Results: Only information obtained up to Week 26 (interim sacrifice) was presented this report.

- Mortality and Clinical Signs - No deaths occurred. No remarkable clinical symptoms were attributable to the treatment.
- Food Consumption and Body Weights - There was no difference in mean accumulated body weight change during Weeks 1-26 between SC-58635 treated and control groups. However, some minor fluctuations in mean body weight change were noted in Group 5 ♀ at Week 3 (↑), Group 4 ♂ Week 26 (↓), and in Group 3 and 7 ♀ at Weeks 4 (↓) and 7 (↓), respectively. Food consumption values were significantly decreased in Group 4 ♂ at Week 15 by 17.4%.
- Rectal Body Temperatures and Respiration Rates - No remarkable differences were noted.
- ECG and - Normal.
- Ophthalmoscopic Examination - No treatment-related effects were seen.
- Clinical Laboratory Pathology - There were some statistically significant changes in hematology and serum chemistry parameters. But these changes were minor and values were within normal reference ranges.
- Gross and Histopathology -

  Gross Pathology:

  Ogan Weights: Significantly ↑ testes/epidimydes and heart to body weight ratios were noted for Groups 4 and 5 ♂, respectively. Group 3 ♀ had significaltly ↓ liver/gallbladder to body weight ratio.

  Microscopic Evaluation: All tissues from Groups 1 and 4 plus the testes and epidymides from Groups 2, 3, and 5 were examined microscopically. There were no treatment-related pathological changes identified.
- PK/TK - Only plasma SC-58635 concentration data of dogs in Groups 2-5 from Days 1 and 178 (Week 26) were included in the current report. Mean PK parameters of SC-58635 on Days 1 and 178 are listed in the following table.

Day	Dose mg/kg	N	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
			♂	♀	♂	♀	♂	♀
1	7.5	8	11.6	14.3	1.82	1.11	12.3	11
	12.5	8	14	14.3	2.17	1.00	20.8	8.49
	17.5	12	14.5	9.25	2.5	1.18	26.8	10.8
	25	8	2.63	2.44	1.36	1.36	15.1	11.6
178	7.5	8	14	11.5	1.15	1.6	12.6	14.4
	12.5	8	12.5	11.3	1.93	3.08	20.6	25.9
	17.5	12	14.9	11	2.79	2.58	29.7	22.3
	25	8	3.75	1.44	0.903	0.586	9.4	4.17

There was a sex difference in the plasma concentrations of SC-58635 on Day 1 of dose administration in the 12.5 (bid) and 17.5 (bid) mg/kg dose groups, with male dogs having higher concentrations of the test article than their female counterparts. There were no apparent differences in the plasma concentrations of SC-58635 between ♂ and ♀ dogs on Day 178 of dose administration.

There was a polymorphism (slow & fast clearance) associated with the metabolism of SC-58635 in dogs. The exposure to SC-58635, as measured by AUC, was greater in dogs characterized as having a slow clearance of SC-58635 than those dogs characterized as having a fast clearance of SC-58635. PK parameters analyzed by the rate of clearance are shown in the below table.

Day	Dose mg/kg	N	T_{max} (hr)				C_{max} (μg/ml)				AUC_{0-24} (μg•hr/ml)			
			Slow		Fast		Slow		Fast		Slow		Fast	
			♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	7.5	4	11.8	14.8	11.5	13.8	2.35	1.68	1.29	0.541	17.9	18.4	6.64	3.68
	12.5	4	15.5	14.5	12.5	14	2.71	1.37	1.63	0.643	28.2	11.9	13.4	5.05
	17.5	6	16	12.3	13	6.17	3.68	1.54	1.32	0.829	42.4	15.1	11.3	6.51
	25	4	3.75	3.13	1.5	1.75	1.99	1.89	0.726	0.821	31.6	17.8	2.67	5.33
178	7.5	4	13	8	15	15	1.55	2.28	0.746	0.918	18.5	2.38	6.75	5.03
	12.5	4	12.5	7.75	12.5	14.8	1.9	3.82	1.95	2.35	24.1	37.8	17.2	14
	17.5	6	15	7.58	14.8	14.5	3.82	3.41	1.77	1.76	47.4	33.8	12	10.9
	25	4	4.5	1.75	3	1.13	1.2	0.699	0.602	0.473	15.3	5.85	3.47	2.48

2.2.2.3. 52-Week Capsule Toxicity Study With SC-58635 In Dogs, Document No.: P30S4425; Date: 03-Mar-1997 (Vol. 1..31-1.32)

Included as an appendix to this report was:
Evaluation Of The SC-58635 Plasma Concentration Data From Week 52 Capsule Toxicity Study With SC-58635 In Dogs, SA4425 (Comparison With 26-Week Data), Document No.: M3097033; Date: 03-Mar-1997

Study Nº: SA4425
Report Nº: M3097033
Study Aim: (1) To identify toxic effects of SC-58635 when administered orally to dogs for at least 52 weeks and reversibility of any toxic effects of the test compound following a 4-week recovery period; (2) To determine the relationship of plasma concentration of test material to the duration of dosing; and (3) To evaluate evidence for sex-related differences in PK parameters.
Compound: SC-58635 (Lot Nº 94K014-A2B)
Vehicle: Empty gelatin capsule
Dosage: 0, 15, 25, and 35 mg/kg/day po for 52 weeks
Animals: 56 & 56 beagle dogs, ~7 months old, weighing 6.6-10.4 kg for ♂ and 4.8-9.3 kg for ♀.

Main and Recovery Study[a]				Satellite PK Study[b]			
Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals/Sex	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals/Sex
1	0	0	12	6	7.5	15	4
2	7.5	15	8	7	12.5	25	4
3	12.5	25	8				
4	17.5	35	12				
5	25.0	25	8				

[a] Dogs in Groups 1-4 & 6-7 received SC-58635 2x/day.
[b] Dogs in Groups 6 & 7 received [^{14}C]SC-58635 as 1st daily dose on Day1 and Weeks 26 and 52.

Study Location:

for the in-life portion of study and
for radioanalysis procedures.

Compliance with GLP/QAU: Yes
Study Date: Dosing started on 9/13/1995 (♂) and 9/20/1995 (♀); interim sacrifice (Groups 1-5, 4/sex/group): 3/14/1996 and 3/21/1996; terminal sacrifice: 9/12 and 9/13/1996 (Groups 1-5, 4/sex/group); recovery sacrifice: 10/17/1996 (Groups 1 and 4, 4/sex/group).
Experimental Design: Dogs were given SC-58635, 0, 7.5x2, 12.5x2, 17.5x2 or 25x1 mg/kg/day in gelatin capsule orally gavage for at least 52 weeks; dosing continued through the day before terminal sacrifice (Weeks 52). Recovery animals were kept without treatment for an additional 4

weeks. Dogs in the companion PK study group received [^{14}C]SC-58635 on Days 1, 176 & 358 and received nonradiolabeled SC-58635 on other days during the study. The following observations were conducted.

- Clinical Signs, Mortality, and Moribundity - 2x/day.
- Body weights - Day 1 Pre-R, and 1x/week afterwards.
- Food consumption - 1x/week.
- Physical examinations (including rectal temperatures and respiration rates) and ECGs (Leads I, II, and III, aVR, aVL, aVF, rV_2, V_2, V_4, and V_{10}) (including heart rates) - 1x before treatment and 1x 1-4 hr postdose during weeks 13, 26, 39 and 52.
- Ophthalmoscopic - pre-R and Weeks 26 and 52.
- Clinical Laboratory Evaluations - 1x pre-R and Weeks 13, 26, 39, 52 and 56. The parameters included in the clinical laboratory analysis are listed in the following table.

HEMATOLOGY				SERUM CHEMISTRY		
aPTT	WBC	MCH	Hb	ALT	Globulin	Glucose
PT	RBC	MCHC	Platelet Count	Albumin	Inorganic Phosphorus	
Differential WBC	Ht	MCV	Reticulocyte Count	Albumin/Globulin Ratio	Potassium	Sodium
URINALYSIS				Alkaline Phosphatase	Total Bile Acid	
Appearance/Color	Occult Blood		Ketones	AST	Total Bilirubin	
Bilirubin	pH		Urine Potassium	Calcium	Total Cholesterol	
Glucose	Protein		Urine Sodium	γ-Glutamyltransferase (γ-GT)	Total Protein	
Microscopic Examination Sediment			Total Volume	Chloride	Triglycerides	
Urobilinogen	Chloride		Urine Osmolality	Creatinine	Urea Nitrogen	

- PK/TK - Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 7, 12, 13, 14, 15, 18 and 24 hr following the ingestion of radiolabeled [^{14}C]SC-58635. Urine and fecal samples were collected for 168 hr after each radiolabeled dose approximate 24-hr intervals.
- Necropsies - all animals at the end of the study. The following organs were weighed. Organ-to-terminal-body-weight and organ-to-brain-weight ratios were calculated.

Adrenals	Liver with Drained Gallbladder	Prostate	Testes with Epididymides
Brain (with Brainstem)	Large Intestine (Cecum and Colon)	Thyroids (with Parathyroid)	
Heart	Ovary	Small Intestine (Duodenum, Jejunum, Ileum)	
Kidneys	Pituitary	Stomach	Uterus with Cervix

The following tissues (when present) from each animal were preserved in 10% neutral-buffered formalin. Microscopic evaluations were performed on all tissues from Groups 1 and 4 animals at all scheduled sacrifice.

Adrenals	Mammary Gland (♀ Only)		Gallbladder	Stomach
Aorta (Thoracic)	Ovaries	Liver	Lung	Thymus
Bone Marrow (Sternum)	Pancreas	Heart	Spinal Cord (Cervical, Mid-Thoracic, and Lumbar)	
Brain With Brainstem (Medulla Pons, Cerebella Cortex, and Cerebral Cortex)			Lymph Nodes (Mesenteric and Retropharyngeal)	
Colon, Cecum, Rectum	Pituitary	Skin	Thyroids (Parathyroid)	Testes with Epididymides
Duodenum, Jejunum, Ileum	Prostate	Spleen	Tongue	Trachea
Esophagus	Salivary Glands (Mandibular)		Urinary Bladder	Lesions
Eyes (Both with Optic Nerve)	Sciatic Nerve/Adjacent Muscle		Uterus with Cervix	Kidneys
Femur with Bone Marrow (Articular Surface of the Distal End)			Vagina	

Results: Only results from terminal and recovery sacrifices were presented in this report.

- Mortality and Clinical Signs - No deaths occurred. No remarkable clinical symptoms were attributable to the treatment. Sporadically, the following abnormal clinical signs were observed: emesis, soft, mucoid or discolored feces and dermological abnormalities.
- Food Consumption and Body Weights - There were no differences in body weights and body weight gains between SC-58635 treated and control dogs. Food consumption values were significantly decreased by17.4% in Group 4 ♂ at Week 15.

- Rectal Body Temperatures and Respiration Rates - No remarkable differences were noted.
- ECG - Normal.
- Ophthalmoscopic Examination - No treatment-related effects were seen.
- Clinical Laboratory Pathology - No significant changes were noted attributable to the treatment.
- Gross and Histopathology - No remarkable pathological changes were attributable to the treatment.
- PK/TK - SC-58635 was absorbed and was systemically available at all doses during the study. The mean PK parameters of SC-58635 on Days 1, 178 and 360 are summarized in the following table. SC-58635 plasma concentrations were similar on Day 178 and 360 indicating that a steady state was maintained during the last 6 months of the 1 year study. There was a sex difference in the plasma concentrations of SC-58635 on Day 1 of dose administration in the 12.5 (bid) and 17.5 (bid) mg/kg dose groups, with male dogs having higher plasma SC-58635 concentrations than female dogs. There were no apparent sex-related differences in the plasma concentrations of SC-58635 between ♂ and ♀ dogs on Days 178 or 360.

Day	Dose mg/kg	N	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
			♂	♀	♂	♀	♂	♀
1	7.5	8	11.6	14.3	1.82	1.11	12.3	11
	12.5	8	14	14.3	2.17	1.00	20.8	8.49
	17.5	12	14.5	9.25	2.5	1.18	26.8	10.8
	25	8	2.63	2.44	1.36	1.36	15.1	11.6
178	7.5	8	14	11.5	1.15	1.6	12.6	14.4
	12.5	8	12.5	11.3	1.93	3.08	20.6	25.9
	17.5	12	14.9	11	2.79	2.58	29.7	22.3
	25	8	3.75	1.44	0.903	0.586	9.4	4.17
360	7.5	4	17.3	12.8	1.26	1.38	14.2	16.1
	12.5	4	16.5	15.0	2.29	2.03	26.6	21.9
	17.5	8	16.9	14.6	2.32	2.26	27.3	21.7
	25	4	2.50	2.13	0.591	0.946	3.83	7.41

There was a polymorphism (slow & fast clearance) associated with the metabolism of SC-58635 in dogs. The exposure to SC-58635, as measured by AUC, was greater in dogs characterized as having a slow clearance of SC-58635 than those dogs characterized as having a fast clearance of SC-58635. PK parameters analyzed by the rate of clearance are shown in the below table.

Day	Dose mg/kg	N	T_{max} (hr)				C_{max} (μg/ml)				AUC_{0-24} (μg•hr/ml)			
			Slow		Fast		Slow		Fast		Slow		Fast	
			♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	7.5	4	11.8	14.8	11.5	13.8	2.35	1.68	1.29	0.541	17.9	18.4	6.64	3.68
	12.5	4	15.5	14.5	12.5	14	2.71	1.37	1.63	0.643	28.2	11.9	13.4	5.05
	17.5	6	16	12.3	13	6.17	3.68	1.54	1.32	0.829	42.4	15.1	11.3	6.51
	25	4	3.75	3.13	1.5	1.75	1.99	1.89	0.726	0.821	31.6	17.8	2.67	5.33
178	7.5	4	13	8	15	15	1.55	2.28	0.746	0.918	18.5	2.38	6.75	5.03
	12.5	4	12.5	7.75	12.5	14.8	1.9	3.82	1.95	2.35	24.1	37.8	17.2	14
	17.5	6	15	7.58	14.8	14.5	3.82	3.41	1.77	1.76	47.4	33.8	12	10.9
	25	4	4.5	1.75	3	1.13	1.2	0.699	0.602	0.473	15.3	5.85	3.47	2.48
360	7.5	2	18.0	10.5	16.5	15.0	1.73	2.10	0.782	0.667	16.7	28.9	7.87	3.35
	12.5	2	16.5	15.0	16.5	15.0	2.48	2.57	2.10	1.49	33.1	33.7	20.1	10.2
	17.5	4	17.3	13.8	16.5	15.5	3.0	3.22	1.64	1.30	41.3	33.2	13.4	10.2
	25	2	3.0	2.0	2.00	2.25	0.859	0.913	0.323	0.979	6.09	8.68	1.58	6.15

In summary, no treatment caused alterations were identified in all parameters examined; the MTD was not achieved in dog 13-, 26/52-week oral toxicity studies.

2.3. CARCINOGENICITY STUDIES

2.3.1. RAT STUDY

2.3.1.1. 104-Week Oral Gavage Carcinogenicity Study In Rats With SC-58635 (SA4367), Document No: P20S4367; Date: 19-Dec-1997 (Vol. 1.42 - 1.50)

Included as an appendix to this report is:
Pharmacokinetic Support For The 104-Week Oral Gavage Carcinogenicity Study In Rats With SC-58635 (SA4367), Document No.: M3097146; Date: 10- Dec-1997 (Vol. 1.50)

Study Nº: SA4367
Report Nº: P20S4367
Study Aims: To determine the carcinogenic potential of SC-58635 to rats by oral gavage for at least 104 weeks.
Compound: SC-58635 suspended in 0.5% Methylcellulose (400 cps) + 0.1% polysorbate 80 (Tween® 80) + distilled water

Lot Nº	Weeks Used	Expiration Date
94K014-A4A	1- 15	Not Indicated.
94K014-A2B	15- 27	August 1995
94K031-A3A	27- 51	November 1995
95K010-A1A	52- 67	May 1997
94K031-A2A	67- 92	November 1997
95K010-A1A	92- 105	May 1998

Vehicle Control: 0.5% methylcellulose (w/v) and 0.1% polysorbate 80 in distilled water.
Dose & Route: 0, 20, 80, and 400 mg/10 ml/kg/day po by gavage; As of Week 18, the dose level for the high-dose females was reduced to 200 mg/kg/day; as of Week 78, the dose levels for the low- and mid-dose females were reduced to 5 and 10 mg/kg/day, respectively, and for the high-dose males to 200 mg/kg/day.
Animals: Sprague-Dawley rats of the Crl:CD®BR strain
~6 weeks of age, weighing 178-273 g for ♂ and 127-197 g.
Study Site: (In-life) and (Plasma PK assessment).
In-Life Observation: 3/16/95 - 3/19/97;
Interim Sacrifice: 3/15/96 (Week 53)
Terminal Sacrifice: 3/14-19/97
GLP/QAC Compliance: Yes
Study Design: Rats were given SC-58635 in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 as a suspension once daily by oral gavage. Dose levels and group assignments are listed in the following table.

Group	Dose mg/kg/day					Nº of Animals		Animal Numbers	
	Wk 1-17	Wk 18-77		Wk 78-104					
	♂ & ♀	♂	♀	♂	♀	♂	♀	♂	♀
MAIN STUDY ANIMALS									
1 (Control)	0	0	0	0	0	80	80	B57665 - B57744	B57745 - B57824
2 (Low)	20	20	20	20	5	80	80	B57825 - B57904	B57905 - B57984
3 (Mid)	80	80	80	80	10	80	80	B57985 - B58064	B58065 - B58144
4 (High)	400	400	200	200	200	80	80	B58145 - B58224	B58225 - B58304
SATELLITE ANIMALS									
5 (Low)	20	20	20	20	5	26	26	B58305 - B58330	B58331 - B58356
6 (Mid)	80	80	80	80	10	26	26	B58357 - B58382	B58383 - B58408
7 (High)	400	400	200	200	200	26	26	B58409 - B58434	B58435 - B58460

* The last ten animals/sex/group were designated for the Week 53 interim sacrifice.

The doses selected in this study were based on the results of a 4-week oral gavage study at doses of 0, 20, 80, 400 and 600 mg/kg in which it was shown that absorption of SC-58635 attained a plateau

at dosages ≥400 mg/kg/day for ♂ rats (AUC_{0-24} for 400 and 600 mg/kg ♂: 195.9 and 97.6 on Day 1 and 60.7 and 58.2 μg•hr/ml on Day 26, respectively) and deaths were seen at 600 mg/kg/day for ♀ rats. The following parameters were monitored:

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - Weeks 1-52, 1x/4 weeks; Weeks 53-104, 1x/2 weeks.
- Body Weight and Food Consumption - 1x/pre-R; Weeks 1-26, 1x/week; Weeks 27-52, 1x/2 weeks; 1x/4 weeks thereafter.
- Ophthalmoscopic Examinations - 1x/pre-R.
- Clinical Pathology - Blood samples were collected at Weeks 53 (interim-sacrifice animals), 79 (all high-dose Main Study and Satellite ♀), and 104 (all surviving Main Study and Satellite animals) for hematology and serum chemistry analyses. Urine specimens were obtained from animals in individual urine collection cages. The specimens for routine urinalysis were obtained following 4 hours (±15 min) of collection. Collections continued for a total of 22 hours (±15 min) and the total volume was recorded after the final collection. The following parameters were determined:

HEMATOLOGY		SERUM CHEMISTRY	
aPTT	MCH	ALT	Inorganic Phosphorus
PT	MCHC	Albumin	Potassium
Differential Count and Cell Morphology	MCV	Albumin/Globulin Ratio	Protein Electrophoresis
WBC	Mean Platelet Volume	Alkaline Phosphatase	Sodium
RBC	Platelet Count	AST	Sorbitol Dehydrogenase
Ht	Reticulocyte Count	Calcium	Total Bilirubin
Hb		Chloride	Total Cholesterol
ROUTINE URINALYSIS		Creatinine	Total Protein
Appearance/Color	Occult Blood	Globulin	Triglycerides
Bilirubin	pH	Glucose	Urea Nitrogen
Glucose	Protein	URINE CHEMISTRY	
Ketones	Urobilinogen	Urine Sodium	Urine Osmolality
Microscopic Sediment		Urine Potassium	Total Volume

- PK/TK - Day 1, Weeks 26, 52, and 78. Whole blood was collected from the satellite study animals (3 /sex/group/time point) at 0.5, 1, 2, 3, 4, 6, 8, and 24 hours after dose administration. The plasma samples were stored at approximately -20°C until shipment to the Sponsor on dry ice. At Week 53, kidneys were collected from the Week 53 interim-sacrifice animals, frozen in liquid nitrogen and stored at -70°C until shipment. Analyses of the plasma, serum or tissue SC-58635 concentrations was performed by The concentrations of SC-58635 in plasma and serum were determined using a validated procedure with an assay sensitivity The concentrations of SC-58635 in kidney were determined using a non-validated procedure with an assay
- Gross and Histopathology - Necropsies were performed on animals sacrificed at moribund and the scheduled sacrificed animals (Weeks 53 and 104/105). The following organs from animals sacrificed at Week 53 were weighed at necropsy. Paired organs were weighed together. Organ-to-terminal-body weight and organ-to-brain weight ratios were determined.

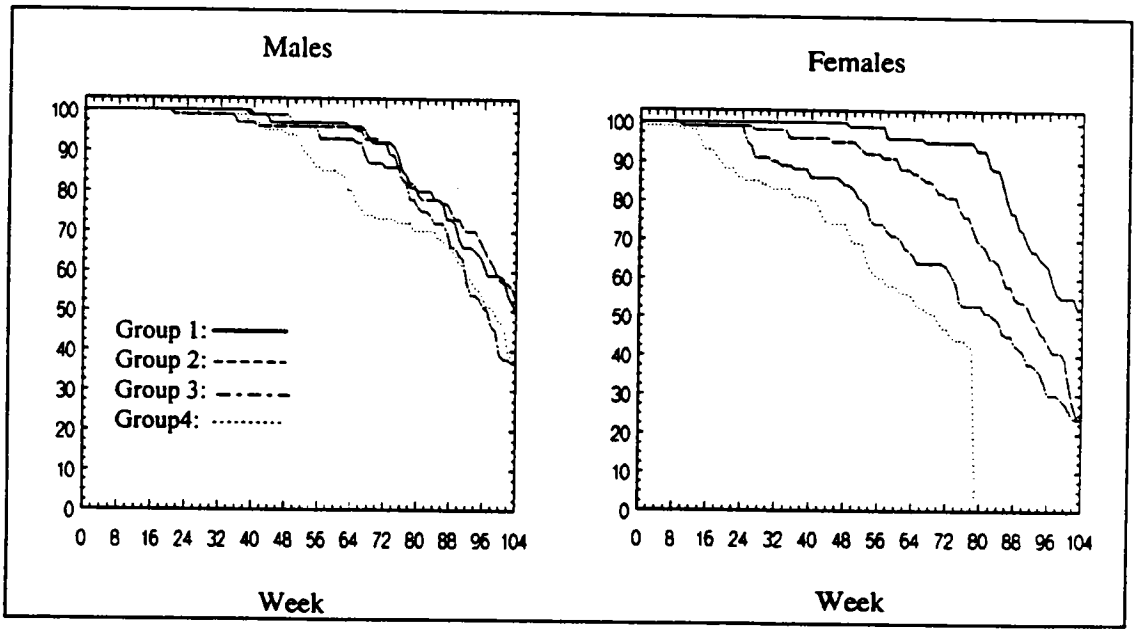
adrenals	ovaries	lung	stomach (empty)		thyroid with parathyroids (postfixation)	
brain (with brainstem)	heart	pituitary (postfixation)	testes with epididymides		uterus	
cecum (empty)	kidneys	prostate	thymus	colon (empty)	liver	spleen

The following tissues (when present) from all Main Study animals and selected Satellite animals were preserved in 10% neutral-buffered formalin. Microscopic examinations were performed on the preserved tissues from all animals in the Main Study and all Satellite animals that died after 4 February 1997 (Day 6 of Week 99).

Adrenals (Both)	Harderian Gland	Pancreas	Testes with Epididymides (Both)	
Aorta (Thoracic)	Heart	Pituitary	Thigh Musculature	
Bone Marrow (Femur and Sternum)	Kidneys (Both)	Prostate	Thymus	Tongue
Brain with Brainstem (Medulla/Pons, Cerebellar Cortex, and Cerebral Cortex)		Salivary Glands (Mandibular)	Thyroid (Parathyroids)	
Colon, Cecum, Rectum	Liver	Sciatic Nerve	Trachea	Urinary Bladder
Duodenum, Jejunum, Ileum	Lung (with Bronchi)	Seminal Vesicle	Ovaries (Both)	Stomach
Esophagus	Mammary Gland with Skin	Spinal Cord (Cervical, Mid-Thoracic, and Lumbar)	Gross Lesions	Spleen
Eyes (Both with Optic Nerve)	Mesenteric Lymph Node	Femur Including Articular Surface	Uterus with Vagina and Cervix	

Results:

- Mortality and Clinical Signs - Treatment-related deaths increased with dose and occurred in the mid- and high-dose ♂ and all treated female groups (Group 2: 4♀; Group 3: 4♂ & 20 ♀; Group 4: 19♂ & 31♀) with confirmed histopathological lesions of gastrointestinal necrosis with inflammation and associated peritonitis. The major clinical observations included higher frequencies of hypoactivity, few feces, cold to touch and dyspnea in the treated groups.



Statistical analyses of survival rates revealed a significant negative trend ($p<0.01$) in survival in both sexes; the mortality rates of the high-dose males and all treated female groups were significantly higher than control. Adjusted survival for ♂ and ♀ was plotted as proportion surviving versus time as shown in the above figures. The life-time mortality, including the survival data of the satellite groups, for each group is presented in the following table.

	Life-Time Mortality			
	Group 1	Group 2	Group 3	Group 4
♂	39/80	50/106	65/106	73/106
♀	37/80	77/106	77/106	60/106[a]

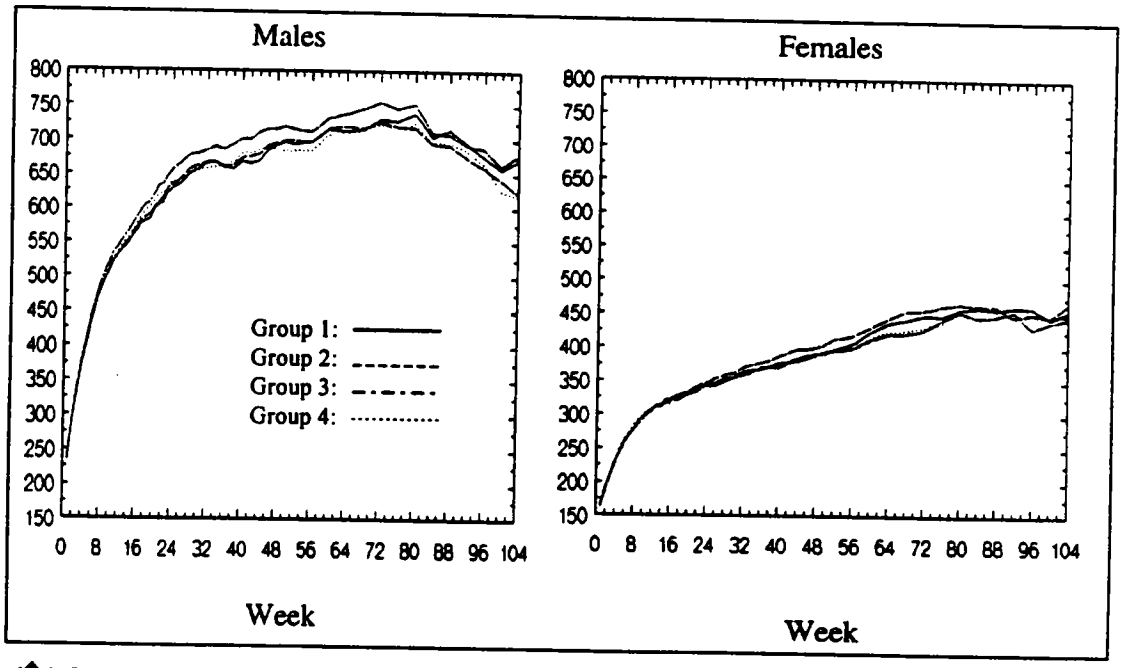
[a] Group 4 ♀ either died or were sacrificed during Week 79.

The incidence of deaths for the main study animals occurred at various stages during the study is listed in the following table. Due to excessive toxicity, high dose females were sacrificed at Week 79.

Group	1		2		3		4	
	♂	♀	♂	♀	♂	♀	♂	♀
UNSCHEDULED DEATHS								
Weeks 1-52	3	1	4	6	3	16	10	25
Weeks 53-78	12	3	11	15	14	20	13	20
Weeks 79-105	24	33	23	38	31	22	26	0
Total Deaths	39	37	38	59	48	58	49	45
SCHEDULED SACRIFICE								
Interim Kill (Week 53)	5	5	5	5	4	4	4	3
Terminal Kill	36	38	37	16	28	18	27	32[a]
Total	80	80	80	80	80	80	80	80

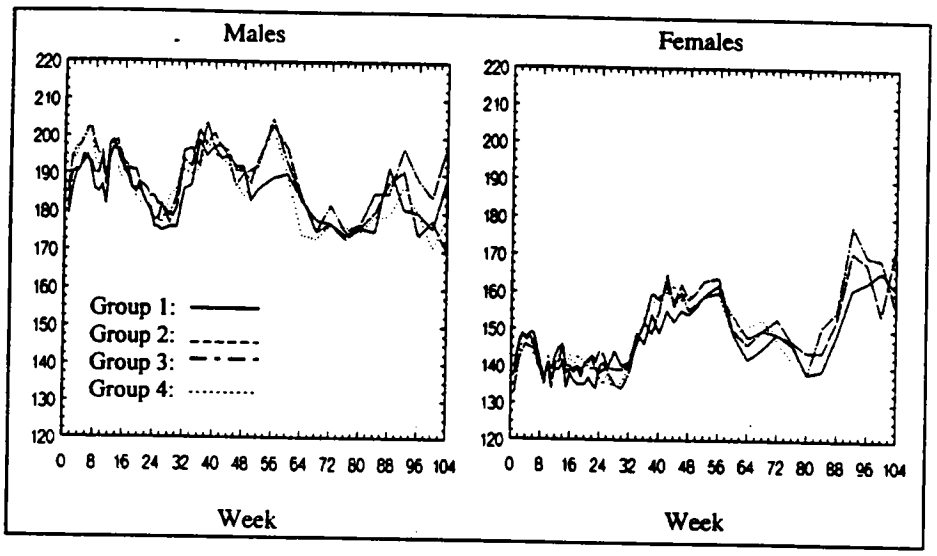
[a] Killed Week 79.

Body Weight and Food Consumption - Mean body weights for each group during the study are illustrated in the following two figures. Group 3 ♂ had significantly higher body weight values



(↑4-5%) during Weeks 18-46. Sporadic significant differences (↑ or ↓) in mean body weight change values were noted in SC-58635 treated groups when compared to the controls. Group 3 ♂ (Weeks 1-18, ↑7.9%) and Group 2 ♀ (Weeks 18-52, ↑23%) had higher interval total body weight change values. Significantly lower interval total body weight change values (↓20%) were observed in Group 4 ♂ at Weeks 18-52.

The mean food consumption values for the Group 3 and 4 ♂ over the first 12 weeks of treatment were higher than control (~5%). Comparable mean food consumption values of both sexes were observed for the rest of study. Interval total food consumption values for Weeks 1-18, 18-53, 1-78, and 1-104 were similar for all groups with the exception of a significantly higher mean value for the Group 3 ♂ at Weeks 1-18 (↑35.8%). Mean food consumption for each group during 2-year study are shown in the following figures.



- Clinical Pathology -

Hematology: No remarkable findings were identified during Weeks 53 and 79 analyses. Significantly ↑ WBC counts were noted all treated ♂ at Week 105 with values of $12.1x10^3/\mu l$, $14.7x10^3/\mu l$, $14.1x10^3/\mu l$, and $16x10^3/\mu l$ for Groups 1, 2, 3, and 4, respectively. In addition, Group 2 ♂ had ↓ in RBC (6.51 vs $8.19x10^6/\mu l$ in controls), Hb (11.5 vs 13.6 g/dl in controls) and Hct (33.9 vs 39.4% in controls) and an ↑ in the absolute reticulocyte count (0.23 vs $0.12x10^6/\mu l$ in controls).

Clinical Chemistry: Slight ↑ in β-globulin in Group 2-4 ♂ and α-2-globulin in Group 3 females were noted at Week 105. These changes were of low magnitude and not biologically significant. Significantly ↑ mean values were observed for inorganic phosphorus (6.6 vs 5.9 mg/dl), sodium (146 vs 145 meq/l), and chloride (102 vs 98 meg/l) in Group 3 ♀ and potassium (5.2-5.3 vs 4.8 meq/l) in Group 2 and 3 ♀ at Week 105. These values were within published biological ranges and might not have biological impacts.

Urinalysis: There were no significant findings between the groups at Weeks 53 and 79 and 105.

- PK/TK - SC-58635 was absorbed systemically. Female rats had higher C_{max} and AUC values than ♂ rats. Mean AUC and C_{max} values for each group on Days 1, 180, 359, and 541 are summarized in the following table. The exposure of the low and mid dose ♀ rats to SC-58635 was 2x of the values observed in ♂ rats. The exposure to SC-58635 in the high dose female rats, as measured by AUC_{0-24} was ~20 and 10x of that observed in humans at the doses of 200 and 400 mg/day, respectively. The exposure of the high dose ♂ rats to SC-58635 was ~10 and 5x of that observed in humans at 200 and 400 mg/day, respectively. At 104 Weeks sacrifice, serum SC-58635 concentrations were 0.321, 3.30 and 5.52 μg/ml for low, mid and high ♂ rats, respectively and were 3.08 and 1.24 μg/ml for the low and mid dose female rats, respectively. At the Week 53 interim sacrifice, kidney concentrations of SC-58635 were 3.37, 9.53 and 15.1 μg/g for ♂ rats and were 4.22, 13.0 and 12.8 μg/g for ♀ rats in the low, mid and high dose groups, respectively. These values were approximately 2-3x times higher than corresponding C_{max} concentrations of SC-58635 in plasma, indicating that the test article was distributed to the kidney.

Group	Dose mg/kg/day	PK Parameter	Day 1 (Wk1)		Day 180 (Wk 26)		Day 359 (Wk 52)		Day 541 (Wk 78)	
			♂	♀	♂	♀	♂	♀	♂	♀
Low	20 5	C_{max} (μg/ml)	1.93	2.65	2.16	3.41	2.00	4.75	1.45	1.11
Mid	80 10		3.42	5.63	3.09	7.46	2.88	7.44	0.893	2.00
High	400 200		6.09	10.1	4.62	7.93	4.71	9.47	4.28	13.0
Low	20 5	AUC_{0-24} (μg•hr/ml)	18.7	39.1	22.6	51.6	24.8	72.8	20.8	17.9
Mid	80 10		42.6	81.2	39.0	111	38.2	114	11.6	27.7
High	400 200		95.1	163	56.8	118	73.4	158	66.7	132

- Gross and Histopathology -

  Organ Weight: Organ weights were only recorded at interim Week 53 sacrifice. Significant increases in the kindey/brain (↑ 13.1%) and liver/body (↑ 12.9%) weight ratios were noted in Group 4 ♂. However, there were no corresponding histopathological lesions found during microscopic evaluations.

  Non-neoplastic Histopathological Findings:

  Unscheduled Deaths

  Dose-dependent GI necrosis/perforation (mainly in the jejunum) with associated abdominal inflammation and pyelonephritis were the only major treatment-related histomorphologic finding in unscheduled deaths during the study. The common causes of fatality are listed as followings:

Most Common Causes of Death	Group							
	1		2		3		4	
	♂	♀	♂	♀	♂	♀	♂	♀
Pituitary Neoplasm	13	20	13	37	12	20	7	4
GI Necrosis/Inflammation	0	0	0	4	4	20	19	31
Mammary Neoplasm (s)	1	9	1	9	0	12	0	1
Chronic Progressive Nephropathy	4	1	3	2	5	0	5	2
Pyelonephritis	0	0	2	0	2	0	4	0
Lymphoma	2	1	4	0	1	0	1	0

Inflammation of the serosal surface of abdominal viscera including the capsule of the spleen, liver, lung, heart (♀ only), pancreas (♀ only), kidneys, urinary bladder, and sex-organs was commonly observed as a secondary effect of test article-related necrosis in the gastrointestinal tract. A low but statistically significant increase in the incidence of pyelonephritis was identified in ♂ rats only (2/38, 5/49, 6/49 in Groups 2, 3, 4, respectively). In addition, dose-dependent pathological changes in the thymus with characteristics of lymphoid depletion, chronic active inflammation and necrosis were noted for ♀ but not ♂. These kind of alterations have been observed in notably stressed rats prior to death or animals treated with compounds possessing immunotoxic properties. Observations in this study were not likely caused by treatment-induced immunotoxicity as there were no similar findings seen in the scheduled sacrificed animals. Incidence of GI pathological changes for each group are listed in the following table.

Microscopic Findings	Unscheduled Deaths	Group 2		Group 3		Group 4	
		♂	♀	♂	♀	♂	♀
GI Necrosis/Inflammation	Weeks 1-52		2		13	2	19
Abdominal Inflammation				1		1	3
GI Necrosis/Inflammation	Weeks 53-78		1	2	7	10	12
GI Necrosis/Inflammation	Weeks 79-105		1	2 (1)[a]	(1)	7 (1)	

[a] Numbers in the parentheses represent data from the Satellite animals.

Interim Sacrifice

No treatment-related microscopic findings were identified in the sections from interim sacrificed rats (Week 53).

Terminal Sacrifice

For rats sacrificed at termination of study, test article-related findings of small intestinal necrosis and inflammation were present in the jejunum of one Group 3 male and in two Group 4 males. In addition, small intestinal necrosis with fibrosis and inflammation were present in two Group 2 females.

The incidence of major non-neoplastic findings (statistically significant at 5 or 1%) for each group, including data from the Satellite animals, during entire period of study are summarized in the following table.

Non-neoplastic Findings	Incidence Rates							
	Group 1		Group 2		Group 3		Group 4	
	♂	♀	♂	♀	♂	♀	♂	♀
Duodenum - Congestion	0/80	0/80	0/95	4/90	1/92	16/90**	5/86**	22/80**
Duodenum - Serosa, Chronic Active Inflammation	0/80	1/80	0/95	2/90	6/92**	5/90	16/86**	6/79*
Jejunum - Congestion	0/80	1/80	0/94	3/90	1/90	12/90**	4/86**	17/79**
Jejunum - Necrosis	0/80	0/80	0/94	4/90	4/90**	18/90**	13/86**	28/79**
Jejunum - Serosa, Chronic Active Inflammation	0/80	0/80	1/94	1/90	10/90**	4/90**	18/86**	5/79**
Ileum - Congestion	0/80	1/80	0/95	1/90	0/92	4/90	3/86**	8/79**
Ileum - Necrosis	0/80	0/80	0/95	7/90*	0/92	15/90**	6/86**	21/79**
Ileum - Serosa, Chronic Active Inflammation	0/80	0/80	1/95	7/90*	6/92**	15/90**	19/86**	21/79**
Stomach, Nonglandular - Hyperplasia	3/79	5/80	8/95	10/90	7/92	6/89	9/86	8/79
Stomach, Nonglandular - Serosa, Chronic Active Inflammation	0/79	0/80	0/95	1/90	3/92*	4/89*	9/86**	19/79**
Stomach, Nonglandular - Necrosis	0/79	0/80	0/95	0/90	1/92	3/89*	3/86*	6/79**
Stomach, Glandular - Erosion	8/79	11/80	9/95	14/90	20/92*	16/90	20/86**	2/79
Stomach, Glandular - Serosa, Chronic Active Inflammation	0/79	0/80	0/95	2/90	5/92**	12/90**	12/86**	16/79**
Colon - Serosa, Chronic Active Inflammation	0/80	0/80	1/95	3/90	8/92**	11/90**	15/86**	20/80**
Cecum - Edema		0/80		2/90		3/90		4/80*
Cecum - Congestion	0/80	1/80	5/95*	6/90	5/92*	3/90	7/85**	4/80
Cecum - Necrosis	0/80	0/80	4/95	5/90	5/92*	3/90	6/85*	7/80*
Cecum - Serosa, Chronic Active Inflammation	0/80	0/80	1/95	2/90	4/92*	13/90**	14/85**	22/80**
Rectum - Serosa, Chronic Active Inflammation		0/80		0/90		1/88		4/80**
Kidney - Capsule, Chronic Active Inflammation	1/80	0/80	0/95	1/90	1/92	7/90**	8/86**	15/80**
Kidney - Pyelonephritis	0/80		4/95		5/92*		6/86*	
Lung - Congestion	30/80	20/80	40/95	44/90**	41/92	42/90**	45/86*	39/80**
Lung - Leukocytosis	5/80	4/80	5/95	6/90	10/92	13/90*	22/86**	14/80**
Lung - Diffuse Pneumonitis	0/80		0/95		6/92**		3/86*	
Lung - Pleura, Chronic Active Inflammation		0/80		1/90		4/90*		6/80**
Lung - Thrombosis	1/80		0/95		2/92		4/86*	
Heart - Epicardium, Chronic Active Inflammation		0/80		3/90		6/90**		7/80**
Spleen - Hyperplasia, Myeloid	0/80	0/80	1/95	3/90	3/92*	1/89	7/86**	9/80**
Spleen - Capsule, Chronic Active Inflammation	0/80	0/80	1/95	1/90	9/92**	16/89**	19/86**	24/80**
Liver - Capsule, Chronic Active Inflammation	0/80	0/80	2/95	3/90	8/92**	18/90**	20/86**	28/80**
Pancreas - Inflammation, Chronic Active	0/80	0/80	3/95	2/88	8/92**	20/89**	24/86**	31/80**
Mesenteric Lymph Node - Lymphangiectasis	1/80		5/93		10/90**		5/85*	
Mesenteric Lymph Node - Hyperplasia, Lymphoreticular	0/80	0/79	3/93	4/89	8/90**	8/90**	15/85**	20/80**
Mesenteric Lymph Node - Inflammation, Chronic Active	0/80	0/79	1/93	3/89	4/90*	11/90**	13/85**	14/80**
Testis - Tunics, Chronic Active Inflammation	0/80		1/95		6/92**		7/86**	
Epididymis - Inflammation, Chronic Active	0/80		1/95		1/92		9/86**	
Seminal Vesicle - Inflammation, Chronic Active	9/80		9/95		13/91		24/86**	
Urinary Bladder - Serosa, Chronic Active Inflammation	1/80	0/78	1/95	1/89	5/92*	12/88**	15/86**	17/80**
Marrow, Sternum - Hyperplasia, Myeloid	21/80		30/95		42/92**		43/86**	
Marrow, Femur - Hyperplasia, Myeloid	21/79		29/95		41/90**		43/86**	
Ovary - Inflammation, Chronic Active		0/79		1/90		15/90**		17/80**
Uterus - Serosa, Chronic Active Inflammation		0/79		3/90		10/90**		9/80**
Cervix - Serosa, Chronic Active Inflammation		0/79		0/90		2/89*		5/78**
Thymus - Congestion	15/71	10/69	23/89	26/79**	22/83	29/81**	26/75*	23/70**
Thymus - Depletion, Lymphoid	7/71	2/69	10/89	5/81	6/83	15/81**	13/75	20/70**
Thymus - Inflammation, Chronic Active		0/69		1/81		2/81		3/70*
Thymus - Necrosis		1/69		0/81		3/81		5/69*
Brain w/ Stem - Congestion	16/80	9/80	16/95	13/90	14/92	21/90*	24/86	20/80**

*p<0.05; **p<0.01

Neoplastic Findings: There were no statistical differences in the incidence of neoplastic lesions between controls and animals treated with SC-58635.

Incidence of major neoplastic findings for each group (including data from the Satellite animals) is listed in the following table.

Neoplastic Findings	Incidence Rates							
	Group 1		Group 2		Group 3		Group 4	
	♂	♀	♂	♀	♂	♀	♂	♀
Adrenal, Medulla - Primary Benign Pheochromocytoma	5/80	0/78	7/95	0/89	6/92	1/89	7/86	0/78
Brain w/ Stem - Primary Benign Granular Cell Tumor	0/80		3/95		1/92		0/86	
Pituitary - Primary Benign Adenoma	43/80	55/80	50/95	65/90	47/90	48/90	36/86	29/80
Pituitary - Primary Malignant Carcinoma	0/80	9/80	1/95	9/90	1/95	4/90	2/86	2/80
Pancreas - Primary Benign Islet Cell Adenoma	5/80	5/80	9/95	4/88	8/92	2/89	6/86	1/80
Pancreas - Primary Malignant Islet Cell Carcinoma	3/80		3/95		7/92		1/86	
Testes - Primary Benign Interstitial Cell Tumor	1/80		3/95		1/92		4/86	
Hematoneoplasia - Primary Malignant Lymphoma	2/80	2/80	6/95	3/90	1/92	1/90	1/86	0/80
Thyroid - Primary Benign "C' Cell Adenoma	8/80	10/80	12/94	10/90	10/91	7/90	8/86	4/80
Uterus - Primary Benign Endometrial Stromal Polyps		0/79		3/90		2/90		0/80
Uterus - Endometrial Stromal Polyps/Carcinoma		1/79		3/90		2/90		0/80
Mammary - Primary Benign Fibroadenoma	2/80	40/78	3/95	32/80	2/92	29/80	3/86	9/79
Mammary - Primary Malignant Carcinoma	1/80	19/78	1/95	13/80	0/92	12/80	0/86	5/79
Mammary - Primary Benign Fibroadenoma and/or Primary Malignant Carcinoma		46/78		41/80		36/80		13/79

Based on presented findings, administration of SC-58635 to rats for 104 weeks did not cause an increase in the incidence for all examined tumors. It did induce GI lesions (necrosis/perforation/inflammation with secondary peritonitis) at all does levels for ♀ and >20 mg/kg/day for ♂. In addition, increased incidence of pyelonephritis were noted in treated male. The NOAEL for ♂ rats was 20 mg/kg. The NOAEL for ♀ rats could not be established under current study since treatment-related deaths occurred at all tested doses.

2.3.2. MOUSE STUDY

2.3.2.1. Dietary Admix Carcinogenicity Study Of SC-58635 In The Mouse (SA4452), Document No: P30S4452; Date: 05- Mar- 1998 (Vol. 1.33 -1.41)

Included as an appendix to this report is:
Evaluation Of Plasma SC-58635 Concentration Data For The Dietary Admix Carcinogenicity Study Of SC-58635 In The Mouse (SA4452), Document No.: M3097237; Date: 10-Mar-1998 (Vol. 1.38)

Study Nº: EHL95107/SA4452
Report Nº: P30S4452
Study Aims: To determine the carcinogenic potential of SC-58635 when administered ad libitum in the diet to mice for at least 104 weeks.
Compound: SC-58635, Lot Nº GDS-4695-042
Dose and Route: 0, 25, 50, and 75 mg/kg/day in the diet for ♂ and 0, 50, 100, and 150 mg/kg/day in the diet for ♀.
Animal: CD-1 mice 5 to 6 weeks of age, weighing 20.8-32.7 g, 90/sex/group for the toxicology, 65/sex/group for the PK study.
Study Site:
In-Life:
Tissue Processing & Microscopic Examinations:

Plasma PK Assessment:
In-Life Observation: 11/28/95 - 12/01-05 & 08/97
Interim Sacrifice: 11/25-26/96 (Days 364 & 365)
Terminal Sacrifice: 12/01-05 & 08/97 (Days 735, 736, 737, 738, 739, and 742)
GLP/QAC Compliance: Yes

Study Design: The dosages and animal grouping are shown in the following table.

Group	Dose (mg/kg)					Animals/Sex/ Group	Animals/Sex		
	♂		♀				Interim Sacrifice	Terminal Sacrifice	
	Wk1-18	Wk 19-104	Wk1-18	Wk19-22	Wk 23-104		Week 53	Week 80	Week 105-106
TOXICOLOGY ANIMALS									
N	0[a]	0	0	0	0	90	10	-	All Survivors
1	25	12.5	50	25	25	90[b]	10	-	All Survivors
2	50	25	100	50	50	90[b]	10	-	All Survivors
3	75	37.5	150	75	150	90	10	All Survivors	-
PHARMACOKINETIC ANIMALS									
4	0	0	0	0	0	20	-	All Survivors	-
5	25	12.5	50	25	25	65	-	-	-
6	50	25	100	50	50	65	-	-	-
7	75	37.5	150	75	150	65	-	All Survivors	-

[a] Control animals received the basal diet only.

[b] Week 92, surviving Pharmacokinetics males in Groups 5 (4♂ & 6♀) and 6 (4♂ & 4♀) were transferred to Toxicology Groups 1 and 2, respectively.

The following observations were conducted.

- Clinical Signs, Mortality and Moribundity - 2x/day.
- Detailed Observations - 1x/week for visible and/or palpable masses.
- Body Weights and Food Consumption - 2x/pre-R; 1x/week 1st 26 weeks (6 months), 1x/2 weeks for the 2nd 6 months, and 1x/4 weeks thereafter.
- Clinical Pathology - Weeks 53, 80, and 105 to 106. Blood was collected from randomly selected 10 animals/sex/group in the Toxicology groups and from all animals in the control PK group (Week 80 only). The following listed variables were determined from the plasma. Parameters in Priority List 1 were analyzed first followed by those in Priority List 2. Blood smears were prepared for all animals sacrificed at Week 53 but not examined.

PRIORITY 1		PRIORITY 2		
ALT	Total Protein	AST	Glucose	Total Bile Acids
Albumin	Alkaline Phosphatase	Chloride	Potassium	Total Bilirubin
BUN	Inorganic Phosphorus	Cholesterol	Sodium	Triglycerides
Creatinine	Calcium	Globulin (Calculated Value)	Sorbitol Dehydrogenase	

- Test Article Bioavailability - Days 3-4 and Weeks 19, 52, and 78. Blood was collected at approximately 2400, 0600, 0900, and 1500 hours from three animals/sex/group in Groups 5, 6, and 7 and at 0900 hours from three animals/sex in Group 4.
- Necropsy - Unscheduled deaths, scheduled interim (Week 53, toxicology study animals, 10/sex/group) and terminal sacrifices (Weeks 105 and 106: toxicology animals, Groups N, 1, 2, 3, and Pharmacokinetics Group 4). Due to poor survival, all surviving high-dose (Group 3) animals were sacrificed during Week 80. In addition, surviving PK control animals (Group 4) were sacrificed at Week 80 to provide age-matched control tissues. The following listed tissues or representative samples were collected and preserved in 10% buffered formalin. Tissues designated with a single asterisk were weighed at the Week 53 scheduled sacrifice. Paired organs were weighed together. All masses and any lesions with possible histopathological correlates were retained. The identity of masses was maintained. Bone marrow smears were prepared and stained with Wright's stain from specimens collected from each animal sacrificed moribund and from all animals at scheduled necropsies. These smears were not examined.

Aorta	*Liver With Gallbladder Drained	Seminal Vesicle
*Adrenal Glands (Weighed Post Fixation)	*Lungs	Skin (Caudal, Abdominal Region)
Bone, Femur (Including Articular Surface)	Lymph Node, Submaxillary	Spinal Cord (Lumbar)
Bone, Sternum (Including Marrow)	Lymph Node, Mesenteric	*Spleen
Bone Marrow Smear (Except for Animals Found Dead)	Mammary Gland (Females Only, Attached To Skin)	*Stomach
*Brain	Nasal Turbinates	*Testes
*Cecum	*Ovaries	*Thymus
*Colon	Pancreas	Tongue
*Epididymides (Both)	*Pituitary Gland (Weighed Post Fixation)	Trachea
Esophagus	*Prostate	Urinary Bladder
Eyes With Harderian Gland	Salivary Gland, Submaxillary	*Uterus (With Cervix)
*Heart	Sciatic Nerve	Vagina
*Intestine, Small (Duodenum, Jejunum, Ileum)	Skeletal Muscle	Lesions And Masses
*Kidneys	*Thyroid Glands (with Parathyroid; Weighed Post Fixation)**	
**The parathyroid was weighed with the thyroid and was examined microscopically if it was included in the section of thyroid.		

- Histopathology - All tissues collected from the Toxicology animals (Groups N, 1, 2, and 3) and the Pharmacokinetics control animals (Group 4) that were sacrificed and necropsied at Week 80, were shipped to for processing and histopathologic examinations. Histological sections of all protocol-defined tissues and all lesions were prepared, stained with haematoxylin and eosin, and examined from all mice sacrificed by design during Weeks 53, 80, and 105-106, and from any Toxicology animal that died or was sacrificed moribund during the study. For each Toxicology animal that died or was sacrificed moribund, an apparent cause of moribundity or death was determined. This evaluation included whether a tumor or tumors contributed to the cause of death.

Results:

- Group Mean Dosages - Test article dosages were calculated using body weight data, food consumption data, and dose formulation information. Based on these calculations, the mean dosages for the study ranged as presented in the following table.

Dose Group	Intended Dosage (mg/kg/day)		Actual Dosage (mg/kg/day)	
	♂	♀	♂	♀
Low	25	50	22.85 - 25.64	40.31 - 55.74[b]
	12.5	25	11.69 - 13.42	19.58 - 27.67
Mid	50	100	45.02 - 51.55[b]	72.83 - 114.65[b]
	25	50	23.48 - 26.58	35.95 - 56.12
High	75	150	67.48 - 84.77	112.62 - 170.08
	37.5	75[a]	33.67 - 40.35	56.26 - 75.48

[a] Weeks 19 through 22

[b] During Weeks 2 and 3, calculated dosages were 70.65 and 70.39 mg/kg/day, respectively, for the mid-dose males; 63.03 and 70.73 mg/kg/day, respectively, for the low-dose females; and 56.38 and 54.52 mg/kg/day, respectively, for the mid-dose females.

- Mortality and Clinical Signs - Test article related-deaths were noted in all SC-58635 treated groups. The incidences of treatment-related deaths increased as the dosage increased. Observations of urine-stained hair, intra-abdominal swelling, distended abdomen, piloerection, decreased defecation, and pale appearance were frequently noted for animals that died or were sacrificed in a moribund condition. Survival for ♂ and ♀ was statistically analyzed by life table methods using the National Cancer Institutes Package[4,5]. Adjusted survival was computed using the Kaplan-Meier product limit estimation method and was plotted as proportion surviving versus time as illustrated in the following figures.

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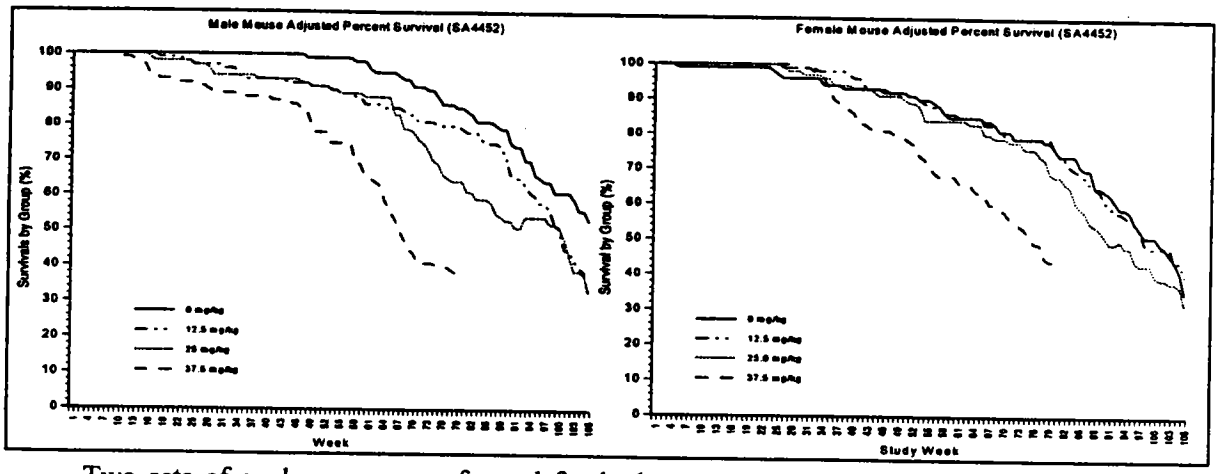
4 D. G. Thomas, N. Breslow, and J.J. Gart, 1977. Trend and homogeneity analyses of proportions and life table data, Comput. Biomed. Res., 10: 373-381.

5 J.J. Gart, D. Krewski, P.N. Lee, R.E. Tarone, and J. Wahrendorf, 1986. Statistical Methods in Cancer Research, Vol. III, The Design and Analysis of Long-Term Animal Experiments, Oxford University Press.



Two sets of analyses were performed for both sexes. In the first set, survival for Groups N through 3 were analyzed through Week 80 (termination of high dose group). In the second set, survival was analyzed for Groups N, 1 and 2 up to Week 106 (terminal sacrifice). Significantly reduced survivals were noted in low-, mid-, and high dose ♂, and high dose ♀. The survivals for each group are summarized in the following table. **Due to excessive toxicity, high dose group animals were sacrificed at Week 80.**

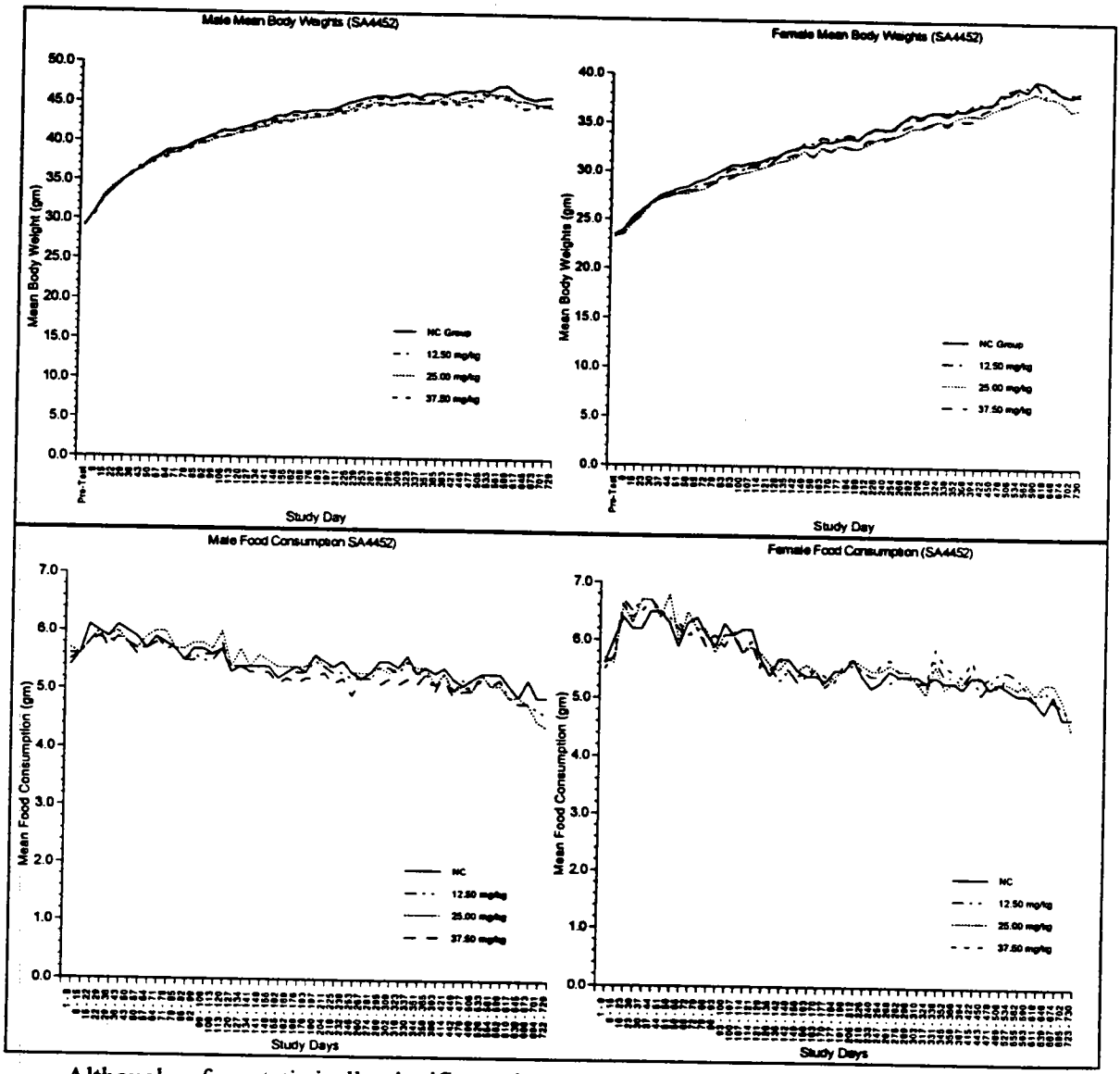
Group	Dose (mg/kg)		Week 80				Week 106			
	♂	♀	♂		♀		♂		♀	
N	0	0	68/79	86%	61/79	77%	39/73	53%	26/73	36%
1	12.5	25	63/80	79%	61/79	77%	26/78	33%**	32/79	41%
2	25	50	50/80	63%	54/80	68%	26/78	33%**	25/78	32%
3	75	150	29/80	36%**	35/80	44%**	-		-	

** Statistically significant, $p<0.01$

- PK/TK - SC-58635 was orally absorbed and systemically available at all doses during the study. Exposure of SC-58635, as measured by C_{max} and AUC_{0-24}, increased with dose and is shown in the following table. Male and female animals within each dose group were similarly exposed to test article on Day 3-4 of the study. However, on subsequent sampling days (Week 19, 52 and 78) plasma concentrations of SC-58635 were lower in female than in male mice when compared within each dose group for the low, mid and high doses.

Week (Days)	Dose (mg/ kg)					T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
	Wk1-18	Wk 19-104	Wk1-18	Wk19-22	Wk 23-80						
	♂		♀			♂	♀	♂	♀	♂	♀
1 (3- 4)	25	12.5	50	25	25	9	9	0.973	0.807	11.1	12.3
	50	25	100	50	50	9	9	1.73	2.73	22.0	29.9
	75	37.5	150	75	150	9	9	2.55	2.65	34.7	33.8
19 (126- 127)	25	12.5	50	25	25	18	9	0. 865	0.555	13.5	7.05
	50	25	100	50	50	9	18	1.75	0. 815	32.8	14.3
	75	37.5	150	75	150	9	9	2.69	0.699	50.8	13.8
52 (357- 358)	25	12.5	50	25	25	9	15	0.328	0. 290	6.43	4.31
	50	25	100	50	50	9	9	0.723	0.558	13.2	8.14
	75	37.5	150	75	150	9	9	1.24	0.967	22.8	17.6
78 (540- 541)	25	12.5	50	25	25	9	9	0.479	0.335	9.22	5.99
	50	25	100	50	50	9	9	0.933	0.813	16.4	12.9
	75	37.5	150	75	150	15	9	1. 22	1.84	25.0	26.5

- Body Weight and Food Consumption - There were no test article-related effects on body weight, cumulative body weight gain, and food consumption as depicted in the following figures.



Although a few statistically significant decreases in mean body weights for mid-and high-dose females (96% to 98% of control) during the first 13 weeks of the study and cumulative body weight gains for the high-dose ♂ and the low-, mid- and high-dose ♀ during 1st week of study, for the mid-dose ♀ at Week 10, and for the high-dose ♀ at Weeks 2 and 3 and Weeks 9 to 13 were observed, these changes were not considered toxicologically significant as the differences were transient, sporadic. There were occasional statistically significant differences (↑ or ↓) in food consumption for all treated groups compared to the control group. All changes seen were within published ranges[6] and were not considered biologically significant.

- Clinical Chemistry - No treatment-related changes in clinical chemistry parameters were observed. Although statistically significant differences were observed in a few parameters, these

6 Andress, J.M, 1992. The Mouse: Toxicology. In: Animal Models in Toxicology, eds., Gad S.C., Chengelis, C.P. New York: Marcel Dekker, Inc., p. 165-232.

changes were either of low magnitude or non-dose dependent and might not have any biological impact. The changes seen were as followings:

Changes	Chemistry Parameter	Group	Week	Observation
↑	Ca	mid- and high-dose ♀	53	↑ 5%
	Globulin	high-dose ♂	80	↑ 22%
	Triglycerides	low-dose ♀	105-106	↑ 49%
	Total Protein	mid-dose ♀	105-106	↑ 11.5%
	K	mid-dose ♀	105-106	↑ 18%
↓	Total Bilirubin	high-dose ♀	80	↓ 36%
	Glucose	high-dose ♀	80	↓ 26%
	Albumin	high-dose ♂ & ♀	80	↓ 10 and 16%, respectively
	Bile Acids	mid-dose ♀	105-106	↓ 37%

Several individual animals in all dose groups (including control) at scheduled or moribund sacrifices showed slight to marked alterations in a few clinical chemistry parameters. These changes usually correlated with the presence of spontaneous, age-related lesions and/or moribundity as evidenced by gross and/or histopathologic evaluations.

- Necropsy Findings -

Unscheduled Deaths (found dead, moribund sacrifice, unscheduled sacrifice): Treatment-caused macroscopic lesions were observed in the GI tract (glandular stomach, small and large intestine). These lesions were characterized as erosion/ulceration and/or perforation of one or more segments of gastrointestinal tract, abdominal visceral adhesions, and abnormal peritoneal contents (due to leakage of gastrointestinal contents into the peritoneal cavity). The following table summarizes the incidence of macroscopic gastrointestinal lesions (erosion/ulceration, perforation and associated changes) in mice that died or were sacrificed in a moribund condition.

Group	N	1	2	3	4	5	6	7
♂	1/35	3/52	14/52	27/51	0/1	0/13	7/13	3/9
♀	1/48	3/48	8/53	33/45	0/3	0/11	3/11	7/14
Total	2/83	6/100	22/105	60/96	0/4	0/24	10/24	10/23

Histologic examinations were performed on Toxicology animals only (Groups N, 1, 2, and 3). Microscopic changes observed in GI included ulceration, erosion, and necrosis of GI mucosa and chronic active inflammation of serosal surfaces (peritonitis) of the abdominal viscera. Morphologic changes as described above were also identified in two control animals; these were considered to be spontaneously occurring age-related lesions occasionally seen in the gastrointestinal tract of aging laboratory mice.

Scheduled Sacrifices:

Week 53 Interim Sacrifice (Groups N, 1, 2, and 3): Treatment-related macroscopic findings included small intestinal (jejunum or ileum) adhesions or mass/nodule in 4 animals (1 Group 1 ♂, 1 Group 3 ♂, 1 Group 2 ♀, and 1 Group 3 ♀). These lesions have microscopic characteristics of chronic active inflammation of the mucosa and/or serosa (peritonitis). The jejunal mass/nodule in another high-dose male was Peyer's patch hyperplasia. All other gross findings were commonly seen in CD-1 mice of this age and occurred with similar incidence among control and SC-58635-treated groups.

Week 80 Terminal Sacrifice (Groups 3 and 4): Treatment-related toxicological findings at Week 80 were gastrointestinal (stomach, jejunum) adhesions and/or ulceration/erosion in the high-dose group (3 ♂ and 6 ♀) with microscopic characteristics of mucosal erosion/ulceration and/or chronic active inflammation of the serosa (peritonitis). All other gross findings were commonly seen in CD-1 mice of this age and occurred with similar incidence among control and SC-58635-treated groups.

Weeks 105-106 Terminal Sacrifice (Groups N, 1, and 2): At terminal necropsy, treatment-related GI changes (gastrointestinal adhesions and/or ulceration/erosion) with microscopic characteristics of mucosal erosion/ulceration and/or chronic active inflammation of the serosa (peritonitis) were seen in Group 2 animals (5♂ & 1♀). All other findings at were commonly seen in CD-1 mice of this age and occurred with similar incidence between control and SC-58635-treated groups.

- Histopathology -

Non-neoplastic Lesions: Treatment-caused histpathological changes were limited to the GI tract. The following table summarizes the incidence of erosion/ulceration in one or more segments of gastrointestinal tract at various sacrifice intervals.

Sacrifice Intervals		N		1		2		3	
		♂	♀	♂	♀	♂	♀	♂	♀
Wk 53	Nº Examined	10	10	10	10	10	10	10	10
	Incidence	0	0	0	0	1	0	1	1
Wk 80	Nº. Examined	0	0	0	0	0	0	29	35
	Incidence	-	-	-	-	-	-	2	5
Wk 105/106	Nº. Examined	45	32	32	38	32	31	-	-
	Incidence	0	1	1	1	2	1	-	-
Unscheduled	Nº. Examined	35	48	52	47	52	53	51	45
Deaths	Incidence	1	1	3	3	6	6	19	20
Total Incidence		1	2	4	4	9	7	22	26

Gastrointestinal tract sites include glandular stomach, duodenum, jejunum, ileum, cecum, and colon. Glandular stomach lesions of animals in this table were all perforating ulcers (Grade 5).

Treatment-related GI lesions (erosion/ulceration with associated chronic active inflammation) were observed in the glandular stomach, duodenum, jejunum, ileum, cecum, and colon at one or more sites, mainly present in the glandular stomach, jejunum and ileum. The severity and distribution of these GI lesions were dose-dependent. GI injury noted in animals that died or were sacrificed at moribund was more severe than those seen at scheduled sacrifice. Chronic active inflammation of the serosal surfaces (peritonitis) of several abdominal organs secondary to the GI injury was also noted. The most common involved tissues in serosal inflammation were: GI tract, adrenals, pancreas, kidney, gall bladder, ovary, uterus, seminal vesicles, urinary bladder, mesenteric lymph nodes, and liver.

Occasionally, microscopic GI lesions were observed in a few animals with no gross morphologic alterations and vice versa. The following table presents the combined total incidence (gross and/or microscopic) of treatment-induced gastrointestinal lesions. Glandular stomach lesions included in this table were perforating ulcers (Grade 5 lesions) only.

	Group		
	1 (Low-Dose)	2 (Mid-Dose)	3 (High-Dose)
♂	5	21	32
♀	4	10	40

The gastrointestinal lesions with or without associated chronic active inflammation of serosal surfaces (peritonitis) of abdominal viscera (as described in SC-58635-treated animals) were also observed in some control animals. These were considered spontaneous lesions occasionally seen in the gastrointestinal tract of aging laboratory mice.

The GI injury was the most common cause of death in high-dose animals. Some animals in the mid- and low-dose groups also died of test article-related GI injury. Other common causes of death as evaluated by macro- and microscopic examinations were: amyloid deposition, lymphoma, and mouse urologic syndrome (a common spontaneous finding in male mice). The incidence of common causes of death, other than treatment-related GI injury, was similar in all

groups or was within the historical data published for CD-1 mice[7,8]. **Amyloidosis occurs frequently in aged CD-1 mice and is the major cause of death. It appears to begin as a deposition of amyloid in the submucosa of the duodenum, jejunum, and ileum. In severe cases, many other organ are also involved; involvement of the glomeruli of kidneys is usually the cause of death in animals that die with amyloidosis[9].**

The following table lists the most common causes of death in male and female mice as evidenced by pathologic evaluations.

Pathological Findings	N		1		2		3	
	♂	♀	♂	♀	♂	♀	♂	♀
Gastrointestinal Lesions[a]	0	1	2	2	8	5	24	30
Amyloid Deposition	5	5	5	0	4	4	3	1
Lymphoma	8	7	4	7	4	8	2	2
Mouse Urologic Syndrome	6	-	17	-	9	-	7	-
Multiple Causes[b]	8	7	15	12	19	7	6	3

[a] Includes animals with erosion/ulceration of the glandular stomach or intestine chronic inflammation of the serosa surfaces (peritonitis) of various abdominal tissues

[b] Multiple causes (include any combination of GI lesions, amyloid deposition, inflammatory lesions in skin, urinary tract, other tissues, and/or lymphoma, and various other neoplasms).

Other common lesions observed in SC-58635-treated male and/or female mice with slightly higher incidence compared with control included: increased hematopoiesis in the spleen, myeloid hyperplasia in the sternal and femoral bone marrow, hematopoiesis in the liver, and leukocytosis in the liver and lung. These findings occurred mainly in animals with gastrointestinal injury and/or prominent neoplastic or inflammatory lesions in various tissues. These findings were considered secondary changes in response to inflammation and/or tissue damage. A decreased incidence of several non-neoplastic (e.g., amyloidosis and mineralization in brain, eye, and testis) lesions was also observed in the high-dose groups (♂: 37.5 mg/kg/day; ♀: 150 mg/kg/day). This decrease was attributable to the shorter lifespans in these groups as high test article-related motality observed and earlier group termination (Week 80). The incidence of test article-related gastrointestinal lesions was statistically significant for ♂ & ♀ in the mid-and high-dose groups. In addition, the incidence of chronic active inflammation of serosal surfaces of abdominal organs, secondary hematopoietic changes in bone marrow, spleen, liver, and lung, and decreased incidence of several spontaneous neoplastic and non-neoplastic lesions were statistically significant in one or more treatment groups. Low and statistically non-significant incidence of pyelonephritis was observed in SC-58635 treated ♂ mice (0/97, 6/94, 2/94, 3/90 for Groups N, 1-3, respectively) that died or sacrificed at moribund. **Although this observation was not dose-related and occured at very low incidence, treatment-attributable nephrotoxicity could not be ruled out as nephropathy was observed in mice treated with this compound at 1000 mg/kg for 2 weeks. In addition, pyelonephritis was commonly seen in animals treated with NSAIDs.**

The incidence of major non-neoplastic findings (statistically significant at 5 or 1%) for each group, including data from the Satellite animals, during entire period of study are summarized in the following table.

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7 Maita, K., Hirano, M., Harada, T., Mitsumori, K., Yoshida, A.; Takahashi, K., Nadashima, N., Kitazawa, T., Enomoto, A., Inui, K., Shirasu, Y,1988. Mortality, major cause of moribundity, and spontaneous tumors in CD-1 mice, Toxicol Pathol, 16(3): 340-349.

8 Chandra, M. and C.H. Frith, 1992. Spontaneous neoplasms in aged CD-1 mice, Toxicol Letters, 61: 67-74.

9 Frith, C.H., Goodman, D.G., and Boysen, B.G., 1992. The Mouse; Pathology. In: Animal Models in Toxicology, eds., Gad S.C., Chengelis, C.P. New York: Marcel Dekker, Inc., p. 165-232.

Non-neoplastic Findings	Incidence Rates							
	Group N		Group 1		Group 2		Group 3	
	♂	♀	♂	♀	♂	♀	♂	♀
Adrenal - Serosa, Inflammation, Chronic Active	1/97	1/95	1/94	3/95	3/94	1/94	13/90**	14/90**
Bone Marrow, Femur - Hyperplasia, Myeloid	19/97	24/95	29/94	34/95	38/94**	26/94	27/90*	43/90**
Bone Marrow, Sternum - Hyperplasia, Myeloid	28/97	26/95	39/94*	34/94	48/94**	31/94	35/90*	43/90**
Brain - Cerebrum, Infiltrate, Lymphocytic, Perivascular	0/97		0/94		2/94		2/90	
Epididymis - Serosa, Inflammation, Chronic Active	1/97		1/94		1/93		3/90	
Gallbladder - Serosa, Inflammation, Chronic Active	0/96	0/91	1/92	1/94	1/90	1/93	4/89*	8/87**
Intestine-large, Cecum - Serosa, Inflammation, Chronic Active	0/97	0/95	1/94	1/94	0/94	2/94	3/90	11/90**
Intestine-large, Colon - Serosa, Inflammation, Chronic Active	0/97	0/94	2/94	0/93	0/94	1/94	3/90	9/90**
Intestine-small, Duodenum - Erosion/Ulceration		0/95		1/94		1/94		2/90
Intestine-small, Duodenum - Serosa, Inflammation, Chronic Active	0/97	0/95	0/94	0/94	5/94	3/94*	1/90	6/90**
Intestine-small, Ileum - Erosion/ulceration	0/97	0/95	1/94	2/95	5/94**	5/94**	6/90**	9/90**
Intestine-small, Ileum - Serosa, Inflammation, Chronic Active	3/97	0/95	1/94	3/95	8/94*	7/94	13/90**	20/90**
Intestine-small, Jejunum - Erosion/ulceration	1/97	2/95	1/94	1/95	5/94*	0/94	6/90**	9/90**
Intestine-small, Jejunum - Serosa, Inflammation, Chronic Active	1/97	2/95	2/94	1/95	11/94**	4/94	11/90**	20/90**
Kidney - Pyelonephritis	0/97		6/94		2/94		3/90	
Kidney - Serosa, Inflammation, Chronic Active	1/97	0/95	1/94	1/95	3/94	3/94	7/90**	7/90**
Liver - Hematopoiesis	4/97	13/95	21/94	16/95	15/94**	18/94	28/90**	33/90**
Liver - Hepatocellular Hypertrophy, Centrilobular	1/97		3/94		3/94		3/90	
Liver - Hepatocellular Necrosis	6/97		5/94		6/94		9/90	
Liver - Leukocytosis	2/97	6/95	2/94	5/95	3/94	7/94	9/90**	20/90**
Liver - Serosa, Inflammation, Chronic Active	1/97	0/95	0/94	2/95	4/94	3/94	9/90**	16/90**
Lung - Leukocytosis	1/97	7/95	1/93	7/95	3/94	8/94	10/90**	17/90**
Lymph Node, Mesenteric - Hyperplasia, Lymphoid	3/95	1/91	6/91	3/94	8/90	5/91*	9/82**	5/86*
Lymph Node, Mesenteric - Inflammation, Chronic Active	6/95	3/91	7/91	3/94	6/90	3/91	8/82	6/86
Lymph Node, Mesenteric - Serosa, Inflammation, Chronic Active	3/95	0/91	0/91	2/94	2/90	3/91	6/82*	15/86**
Mammary Gland - Inflammation, Chronic Active		0/94		0/95		0/91		4/89*
Nasal Turbinate - Respiratory Mucosa, Cyst	0/96		0/92		0/91		4/83**	
Ovary- Serosa, Inflammation, Chronic Active		2/94		2/95		3/93		15/90**
Pancreas - Serosa, Inflammation, Chronic Active	2/97	2/95	2/94	2/95	9/94**	5/94	17/90**	24/90**
Seminal Vesicle - Serosa, Inflammation, Chronic Active	0/97		3/94		1/94		10/90**	
Spleen - Hematopoiesis, Increased	21/97	52/95	36/93*	55/94	48/92**	46/93	39/90**	66/90*
Spleen - Serosa, Inflammation, Chronic Active	1/97		2/93		0/92		5/90*	
Stomach - Glandular, Erosion/Ulceration		5/95		5/95		9/94		26/90**
Stomach - Glandular, Inflammation, Chronic Active		0/95		0/95		3/94*		2/90*
Stomach - Serosa, Inflammation, Chronic Active	2/97	1/95	3/94	3/95	6/94	6/94*	23/90**	34/90**
Urinary Bladder - Concretion	0/97		0/94		0/94		3/90*	
Urinary Bladder - Serosa, Inflammation, Chronic Active	1/97	0/94	0/94	0/95	0/94	1/93	6/90**	11/90**
Uterus - Serosa, Inflammation, Chronic Active		0/95		0/95		3/94*		7/90**

*p<0.05; **p<0.01

Neoplastic Lesions: Treatment of SC-58635 did not increase the incidence of all examined tumors. The incidence of spontaneous common neoplasms was similar and statistically non-significant between control and SC-58635 treated groups. An apparent positive trend in the incidence of pars distalis adenoma of the pituitary in the females (p=0.0192) was observed. It is not statistically significant as pituitary adenoma is a common tumor in female CD-1 mice (0-8% with a mean of approximately 4%). All other neoplastic lesions did not exhibit a clear dose-related increase in incidence or severity. The following table shows major neoplastic findings (incidence rates) for each group.

Neoplastic Findings	Group N		Group 1		Group 2		Group 3	
	♂	♀	♂	♀	♂	♀	♂	♀
Adrenal Gland: Subcapsular Cell Adenoma (I)	3/97	0/95	2/94	1/95	6/94	0/94	0/90	1/90
All Tissues: Lymphoma (I+F)	11/97	14/95	11/94	17/95	8/94	13/95	3/90	3/90
All Tissues: Hemagioma	0/97	3/95	3/94	1/95	1/94	3/94	0/90	0/90
All Tissues: Hemagiosarcoma	4/97	5/95	3/94	3/95	10/94	4/94	2/90	1/90
Lung: Bronchiolar/Alveolar Adenoma/Carcinoma (I+F)	32/97	18/95	32/93	26/95	29/94	19/94	10/90	3/90
Pituitary, Pars Distalis Adenoma (I+F)	1/94	2/92	0/94	4/93	1/92	5/89	1/90	2/88*

I = Incidental; F = Fatal.

Therefore, dietary administration of SC-58635 to mice for ≥104 weeks caused gastrointestinal toxicity and mortality in all dose groups and it is not carcinogenic as similar incidence of examined tumors was noted in all groups. Non-dose dependent pyelonephritis was only observed in drug-treated ♂ with low incidence rates. The dosages used in this carcinogenicity assessment study exceeded a Maximum Tolerated Dose (MTD) in all treatment groups and the NOAEL for either ♂ or ♀ could not be determined.