA statistician used exact permutation tests (trend or pair-wise) for all comparisons, assigning 0.05 for rare and 0.01 for common tumors as critical p- values for evaluating significance.

TABLE 3.3.1.11
24-MONTH ORAL CARCINOGENICITY STUDY OF OLMESARTAN MEDOXOMIL IN RATS
KIDNEY HISTOPATHOLOGICAL FINDINGS IN INDIVIDUAL MALES

Findings	200 mg/kg/day	600 mg/kg/day	2000 mg/kg/day
Thickening of arterial wall	All	All	All
Chronic nephropathy	1,2,3,4,5,6,7,9,10,11,12,13, 14,15,16,18,19,20,22,23,24, 25,26,27,28,29,30,31,32,33, 34,35,36,37,38,40,41,42,43, 44,45,47,48,49,50	1,2,3,4,5,6,7,8,9,10,11,12, 13,14,15,16,17,18,19,20,21, 23,25,26,27,29,30,31,32,33, 34,35, 36,37,38,39,40,41,42, 44,45,46,47,48,49,50	1,2,4,5,6,7,8,9,10,11,12,13, 14,15,16,17,19,20,21,22,23, 24,25,26,27,28,29,30,31,32, 33,34, 35,36,37,38,39,40,41, 42,43,44,45,46,47,49,50
Cyst	1,2,18,20,28,30,31,39,	10,22,34,42,47,48,	6,9,14,25,32,49
Tubular cell hyperplasia	2,4,7,16,25,27,28,30,35,37, 38,41,42,44,	2,6,7,14,24,25,29,34,35,42, 48,49,50	1,9,10,11,12,13,20,21,23,27, 37,38,39,41,42, 43,44,45,50
Transitional cell papilloma	8		
TUBULAR CELL ADENOMA	**21, 43¶**	**24, 30, 33**	**2**
TUBULAR CELL CARCINOMA		**26**	**24**
Moribund sacrifice	11,17,23,26,46,47,	10,11,18,19,26,32,	2,18,19,31,34,46,47,48,
Death	15,29,33,	12,37,43,	26,30

¶: multiple

The most frequent neoplastic finding was large granular lymphocytic (LGL) leukemia. The main causes of death and moribundity were neoplastic lesions such as LGL leukemia and pituitary tumors in both males and females. LGL leukemia incidence was analyzed by site and irrespective of site (as suggested by McConnell, *et al.* JNCI 76: 283-289, 1986) by the FDA statistician (Table 3.3.1.13). For the male rats, leukemia in the forestomach, jejunum, ileum, colon, rectum (by trend tests), and leukemia in the submandibular lymph node (pair-wise test) were observed as rare tumors and reached statistical significance at p= 0.05, according to the FDA statistical analyses. For each site, occurrence at the high dose was limited to two animals with the exception of leukemia in the submandibular lymph node, where four high dose animals were affected. There was no significant increase in incidence of leukemia when an "all site" analysis was performed (p >0.05). For female rats, according to the sponsor, the incidence of uterine endometrial polyps at 200 mg/kg/day was significantly higher than concurrent control (p

<0.05) but the incidence at 600 mg/kg/day was the same as the incidence in the untreated group. The FDA analysis shows a marginally significant increasing trend in the incidence of endometrial sarcoma in the uterus (p = 0.0511). But the incidence at the high dose did not differ from control (p=0.167). There were one and two animals with this finding in the mid and high dose groups, respectively. Similarly, a nominal increase in the incidence of renal tubular neoplasia in treated males (adenomas and carcinomas which were not seen in the concurrent control rats, and are relatively rare on the basis of historical control data for the strain (0.8%)) was not statistically significant or dose-dependent (Table 3.3.1.11 and 3.3.1.13). A detailed tumor incidence summary is given in Table 3.3.1.14.

TABLE 3.3.1.12
24 MONTH CARCINOGENICITY STUDY IN RATS. SUMMARY OF NEOPLASTIC FINDINGS

Dose (mg/kg/day)	Control		200a		600a		2000	
Sex	m	f	m	f	M	f	m	f
No. of animals examined	50	49	50	50	50	50	50	50
No. tumor-bearing animals	50	45	23	25	27	20	49	44
(% incidence)	(100)	(92)	(46)	(50)	(54)	(40)	(98)	(88)
Benign	30	29	14	17	19	7	31	33
Malignant	0	6	5	6	3	9	2	4
Benign + Malignant	20	10	4	2	5	4	16	7
No. with multiple tumors	40	21	6	7	9	4	39	25
(% incidence)	(80)	(43)	(12)	(14)	(18)	(8)	(78)	(50)
No. primary tumors	140	73	30	34	42	25	108	84
Benign	116	57	21	25	34	12	90	71
Malignant	24	16	9	9	8	13	18	13

a: For the 200 and 600 mg/kg/day groups, only the liver, kidney, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, adrenal and uterus were examined in scheduled sacrifice animals. All organs were examined in dead or moribund animals.

TABLE 3.3.1.13
24 MONTH CARCINOGENICITY STUDY IN RATS. P-VALUES FOR SELECTED TISSUE OR TUMOR COMBINATIONS FOR RATS (FDA ANALYSIS)

SEX	TISSUE	TUMOR	INCIDENCE				P (TREND)	P (PAIR WISE)
			Control	200	600	2000		
Male	All Organs*	Leukemia-LG	12			12	---	0.507
	Thyroid	C-cell Adenoma + Carcinoma	14			11	---	0.839
	Thyroid	F-cell Adenoma + Carcinoma	1			4	---	0.169
	Kidney	Adenoma + Carcinoma	0	2	4	2	0.311	
	Liver	Adenoma + Carcinoma	4	1	1	1	0.870	
Female	All Organs*	Leukemia-LG	11			5	---	0.949
	Thyroid	C-cell Adenoma + Carcinoma	13			9	---	0.925
	Thyroid	F-cell Adenoma + Carcinoma	0			2	---	0.285
	Kidney	Adenoma + Carcinoma	0	0	0	0		
	Liver	Adenoma + Carcinoma	2	0	0	2	0.293	
	Uterus	Adenoma + Carcinoma	2	2	1	4	0.173	
	Uterus	Sarcoma + Polyps	4	12	4	12	0.088	

*Includes target and non-target organs

TABLE 3.3.1.14
24 MONTH CARCINOGENICITY STUDY IN RATS. INCIDENCE OF PRIMARY NEOPLASMS

ORGAN SYSTEM Organ/Tissue Neoplasm	TD	Dose level (mg/kg/day)							
		0		200[a]		600[a]		2000	
		m	f	m	f	m	f	m	f
# of animals in the study		**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
CIRCULATORY SYSTEM									
Heart (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Endocardial schwannoma	MA	2	0	0	0	0	0	1	0
DIGESTIVE SYSTEM									
Liver (n)		**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
Hepatocellular adenoma	BE	2	2	1	0	1	0	1	2
Hepatocellular carcinoma	MA	2	0	0	0	0	0	0	0
Hemangioendothelioma	BE	1	0	0	0	0	0	1	0
Hemangioma	BE	1	0	0	0	0	0	0	0
Histiocytic sarcoma	MA	0	1	0	0	0	0	0	0
Mesothelioma	BE	0	0	0	1	0	0	0	0
Forestomach (n)		**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
Squamous cell papilloma	BE	1	0	0	0	0	0	0	0
Glandular stomach (n)		**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
Adenomatous polyp	BE	0	0	0	0	0	0	0	1
Jejunum (n)		**49**	**49**	**49**	**50**	**49**	**48**	**50**	**48**
Adenoma	BE	0	0	0	0	1	0	1	0
Leiomyoma	BE	0	0	0	0	0	0	0	1
Colon (n)		**49**	**49**	**49**	**49**	**50**	**48**	**50**	**49**
Adenoma	BE	0	0	0	1	0	0	0	0
Pancreas (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Islet cell adenoma	BE	4	0	0	0	1	0	0	1
ENDOCRINE SYSTEM									
Pituitary (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Adenoma	BE	26	24	1	2	5	3	14[1)]	24
Adrenal (n)		**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
Cortical adenoma	BE	0	4	1	2	2	1	1	4
Cortical carcinoma	MA	0	0	0	1	0	0	0	1
Pheochromocytoma	BE	5	1	8	3	8	2	10	3
Malignant pheochromocytoma	MA	0	0	1	0	1	0	0	1
Thyroid (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
C-cell adenoma	BE	14	13	0	2	1	0	10	8
C-cell carcinoma	MA	0	0	0	0	0	0	1	1
Follicular cell adenoma	BE	1	0	0	0	1	0	2	1
Follicular cell carcinoma	MA	0	0	0	0	0	0	2	1
Parathyroid (n)		**49**	**48**	**9**	**11**	**8**	**11**	**50**	**47**
Adenoma	BE	0	0	0	0	0	0	0	1

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

ORGAN SYSTEM Organ/Tissue Neoplasm	TD	Dose level (mg/kg/day)							
		0		200[a]		600[a]		2000	
		m	f	m	f	m	f	m	f
# of animals in the study		**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
HEMATOPOIETIC SYSTEM									
Spleen (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Hemangioendothelioma	BE	0	0	0	0	0	0	1	0
Malignant hemangioendothelioma	MA	1	0	0	0	0	0	0	0
Thymus (n)		**50**	**49**	**7**	**11**	**6**	**11**	**50**	**49**
Thymoma	BE	0	0	0	0	0	1	0	0
Malignant thymoma	MA	0	1	0	0	0	0	0	0
Bone marrow (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Hemangioma	BE	1	0	0	0	0	0	1	0
Generalized tumors (n)		**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
Histiocytic sarcoma	MA	0	0	1	0	1	0	0	0
Leukemia, LGL	MA	12	11	3	6	5	10	12	5
INTEGUMENTARY SYSTEM									
Skin (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Amelanotic melanoma	BE	0	1	0	0	0	0	0	0
Keratoacanthoma	BE	4	0	0	0	0	0	0	0
Squamous cell papilloma	BE	0	0	0	1	0	0	0	1
Trichoepithelioma	BE	1	0	0	0	0	0	0	0
Subcutis[•] (n)		**3**	**0**	**2**	**0**	**1**	**0**	**0**	**2**
Fibroma	BE	3	0	2	0	1	0	0	2
NERVOUS SYSTEM									
Cerebrum (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Malignant reticulosis	MA	2	0	0	0	0	0	0	0
Cerebellum (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Malignant meningioma	MA	0	0	0	0	0	1	0	0
REPRODUCTIVE SYSTEM									
Mammary gland[§] (n)		**4**	**49**	**0**	**11**	**2**	**11**	**1**	**50**
Adenoma	BE	0	3	0	1	0	1	0	4
Fibroadenoma	BE	0	3	0	0	0	0	0	2
Preputial gland (n)		**50**		**9**		**9**		**50**	
Adenoma	BE	3		0		1		0	
Adenocarcinoma	MA	0		1		0		0	
Keratoacanthoma	BE	1		0		0		0	
Clitoral gland[•] (n)			**0**		**0**		**0**		**1**
Adenoma	BE		0		0		0		1
Prostate (n)		**50**		**9**		**9**		**50**	
Adenocarcinoma	MA	1		0		0		0	
Testis (n)		**50**		**9**		**9**		**50**	
Interstitial cell adenoma	BE	41		3		7		40	
Vagina (n)			**49**		**11**		**10**		**50**
Vaginal polyp	BE		1		0		0		0

ORGAN SYSTEM Organ/Tissue Neoplasm	TD	Dose level (mg/kg/day)							
		0		200[a]		600[a]		2000	
		m	f	m	f	m	f	m	f
# of animals in the study		**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
REPRODUCTIVE SYSTEM									
Uterus (n)			**49**		**50**		**50**		**50**
Endometrial adenoma	BE		1		0		1		2
Endometrial adenocarcinoma	MA		1		2		0		2
Endometrial stromal polyp	BE		4		12[2)]		3		10
Endometrial stromal sarcoma	MA		0		0		1		2
Ovary (n)			**49**		**11**		**11**		**50**
Malignant granulosa cell tumor	MA		1		0		1		0
RESPIRATORY SYSTEM									
Lung (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Alveolar/Bronchiolar adenoma	BE	6	0	0	0	0	0	4	1
Alveolar/Bronchiolar carcinoma	MA	1	0	0	0	0	0	0	0
SPECIAL SENSE ORGANS									
Harderian gland (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Adenoma	BE	0	0	0	0	0	0	1	0
Zymbal gland* (n)		**1**	**0**	**3**	**0**	**0**	**0**	**0**	**0**
Adenocarcinoma of Zymbal gland	MA	0	0	1	0	0	0	0	0
Squamous cell papilloma	BE	0	0	1	0	0	0	0	0
Squamous cell carcinoma	MA	1	0	1	0	0	0	0	0
URINARY SYSTEM									
Kidney (n)		**50**	**49**	**50**	**50**	**50**	**50**	**50**	**50**
Transitional cell papilloma	BE	0	0	1	0	0	0	0	0
Tubular cell adenoma	BE	0	0	2	0	3	0	1	0
Tubular cell carcinoma	MA	0	0	0	0	1	0	1	0
Urinary bladder (n)		**50**	**49**	**9**	**11**	**9**	**11**	**50**	**50**
Transitional cell papilloma	BE	1	0	0	0	0	0	2	2
Transitional cell carcinoma	MA	0	0	1	0	0	0	0	0
Urinary bladder polyp	MA	1	0	0	0	0	0	0	0
Leiomyosarcoma	MA	0	0	0	0	0	0	1	0
BODY CAVITIES									
Scrotal cavity* (n)		**0**		**1**		**2**		**2**	
Mesothelioma	BE	0		1		2		2	
Cranial cavity* (n)		1	1	0	0	0	0	0	0
Osteosarcoma	MA	1	1	0	0	0	0	0	0

TD: Tumor designation, BE: Benign, MA: Malignant

a: The liver, kidney, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, adrenal and uterus were examined in scheduled sacrifice animals. All organs were examined in dead or moribund animals.

2) Statistically significant increase ($p<0.05$) compared to control group

(n) The numbers in each row for an organ or tissue indicate the number of animals examined

* Organ or tissue that was examined due to abnormal macroscopic finding.

§ Mammary glands of males that have abnormal macroscopic finding were examined

The plasma concentrations of olmesartan increased in a dose-dependent manner, and the concentration showed a tendency to increase with prolongation of the administration period. Plasma concentrations were lower in samples taken in the afternoon compared to the morning samples (Table 3.3.1.15). The higher plasma concentration in the morning is probably due to higher food intake of the rats at nighttime than at daytime. No significant differences in olmesartan plasma concentrations were noted between males and females. In normal healthy male volunteers, 10 daily oral doses of 40 mg olmesartan medoxomil achieved a mean C_{max} (on the 10^{th} day) of 0.73 µg/ml (study #866-102). Thus, at the high dose of 2000 mg/kg/day in male rats, systemic exposure to olmesartan (average plasma concentration 5.8 µg/ml) was 8 times the exposure for humans.

TABLE 3.3.1.15
24 MONTH CARCINOGENICITY STUDY IN RATS. TOXICOKINETICS

Time	Arithmetic mean plasma concentrations of olmesartan (µg/ml), n=5					
	200 mg/kg/day		600 mg/kg/day		2000 mg/kg/day	
	Males	Females	Males	Females	Males	Females
Week 3						
$C_{a.m.}$	0.82	0.82	2.34	2.04	3.10¶	3.20
$C_{p.m.}$	0.39	0.40	1.05	0.94	2.82	2.13
Week 13						
$C_{a.m.}$	1.10	0.93	2.67	2.39	5.08	4.17
$C_{p.m.}$	0.40	0.40	0.88	1.08	3.87	2.53
Week 26						
$C_{a.m.}$	1.25	1.04	2.88	2.98	5.35	5.32
$C_{p.m.}$	0.62	0.48	1.84	1.59	3.44	4.81
Week 39						
$C_{a.m.}$	1.87	1.24	3.79	3.30	6.87	5.10
$C_{p.m.}$	0.59	0.64	1.62	1.94	4.73	3.24

¶: n=3

3.3.2. SUPPLEMENTAL EVALUATION OF 2-YEAR RAT CARCINOGENICITY STUDY OF OLMESARTAN MEDOXOMIL

1. ***Expert Report (dated May 29, 2001) on Renal histopathologic changes in the 2 year rat carcinogenicity with olmesartan medoxomil (Author: [redacted]):*** The slides examined (unblinded) by [redacted] were the original kidney slides from all male and female rats. The group incidences of proliferative and other OM treatment-related renal changes in the male rats are summarized in Tables 3.3.2.2 and 3.3.2.3. Chronic progressive nephropathy (CPN) in male rats was graded for severity on a scale of 0 (no lesions) to 8 (end-stage) using a semi-quantitative system based on lesion pathogenesis. The incidence in all groups was 100% and the most frequent grade in each group was 5 (high moderate) (Table 3.3.2.1).

TABLE 3.3.2.1

GROUP INCIDENCE OF CHRONIC PROGRESSIVE NEPHROPATHY (CPN) IN MALE RATS

		CPN GRADE								
CS-866 dose (mg/kg)	Effective No.*	0	1	2	3	4	5	6	7	8
0	47	0	0	1	7	15	21	1	1	1
200	49	0	0	0	0	12	31	4	1	1
600	48	0	0	0	0	4	32	12	2	0
2000	49	0	0	0	0	7	29	11	2	0

*** Effective no. represents rats in which CPN grade could be evaluated.**

[redacted] observations:

"The only compound-related renal changes observed in the rats of this carcinogenicity study with OM administered in the diet were vessel wall hypertrophy and renal tubule cell hypertrophy, the latter probably involving the distal tubule in the vicinity of the *macula densa*. The lesions originally diagnosed as tubule hyperplasia were consistent with tubule hypertrophy and not hyperplasia. Tubule cell hypertrophy is not a proliferative lesion, but usually indicative of an adaptive or compensatory response. There was also no histological evidence that OM was cytotoxic for the rat kidney because of the absence of single cell death, cytoplasmic vacuolation, cell detachment into the tubule lumen, increase in mitotic activity, simple tubule hyperplasia, or karyomegaly."

"Renal tubule adenomas or carcinomas were present in low incidence in all treated male groups, showing no dose response relationship (low-dose 2, mid-dose 3, high-dose 2). Furthermore, there was no background incidence of atypical tubule hyperplasia, which is an obligatory precursor stage of renal tubule tumors. In 3 of the 7 rats with renal tumors, a distinctive eosinophilic tumor phenotype that has been associated with familial occurrence was represented. Such eosinophilic tumors are one of the typical findings in the mutant Eker rat, which carries a hereditary predisposition for spontaneous renal tubule tumor development. They have also been encountered as spontaneous findings in conventional rat strains at a relatively young age, but to

date, have not been recorded as being induced *de novo* by any chemical. One of the tumor-bearing male rats at the low dose had multiple adenomas and carcinomas, comprising both eosinophilic (familial) and basophilic types, which is also typical of the Eker rat analogy. Historical control data from 5 control groups in 3 carcinogenicity studies with the F344/DuCrj rat at the Sankyo Research Laboratories reveals 1/50 renal tubule carcinomas in male rats in each of two of the studies, but no occurrence of adenomas, or renal tumors in females. Thus, the historical control incidence in this rat strain is 2/250, representing a spontaneous incidence of 0.8 %. Because of all of the above points, the occurrence of renal tumors in this study is considered to be spontaneous and unrelated to treatment."

It should be noted that [redacted] failed to confirm the original diagnosis of a carcinoma from a mid dose animal (03M26). The expert pathologist concludes that the occurrence of renal tumors in this study is incidental and not related to drug treatment. His conclusion is based on the "absence of any cellular changes to the tubules consequent upon treatment, the absence of a background of pre-neoplastic lesions (atypical hyperplasia), the presence in 3 of the 7 rats of a tumor phenotype consistent with spontaneous origin, the very low incidence of tumors in the treated groups lacking a dose-response relationship, and a historical control incidence for the male rat renal carcinoma in the sponsor's laboratory of close to 1%". Further, the original diagnosis of tubule hyperplasia was not confirmed by [redacted] but rather, was found by him "to represent an adaptive change of renal tubule hypertrophy". PCNA (proliferating cell nuclear antigen) staining further corroborated the lack of a drug-induced proliferative lesion. (Tissues from the proximal and distal tubules of control animals and tissues from areas of "hyperplasia" from each of the 3 treated groups was stained with PCNA to obtain a numerical index of a proliferating lesion. No statistical significant difference was observed in cell proliferating activity between the lesion diagnosed as tubular cell hyperplasia and the control proximal or distal tubules. Report #APR-148-074, Amendment of August 30, 2001).

2. ***Expert Report by NIEH Pathologists, Drs. Gary A. Boorman and Robert R. Marenpot***: At the request of the FDA, a peer review of the kidneys from the male rats was conducted by Drs. Boorman and Marenpot (Laboratory of Experimental Pathology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC). This peer review was conducted on 13 blinded kidney slides, including all 8 of the slides from rats originally diagnosed with renal tubular neoplasia. In their opinion (report dated July 25, 2001), the tubular hyperplasia that was seen reflects tubular regeneration secondary to nephropathy. Further, they add that it is unlikely that those lesions are part of the neoplastic process. They concur with the observations made by the original study pathologist (Table 3.3.2.2) except for a low dose male rat (02M21) which they diagnosed with carcinoma rather than adenoma.

3. ***Histopathological Examination of Step-Sections of the Male Kidney from the OM Rat Carcinogenicity Study (Report #APR-148-080)***: This GLP examination was conducted at Medicinal Safety Research Laboratories, Sankyo Co. Lrd., Fukuroi, Shizuoka 437-0065, Japan, between July 25 and September 10, 2001. At the request of the FDA, kidneys from all groups of male rats (n=50/group) were evaluated using the National Toxicology Program step-sectioning protocol. Six kidney slides were prepared from each animal (total of 1200 slides), and histopathological examination was performed in a blinded manner. Diagnostic criteria were the same as used in the original study report.

In comparison with the original (single section) evaluation (section 3.3.1), 4 additional animals (all from OM treated groups) had tumors (tubular adenomas) when evaluated using the step sectioning protocol. One low dose rat, originally diagnosed with tubular cell adenoma, was diagnosed with both adenoma and carcinoma when evaluated using the step-sectioning protocol. A total of 3, 4 and 3 tubular cell adenomas were observed in the 200, 600 and 2000 mg/kg/day groups, respectively. Tubular cell carcinomas were observed in one mid and one high dose animal (Table 3.3.2.2). The total number of tumor bearing animals was 3, 5 and 4 in the low, mid and high dose groups, respectively. Though the number of tumor bearing animals in the step-section analysis increased from 8 to 12, the sponsor still contends that the incidence is not significantly different from the concurrent control group incidence (0%) and that the incidence for each treated group is within the range of historical control group values for the step-section protocol, which according to Eustis *et al.*, has an overall renal tumor incidence rate of 4.62% (30/649) and individual study rates ranging from 0-16% (Eustis, S.L. *et al.* The utility of multiple-section sampling in the histopathological evaluation of the kidney for carcinogenicity studies. *Toxicol. Pathol.*, 22: 457-472, 1994). The FDA analysis of the step-section data revealed no statistically significant increased trend in the incidence of adenomas and carcinomas that could be attributed to treatment with OM (p=0.12). But, pair-wise comparisons (mortality adjusted or unadjusted) resulted in a statistically significant differences between control and the mid dose group (p =0.02). Furthermore, control versus all treated males (combined) resulted in a p-value of ≤ 0.02. All non-neoplastic lesions (thickening of the arterial wall, chronic nephropathy and tubular cell hyperplasia) showed significantly increased incidence in the treated groups relative to the control group (Table 3.3.2.3).

TABLE 3.3.2.2
24-MONTH ORAL CARCINOGENICITY STUDY OF OLMESARTAN MEDOXOMIL IN RATS
RENAL TUBULE NEOPLASTIC FINDINGS IN INDIVIDUAL MALE RATS

Dose mg/kg/day	Animal #	Original results[1]	Expert report by [redacted]	NIEHS review[3]	Step-section analysis[4]
200	02M06				Adenoma
	02M21	Adenoma	**Carcinoma**	**Carcinoma**	Adenoma
	02M43	Adenoma	Adenoma and **Carcinoma**[a]	Adenoma and **Carcinoma**[a]	Adenoma
600	03M10				Adenoma
	03M24	Adenoma	**Carcinoma**	Adenoma[b]	Adenoma
	03M26	**Carcinoma**		**Carcinoma**	**Carcinoma**
	03M30	Adenoma	Adenoma	Adenoma	Adenoma
	03M33	Adenoma	Adenoma	Adenoma	Adenoma
2000	04M02	Adenoma	Adenoma	Adenoma	Adenoma
	04M21				Adenoma
	04M24	**Carcinoma**	**Carcinoma**	**Carcinoma**	**Carcinoma**
	04M40				Adenoma

1: Original study #97-0022, Report #TR 146-570
2: At the request of the sponsor, [redacted] did unblinded review. Report prepared May 29, 2001
3: At the request of the FDA, Drs. G.A. Boorman and R.R. Marenpot of NIEHS reviewed 13 slides, 8 of them originally diagnosed as renal tubular neoplasia, the rest as renal tubular hyperplasia. Report dated July 25, 2001
4: At the request of the FDA, kidneys of all groups of male rats were evaluated using the NTP step-sectioning protocol at the sponsor's (Sankyo, Japan) laboratory (report #APR-148-080).
[a]: multiple adenomas and carcinomas
[b]: characterized as carcinoma by Dr. Boorman and adenoma by Dr. Marenpot

TABLE 3.3.2.3
24-MONTH ORAL CARCINOGENICITY STUDY OF OLMESARTAN MEDOXOMIL IN RATS
GROUP INCIDENCE OF KIDNEY HISTOPATHOLOGICAL FINDINGS OTHER THAN TUMORS IN MALE RATS

Findings	Dosage (mg/kg/day)															
	0				200				600				2000			
	Orig[1]	[redacted]	SS[3]	Combined[4]	Orig[1]	[redacted]	SS[3]	Combined[4]	Orig[1]	[redacted]	SS[3]	Combined[4]	Orig[1]	[redacted]	SS[3]	Combined[4]
Rats in group	50	47	50	50	50	49	50	50	50	48	50	50	50	49	50	50
Thickening of arterial wall[a]	0	0	0	0	50**	50	50**	50**	50**	50	50**	50**	50**	50	50**	50**
Chronic nephropathy[b]	21	47	36	38	45**	49	50**	50**	46**	48	49**	49**	47**	49	49**	50**
Tubular cell hyperplasia[c]	0	1	13	13	14**	25	39**	40**	13**	15	38**	40**	19**	20	41**	42**
Cortical/medullary cyst	0	0	1	1	8**	9	11**	17**	7**	9	6	12**	6*	5	10	14**

*: significantly different from control, $p < 0.05$
**: significantly different from control, $p < 0.01$
1: Original study #97-0022, Report #TR 146-570. Single section
2: At the request of the sponsor, . [redacted] Expert Pathologist, did unblinded review. Data was not analyzed statistically.
3: At the request of the FDA, kidneys of all groups of male rats were evaluated by the sponsor using the NTP step-sectioning protocol. Report #APR-148-080.
4. Single and multiple sections combined. [redacted] findings (see above, #1) are not included in the combined results.

a: blood vessel wall thickening appeared to represent hypertrophy and hyperplasia of the vascular smooth muscle.
b: [redacted] has graded CPN for severity on a scale of 0 (no lesions) to 8 (end stage) based on lesion pathogenesis. According to him, the incidence in all groups was 100% and the most frequent grade in each group was 5 (high moderate) (for details, see Table 3.3.2.1). Though there was an increased extension into higher grades at the mid and high doses, [redacted] does not consider OM to cause a remarkable exacerbation of this spontaneous disease.
c: tubule hyperplasia, a precursor of tumor, as originally reported in the study, has been disputed by the experts (both [redacted] and NIEHS scientists). It was determined to be tubular regeneration secondary to nephropathy by NIEHS investigators and 'tubule cell hypertrophy' by [redacted]

3.3.3. 26-Week Oral Carcinogenicity Study of Olmesartan Medoxomil in p53(+/-) Transgenic Mouse (Study #6839-105, Report #TRC 146-030) Vol. 23, 24

This GLP study was conducted by [redacted] for Laboratory Animal Science & Toxicology Laboratories at Sankyo Co., Ltd., Horikoshi, Fukuroi, Shizuoka-ken, Japan, between May 13 and November 13, 1998. This study was conducted to assess the potential toxicity and carcinogenic effects of olmesartan medoxomil (OM) when administered orally to p53(+/-) transgenic mice for 26 weeks. An additional group included with the study received the bladder carcinogen, *p*-cresidine, to confirm the model response to a known carcinogen.

Male and female C57BL/6TacfBR-[KO]N5 p53(+/-) heterozygous mice were used in the study. The animals were approximately 8 weeks old and weighed 18.5-26.8 g (males) or 16.3-21.6 g (females) at the time dosing was initiated. The animals were individually housed and received food and water *ad libitum*. The mice were assigned to five main study groups (15/sex/group) and four satellite (toxicokinetic) groups (3/sex/group). OM (lot No. NH206C) was suspended in 0.5% CMC and administered orally by gavage (10 ml/kg) to groups 2, 3 and 4 in the main study and satellite study at doses of 100, 300 or 1000 mg/kg/day, respectively (doses approved by the CAC; see attachment #2). Group 1, the negative control, received the vehicle. The remaining group (#5) in the main study was dosed with the positive control, *p*-cresidine (in corn oil), a urinary bladder carcinogen, at a dose of 400 mg/kg/day.

Observations and Measurements

All animals were observed twice daily for evidence of mortality and moribundity. Body weight and food consumption were recorded prior to treatment (day 1) and weekly thereafter. Hematology parameters were determined in all surviving rats (fasted overnight) at the end of the study. (Clinical chemistry parameters were not studied.) Blood samples were obtained from the orbital sinus under anesthesia. For toxicokinetics study, blood samples were collected from the abdominal vena cavas of anesthetized satellite mice 2 hr postdose during week 26. These animals were euthanized and discarded without further examination.

All animals in the main study that were found dead or sacrificed *in extremis* were weighed and subjected to a gross pathological examination. All surviving main study animals were weighed the day of scheduled necropsy. Selected organs were removed and weighed for all the rats. Histopathological examination was conducted on all organs and tissues from all animals in the control and the high dose groups and for any animal (any group) that died or was moribund sacrificed (Table 3.3.3.1). Histopathological examination of organs/tissues in the remaining low and mid dose group animals was limited to lung, liver, kidney and gross lesions. Only the urinary bladder (target tissue) was examined from the positive control group. Other preserved tissues were retained for possible future examination.