during the 24-hr period following Day 1 and 2x during the 24-hr period following Days 37 and 86. Fecal and urine samples (3/sex/group) were collected for 7 days after dosing with [^{14}C]SC-58635 (Days 1, 37, and 86).

- Necropsy - Days 93/94, the end of the study; the following organs (from scheduled sacrifice animals only) were weighed at necropsy: adrenals, brain (with brainstem), cecum (empty), colon (empty), heart, kidneys, liver, lungs, ovaries, pituitary (postfixation), prostate, spleen, stomach (empty), testes with epididymides, thymus, thyroid with parathyroids (postfixation), uterus; the following tissues (when present) from each main and recovery study animal were preserved in 10% neutral-buffered formalin: adrenals (both), aorta bone marrow (femur and sternum), brain with brainstem (medulla/pons, cerebellar cortex, and cerebral cortex), colon, cecum, rectum, duodenum, jejunum, ileum, esophagus, eyes (both with optic nerve), femur including articular surface, harderian gland, heart, kidneys (both), lesions, liver, lungs (with bronchi), mammary gland with skin, mesenteric lymph node, ovaries (both), pancreas, pituitary, prostate, salivary glands (mandibular), sciatic nerve, seminal vesicle, spinal cord (cervical, mid-thoracic, and lumbar), spleen, stomach, testes with epididymides (both), thigh musculature, thymus, thyroid (parathyroids), tongue, trachea, urinary bladder, uterus with vagina and cervix.

Results:

- Mortality & Clinical Observation - Two rats, 1♂ at 20 mg/kg/day and 1♀ at 80 mg/kg/day, died during the study due to blood sampling accident and gavage error, respectively. No other clinical findings were remarkable.
- Body Weight & Food Consumption - Group 4 ♂ had significantly higher mean body weight values during Weeks 4 (Day 26) and 11 and significantly higher mean body weight changes during Weeks 1 (Days 5-8), 4 (Days 22-26), 5, and 10. During the recovery phase, significantly higher mean body weight values were noted for Group 2 males at Weeks 15, 16, 17, and 18. Group 4 ♂ had significant increases in mean food consumption (Weeks 1, 2, 3, 4, 9, 10, 11, and 12) and total food consumption (Weeks 1-13).
- Ophthalmology - No remarkable treatment-related changes were noted.
- Clinical Pathology - One male each at 20 and 80 mg/kg had marked elevations in ALT (524 and 574 U/l, respectively), AST (640 and 815 U/l, respectively), and sorbitol dehydrogenase (SDH) (134 and 136, respectively) at Week 18. Similarly, elevated ALT, AST, and SDH (~2-3x relative to control values) were noted in females at Weeks 6 and/or 14 (1 @ 20, 2 @ 80 and 3 @ 400 mg/kg). Although correlated histopathological lesions were not identified, these changes as results of the administration of the test article could not be ruled out. The urinalysis findings were generally unremarkable and comparable between the groups at Weeks 6, 14, and 18.
- Pathology & Histology - Test article-related histomorphologic alterations were observed in the liver and kidneys at the terminal sacrifice. Minimal to slight change in the liver with centrilobular to midzonal hepatocellular enlargement was seen in both high dose ♂ and ♀ rats. Minimal or slight degeneration of the renal papilla was noted in 1♂ @ 80 mg/kg/day and 3♂ @ 400 mg/kg/day but not in ♀ or rats in recovery phase. There were no treatment-related microscopic changes in the GI tract.
- PK/TK -

  Absorption: SC-58635 was absorbed systemically. Exposure of SC-58635, as measured by AUC and Cmax increased with dose but the increases were not dose-proportional. There were differences in the pharmacokinetics of SC-58635 between male and female rats in that plasma SC-58635 concentrations (C_{max} and AUC) were higher in ♀ rats than ♂ rats. The pharmacokinetics of SC-58635 did not change as a result of repetitive dose administration except in the 400 mg/kg dose group where plasma SC-58635 levels decreased with duration of dosing. The mean PK parameters are shown in the following table.

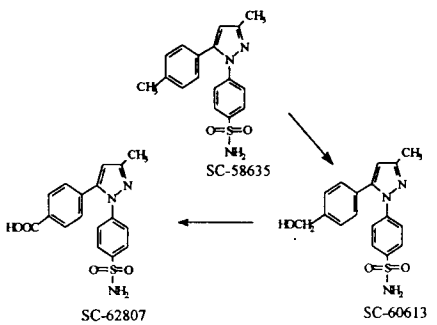
Day	Dose	T_{max} (hr)			C_{max} (μg/ml)			$AUC_{0-\infty}$ (μg•hr/ml)		
	mg/kg	♂	♀	♂ + ♀	♂	♀	♂ + ♀	♂	♀	♂ + ♀
1	20.0	3.00	13.00	3.00	2.47	2.91	2.69	22.0	38.3	30.1
	80.0	6.00	6.00	6.00	3.79	5.99	4.89	42.4	83.5	62.9
	400	6.00	6.00	6.00	6.50	11.6	9.05	78.8	149	114
42	20.0	3.00	3.00	3.00	1.68	3.06	2.37	17.6	36.9	27.3
	80.0	4.00	3.00	3.00	2.58	6.86	4.53	23.4	90.3	56.8
	400	8.00	4.00	4.00	4.36	6.80	5.25	66.1	100	83.2
91	20.0	3.00	6.00	3.00	1.75	2.20	1.89	18.9	34.2	26.5
	80.0	4.00	6.00	2.00	2.49	4.26	3.28	36.3	75.4	55.8
	400	8.00	2.00	2.00	3.91	7.19	5.32	58.3	105	81.5

Radioactivity in Plasma and RBC: Concentrations of radioactivity in the cellular fraction of blood were much higher than in plasma. Following oral administration of 20, 80, and 400 mg/kg of [^{14}C]SC-58635 to animals on Day 1 and Weeks 6 and 13, plasma C_{max} occurred from 3 to 8 hours postdose. The plasma C_{max} increased non-proportionally with increasing dose concentrations. Plasma T_{max} increased with dose. The peak levels were higher in females than males. The T_{max} radioactivity in red blood cells occurred from 2 to 8 hours postdose. The C_{max} were higher in ♀ than ♂.

Excretion: The major route of excretion of radioactivity was through the feces. Following administration of 20, 80, and 400 mg/kg of [^{14}C]SC-58635 on Day 1 and Weeks 6 and 13, the percentage of the dosed radioactivity excreted in the feces ranged from 72.1% to 92.2% over the 168-hour collection period with urinary excretion accounting for 1.51% to 9.18%. As the dose increased, the percentage of dosed radioactivity excreted in the feces generally increased. No changes were observed in the excretion pattern following Day 1 and Weeks 6 and 13 of the dosing regimen. The following table reveals % of radicactive dose in urine, feces, cage rinse, cage wash, cage wipe, and urine wipe at specified intervals postdose for rats following a single oral dose of [^{14}C]SC-58635 on Day 1 and Weeks 6 and 13.

	% of Radioactive Dose								
	Dose	Urine		Feces		Cage Rinse		Total	
	mg/kg	♂	♀	♂	♀	♂	♀	♂	♀
Day 1	20	5.48 ± 2.45	7.59 ± 3.70	87.7 ± 3.42	72.1 ± 11.7	5.66 ± 3.69	15.4 ± 11.6	99.2 ± 0.90	95.9 ± 0.05
	80	3.34 ± 0.42	3.66 ± 1.15	81.5 ± 22.5	80.9 ± 8.48	12.2 ± 17.2	10.6 ± 8.2	98.0 ± 4.77	95.4 ± 1.66
	400	2.11 ± 1.83	1.69 ± 0.87	79.7 ± 17.4	87.4 ± 6.02	9.12 ± 12.5	5.25 ± 2.34	91.5 ± 2.88	94.8 ± 3.11
Week 6	20	9.18 ± 3.10	6.70 ± 1.74	88.5 ± 2.01	78.7 ± 12.9	1.59 ± 0.49	9.37 ± 7.40	99.9 ± 1.98	97.3 ± 2.47
	80	4.90 ± 3.67	3.42 ± 0.91	84.8 ± 2.53	83.3 ± 7.87	4.80 ± 4.32	5.35 ± 2.95	95.1 ± 0.31	93.5 ± 5.45
	400	1.51 ± 0.47	1.71 ± 0.21	90.2 ± 1.92	90.5 ± 6.47	1.62 ±2.25	4.05 ± 0.85	93.6 ± 1.74	97.1 ± 5.57
Week 13	20	9.06 ± 5.39	4.74 ± 1.98	82.4 ± 1.80	83.8 ± 3.49	1.79 ± 1.19	3.09 ± 1.97	94.1 ± 3.96	92.5 ± 2.32
	80	2.69 ± 1.34	3.28 ± 0.65	88.5 ± 3.90	85.7 ± 6.20	1.89 ± 2.26	3.34 ± 2.23	93.7 ± 3.61	94.2 ± 1.04
	400	1.93 ± 0.83	1.56 ± 0.96	90.6 ± 6.87	92.2 ± 4.74	3.93 ± 5.12	3.47 ± 2.85	96.5 ± 1.11	97.5 ± 1.17

Metabolic Profiles in Blood, Urine and Feces: The majority of the radioactivity circulating in plasma was [^{14}C]SC-58635. [^{14}C]SC-60613, the hydroxylated metabolite of [^{14}C]SC-58635, was also found to circulate in plasma at approximately 1-10% of plasma radioactivity. There were no detectable differences in high performance liquid radiochromatography (HPLRC) distribution of plasma radioactivity between doses or duration of dosing. The majority of the 0-24 hr urine radioactivity was excreted as [^{14}C]SC-62807 (carboxylated metabolite) with no significant differences between sex, dose or duration of dosing. The majority of the fecal radioactivity excreted in the feces was [^{14}C]SC-62807 and [^{14}C]SC-58635 (hydroxylate metabolite). Mean percentages of dose excreted as



[^{14}C]SC-58635, [^{14}C]SC-60613 and [^{14}C]SC-62807 in feces on Days 1, 42, and 91 are summarized as follows.

Day	Dose (mg/kg)	% SC-62807		% SC-60613		% SC-58635	
		♂	♀	♂	♀	♂	♀
1	20	48.7	43.0	1.31	0.730	31.9	26.8
	8	31.6	26.3	1.05	1.09	47.5	50.0
	400	12.2	9.60	0.334	a	65.6	77.0
42	20	62.8	47.4	1.48	3.07	23.1	25.7
	80	33.2	28.0	1.09	2.47	41.0	50.5
	400	2.36	13.2	0.918	0.450	85.3	75.6
91	20	38.3	35.8	0.940	2.67	39.6	42.1
	80	19.5	22.2	0.662	2.26	67.6	60.2
	400	9.40	9.38	a	0.459	78.6	81.2

a No peak detected.

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DOG STUDIES

2.2.1.6. Four Week Oral Capsule Toxicity Of SC-58635 In The Dog With Reversal, Document No: PSA-95S-4260; Date: 18-Jan-1995 (Vol. 1.15-1.16)

Included as an appendix to this report were:

1. Evaluation Of The SC-58635 Plasma Concentration Data From The Four Week Toxicity Study Of SC-58635 In The Dog, SA4260, Document No.: MRC-94S-0185; Date: 17-Nov-1994
2. Report Amendment No. 1: Four-Week Oral Capsule Toxicity Of SC-58635 In The Dog With Reversal Document No.: PSA95S-31-SA4260; Date: 17-May-1995

Study Nº: SA4260
Report Nº: PSA-94S-4260
Study Aim: To evaluate the potential toxic effects of SC-58635 and to assess the reversibility of potential toxic effects
Compound & Dose Form: SC-58553 (Lot Nº 94K014-A1B) in gelatin capsule
Dose & Route: 20, 25, 50, 100 and 250 mg/kg/day in gelatin capsule, oral
Animals: ♂ & ♀ beagle dogs, 9 - 11 months old, weighing 9.5 to 14.3 kg, 4 or 8/sex/group
Study Location: G.D. Searle, Skokie, IL
Compliance with GLP/QAU: No
Study Design:

Group		Dose (mg/kg)	Nº Animals /Sex/Group	Nº Animals/Sex Sacrificed	
				Day 17	Days 29-31
Toxicology Study	1	0	4 (4)*	-	8
	2	25	4	-	4
	3	50	4	-	4
	4	100	4 (4)*	4	4
	5	250	4 (4)*	4	4
PK Study**	6	25	2		
	7	100	2		

*The number in the parenthesis indicating the number of animals were used in the 2 week reversal phase study.
**Animals in group 6 & 7 were treated with [^{14}C]SC-58635.

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The animals in group 4, 5 and 7 and 4/sex from group 1 were treated 15 doses. The animals in group 2, 3, 6 and the remaining 4/sex from group 1 were treated a minimum of 28 doses. The following parameters were monitored:

- Clinical signs and mortality - 2x/day
- Body Weight - 2x before dosing, Day 1 and 1x/week thereafter.
- Food Consumption - 1x/week.
- Ophthalmological Examination - Days -2 and 28.

- EEG (10 lead: I, II, III, aVR, aVL, aVF, rV2, V2, V4, and V10) - Days -15/-16, 8, and 23.
- Hematology & Clinical Chemistries - Days -6/-7, 2, 9, 10, and 29/30/31.
- Urinalysis - Days-14/-15 and 29/30/31.
- Template Bleeding Time - Days -6/-7, 17, and 29/30/31.
  The whole blood was analyzed for the following parameters: activated partial thromboplastin time and prothrombin time. The following table listed the parameters performed during clinical pathology analysis.

HEMATOLOGY PARAMETERS			URINALYSIS PARAMETERS	
White Blood Cells		MCH	Bilirubin	pH
Differential WBC		MCHC	Glucose	Protein
Red Blood Cells		Mean Platelet Volume	Ketones	Urobilinogen
Hemoglobin (Hb)		Platelets	Occult Blood	Volume
Hematocrit (Ht)		Reticulocytes	Osmolality	Urine Sediment Microscopic Examination
MCV		(Days 16 And 29-31)		
CLINICAL CHEMISTRY PARAMETERS				
ALT	Albumin	Creatinine	Potassium	Total Bilirubin
Alkaline Phosphatase		Globulin	Sodium	Total Protein
AST	Calcium	Glucose	Sorbitol Dehydrogenase	Triglycerides
Chloride	Cholesterol	Inorganic Phosphorus	Total Bile Acids	Urea

- PK/TK - Non-radioactive Component: Days 1 (Groups 1-5) and 27 (Groups 1-3) at 30 minutes and 1, 1.5, 2, 2.5, 3.5, 5, 7 and 24 hr after dosing; Day 15 (Groups 4 and 5) at 2.5, 3.5 and 24 hr; and Days 29-31 prior to necropsy. Radioactive Component: Days 1 & 28 (Group 6) and Days 1 & 15 (Group 7 animals) at ~30 min, and 1, 1.5, 2, 2.5, 3.5, 5, 7 and 24 hr after administration of the radioactive dose. Feces and urine samples were collected for 7 days after the ^{14}C administration.
- Necropsy - Days 17 (interim sacrifice) and 29/30/31. The following listed tissues (when present) or representative samples were collected from all animals and preserved in 10% buffered formalin. The organs (when present) marked with an asterisk were weighed at scheduled necropsy; organs of animals found dead or moribund sacrificed were not weighed. Paired organs were weighed together.

Aorta	*Heart	Pancreas	*Stomach
*Adrenal Glands (Both)	Intestine, Small (Duodenum, Jejunum, Ileum)		*Testes (Both)
Bone, Femur (Including Articular Surface)	*Intestine, Large (Cecum, Colon)	*Pituitary Gland	*Thymus
Bone, Sternum (Including Marrow)	*Kidneys (Both)	*Prostate	*Thyroid Glands** (Both)
Bone Marrow Smear (Not Examined)	*Liver	Salivary Gland, Mandibular	Tongue
*Brain	*Lungs (Both)	Sciatic Nerve	Trachea
*Epididymides (Both)	Lymph Node, Retropharyngeal	Skeletal Muscle	Urinary Bladder
Esophagus	Lymph Node, Mesenteric	Skin	*Uterus
Eyes (Both)	Mammary Gland (♀ Only)	Spinal Cord (Lumbar)	Vagina
Gallbladder	*Ovaries (Both)	*Spleen	Lesions

**The parathyroids were weighed with the thyroids and examined microscopically if they were included in the thyroid sections.

Results:

- Clinical Observation and Mortality - One ♂ & ♀ dogs dosed at 25 mg/kg had black stool during on Days 18 & 19. One ♂ & ♀ dogs receiving 50 mg/kg exhibited black stool during Week 2. **All animals in group 4 & 5 had black stool beginning on Day 5, and pale gums starting on Day 9; these clinical signs persisted throughout the treatment period**. No deaths were seen in Groups 1 and 2. One ♀ receiving 250 mg/kg died on Day 12 as a result of a perforated pyloric ulcer with secondary fibrinous peritonitis. Five animals (1♂ @ 50 mg/kg, 2♂ & 1♀ @ 100 mg/kg, and 1♂ @ 250 mg/kg) were sacrificed in a moribund condition between Days 11 and 14 with clinical signs of black stool; pale gums; difficulty in standing; lateral recumbency; thin appearance; reduced activity; cold to touch; tremors/shivering; stool with white/tan pieces; watery stool; and mucoid stool. One ♂ (250 mg/kg) in reversal phase was also sacrificed on Day

23 (Day 7 of the reversal phase). The following table lists the incidence of mortality including dogs sacrificed at moribund and the numbers of dogs sacrificed at different stages.

Fate	Study Day	0 mg/kg		25 mg/kg		50 mg/kg		100 mg/kg		250 mg/kg	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Found Dead	12	0	0	0	0	0	0	0	0	0	1
Moribund	11-14	0	0	0	0	1	0	2	0	2	0
Interim Sacrifice	17	0	0	0	0	0	0	3	4	3	3
Terminal Sacrifice	29-31	8	8	4	4	3	4	3[a]	4[a]	3[a]	4[a]

[a] These dogs were dosed with SC-58635 for 15 days and had a 2-week recovery phase.

- Body Weight and Food Consumption - There were no significant differences in mean body weight changes in groups treated with 25 and 50 mg/kg. There was a significant decrease (11.1%) in mean body weight for ♂ @ 250 during week 3. Significant weight losses were noted in ♂ @ 100 and 250 mg/kg during Week 2 with values of 0.3 and 0.7 kg, respectively. On Day 28 (during reversal phase), significant increased in weight gains (0.5 kg) were seen in ♂ & ♀ in the 250 mg/kg reversal group. Mean food consumption was decreased significantly during week 2 for animals @ 250 mg/kg (♂: ↓54.1%; ♀: ↓35.7%). Contrarily, during Week 4, dogs @ 250 mg/kg had increased food consumption by 36.2% (♂) to 51.1% (♀). There was no changes in rectal temperature.
- Ophthalmological Examination & EEG - No ocular abnormalities were noted during week 4. EEG showed no cardiac disorders during Weeks 2 & 4.
- Clinical Pathology - Normal buccal mucosal bleeding times were seen in all animals. There were no changes in clinical pathology parameters in animals receiving 25 mg/kg treatment. Significant and dose-related changes in the values of clinical parameters were seen in animals given 50, 100 and 250 mg/kg. Most of these changes were secondary to intestinal bleeding. **Most notable changes were the progressive and dose-associated ↓ in RBC counts (↓9-23%), hematocrit (↓9-24%), Hb (↓23-32%) and serum proteins (panhypoproteinemia) (albumin: ↓31-54%; globulin: ↓23-26%).** Low serum calcium (↓~20% but within lower normal limit values), higher WBC counts (↑1.7-2x) with higher absolute PMN counts (↑~2x) were also observed. No treatment caused changes in urinalysis parameters.
- Gross Pathology -
  Unscheduled Sacrifices: GI (pylorus, jejunum, distal duodenum and proximal ilum) ulcers/erosions with or without diffuse fibrinosis peritonitis and moderate acute multifocal medullary (papillary) necrosis (1♂ @ 50 mg/kg) were major pathological findings in the animals that died or were sacrificed moribund during Days 11-14. One ♂ @ 250 mg/kg was sacrificed at moribund on Day 23, (Day 7 of the reversal phase of the study) with gross findings of a small focal pyloric ulcer (6 mm in diameter) and numerous ulcers in the mid duodenum, jejunum, and proximal ileum. Other macroscopic observations included interdigital pyoderma (1♂ @ 50 and 2♂ @ 100 mg/kg) and focal areas of subcutaneous inflammation (cellulitis) with necrosis and abscessation in the caudal-ventral neck (2♂ @ 100 and 1♂ @ 250 mg/kg). The sponsor concluded that these cutaneous inflammatory processes were not associated with administration of the test article. **Interdigital pyoderma is a common bacterial infection of the skin of the feet of short-hair breeds of dogs[1]. But, it is seldom seen in the dogs maintained in the experiment control enviroment settings[2]. Therefore, the review pharmacologist does not concur with this conclusion as similar findings of cutaneous lesions were observed in dogs treated with other COX-2 inhibitors[3]. Although these observations occured at low**

1 Muller G.H., Kirk R.W, 1976. Interdigital Pyoderma (Interdigital "Cysts"). Small Animal Dermatology. pp:253-255. W.B. Saunders Co., Philadelphia, PA..

2 Personal experience.

3 [redacted]

incidence and not appeared to be dose-dependent in the present study, test-article caused toxicity through the mechanism by inhibiting phagocytic cell functions could not be ruled out.

Interim Sacrifices: A total of 13 dogs (100 mg/kg: 3 ♂ & 4♀; 250 mg/kg: 3♂ & 3♀) were sacrificed on Day 17. Major GI lesions included: pyloric ulcers (1♂ & 1♀ @ 250 mg/kg), segmental intestinal erosions and ulcers (0.5-2.0 cm) (100 mg/kg: 2/3♂ & 4/4♀; 250 mg/kg: 3/3♂ & 3/3♀). Commonly, the jejunum was most affected with lesser involvement of the distal duodenum and proximal ileum. Other pathological changes identified were blood in colonic contents (1♂ & 2♀ @ 100 mg/kg and 1♀ @ 250 mg/kg), mild bilateral renal papillary necrosis (1♀ @ 100 mg/kg), moderate splenic enlargement (1♀ @ 100 mg/kg and 1♂ @ 250 mg/kg), ascites and hydrothorax (25-100 ml) secondary to hypoalbuminemia (2♀ @ 100 mg/kg and 1♀ @ 250 mg/kg), and interdigital pyoderma (1♂ @ 100 mg/kg).

Recovery Sacrifices (Groups 4 & 5): Recovery dogs in Groups 4 (3♂ & 4♀) and 5 (3♂ & 4♀) were dosed with SC-58635 for 15 days with a 2-week recovery phase and were necropsied on Days 29-31. Three to 15 small chronic (healing) jejunal ulcers (0.25-0.50 cm in diameter) were identified in 2♂ @ 100 mg/kg and 1♀ @ 250 mg/kg group.

Macroscopic Observations	0		25		50		100[a]		250	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Stomach (Pylorus) - Ulcer/Erosion					1		1	1	3	2
Small Intestine - Ulcer/Erosion					3	1	6	4	5	5
Large Intestine - Blood in Contents					1		2	3		1
Kidney- Papillary Necrosis					1					
Skin- Interdigital Pyoderma					1		2			1
Subcutis Abscess - Caudal Ventral Neck							2	1	1	
Asites (75-100 ml)								2		1
Hydrothorax/Hydropericardium								1		1

[a] One Group 7 (PK) ♀ dog sacrificed at moribund on Day 12 was included in the Macroscopic analysis.

- Microscopic Findings - There were no treatment-related microscopic findings in dogs given 25 mg/kg of SC-58635 for ≥28 days. The predominant treatment-caused microscopic lesions limited to the GI tract and were characterized by pyloric ulceration, segmental intestinal ulceration, multifocal blunting areas of villus with hyperemia, severe diffuse fibrinopurulent peritonitis (fibrinous inflammation of mesentery and serosa of most abdominal organs (liver, pancreas, urinary bladder, spleen, kidney, large and small intestines). Bone marrow hyperplasia and extramedullary hematopoiesis in the spleen and occasionally the liver were identified in several unscheduled sacrificed dogs, an indicative of regenerative hematopoiesis. There were lesions seen in the brain were characterized as slight→mild chronic multifocal periventricular and perivascular and/or subependymal infiltrates of lymphocytes and macrophages with fewer plasma cells. These changes were seen slightly more frequent in the SC-58635-treated dogs. **Theses pathological changes with perivascular/periventricular lymphocytic infiltrate in brain are often seen in dogs with viral infection such as canine distemper. Data from a rat study (See 1.5.17; Document Nº BRD97D1852) implied that SC-58635 could pass blood-brain-barrier (BBB) and rapidly distribute into CNS tissues as the levels of SC-58635 in CNS were higher than blood following an oral administration of 10 mg/kg. Therefore, the observations of theses changes may be attributable to drug-caused toxicity. It would require additional study to distinguish whether such lesions are drug-induced or due to underlying viral inflammatory diseases of the CNS or other causes.** The incidence of major microscopic observations are shown in the following table.

Microscopic Observations	0		25		50		100		250	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Stomach - Pylorus Ulceration					1		1		3	2
Small Intestine - Ulceration/Erosion/Necrosis					2	1	6	3	5	5
Segmental Villus Blunting/Atrophy					2		3			
Kidney - Papillary Necrosis/Pyelitis							2	1		1
Interstitial Suppurative Nephritis/Fibrosis				1						
Brain - Chronic Perivascular/Periventricular Lymphocytic Infiltration	1	1				2	1	3	2	1
Leptomeninges, Lymphocytic Infiltration,			1							1
Sternum Bone Marrow Hyperplasia			1				4	7	7	5
Skin - Suppurative Subcutis Inflammation					1		1	1		1

- PK Analysis - SC-58635 was absorbed and systemically available at all doses in both sexes during 4 week oral toxicity study. The C_{max} and $AUC_{0-24\ hr}$ values for ♀ & ♂ following repetitive dosing were higher than C_{max} and AUC values on Day 1 study, indicating that accumulation of SC-58635 occurred after repetitive dosing. Although highly variable values were seen among dogs, there was a trend that SC-58635 C_{max} and AUC were higher in female dogs than those in male dogs. Mean PK parameters following are presented in the following table.

Sampling Day	Dose mg/kg	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀
Day 1	25	1.8	2.0	1.72	1.90	18.65	21.68
	50	13.3	3.5	1.94	4.15	25.41	47.70
	100	3.2	6	3.96	6.89	71.02	103.64
	250	6.1	8.8	8.44	10.31	119.53	153.37
Day 27	25	1.9	1.6	2.20	4.6	22.79	71.53
	50	1.8	1..9	4.66	6.77	60.56	83.73
Day 15	100	10.2	5.7	8.72	8.35	103.72	117.25
	250	2.3	2.7	11.98	7.72	210.98	135.42

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In conclusion, oral treatment of 25 mg/kg of SC-58635 to dogs appeared to be safe and results in no toxicological effects on survival, body weight and body weight gains and feed consumption. No treatment-related changes in any clinical and anatomical pathology parameters were seen. Dosages of 50, 100 and 250 mg/kg of SC-58635 were not tolerated. Ulceration of small intestine (mainly pylorus, jejunum duodenum and ileum) was the major test-related lesion in these animals. Dogs were more sensitive to SC-58635 induced GI toxicity as compared to rats. It was worthy to note that low incidence of interdigital pyoderma and subcutis abscess was identified in dogs at @ ≥50 mg/kg/day. Inconclusive histopathological changes in the brain (mild→moderate periventricular/perivascular lymphocytic infiltration) were noted.

2.2.1.7. 13-Week Capsule Toxicity Study With SC-58635 In Dogs, Document No: PSA95C-30-SA4324; Date: 01-Dec-1995 (Vol. 1.22-1.24)

Included as an appendix to this report were:

1. Evaluation Of The SC-58635 Plasma Concentration Data From The 13-Week Capsule Toxicity Study With SC-58635 In Dogs, Document No.: MRC95S-30-950261; Date: 20-Nov-1995
2. Metabolism Support For A 13-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4324, Document No.: MRC95S-30-950263; Date: 27-Nov-1995
3. Final Report Amendment No. 1: Metabolism Support For A 13-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4324, Document No.: M3196263; Date: 24-Sep-1997
4. Evaluation Of The Total 14-Carbon Analyses And Liver Microsomal And Postmitochondrial Supernatant Preparation In A 13-Week Capsule Toxicity Study With SC-58635 In Dogs (SA4324), Document No.: MRC95C-30-950253; Date: 27-Nov-1995

Report Nº: HWI 6127-233/PSA95C-30-SA4324, MRC95S-30-950263 (companion PK study), MRC95C-30-950253 (companion liver microsome study)
Study Nº: HWI 6127-233/SA4324
Study Aim: To identify toxic effects of SC-58635 when administered orally to dogs for at least 13 weeks and reversibility of any toxic effects of the test compound following a 4-week recovery period.
Compound: SC-58635 (Lot Nº 94K014-A2B) and [^{14}C]SC-58635 (Lot Nº GDS 4404-164 & GDS 4404-165) in gelatin capsule
Vehicle: Empty gelatin capsule
Dosage: 0, 15, 25, and 35 mg/kg/day po for ≥ 13 weeks
Animals: 30♂ & 30♀ beagle dogs, ~7-9 months old, weighing 8.2-12.2 kg

Main and Recovery[a] Study				Satellite PK Study			
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
1[a]	0	0	6[c]	6[a,b]	7.5	15	3
2[a]	7.5	15	4	7[a,b]	12.5	25	3
3[a]	12.5	25	4	[a]Animals in Group 1-4, 6 and 7 were dosed twice daily at 12-hr intervals for ≥ 13 weeks.			
4[a]	17.5	35	6[c]	[b]Two animals/sex in group 1, 4, and 5 had a recovery phase for 28 days after a 13-week treatment.			
5	25	25	4[c]	[c]Animals in group 6 and 7 received [^{14}C]SC-58635 at the first daily dose on Day 1 and once during weeks 6 and 13.			

Study Location: (b)(4)(CC) [redacted]

Study Date: March 10, 1995 - July 10, 1995
Compliance with GLP/QAU: Yes
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 13 weeks; dosing continued through the day before terminal sacrifice (Day 93/94). 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, 39, 88 and received nonradiolabeled SC-58635 on other days during the study. The following observations were conducted:

- Clinical Signs and Mortality - 2x daily.
- Body Weights - Day 1, and weekly afterwards.
- Food Consumption - 1x/week.
- Physical examinations and ECGs (including heart rates) - 1x pre-Rx and once ~1-4 hr postdose during weeks 4, 8, and 13; and once during week 17 for the recovery animals.
- Ophthalmoscopic Examination - pre-Rx and during Weeks 8 and 12, and 17 (recovery animals).
- Clinical Laboratory Evaluation - pre-Rx and during Weeks 4, 8, 12, and week 17 (recovery animals). The parameters included in the clinical laboratory analysis are listed in the following table.

HEMATOLOGY				SERUM CHEMISTRY		
aPTT	WBC	MCH	Hb	ALT		Potassium
PT	RBC	MCHC	Platelet Count	Albumin		Sodium
Differential WBC	Ht	MCV	Reticulocyte Count	Alkaline Phosphatase		Total Bile Acid
URINALYSIS				AST		Total Bilirubin
Appearance/Color	Microscopic Examination Sediment			Calcium	Chloride	Total Cholesterol
Bilirubin	Protein	Volume		Creatinine	Glucose	Total Protein
Glucose	pH	Specific Gravity		Globulin		Triglycerides
Ketones	Urobilinogen			Inorganic Phosphorus		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 on Days 1, 39, and 88. Urine and fecal samples were collected for 168 hr after each radiolabeled dose approximate 24-hr intervals.
- Necropsies - were performed on all animals at the end of the study (Week 13, 4/sex from Groups 1-4 and 2/sex from Group 5; Week 17, 2/sex from Groups 1, 4, and 5). At necropsy, the following organs (when present) were weighed. Paired organs were weighed together; the intestines were rinsed and blotted before weighing. Samples of liver (30-40 g) were collected for microsomal protein and cytochrome P450 content analyses.

Adrenals	Intestine (small, cecum and colon)	Ovaries	Testes
Brain	Kidneys	Pituitary	Thymus
epididymis	Liver	Prostate	Thyroids with parathyroid
Heart	Lungs	Stomach	Uterus with cervix

The following (when present) or representative samples were preserved in 10% phosphate-buffered formalin from animals in Groups 1-5 sacrificed after 13 weeks of treatment, unless otherwise specified:

Adrenals	Liver	Spinal Cord (Lumbar)
Aorta	Lungs	Spleen
Brain	Lymph Nodes (Mesenteric and Retropharyngeal)	Sternum with Bone Marrow
Cervix	Mammary Gland (♀ Only)	Stomach
Epididymides	Ovaries	Testes
Esophagus	Pancreas	Thymus
Eyes (Preserved in Davidson's Fixative)	Pituitary	Thyroids with Parathyroid
Femur with Bone Marrow (Articular Surface of the Distal End)	Prostate	Tongue
Gallbladder	Rectum	Trachea
Heart	Salivary Gland (Mandibular)	Urinary Bladder
Intestine, Small (Duodenum, Jejunum, Ileum)	Sciatic Nerve	Uterus
Intestine, Large (Cecum, Colon, Rectum)	Skeletal Muscle	Vagina
Kidneys	Skin	Lesions

Tissues sections from above list of each dog in Groups 1, 4, and 5 were examined microscopically.

Results:

- Mortality & Clinical Observation - No deaths occurred. No remarkable clinical symptoms were treatment-related.
- Body Weight & Food consumption - No significant changes in mean body weights, cumulative body weight gains and food consumption.
- Ophthalmology - No significant findings were attributable to the treatment of SC-58635.
- ECG - Except 1♀ @ 25 mg/kg/day had a second degree AV block, all other dogs had normal ECG readings.
- Clinical Pathology - One ♂ @ 7.5 mg/kg bid had significantly elevated ALT activity (192 IU/l) during Week 4 analysis and had normal ALT values during the subsequent analyses (Weeks 8 and 12). A Group 5 ♂ (25 mg/kg qd) had significantly increased WBC ($31 \times 10^3/\mu l$) and absolute PMN counts ($27.5 \times 10^3/\mu l$) during Week 8, an indicative of ongoing inflammation. An abscess was found in the area of lower right mandible of this dog. Leukogram of this dog at Week 12 was normal.
- Pathology & Histology - No treatment related alterations were noted macro- or microscopically.
- Toxicokinetics -

<u>Absorption</u>: Oral administration of SC-58635 was absorbed and systemically available. Plasma concentrations of SC-58635 and the exposure to SC-58635, as measured by AUC, increased with dose. The mean plasma concentration and AUC on Day 88 are shown in the following table.

Group	Dose (mg/kg)	Dosage (mg/kg/day)	C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
			♂	♀	♂	♀
2	7.5	15	1.32 ± 0.376	1.67 ± 0.570	13.8 ± 4.54	14.2 ± 5.27
3	12.5	25	1.83 ± 0.358	1.64 ± 0.337	18.0 ± 4.23	15.8 ± 6.14
4	17.5	35	2.59 ± 0.525	2.68 ± 0.427	25.7 ± 5.66	29.4 ± 6.75
5	25	25	0.875 ± 0.310	0.473 ± 0.040	10.1 ± 5.28	3.98 ± 1.52

Summary of C_{max}, T_{max}, and AUC of plasma and erythrocyte radioactivity concentrations following a single oral dose of [^{14}C]SC-58635 to male and female dogs on Day 1, and during Weeks 6 and 13 of a 13-Week dosing regimen are shown in the following table.

Sample	Dose mg/kg/day	Duration	C_{max} (μg eq./g)		T_{max} (hr)		AUC_{0-t} (μg eq.•hr/g)	
			♂	♀	♂	♀	♂	♀
Plasma	7.5	Day 1	0.370	0.226	5.7	12.7	3.40	1.87
		Week 6	0.331	0.311	9.7	6.0	3.32	3.16
		Week 13	0.248	0.338	5.7	5.7	2.19	3.30
	12.50	Day 1	0.390	1.140	9.3	4.0	4.42	10.0
		Week 6	0.212	0.812	7.0	10.0	2.52	7.98
		Week 13	0.270	0.851	5.0	9.7	2.26	7.63
RBC	7.50	Day 1	0.768	0.504	5.7	12.7	7.78	4.87
		Week 6	0.677	0.659	9.7	6.0	7.16	6.22
		Week 13	0.521	0.727	5.7	13.0	5.09	6.70
	12.50	Day 1	0.828	2.730	9.7	4.3	10.20	19.50
		Week 6	0.505	1.380	7.0	9.7	5.74	13.90
		Week 13	0.664	1.610	5.0	9.7	4.99	14.4

A summary of C_{max}, T_{max}, and AUC of plasma and erythrocyte radioactivity concentrations following a single oral dose of [^{14}C]SC-58635 on Day 1, and during Weeks 6 and 13 of a 13-Week dosing regimen in dogs classified as fast or slow metabolizers of SC-58635 is given in the table below.

Sample	Dose mg/kg/day	Duration	C_{max} (μg eq./g)		T_{max} (hr)		AUC_{0-t} (μg eq.•hr/g)	
			Fast	Slow	Fast	Slow	Fast	Slow
Plasma	7.5	Day 1	0.322	0.274	10.7	7.7	2.40	2.87
		Week 6	0.270	0.373	6.0	9.7	2.39	4.09
		Week 13	0.231	0.350	5.7	5.7	2.12	3.37
	12.50	Day 1	0.213	1.310	5.7	7.7	1.42	13.00
		Week 6	0.214	0.809	9.7	7.3	1.99	8.51
		Week 13	0.444	0.677	8.7	6.0	3.01	6.88
RBC	7.50	Day 1	0.771	0.501	10.7	7.7	7.37	5.27
		Week 6	0.652	0.684	6.0	9.7	5.99	7.40
		Week 13	0.581	0.667	13.0	5.7	5.60	6.20
	12.50	Day 1	1.230	2.320	6.7	7.3	5.16	24.60
		Week 6	0.561	1.320	9.7	7.0	5.14	14.50
		Week 13	1.180	1.100	8.7	6.0	7.51	11.90

Excretion: The major excretion route was through feces. A summary of the percent of radioactive dose excreted in urine and feces of dogs (Groups 6 and 7) following a single oral dose of [^{14}C]SC-58635 on Day 1, and During Weeks 6 and 13 of a 13-Week dosing regimen is listed in the following table.

Group	Dose mg/kg/day	Dosing Interval	% Radioactive Dose					
			Urine		Feces		Total	
			♂	♀	♂	♀	♂	♀
6	7.50	Day 1	0.49	0.56	96.2	105	96.9	106
		Week 6	0.77	0.73	91.8	92.2	92.8	93.2
		Week 13	0.41	0.87	94.1	90.9	94.8	92.4
7	12.50	Day 1	0.64	1.25	93.9	92.5	95.1	94
		Week 6	0.43	1.06	90.8	96.4	91.3	97.9
		Week 13	0.37	1.35	92.2	90.3	93.3	92.3

Metabolic Profile in Urine and Feces: Majority of drugs excreted in the feces were as unchanged (57-83%) parent drug and SC-62807 (10-29%), the carboxylated metabolite. Mean (±SEM) percent of dose excreted in feces (0-72 hr) as SC-58635 and SC-62807 on Weeks 1, 6 and 13 in dogs characterized as having a fast or a slow SC-58635 clearance are presented as follows:

Group	Week	% of dose excreted as SC-58635		% of dose excreted as SC-62807	
		Fast	Slow	Fast	Slow
6	1	78 ± 11.5	84.7 ± 1.63	26.7 ± 10.8	9.78 ± 4.4
7		82.9 ± 1.0	57.1 ± 9.7	10.3 ± 1.5	29.2 ± 13
6	6	68.9 ± 13.2	66.4 ± 11.2	20.9 ± 10.8	25.4 ± 10.9
7		75.5 ± 2.6	68.8 ± 9.7	13.7 ± 3.4	26.5 ± 16.8
6	13	70.7 ± 7.7	78 ± 11.7	20.6 ± 8.2	14.9 ± 9.7
7	3	68.9 ± 12	72 ± 13	21.4 ± 10.5	19.1 ± 12

The following table shows mean (±SEM) percent of dose excreted in feces (0-72 hours) as SC-58635 and SC-62807 on Weeks 1, 6 and 13 of dose administration in male and female dogs.

Group	Week	% of dose excreted as SC-58635		% of dose excreted as SC-62807	
		♂	♀	♂	♀
6	1	75.6 ± 9.9	87.1 ± 3.8	19.4 ± 9.5	17.1 ± 10.8
7		77.4 ± 4.6	62.6 ± 13.6	11.5 ± 0.7	27.9 ± 13.9
6	6	65.6 ± 12	69.7 ± 12.5	24 ± 9.6	22.3 ± 12.2
7		75.8 ± 2.7	68.4 ± 9.5	14.6 ± 2.8	25.6 ± 17.2
6	13	78.2 ± 11.5	70.5 ± 7.8	15.6 ± 10.4	19.9 ± 7.6
7		77.3 ± 12.7	63.7 ±10.4	14.3 ± 11.1	26.1 ± 9.9

Metabolism: It apperaed that higher portions of SC-58635 transformed into SC-60613, a hydroxyl metabolite, in the microsomes obtained from fast metabolizers. The following table lists mean (±SEM) percent of SC-58635 and SC-60613 in dog liver microsomes incubated with [^{14}C]SC-58635 from ♂ and ♀ dogs characterized as having a fast or slow SC-58635 clearance.

Dose	% SC-60613				% SC-58635			
(mg/kg/day)	Male	Female	Fast	Slow	Male	Female	Fast	Slow
Control	14.60 ± 4.40	14.00 ± 1.40	16.10 ± 2.50	9.00	71.30 ± 6.00	78.10 ± 1.70	73.70 ± 4.00	77.70
15.00	15.50 ± 5.30	14.80 ± 4.60	22.40 ± 3.70	7.88 ± 0.62	77.90 ± 5.70	84.50 ± 4.70	73.70 ± 4.30	88.70 ± 2.10
35.00	19.70 ± 6.70	10.80 ± 1.20	22.10 ± 5.30	8.45 ± 0.28	79.60 ± 6.70	88.90 ± 1.20	77.40 ± 5.40	91.20 ± 0.30

Microsome Induction: Similar levels of total cytochrome P450 content, microsomes and total protein yield of dog liver were obtained as shown in the following table.

Group	Dose mg/kg/day	P450 (nmole/mg protein)		Microsome Yield (mg/g liver)		Total Protein Yield	
		♂	♀	♂	♀	♂	♀
1[a]	Control	0.641 ± 0.0526[b]	0.606 ± 0.0387	14.5 ± 0.96	17.0 ± 1.52	99.8 ± 7.19	97.3 ± 5.91
2	15	0.577 ± 0.0659	0.613 ± 0.0668	17.9 ± 1.94	15.3 ± 2.42	107 ± 4.79	95.7 ± 8.93
3	25	0.620 ± 0.0313	0.586 ± 0.0400	16.9 ± 2.01	17.5 ± 1.31	103 ± 8.33	112 ± 6.60
4	35	0.619 ± 0.0780	0.597 ± 0.0410	18.2 ± 3.34	15.2 ± 2.33	109 ± 7.02	101 ± 7.87
5	25	0.69	0.65	15.10	16.90	105	107

[a] Total daily dose administered. Animals in Groups 1 through 4 were dosed twice daily for at least 13 weeks. Animals in Group 5 were dosed once daily for at least 13 weeks.
[b] Mean ± SD.

No treatment-associated changes were observed in all dose groups. Therefore, the MTD was not achieved in present study.

2.2.1.8. Seven-Day Exploratory Intravenous Toxicity Study Of SC-58635 In The Dog (EX4381), Document No.: P30E4381; Date: 26-Nov-1997

Included as an appendix to this report was:

Evaluation Of Plasma Concentration Data From The Seven Day Exploratory Intravenous Toxicity Study Of SC-58635 In The Dog, EX4381, Document No.: M3095222; Date: 12-Aug-1996

Study Nº: EX4381
Report Nº: P30E4381
Study Aims: To assess the relationship of plasma levels of SC-58635 to gastrointestinal injury in the dog and to establish a correlation between plasma levels of SC-58635 and biochemical changes (i.e., prostaglandin levels) in potential target organs.
Compound: SC-58635 (Lot Nº 94KO14-A3B in Phase 1; Lot Nº GDS-4695-042 in Phase 2).
Vehicle Control: PEG/sterile H_2O (2:1 on Day 1 of Phase 1 or 3:1 on Days 2-7 of Phase 1 and all of Phase 2)
Dose & Route: 0, 15 or 40 mg/kg/ml iv for 7 days
Animals: ♂ & ♀ Beagle dogs, ~ 9 - 21 months of age, weighing 8.0 - 15.3 kg for Phase 1 study; 12-21 months old and weighing 10.3 to 14.7 kg for Phase 2 study.
Study Location: Searle R&D, Skokie, IL (in-life & pathology) and CEDRA Corporation, Austin, TX (analysis of plasma concentrations of SC-58635).
Study Date: Phase 1 - treatment: 7/6-7/12/95; Sacrificed: 7/13/95.
Phase 2 - Treatment: 11/30-12/6/95; Sacrificed: 12/7/95.
GLP/QAU Compliance: N/A
Study Design: Groups of 3 dogs, randomly assigned to dose groups as shown in the following table, were administered intravenously (iv) with SC-58635 at 0, 15 or 40 mg/kg daily for 7 days.

Group	Dose (mg/kg)	Nº of Animals
PHASE 1 STUDY		
1	0	3
2	15	3
PHASE 2 STUDY		
1	0	3
2	40	3

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The following observations were conducted. The concentrations of SC-58635 in plasma were determined using a validated (b)(4)(C) procedure.

- Physical Examinations - Day 1 pre-℞.
- Mortality & Clinical Signs - 2x/day; pre-℞ and ~1-3 hr after dosing.
- Body Weights - 2x pre-℞ and 2x during the treatment.
- PK - Blood samples for pharmacokinetic assessments were collected from each dog in Phases 1 and 2 at 5, 15, and 30 min and 1, 2, 4, 6, 8 and 24 hr after dosing on Days 1 and 7.
- Ex Vivo Analysis for Inhibition of COX-1 and COX-2 Activities in Blood - Days 1, 4, and 7; pre-℞ and 24 hr after dosing.
- Clinical Pathology - Day 8 before necropsy. The following parameters were analyzed.

HEMATOLOGY PARAMETERS			COAGULATION PARAMETERS	CHEMISTRY PARAMETERS
White Blood Cells		MCV	Activated Partial Thromboplastin Time	Alanine Aminotransferase
Differential WBC		MCH	Prothrombin Time	Total Protein
Red Blood Cells		MCHC	Fibrinogen	Albumin
Hb	Ht	Platelets		Calcium

- Necropsy - Day 8. Macroscopic observations were recorded. Specified organs and selected tissues as shown in the following table were collected and preserved for microscopic evaluation. Tissues designated with an asterisk were weighed and paired organs were weighed together.

*Large Intestine (Colon and Cecum-Opened, Washed and Weighed Separately)	*Kidneys (Both)	Lesions
*Intestine, Small (Duodenum, Jejunum, Ileum-Opened, Washed and Weighed Together)	*Stomach	

- Prostaglandin Analysis - Approximately 5 grams of stomach, jejunum, colon, and kidney were frozen in liquid nitrogen for analysis of prostaglandin content.

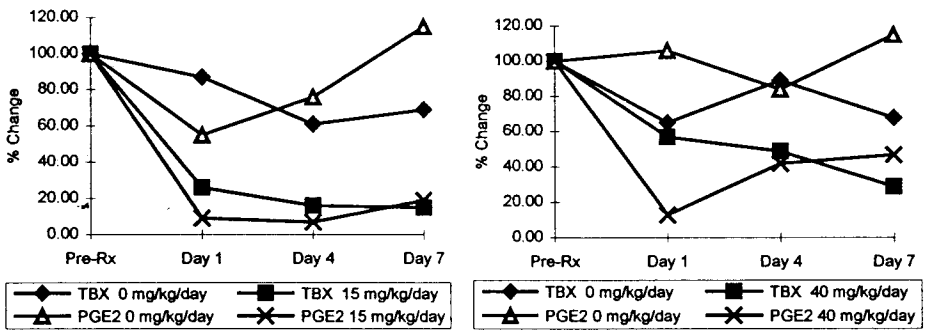
Results:

- Clinical Signs and Mortality - No deaths occurred. Swelling of the forelimbs was seen in dogs receiving test article. This forelimb swelling was more extensive in Phase 2 animals. Moreover, in one animal, the swelling extended from the forelimbs to involve the chest, ventral thorax, and neck.
- Body Weights - No significant changes were noted.
- Clinical Pathology - Elevated ALT values were noted in one dog each @ 0 (~2x ↑) and 15 mg/kg (4x ↑) on Day 8 of Phase I study. Increases in relative (82 vs 57%) and absolute neutrophil (16.57 vs 6.33 x$10^3/\mu l$) and total WBC (11.1 vs 20.5 x$10^3/\mu l$) counts, and ↓ in mean total protein (↓11%) and albumin (↓16%) values were noted in the dogs at 40 mg/kg on Day 8 during Phase II study.
- Tissue PGE_2 Levels (pg/g tissue)-

Tissue	PHASE 1		PHASE 2	
	0 mg/kg/day	15 mg/kg/day	0 mg/kg/day	40 mg/kg/day
Stomach	3406.2 ± 1677	1163.1 ± 194	1950 ± 283	1195 ± 509
Kidney	111.2 ± 48.3	42.7 ± 16.9	148.4 ± 52.3	28.0 ± 10.7
Jejunum	462.6 ± 22.2	413.9 ± 115	959.7 ± 122	604.8 ± 171
Colon	1022.9 ± 54.8	977.9 ± 232	1068.1 ± 463	893.3 ± 90.7

- Ex Vivo Analysis for Inhibition of COX-1 (TBX Levels) and COX-2 (PGE_2 Levels) Activities in Blood - The levels and percent changes of TBX and PGE_2 in the blood on different days during Phase I and II studies are shown in the following table and figures.

Sampling Day	Blood TBX Levels (ng/ml)				Blood PGE_2 Levels (ng/ml)			
	0 mg/kg/day	15 mg/kg/day	0 mg/kg/day	40 mg/kg/day	0 mg/kg/day	15 mg/kg/day	0 mg/kg/day	40 mg/kg/day
Pre-Rx	41.4	150.5	43.4	19.5	3225	2626	900	442
Day 1	36.0	39.3	28.0	11.2	1782	235	954	57
Day 4	25.3	23.3	38.7	9.5	2440	190	758	187
Day 7	28.7	22.5	29.4	5.7	3696	497	1031	208



- Mean PK (±SEM) parameters for SC-58635 on Days 1 and 7 following iv administration of SC-58635 to the dog are summarized in the following table.

Dose (mg/kg)	Day	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg•hr/ml)
15.0	1	2.17 ± 1.92	3.38 ± 0.09	59.1 ± 8.4
15.0	7	3.50 ± 1.61	5.35 ± 1.08	74.7 ± 11.8
40.0	1	0.08 ± 0	32.8 ± 2.3	137 ± 5
40.0	7	0.08 ± 0	32.5 ± 3.8	143 ±11

- Gross and Histopathology - There were no remarkable changes in organ weights. Moderate edema of the subcutis and musculature of the right forelimb, a response to perivascular leakage

of test article/vehicle, was observed in one Phase 1 and all Phase 2 SC-58635 treated dogs. Two shallow ulcers (approximately 1 cm in diameter) were identified in the proximal duodenum (pyloric-duodenal junction) of one animal given 40 mg/kg SC-58635. Other gross findings in this animal included the abundant dark black contents (melena) in the ileum and colon, swollen kidneys, pallor of the renal papilla, edema around the kidneys (perirenal) and omentum, and enlarged mesenteric lymph nodes. Treatment-related histomorphologic changes correlated with the lesions noted macroscopically, were moderate focal subacute ulceration in the proximal small intestine at the pyloric duodenal junction of one Phase 2 dog receiving 40 mg/kg SC-58635. Microscopic evaluation of the forelimb injection sites of 2 Phase 2 animals revealed moderate to marked subacute necrotizing vasculitis with thrombosis involving primarily large veins, moderate to marked diffuse edema with multifocal hemorrhages, and multifocal infiltrates of a mixed population of inflammatory cells (predominantly neutrophils and macrophages).

Based on presented results, it appeared to be high levels of PGE_2 present in the stomach and colon. Treatment with SC-58635 caused decreases in blood TBX and PGE_2 levels. At a dose of 40 mg/kg, SC-58635 caused GI lesions (pyloric-duodenal ulcer/erosion) in the dog after repeated dosing for 7 days.

2.2.2. CHRONIC TOXICITY STUDIES

2.2.2.1. 26-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635 (SA 4366), Document No: P30S4366; Date: 16-Sep-1996 (Vol. 1.26-1.28)

Included as an appendix to this report was:

1. Pharmacokinetics And Metabolism Support For A 26-Week Oral Toxicity Study Of SC-58635 In Rat, Document No.: M3096054; Date: 04-Jun-1996
2. Final Report Amendment No. 1: Pharmacokinetics And Metabolism Support For A 26-Week Oral Toxicity Study Of SC-58635 In The Rat, SA4366, Document No.: M3196054; Date: 07-Oct-1997
3. Final Report Amendment No. 1: 26-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635 (SA4366), Document No.: P31S4366; Date: 07-Oct-1997

Report Nº: M3096054
Study Nº: SA4366/CHV 700-331
Study Aim: To evaluate the chronic toxicity of SC-58635 in rats following a daily oral gavage administration for ≥26 weeks.
Compound: SC-58635 (Lot Nº 94K014-A2B), [^{14}C]SC-58635 (Lot Nº GDS4021-68, specific activity 7.68 μCi/mg & Lot Nº 4404-145, specific activity 143 μCi/mg)
Control Vehicle: 0.5% (w/v) methylcellulose and 0.1% Polysorbate 80 in distilled H_2O
Dose & Route: 0, 20, 80, 400 mg/kg/day po by gavage
Animals: Sprague-Dawley rats, Crl:CD®(SD)BR, ~6 weeks of age, weighing 194-268 g for ♂ and 131-192 g for ♀, 25/sex/group for main (15/sex/group) and recovery (10/sex/group) studies, 18/sex/group for satellite PK study.
Study Location: Corning Hazleton Inc., 9200 Leesburg Pike, Vienna, VA 22182.
GLP/QAU Compliance: Yes
Study Date: 03/06/95 - 10/12/95
Study Design: Animals were given SC-58635, 0, 20, 80, or 400 mg/kg/day by oral gavage once daily for at least 26 weeks. Ten rats/sex from groups 1-4 were allowed to have a 4-week recovery period after the last dosing. Animal group designation and dosing levels are shown in the following table. On Days 1 and 177, [^{14}C]SC-58635 was given to Groups 5, 6, and 7 animals. Blood samples

were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, and 24 hr post dosing from 3 rats/sex/time point. Urine and fecal samples were collected over 168 hr after dosing with [^{14}C]SC-58635 in 24 hr intervals.

Main and Recovery[a] Study				Satellite PK Study			
Group	Dose (mg/kg/day)	Nº of Animals ♂	Nº of Animals ♀	Group	Dose (mg/kg/day)	Nº of Animals ♂	Nº of Animals ♀
1	0 (MC)	25	25	5	20 (Low)	18	18
2	20 (Low)	25	25	6	80 (Mid)	18	18
3	80 (Mid)	25	25	7	400 (High)	18	18
4	400 (High)	25	25	[a]The recovery group comprised of 10/sex/group			

The following observations were conducted:

- Mortality and Clinical Signs - 2x/day during treatment and 1x/day during recovery phase.
- Body Weights - Day 1 pre-℞, 2x/week up to Week 4, and 1x/week thereafter.
- Food Consumption - 1x/week.
- Ophthalmoscopic Examinations - Pre-℞ and Week 26.
- Clinical Pathology (Groups 1-4) - Weeks 13 (10/sex/group), 27 (terminal sacrifices) and, 31 (recovery sacrifices). 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 - Blood was collected from Groups 5-7 (3/sex/time point) on Days 1 and 177 at 0.5, 1, 2, 3, 4, 6, 8, and 24 hr post radiolabeled dose. Fecal and urine samples were collected from the designated animals (3/sex/group) in Groups 5-7 for 7 days after [^{14}C]SC-58635 administration.
- Necropsy - Necropsy was performed on all unscheduled deaths and surviving animals in Groups 1-4. The following organs (from post-treatment and recovery sacrifice animals) were weighed at necropsy.

Adrenals	Kidneys	Ovaries	Stomach (Empty)	Uterus
Brain (with Brainstem)	Heart	Pituitary (Postfixation)	Testes with Epididymides	
Cecum (Empty)	Liver	Prostate	Thymus	
Colon (Empty)	Lung	Spleen	Thyroid with Parathyroids (Postfixation)	

The following tissues (when present) from each main and recovery study animal were preserved in 10% neutral-buffered formalin. Tissues from the main and recovery study animals in Groups 1 and 4 and animals in Groups 1-4 that were found dead or sacrificed in extremis were examined microscopically. In addition, the liver, kidneys, small intestines, and large intestines animals in Groups 2 and 3 were examined. Gross lesions were examined from all animals.

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

Results:

- Mortality and Clinical Signs - There were a total of 7 treatment-related deaths (1♀ @ 80 mg/kg, Week 25; 6♀ @ 400 mg/kg, Weeks 15-22) as a result of GI injury (GI necrosis with moderate→severe peritonitis). One ♀ at 80 mg/kg died of pulmonary hemorrhage due to gavage accident during Week 15. No remarkable clinical symptoms were attributable to the treatment. The survivals for each group at Week 26 are listed in the following table.

	Dose (mg/kg/day)			
	Control	20	80	400
♂	25/25	25/25	25/25	25/25
♀	25/25	25/25	23/25	19/25

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- Body Weights and Food Consumption - Comparable mean body weight values were noted for rats in all groups. Significantly higher values in mean body weight changes were noted in Group 3 ♂ during Weeks 1 (↑ 26%), 11 (↑ 27%), and 22 (↑ 600%) and Group 4 ♀ during Week 3 (Days 19-22) (↑ 71%). Significantly lower mean body weight gains were noted in Group 4 ♂ during Weeks 14 (↓ 50%) and 17 (↓ 70%) and Group 3 ♀ during Week 11 (↓ 60%). However, there were no significant differences in total body weight change values during treatment (Weeks 1-26). As for food consumption, sporadically significant changes were noted (↑6% and 11%, respectively in Group 4 ♀ during Weeks 4 and 18; ↓7% in Group 4 ♂ during week 25).
- Ophthalmology - No treatment related changes were observed.
- Clinical Pathology - There were no significant changes in hematology and serum chemistry analyses. No remarkable findings were noted in urinalysis. Elevated osmolality (20-69%) with higher values in urine K^+ (42-87%) were noted in SC-58635 treated 4 ♂ during Week 13 analysis. These changes might not have biological impacts as they were not observed in the subsequent analyses (Weeks 27 terminal sacrifices and 31 recovery sacrifices).
- PK/TK -

  Absorption: SC-58635 was absorbed systemically following oral administration. Mean PK parameters for SC-65872 on Day 182 are presented in the following table. Dose-dependent but not proportional increases in AUC and C_{max} values were noted. Higher exposure of SC-58635, as measured by AUC and C_{max}, was seen in female rats.

Parameters	Dose Levels (mg/kg)					
	20		80		400	
	♂	♀	♂	♀	♂	♀
C_{max} (μg/ml)	2.03	4.05	2.97	6.94	5.12	10.5
AUC_{0-24} (μg•hr/ml)	26.5	52.5	41.5	101	54.6	150
T_{max} (hr)	2	4	2	6	1	3

Relationship between Plasma Concentrations and Dose: Majority (85-100%) of the radioactivity circulating in plasma on Day 177 was [^{14}C]SC-58635. Small percentages of radioactivity circulating in plasma from rats in the 20 and 80 mg/kg dose groups were the hydroxylated

metabolite, SC-60613 (5-8%) and the carboxylated metabolite, SC-62807 (0.5-9%). Only unchanged drug, [^{14}C]SC-58635, was detected in the plasma from animals @ 400 mg/kg.
Excretion and Metabolic Profiles in Urine and Feces: The majority of radioactivity excreted in urine (0-48 hr) was [^{14}C]SC-62807 representing 1.11-9.00% of the dose. Less than 1% of the dose was excreted as unchanged drug in the urine. The majority of the fecal radioactivity excreted in feces (0-72 hr) was [^{14}C]SC-58635 and [^{14}C]SC-62807 representing 23.1-80.1% and 7.70-53.2% of the dose, respectively. A higher percentage of the dose was excreted as [^{14}C]SC-58635 and a lower percentage of the dose was excreted as [^{14}C]SC-62807 with increasing dose level.

- Histopathology - The major treatment-related pathological changes were limited to GI tract. These alterations were characterized as severe necrosis in jejunum (Group 3: 1♂ & 1♀; Group 4: 4♀) and various degree of chronic active inflammation of the abdominal serosal surface.

Therefore, treatment of SC-58635 to rats for 26 weeks by oral gavage caused deaths and GI injury at doses ≥80 mg/kg/day.

2.2.2.2. 52-Week Capsule Toxicity Study With SC-58635 In Dog, (SA 4425) (26-Week Interim Evaluation), Document No: P3IS4425; Date: 23-Sep-1996 (Vol. 1.29-1.30)

Included as an appendix to this report was:
Evaluation Of The SC-58635 Plasma Concentration Data From The 52-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4425, Document No.: M3096285; Date: 18-Sep-1996

Study Nº: SA4425/6127-190/700-338
Report Nº: P3IS4425
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				Satellite PK Study			
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/sex from Groups 1-5 were sacrificed at Week 26.			
4	17.5	35	12	Dogs in Groups 1-4 & 6-7 received SC-58635 2x/day.			
5	25.0	25	8	Dogs in Groups 6 & 7 received SC-58635 as 1st daily dose on Day1 and Weeks 26 and 52.			

Study Location: (b)(4)(CC) [redacted]

Compliance with GLP/QAU: Yes
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 (Week 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-℞, 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 Pre-℞ and 1x 1-4 hr postdose during weeks 13, 26, 39 and 52.
- Ophthalmoscopic - pre-℞ and Weeks 26 and 52.
- Clinical Laboratory Evaluations - 1x pre-℞ and Weeks 13, 26, 39, 52 and 56. The parameters included in the clinical laboratory analysis are listed in the following table.
  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	

- 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 - Week 26 (interim sacrifice: Groups 1-5, 4/sex/group). The following organs were weighed. Organ-to-terminal-body-weight and organ-to-brain-weight ratios were calculated.

Adrenals	Large Intestine (Cecum and Colon)	Small Intestine (Duodenum, Jejunum, Ileum)
Brain (with Brainstem)	Ovary	Stomach
Heart	Pituitary	Testes With Epididymides
Kidneys	Prostate	Thyroids (with Parathyroid)
Liver with Drained Gallbladder		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 animals in Groups 1 and 4 sacrificed at Week 26.

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 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 -

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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

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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: (b)(4)(CC) [redacted]

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

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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.

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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

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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 (Charles River Laboratories, Inc., Raleigh, NC), ~6 weeks of age, weighing 178-273 g for ♂ and 127-197 g.

Study Site: (b)(4)(CC) [redacted]

In-Life Observation: 3/16/95 - 3/19/97;
Interim Sacrifice: 3/15/96 (Week 53)
Terminal Sacrifice: 3/14-19/97

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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 (b)(4)(CC) [redacted] The concentrations of SC-58635 in plasma and serum were determined using a validated (b)(4)(C procedure with an assay sensitivity of 0.0250 μg SC-58635/ml for a 0.300 ml sample. The concentrations of SC-58635 in kidney were determined using a non-validated (b)(4)(C procedure with an assay range of 0.500 to 10.0 μg SC-58635/g tissue.
- 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.

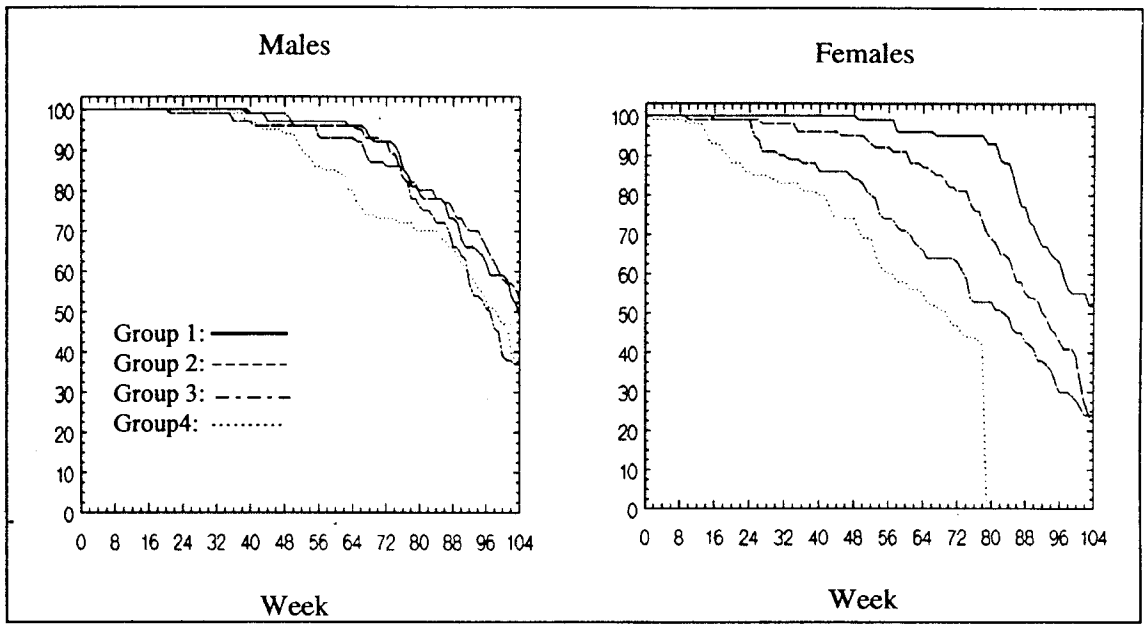
adrenals	ovaries	lung	stomach (empty)	thyroid with parathyroids (postfixation)		
brain (with brainstem)	heart	pituitary (postfixation)	testes with epididymides	uterus		
cecum (empty)	kidneys	prostate	thymus	colon (empty)	liver	spleen

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.

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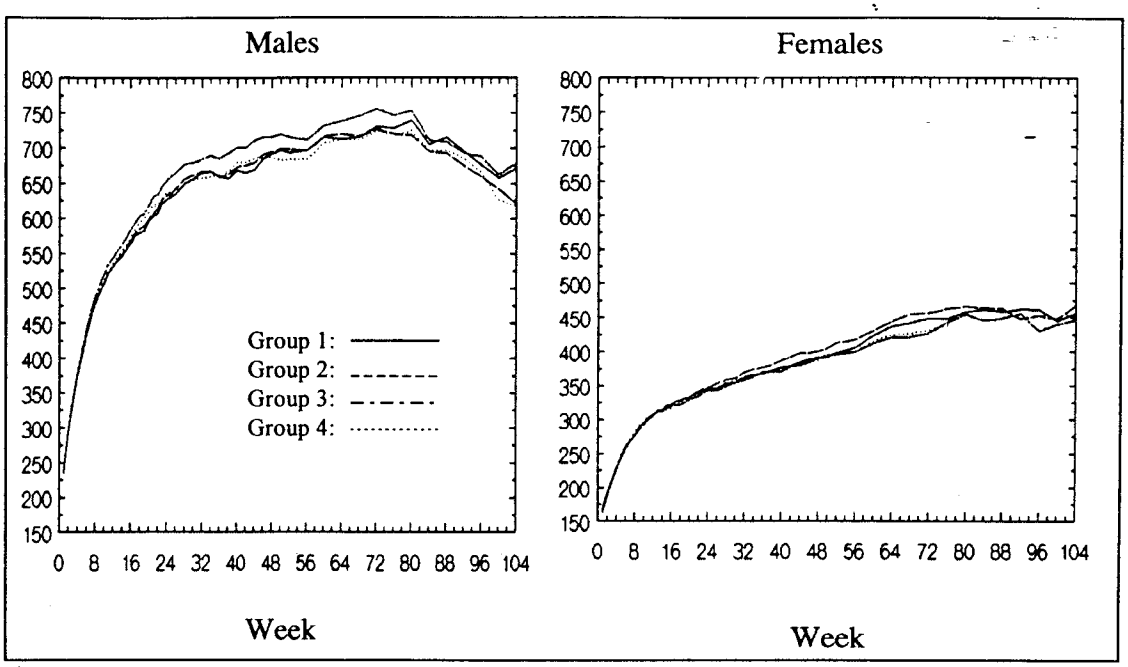
The incidence of deaths for the main study animals occurred at various stages during the study is listed in the following table. Due to excessive toxicity, high dose females were sacrificed at Week 79.

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

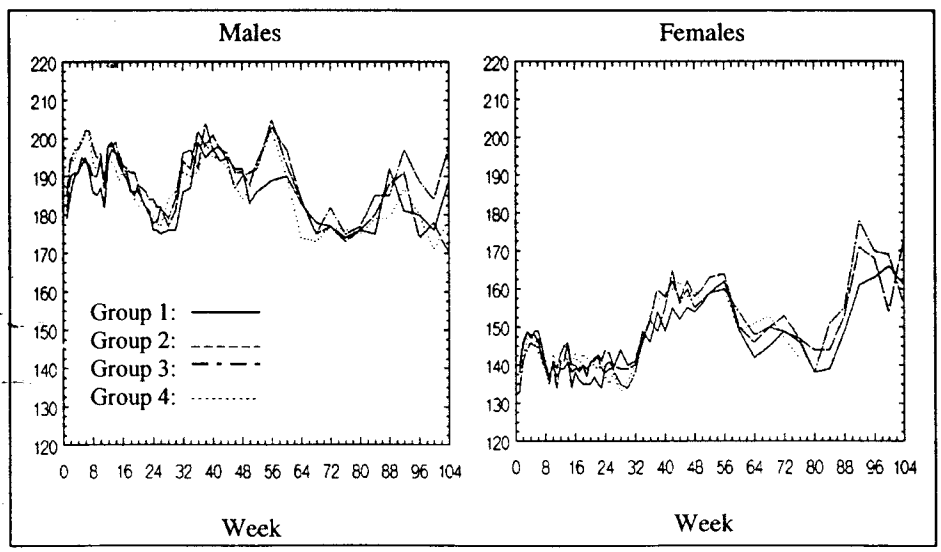
[a] Killed Week 79.

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 $12.1 \times 10^3/\mu l$, $14.7 \times 10^3/\mu l$, $14.1 \times 10^3/\mu l$, and $16 \times 10^3/\mu l$ for Groups 1, 2, 3, and 4, respectively. In addition, Group 2 ♂ had ↓ in RBC (6.51 vs $8.19 \times 10^6/\mu l$ 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 $0.12 \times 10^6/\mu l$ 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

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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.

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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.

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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: Charles River CD-1 mice (Charles River Laboratories, Inc., Portage MI), 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: (b)(4)(CC) [redacted]
Tissue Processing & Microscopic Examinations: (b)(4)(CC) [redacted]
(b)(4)(CC) [redacted]
Plasma PK Assessment: (b)(4)(CC) [redacted]
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-Rx; 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 (b)(4)(CC) [redacted] 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.

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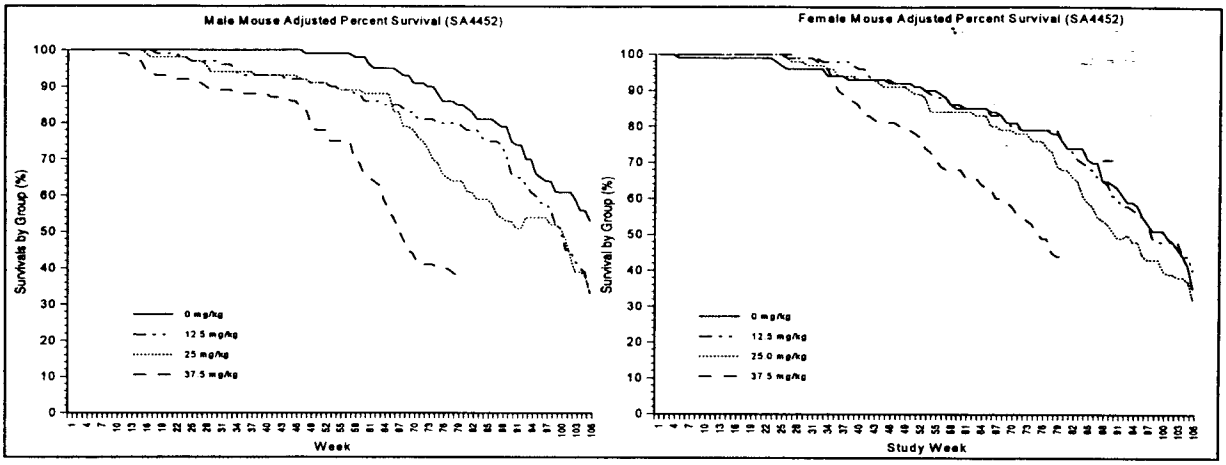
- Mortality and Clinical Signs - Test article related-deaths were noted in all SC-58635 treated groups. The incidences of treatment-related deaths increased as the dosage increased. Observations of urine-stained hair, intra-abdominal swelling, distended abdomen, piloerection, decreased defecation, and 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

[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.

the Kaplan-Meier product limit estimation method and was plotted as proportion surviving versus time as illustrated in the following figures.



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.**

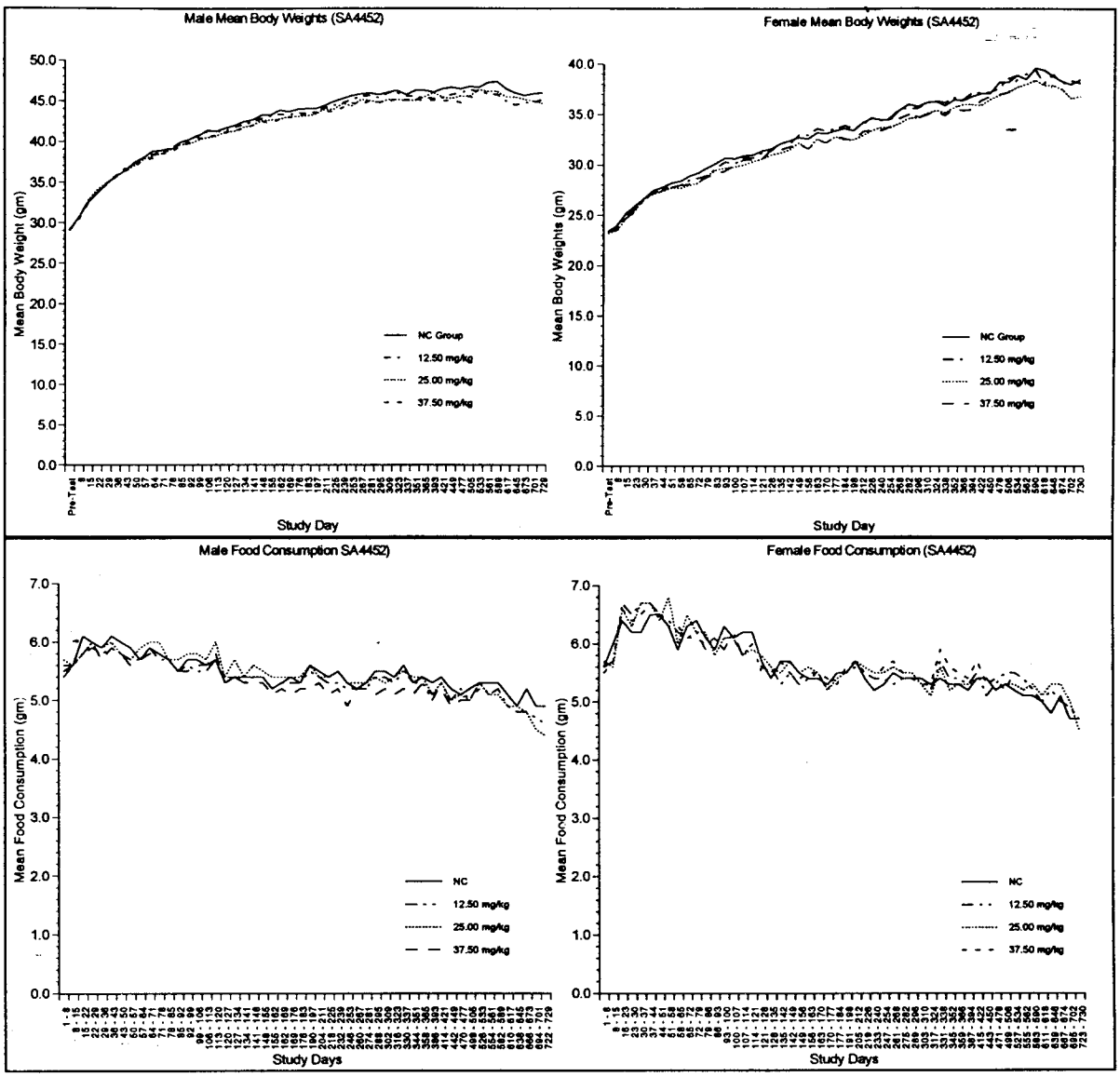
Group	Dose (mg/kg)		Week 80				Week 106			
	♂	♀	♂		♀		♂		♀	
N	0	0	68/79	86%	61/79	77%	39/73	53%	26/73	36%
1	12.5	25	63/80	79%	61/79	77%	26/78	33%**	32/79	41%
2	25	50	50/80	63%	54/80	68%	26/78	33%**	25/78	32%
3	75	150	29/80	36%*	35/80	44%**	-		-	

* 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 Deaths	Nº. Examined	35	48	52	47	52	53	51	45
	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

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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).

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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.

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2.4. REPRODUCTIVE TOXICOLOGY

2.4.1. FERTILITY STUDIES

2.4.1.1. Study Of Fertility And Early Embryonic Development To Implantation With SC-58635 By Oral Administration In The Rat, Document No.: PSA95C-30-SA4294; Date: 15-May-1995 (Vol. 1.55, p. 1-339 & Vol. 1.56, 1-230)

Included as an appendix to this report was:
Evaluation Of The SC-58635 Plasma Concentration Data From The Study Of Fertility And Early Embryonic Development To Implantation With SC-58635 By Oral Administration In The Rat, SA4294, Document No.: MRC-95S-0086; Date: 27-Apr-1995 (Vol. 1.56, p. 179-193)

Study Nº: SA4294/B 95723
Report Nº: PSA95C-30-SA4294
Study Aim: To evaluate the effects of SC-58635 on fertility and early embryonic development in Sprague-Dawley rats
Compound: SC-58553 (Lot Nº 94K014-A1B, -A3B) suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O
Dose & Route:
♂: 0, 60, 300, and 600 mg/kg/day po, at least 28 days prior to mating, throughout the study.
♀: 0, 60, 300, and 600 mg/kg/day po, 14 days prior to placement for mating, during the mating period and in gestation from Day 0 to 7.
Control Vehicle: 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O
Animals: 115♂ & 115♀ Sprague-Dawley rats, strain Crl:CD®(SD)BR; Age: 12 & 10 wk old for ♂ and ♀, respectively; weighing 367 - 444 g for ♂ and 191 - 267 g for ♀ rats.
Study Location: (b)(4)(CC) [redacted]
Study Date: 10/4/1994 - 1/23/1995
Compliance with GLP/QAU: Yes
Study Design:

Group	Dose (mg/kg/day)	Nº of Rats		
		Treated		Untreated
		♂	♀	♀
Vehicle Control	0	25	25	25
SC-58635	60	25	25	24*
SC-58635	300	25	25	25
SC-58635	600	25	25	25

*Assigned male died prior to mating with untreated females.

The following parameters were investigated: clinical signs; body weight (measured on Gestation Days 0, 3, 7, 10 and 13); food consumption recorded for the mated females (treated and untreated) during gestation intervals 0-3, 3-7, 7-10 and 10-13; estrous cycles; uterine examination on Gestation Day 13; PK; and terminal gross pathological examinations; sperm mortality; spermatozoa counts and morphology of spermatozoa.

Results: One ♂ in both the control and the 60 mg/kg/day groups died of unknown causes during the study. One ♂ in 600 mg/kg/day was killed on Day 102 in a moribund condition as a result of esophageal perforation. No treatment related clinical findings were noted for the male or treated females. There was no effects on body weights. Food consumption was increased for males receiving 300 mg/kg/day from weeks 2 to 3 and for females from weeks 1 to 2 of the premating

period. No gross pathological findings were treatment related. The estrous cycles of the SC-58635 treated females were not affected. The mating and fertility indices, conception rates and mean day of mating were unaffected in all animals. Sperm motility, spermatozoa counts and morphology were not changed by the treatment. The number of live fetuses and implantation sites were significantly lower in all SC-58635 treated groups. Significantly higher preimplantation losses were seen for the all treated females and this SC-58635 induced preimplantation loss was dose-dependent.
In conclusion, male fertility was not affected by SC-58635 treatment at the dose levels up to 600 mg/kg/day. For the treated females, the number of live fetuses was significantly lower and significantly higher preimplantation losses at dose levels ≥60 mg/kg/day.

2.4.1.2. Study Of Fertility And Early Embryonic Development To Implantation With SC-58635 By Oral Administration In The Female Rat, (SA 4345), Document No.: P30S4345; Date: 04-Nov-1996 (Vol. 1.57, 1-272)

Study Nº: SA4345/95813
Report Nº: P30S4345
Study Aims: To investigate the effects of SC-58635 on fertility and early embryonic development in female rats after oral administration.
Compound: SC-58635 (Lot Nº: 94K014-A3B, 99.8% purity)
Vehicle: 0.5% Methylcellulose

Group	Dose (mg/kg/day)	Nº of ♀
1 (Vehicle Control)	0	25
2	15	25
3	30	25
4	50	25
5	300	25

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Dose and Route: 15, 30, 50, and 300 mg/10 ml/kg/day po by gavage
Animals: 125♀ Sprague-Dawley rats, Crl:CD®(SD)BR, 10 weeks of age, weighing 211-258 g, 25/group.
Study Date: 2/7/95 (1st day of treatment) - 3/26/95 (necropsy)
Study Site: (b)(4)(CC) [redacted]
GLP/AUC: Yes
Study Design: The female rats were given SC-58635 or vehicle control daily from 14 days prior to mating, throughout the mating and through Gestation Day 7. The following observations were conducted:

- Clinical Signs and Mortality - 2x/day.
- Body Weight and - 1x/week during premating treatment period and Gestation Days 0, 3, 7, 10, and 13.
- Food consumption - 1x/week during premating treatment period and Gestation Days 0-3, 3-7, 7-10, and 10-13.
- Necropsy - on Gestation Day 13. The reproductive tract was removed and the corpora lutea were counted. The uterine contents were examined. The following tissues were preserved: uterus, mammary glands (cervical and inguinal), vagina, ovaries, and any abnormalities.
- Mating and fertility indices, and the conception rates were calculated as follows:
  Mating Index (%) = (Nº of females mating)/(Nº of females placed for mating) x 100
  Fertility Index (%) = (Nº of females pregnant)/(Nº of females placed for mating) x 100
  Conception Rate (%) = (Nº of pregnant females)/(Nº of mated females) x 100
- Reproductive Indices were calculated as follows:
  Preimplantation loss (%) = (Nº of corpora lutea - Nº of implants)/(Nº of corpora lutea) x 100

Post implantation loss (%) = (Nº of implants - Nº of live embryos)/(Nº of implants) x 100

Results:

- Mortality and Clinical Findings- One ♀ @ 50 mg/kg/day died on study Day 29 prior to mating due to the handling error with macroscopic findings of pulmonary edema and fluid in the tracheal lumen and a clot in the cranial cavity. Because mating was not observed, a ♀ @ 50 mg/kg/day was sacrificed at the end of the mating period and was found to be pregnant. No remarkable clinical signs were noted attributable to the treatment.
- Body Weight and Food Consumption - No treatment related effects were observed. Food consumption values for the 15 mg/kg/day treated females were significantly lower during the prestudy period.
- Gross Pathological Findings - Adhesion between the liver and adjacent structures, such as the diaphragm or intra-abdominal fat was seen in 3 females @ 300 mg/kg/day. This change was associated with intrahepatic abnormalities, such as depressed and/or dark and/or pale area(s). The sponsor stated that these findings were incidental. Dark mucoid material in the vaginal lumen was the most frequent observation in all groups.
- Estrous Cycles - Not affected.
- Reproductive Performance and Parameters - The mating and fertility indices, conception rates and mean day of mating were unaffected. The numbers of corpora lutea were significantly ↓ for the 300 mg/kg/day group. Significantly decreased numbers of implantation sites and live embryos were seen in the females @ 50 and 300 mg/kg/day. These reductions resulted in significantly ↑ pre- and post implantation losses (%) in these groups. The following table shows reproductive indices for each group.

Reproductive	Dose (mg/kg/day)				
Indices	Vehicle Control	15	30	50	300
Nº of Corpora Lutea	17.5±2.04	17.3±3.15	17.6±2.33	17.2±2.80	15.7±2.42**
Nº of Implantation Sites	16.5±1.90	16.3±2.65	16.9±2.09	14.0±3.76*	11.4±4.56***
Nº of Live Embryos	15.4±1.74	14.4±3.33	14.9±2.61	11.6±4.41***	9.4±4.18***
Nº of Dead Embryo	0.0±0.21	0.0±0.00	0.0±0.00	0.1±0.23	0.0±0.00
Nº of Early Resorption	1.0±1.17	1.9±1.94	2.0±1.61	2.4±3.55	2.0±1.93
% Preimplantation Loss	5.8±6.52	5.7±7.37	4.0±5.12	18.0±19.21*	27.7±25.40***
% Post Implantation Loss	6.4±6.67	11.9±12.81	12.0±9.34	16.7±21.02*	20.3±21.90**

Significantly different from control value: *p<0.05; **p<0.01; ***p<0.001 (Mann-Whitney).

- In conclusion, no evidence of SC-58635 induced toxicity was observed in the females at any dose level. There was no affect on mating and fertility indices, conception rates or the mean day of mating when female rats were treated with SC-58635 at dose levels up to 300 mg/kg/day. For the treated females, the numbers of implantation sites and live embryos were significantly ↓ at dose levels of ≥50 mg/kg/day that resulted in significantly ↑ pre- and post-implantation losses. In addition, significant reductions in the numbers of corpora lutea were seen in the ♀ @ 300 mg/kg/day. Therefore, the NOAEL was 30 mg/kg/day for female rats in this study.

2.4.1.3. Study Of Fertility And Early Embryonic Development Through Implantation With SC-58635 In The Female Rat (2 Week Oral Administration Followed By 2 Week Reversal Prior To Mating)(SA 4402), Document No.: P30S4402; Date: 26-Aug-1996 (Vol. 1.57, p. 273-464)

Report Nº: P30S4402
Study Nº: SA4402
Study Aim: To evaluate the reversibility of SC-58635 induced effect on fertility and early embryonic development in female rats
Compound: SC-58635 (Lot Nº 94K014-A3B)

Vehicle Control: 0.5% (w/v) methylcellulose and 0.1% Polysorbate in distilled and deionized H_2O

Dose & Route: 0, 60 and 300 mg/kg/day po by gavage

Animals: 75 ♀ Sprague-Dawley rats, Crl:CD•(SD)BR, weighing 177-245 g, 8-9 weeks of age, 25/group

Group	Dose (mg/kg/day)	Nº of ♀
1	0	25
2	60	25
3	300	25

Study Location: (b)(4)(CC) [redacted]

Compliance with GLP/QAU: Yes

Study Date: 6/13/95 - 8/6/95

Study Design: The animals were orally dosed with SC-58635 daily for 14 days followed by a 14-day reversal period before mating. The following parameters were monitored.

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - 1x/week.
- Body Weight & Food Consumption - Gestation Days 0, 3, 7, 10, and 13.
- Necropsy - Gestation Day 13.
- Estrous Cycles - The estrous cycles were determined for 10 days prior to mating.
- Mortality and Clinical Signs - No death occurred. No treatment-related clinical signs were noted.
- Body Weight & Food Consumption - No SC-58635 treatment related effects were noted.
- Estrous Cycles - The estrous cycles were not altered.
- Maternal Reproductive Performance - Neither mating nor fertility indices were affected. Conception rates in the treated ♀ were comparable to the control. There were no significant changes in the numbers of corpora lutea, implantation sites, live and dead fetuses, early absorption or pre and post implantation losses.
- Necropsy - No remarkable findings were obtained during gross pathological examination.

Results: In the previous study (Study Nº SA4294)(2.3.1.1.), results showed that SC-58635 at doses ≥60 mg/kg caused a significant ↓ in the numbers of live fetuses and ↑ in the preimplantation losses when ♀ rats were treated with SC-58635 14 days before mating, and through Gestation Day 7. These effects were not observed in the present study when treated females were allowed to have a 14-day recovering period before mating. The length of treatment with SC-58635 in the current study was shorter than that indicated in the Study Nº SA4294. Therefore, under the current study condition, the effects of SC-58635 on female reproductive performance might be reversible.

2.4.2. TERATOLOGY STUDIES

2.4.2.1. An Embryo-Fetal Developmental Toxicity Study Of SC-58635 In Rats, SA 4362, Document No.: PSA95S-30-SA4362; Date: 06-Dec-1995 (Vol. 1.58, p. 1-172)

Included as an appendix to this report was:
Evaluation Of Plasma SC-58635 Concentrations In An Embryo-Fetal Developmental Toxicity Study In Rats, SA 4362, Document No.: MRC95S-30-950168; Date: 22-Sep-1995 (Vol. 1.58, p. 146-168)

Study Nº: SA4632

Report Nº: PSA95S-30-SA4632

Study Aim: To determine the possible adverse effects on the pregnant female rats and on the development of the embryo and fetus following multiple oral administration of SC-58635 on Gestation Days 7-18.

Compound: SC-58635 (Lot Nº 94K014-A3B) suspension in 0.5% methylcellulose (w/v), 0.1% polysorbate 80 (v/v) in dist. H_2O

Dosage & Route: 0, 10, 30, and 100 mg/kg/day, 10 ml/kg po from Gestation Days 6-17 for 12 days

Animals: ♀ Charles River (VAF) CD strain rats, weighing 182-288g, ~4 months of age, 20/group for the Study Nº SA4632, and 6/group and 2 in the control group for the companion PK study

Study Location: G.D. Searle, Skokie, IL

Compliance with QAU: Yes

Study Design: Pregnant female rats were dosed with SC-58635 at 0, 10, 30, or 100 mg/kg/day for 12 days (Gestation Days 6-17). All animals were observed for clinical signs at least once daily. All animals were sacrificed on Gestation Day 20. All maternal and fetal data were collected at necropsy. Blood samples were collected on Gestation Days 6 & 16 at 2, 3, 4, and 24 hr post dosing. Plasma SC-58635 concentrations were determined by a validated (b)(4)(C method.

Results:

- Clinical Observations & Mortality - One at 100 mg/kg in the companion PK study died due to dosing error. Two animals in the control group were excluded from the study due to inadvertent deprivation of H_2O intakes. No remarkable treatment-related clinical signs were noted.
- Food Consumption and Body Weight - No treatment-related changes were seen.
- Maternal Reproductive Performance - The data from any reproductive indices (Nº of corpora lutea, implantations, resorptions, dead fetuses, preimplantation loss, and postimplantation loss) were comparable across all dose groups. There was a slight but not statistical significant decrease in the of live fetuses observed in the 100 mg/kg group. The mean (±SD) live fetuses for control, 10, 30, and 100 mg/kg Groups were 13.7±2.1, 13.8±2.0, 13.5±2.0, and 12.1 ±3.0, respectively.
- Toxicokinetics - Dose-dependent but not dose-proportional increases in C_{max} and AUC were noted on Gestation Days 6 & 16. The summarized PK parameters obtained on Gestation Days 6 & 16 are presented in the following table. C_{max} and AUC values were higher on Gestation Day 16 than those values obtained on Gestation Day 6 for the animals receiving 10 and 30 mg/kg/day indicating that accumulation of SC-58635 had occurred after repeated dosing.

Parameter	10 mg/kg		30 mg/kg		100 mg/kg	
	Gestation Day 6	Gestation Day 16	Gestation Day 6	Gestation Day 16	Gestation Day 6	Gestation Day 16
AUC_{0-24} (μg•hr/ml)	20.3	37.1	43.9	67.0	134	115
AUC/Dose	2.03	3.71	1.46	2.23	1.34	1.15
C_{max} (μg/ml)	1.79	2.81	3.01	5.03	6.37	7.45
C_{max}/Dose	0.179	0..81	0.100	0.168	0.0637	0.0745
T_{max} (hr)	3.00	3.00	3.00	3.00	4.00	4.00

- Fetal Parameters - Live fetal body weights were similar among treated and control groups. Fetal external and visceral examination revealed that one fetus in the 10 mg/kg group with major malformation (elongated nose, right anophthalmia, displaced left eye, displaced ears, no mouth opening, a papillated left flap of tissue located next to the left eye, and missing the left kidney and ureter). Skeletal examination of this particular fetus also showed some alterations (malformations) with the characteristics of split, misshaped, and unossified skull bones. **Based on the data from skeletal examination, the incidence in the wavy ribs appeared to increase in the fetuses at 30 and 100 mg/kg groups with values of 7 in 4 litters and 23 in 7 litters respectively as compared with 5 in 2 litters in the control group.** It should be noted that data from the historical controls should be employed to compare the incidence for alterations (malformations) and variations in the external, visceral, and skeletal examinations.

Therefore, the no-observable-adverse-effect-level (NOAEL) for the maternal, reproductive, and fetal development in the present study was 100, 30, 10 mg/kg/day, respectively.

2.4.2.2. An Oral Study Of Embryo-Fetal Development In The Rat Administered SC-58635 (SA 4599), Document No.: P20S4599; Date: 03-Dec-1997 (Vol. 1.59, p. 1-375)

Included as an appendix to this report was:
Pharmacokinetics Of SC-58635 in An Oral Study Of Embryo-Fetal Development in The Rat Administered SC-58635 (SA4599), Document No.: M3097210; Date: 04-Sep-1997 (Vol. 1.59, p. 353-369)

Study Nº: SA 4599/COV6127-353
Report Nº: P20S4599
Study Aim: To evaluate the maternal and embryo-fetal toxicity and teratogenic potential of SC-58635 when administered once daily via oral gavage to pregnant rats during the period of organogenesis.
Compound: SC-58553 (Lot Nº 95K010-A1A) suspension in 0.5% methylcellulose (w/v) (400 cps) & 0.1% polysorbate 80 (v/v) in H_2O
Dose & Route: 0, 10, 30 and 100 mg/kg/day, 10 ml/kg for 12 days (Gestation Days 6-17) by gavage
Control vehicle: 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O, 10 ml/kg
Animals: ♀ Crl:CD®BR rats (Charles River, Kingston, New York), ~ 10-11 weeks of age, weighing 208 - 298 g at time of mating, 30/group for Toxicology study and 2-6/group for PK study.
Study Location: (b)(4)(CC)
Study Date: 6/3/97 - 6/20/97
Compliance with GLP/QAU: Yes
Study Design: Groups of 32-36 pregnant rats were dosed with SC-58635 or vehicle once daily for 12 days (Gestation Days 6-17) by oral gavage. Group assignments and dose levels are as follows:

Group	Dose	Nº Rats/Group	
	(mg/kg/day)	Toxicology Study	PK Study
1 (Control)	0	30	2
2 (Low)	10	30	6
3 (Mid)	30	30	6
4 (High)	100	30	6

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The following parameters were monitored.

- Mortality and Clinical Signs - 2x/day.
- Body Weight & Food Consumption - Gestation Days 0, 6, 8, 10, 12, 14, 16, 18 and 20.
- PK - on Gestation Days 6 and 17 at 0, 2, 3, 4 and 24 hr post dose.
- Cesarean Section and Necropsy - Gestation Day 20. Each animal were examined for cervical, thoracic, or abdominal visceral abnormalities. Abnormal viscera were preserved in 10% neutral-buffered formalin. The uterus from each gravid female was excised, weighed, and examined for the number and placement of implantation sites, live and dead fetuses, early and late resorptions, and any abnormalities. The uteri of apparently non-pregnant females were stained with ammonium sulfide for verification of pregnancy status. The ovaries were examined for the number of corpora lutea.
- Fetal Examination - Each fetus was sexed, weighed, examined for external abnormalities and sacrificed. Visceral examination was performed on ½ of the fetuses from each litter for assessing soft tissue development. The remaining fetuses were processed for skeletal examination using

the Alizarin Red S staining method. This evaluation included examination of the skull, long bones, vertebral column, rib cage, extremities, and pectoral and pelvic girdles. Bone alignment and degree of ossification were assessed. All fetuses were kept in Bouin's fixative (fetuses examined for visceral abnormalities) or glycerin (fetuses examined for skeletal abnormalities).

Results:

- Clinical Observations and Mortality - One ♀ @ 10 mg/kg was found dead on Gestation Day 20 as a result of dosing error (perforated esophagus) with clinical signs of swollen dorsal cervical area, swollen right shoulder, and few or no feces.
- Body Weights and Food Consumption - Significantly lower mean body weight (↓ 4% relative to control) and body weight change (↓ 28.5%) values were noted for the animals @ 30 mg/kg during the pretreatment interval (Gestation Days 0-6). A significant reduction (↓13.6 %) in food consumption was observed for the high dose group during Gestation Days 6-8.
- Gross Pathology - The Group 2 ♀ that died on Gestation Day 20 had a perforated esophagus, a large amount of food in the thoracic cavity and enlarged adrenals. Another Group 2 ♀ had a diaphragmatic hernia. There were no treatment related changes in gravid uterine weights, corrected terminal weights, and net body weight gains. The pregnancy rates were 97, 100, 100, and 100% for the main study females in Groups 1-4, respectively. The mean numbers of corpora lutea and implantation sites and percent preimplantation loss values of the SC-58635-treated animals were comparable to those of the control group. Values for the mean percent of early, late, and total resorptions and viable fetuses were comparable among all groups. There were no dead fetuses and the sex ratios and mean covariate fetal weights were similar among all groups.
- Fetal Evaluations - **A dose dependent increase in diaphragmatic hernia (soft tissue malformation) was noted.** The fetal and litter incidences for diaphragmatic hernia in each group are presented in the following table.

		Dose (mg/kg)			
		0	10	30	100
VISCERAL EVALUATION					
Litters Evaluated		29	29	30	30
Fetuses Evaluated		209	215	216	221
Soft tissue Malformations					
Diaphragmatic Hernia	Fetal Incidence	0	0	8 (3.7%)	31 (14%)
	Litter Incidence	0	0	6 (20%)	13 (43%)
SKELETAL EVALUATION					
Litters Evaluated		29	29	30	30
Fetuses Evaluated		207	218	211	222
Skeletal Variations					
Unossified Vertebral Centrum	Fetal Incidence	5 (2.4%)	0	3 (1.4%)	11 (5.0%)
	Litter Incidence	4 (14%)	0	3 (10%)	7 (23%)
Bipartite Vertebral Centrum	Fetal Incidence	5 (2.4%)	4 (1.8%)	1 (0.5%)	8 (3.6%)
	Litter Incidence	4 (14%)	3 (10%)	1 (3.3%)	7 (23%)
5th Sternebrae Incomplete Ossification	Fetal Incidence	64 (31%)	71 (33%)	88 (42%)	109 (49%)
	Litter Incidence	23 (79%)	22 (76%)	25 (83%)	29 (97%)
Sternebrae Asymmetrically Ossified	Fetal Incidence	3 (1.4%)	1 (0.5%)	12 (5.7%)	9 (4.1%)
	Litter Incidence	2 (6.9%)	1 (3.4%)	9 (30%)	8(27%)
Skeletal Malformations					
Absent Bone in Skull	Fetal Incidence	0	0	0	1 (0.5%)
	Litter Incidence	0	0	0	1 (3.3%)
Vertebral Anomaly with/without Rib Anomaly	Fetal Incidence	0	0	0	1 (0.5%)
	Litter Incidence	0	0	0	1 (3.3%)

- PK - SC-58635 was absorbed systemically and plasma levels of SC-58635 increased non-proportionally with dose. The mean PK parameters are presented in the following table.

PK Parameter	10 mg/kg		30 mg/kg		100 mg/kg	
	Gestation Day 6	Gestation Day 17	Gestation Day 6	Gestation Day 17	Gestation Day 6	Gestation Day 17
AUC_{0-24} (μg•hr/ml)	45.7	47.6	54.3	104	140	115
AUC/Dose	4.57	4.76	1.81	3.47	1.4	1.15
C_{max} (μg/ml)	3.79	3.20	4.91	5.43	7.66	- 7.41
C_{max}/Dose	0.379	0.320	0.164	0.181	0.0766	0.0741
T_{max} (hr)	3.00	3.00	3.00	4.00	4.00	3.00

2.4.2.3. A Range-Finding Study of SC-58635 In Pregnant Rabbits, Document No.: PSA95S-30-EX4310; Date: 27-Mar-1995 (Vol. 1.60, p. 1-69)

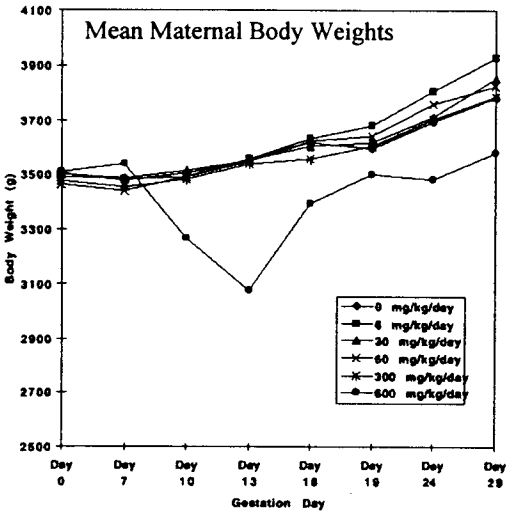
Included as an appendix to this report was:
Searle Memo Report Of SC-58635 Plasma Concentrations In A Range-Finding Study Of SC-58635 In Pregnant Rabbits, EX4310, Document No.: MRC-95S-0032; Date: 26-Jan-1995 (Vol. 1.60, p. 58-64)

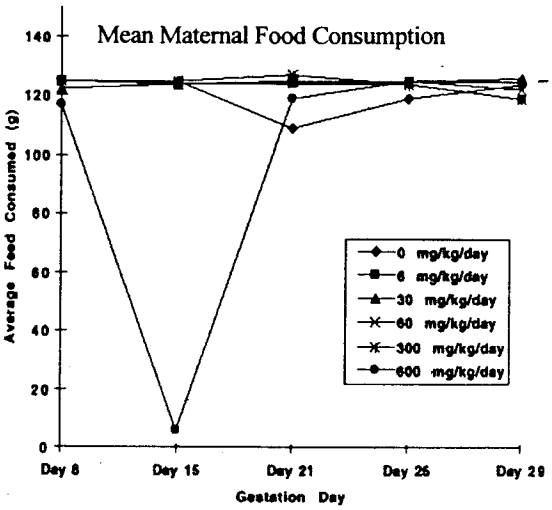
Study Nº: EX4310
Report Nº: PSA-95S-30-EX4310
Study Aim: To evaluate the potential toxic effects of SC-58635 on fetal viability in rabbits
Compound: SC-58553 (Lot Nº 94K014-A3B) suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O
Dose & Route: 6, 30, 60, 300, and 600 mg/kg/day, 10 ml/kg for 12 days by gavage
Control vehicle: 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O, 10 ml/kg
Animals: 36 nulliparous ♀ New Zealand White rabbits, approximately 5 mon of age; Strain Hra:(NZW)SPF; Weight: 3045 - 3929 g; 6/group
Study Location: G.D. Searle, Skokie, IL
Study Date: 11/28/94 - 12/20/94
Compliance with GLP/QAU: No
Study Design: Pregnant rabbits, 6 groups of 6, were orally administered with SC-58635 (6, 30, 60, 300, or, 600 mg/kg) or vehicle via gavage for 12 days from Gestation Days 7-18. Animals were examined daily for mortality and clinical signs starting on Gestation Day 7. Body weights were measured on Gestation Days 0, 7, 10, 13, 16, 19, 24, and 29. Food consumption was measured for the 24 hr interval on Gestation Days 7-8, 14- 20-21 24-25, and 28-29. Blood samples was taken on Gestation Days 7 and 17 at selected time points for the determination of plasma SC-58635 levels. All surviving animals were sacrificed on Gestation Day 29. Gross pathological examine was performed and the reproductive tracts were evaluated to acquire the numbers of corpora lutea, implantations, resorptions, and live and dead fetuses. All fetuses were individually weighed and examined.

Results:

- Clinical Signs and Mortality - No treatment-related mortality occurred at any dosage level. One rabbit from each of 6 and 300 mg/kg/day group died from gavage error on Gestation Day 11. Post mortem examinations showed foamy, fluid-filled lungs. One female in 600 mg/kg/day group aborted on Gestation Day 24. Two rabbits in the same group showed clinical sings of red materials.

- Body Weight and Food Consumption - Decreased body weights during treatment period, Gestation Days 7 - 18 and a marked decrease in food consumption between Gestation Days 14-15 were noted in rabbits receiving SC-58635 600 mg/kg/day group as depicted in the following figure.





- Female Reproductive Parameters - It appeared that no drug related effects on the mean numbers of corpora lutea, implantations, resorptions, fetal weights and live or dead fetuses were noted in groups of rabbits receiving ≤300 mg/kg/day. In the 600 mg/kg/day group, significantly increased post-implantation losses ($p \leq 0.003$) and decreased live fetuses ($p \leq 0.014$) were noted. External examination of fetuses revealed no SC-58635 treatment associated changes. In conclusion, SC-58635 had significant maternal toxicity and embryo-fetal toxicity at the level of 600 mg/kg/day by the evidence of weight losses, reduced food consumption, clinical signs, significantly higher post-implantation loses, and significantly reduced live fetuses.
- PK- SC-58635 could be detected in all plasma samples indicating that it was systemically available at all dosage levels. Mean plasma SC-58635 concentrations on treatment Days 1 and 11 (Gestation Days 7 and 17) are listed in the following table.

Dose (mg/kg)	Plasma SC-58635 Concentration (μg/ml)							
	2 hr		3 hr		4 hr		24 hr	
	Day 1	Day 11	Day 1	Day 11	Day 1	Day 11	Day 1	Day 11
6	0.108	0.167	0.132	0.155	0.125	0.173	-	0.0132
30	0.49	0.454	0.535	0.462	0.559	0.673	0.0591	0.0663
60	0.838	0.655	1.17	1.02	0.837	0.737	0.227	0.212
300	1.64	2.65	1.94	3.45	1.89	2.97	1.69	1.95
600	2.1	10.1	2.83	8.49	2.54	10.2	2.64	6.25

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2.4.2.4. A Pilot Study Of SC-58635 In Rabbits, Document No.: PSA95S-30-EX4309; Date: 20-Feb-1995 (Vol. 1.60, p. 70-85)

Included as an appendix to this report was:
Searle Memo Report Of SC-58635 Plasma Concentrations In The Pilot Study Of SC-58635 In Pregnant Rabbits, EX4309, Document No.: MRC-95S-0031; Date: 23-Jan-1995 (Vol. 1.60, p. 83-85)

Study Nº EX4309
Report Nº PSA95S-30-EX4309
Study Aim: To evaluate the potential toxic effects of SC-58635 and to establish PK data for dosage selection in a range-finding study in rabbits

Compound: SC-58553 (Lot Nº 94K014-A1B) suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O
Dose & Route: 200, 400, and 600 mg/kg/day, 10 ml/kg for 4 days by gavage
Animals: 6 mated ♀ New Zealand White rabbits (Gestation Days 19-21), 6 to 7 months of age; Strain Hra:(NZW)SPF; Weight: 3494 - 4267 g; 2/group
Study Location: G.D. Searle, Skokie, IL
Study Date: 11/7-11/1994
Compliance with GLP/QAU: No
Study Design: Female rabbits, 2/group, were given SC-58635 suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O at levels of 200, 400, or 600 mg/kg/days for 4 days by gavage. Clinical signs and mortality were monitored daily. Blood sampling was taken for plasma SC-58635 determination at approximately 2, 3, 4, and 24 hr following the first dosing and 24 hr following the last dosing. Animals were subjected to post-mortem examinations on day 5.

Results: Animals receiving 600 mg/kg/day had decreased body weights (↓ 5% on Day 5) with signs of few, soft, and small or no feces. No significant changes were attributable to the treatment at post-mortem. Plasma SC-58635 concentrations were as followings:

Dose	Mean Plasma SC-58635 Levels (μg/ml)				
(mg/kg/day)	Day 1				Day 4
	2 hr	3 hr	4 hr	24 hr	24 hr
200	3.44 ± 0.51	3.52 ± 0.97	2.77 ±0.61	1.97 ± 0.41	1.75 ± 0.82
400	3.86 ± 0.86	3.46 ± 0.42	3.78[a]	3.61 ± 0.69	3.70 ± 0.78
600	3.55 ± 0.17	4.93 ± 0.98	3.73 ± 0.15	5.72 ± 0.56	5.99 ± 2.76

[a]Data was obtained from a single animal.

Based on data presented in the current study, SC-58635 was considered to be toxic at 600 mg/kg/day level.

2.4.2.5. A Segment II Developmental Toxicity Study Of SC-58635 In Rabbits, Document No.: PSA95S-30-SA4342; Date: 25-Oct-1995 (Vol. 1.60, p. 86-255)

Included as an appendix to this report were:

1. Evaluation Of Plasma SC-58635 Concentrations In A Segment II Developmental Toxicity Study Of SC-58635 In Rabbits (SA4342), Document No.: MRC95S-30-950134; Date: 24-Jul-1995 (Vol. 1.60, p. 223-245)
2. Final Report Amendment No. 1: A Segment II Developmental Toxicity Study Of SC-58635 In Rabbits (SA4342), Document No.: P31S4342; Date: 16-Oct-1997 (Vol. 1.60, p. 249-255)

Study Nº: SA4342
Report Nº: PSA95S-30-SA4342
Study Aim: To determine the possible adverse effects on the pregnant female rabbits and on the development of the embryo and fetus following multiple oral administration of SC-58635 on Gestation Days 7-18.
Compound: SC-58635 (Lot Nº 94K014-A3B) suspension in 0.5% methylcellulose (w/v), 0.1% polysorbate 80 (v/v) in dist. H_2O
Dosage & Route: 0, 60, 150, and 300 mg/kg/day, 10 ml/kg po from Gestation Day 7-18 for 12 days
Animals: New Zealand White ♀ rabbits (Hra:SPF), weighing 2821-4821 g, 4-6 months of age, 20/group
Study Location: G.D. Searle, Skokie, IL
Study Date (In-Life): 2/5/95 - 3/3/1995.

Compliance with QAU: Yes

Study Design: Pregnant female rabbits were dosed with SC-58635 at 0, 60, 150, or 300 mg/kg/day for 12 days (from Gestation Days 7-18). All animals were observed for clinical signs at least once daily. All rabbits were sacrificed on Gestation Day 29 and all maternal and fetal data were collected. Blood samples were collected on Gestation Days 7 & 19 at 1, 2, 3, 4, 8, and 24 hr post dosing. Plasma SC-58635 concentrations were determined by a validated HPLC method.

Results:

- Clinical Observations & Mortality - Two in each of 60 and 300 mg/kg groups were found dead as results of dosing errors. Reduced feces, soft stool and fecal tinted fur were seen scattered across all groups.
- Food Consumption and Body Weight - Food intake and body weight gains were comparable among treated and control animals.
- Toxicokinetics - Dose-dependent but not dose-proportional increases in C_{max} and AUC were noted on Gestation Days 7 & 19. The following table showed summarized PK parameters obtained on Gestation Days 7 & 19. C_{max} and AUC values were higher on Gestation Day 19 than those values obtained on Gestation Day 7 indicating that accumulation of SC-58635 had occurred after repeated dosing.

Parameter	60 mg/kg		150 mg/kg		300 mg/kg	
	Gestation Day 7	Gestation Day 19	Gestation Day 7	Gestation Day 19	Gestation Day 7	Gestation Day 19
AUC (μg•hr/ml)	14.9	22.5	24.5	41.5	37.4	89.0
AUC/Dose	0.249	0.375	0.164	0.227	0.125	0.297
Cmax (μg/ml)	0.951	1.49	1.41	2.37	1.76	5.14
C_{max}/Dose	0.0158	0.0248	0.00942	0.0158	0.00585	0.0171
T_{max} (hr)	8.00	8.00	8.00	8.00	4.00	8.00

- Fetal Parameters - External and visceral fetal examination showed a slight increase in sternebrae fused of the fetuses at 150 mg/kg group. There was a slight and dose-dependent increase in the incidence of misshapen sternebrae in the fetuses at 150 and 300 mg/kg groups during skeletal examination.

	Dose (mg/kg/day)			
	Control	60	150	300
Nº. Live Fetuses Examined	177	121	153	111
Nº Litter Examined	20	17	20	16
TYPE AND NUMBER OF FETAL ALTERATIONS: (Nº of Fetuses/Nº of Litters)				
Ribs Fused (M)	1 (0.6%)/1	2 (1.7%)/1	2 (1.3%)/2	4 (3.6%)/4
Sternebrae fused (M)	1 (0.6%)/1	2 (1.7%)/2	13 (8.5%)/10	5 (4.5%)/4
Sternebrae Misshapen (V)	2 (1.2%)/2	3 (2.5%)/3	6 (3.9%)/4	5 (4.5%)/2

- Maternal Reproductive Performance - Oral administration of SC-58635, at dosages of 150 mg/kg/day, to pregnant rabbits did not have adverse effects on the average of corpora lutea, implantations, resorption and live or dead fetuses. In contrast, at the dose level of 300 mg/kg, SC-58635 caused significant decreases in the numbers of live fetuses and significant post-implantation losses (resorption and dead fetuses) as shown in the following table.

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REPRODUCTIVE STATUS OF PREGNANT FEMALES AT SACRIFICE

DOSE GROUP		FETAL OBSERVATIONS						
		CORPORA LUTEA	IMPLAN-TATIONS	RESORP-TIONS	LIVE FETUSES	DEAD FETUSES	PREIMP. LOSS(a)	POSTIMP LOSS(b)
CONTROL	MEAN	11.2	9.6	0.8	8.9	0.0	1.6	0.8
	IMN(c)	10.9	9.6		8.9		1.1	0.6
	STD	2.1	2.4	1.1	2.2	0.0	1.6	1.1
	N	20	20	20	20	20	20	20
60 MG/KG SC-58635	MEAN	10.2	8.1	1.0	7.1	0.0	2.1	1.0
	IMN(c)	10.0	8.3		7.4		1.4	0.7
	STD	1.8	2.2	1.5	2.3	0.0	2.6	1.5
	N	17	17	17	17	17	17	17
	P-VALUE (TREND)				.025*			
150 MG/KG SC-58635	MEAN	9.9	8.9	1.3	7.7	0.0	1.0	1.3
	IMN(c)	9.6	9.0		7.9		0.8	0.9
	STD	1.7	2.1	1.4	2.6	0.0	1.0	1.4
	N	20	20	20	20	20	20	20
	P-VALUE (TREND)				.025*			.17
300 MG/KG SC-58635	MEAN	10.9	9.5	2.6	6.9	0.1	1.4	2.6
	IMN(c)	10.4	9.4		7.2		0.9	2.1
	STD	2.7	3.0	2.0	3.2	0.3	1.8	2.0
	N	16	16	16	16	16	16	16
	P-VALUE (TREND)	(d)	.21	(e)	.018*	(e)	1.0	.001*

(a) Calculated as Corpora Lutea - Implantations
(b) Calculated as Resorptions + Dead
(c) IMN computed only for those parameters statistically analyzed
(d) Tested only for global homogeneity, p-value = .19
(e) Parameter not statistically analyzed

Therefore, the lowest no-observable-effect level (NOEL) for maternal, reproductive, and developmental toxicity in the rabbits were 300, 150 and 60 mg/kg, respectively.

2.4.3. PERINATAL/POSTNATAL STUDY

2.4.3.1. A Study Of Pre And Postnatal Development With SC-58635 By Oral Administration In The Rat, (SA 4404), Document No.: P30S4404; Date: 21-Mar-1997 (Vol. 1.61-1.64)

Included as an appendix to this report was:
Evaluation Of Plasma Concentration Data In A Study Of Pre And Postnatal Development With SC-58635 By Oral Administration In The Rat, SA4404, Document No.: M3096141; Date: 28-Oct-1996 (Vol. 1.64, p. 202-218)

Study Nº:	SA4404/95903
Report Nº:	P30S4404
Study Aims:	To examine the effects of SC-58635 on gestation, parturition and lactation in the dams and the development, survival, physical development, behavior and reproductive performance of the pups.
Compound:	SC-58635 (Lot Nº 95K010-A1A)
Vehicle:	0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) in dist. H_2O
Dosage & Route:	0, 10, 30, or 100 mg/10 ml/kg po by gavage from Gestation Day 6 to Days 21-23 post partum
Animals:	Sprague-Dawley rats, Crl:CD®(SD)BR, 12 weeks of age, weighing 212-292 g, 25 ♀/group

Study Date (In-Life): 10/2/95 - 2/20/96
Study Site: (b)(4)(CC) [redacted]

GLP/AUC: Yes

Study Design: Group of 25 pregnant ♀ (F_0) were given SC-58635 at doses of 10, 30, and 100 mg/10 ml/kg/day from Gestation Day 6 through Days 21-23 post partum by oral gavage. F_1 generation (1/sex from each litter), weaned on Day 21 post partum, was examined for physical, reflex/sensory development, behavior and reproductive performance. All non-selected pups were subjected to a gross examination. The following observations were performed.

Group	Compound	Dose (mg/kg/day)	Nº of mated ♀
1	Vehicle Control	0	25
2	SC-58635	10	25
3	SC-58635	30	25
4	SC-58635	100	25

F_0 Generation:
- Clinical Signs and Mortality - 2x/day
- Body Weight - Gestation Days 0, 6, 9, 12, 15, 18, and 20 and Post Partum Days 0, 4, 7, 10, 14, 17 and 21.
- Food Consumption - Gestation Days 0-6, 6-9, 9-12, 12-15, 15-18, and 18-20.

F_1 Litter Observation:
- Clinical Condition - 1x/day during the lactation period.
- Body Weight - Days 4, 7, 10, 14, 17, and 21 post partum.
- Culling - On Day 4 post partum, the litter was culled to 8 pus (4♂ & 4♀)
- Physical Development - Day 1 post partum and on onward: pinna unfolding; Day 7 post partum and on onward: tooth eruption; Day 12 post partum and on onward : eye opening.
- Reflexological Development - Days 2 and on onward or 4 post partum.
- Weaning and Selection for F_1 Adult Generation - Day 21 post partum, 1♂ and 1♀ were selected from each litter to form F_1 adult generation.

F_1 Adult Observation:
- Clinical Condition - 2x/day
- Body Weight - Gestation Days 0, 6, 9, 12, 15, 18, and 20.
- Physical Development - ♀: Day 26 post partum and on onward, assessment of vaginal opening; ♂: Day 35 and on onward, assessment of preputial separation.
- Visual Function (pupillary closure and visual placing)- Day 21 post partum
- Behavior Performance -
  Motor Activity: Figure 8 mazes assessment on Days 35 (±1) and 60 (±2) post partum.
  Auditory Startle Habituation: startle habitation assessment on Day 55 (±2) post partum.
  'E' Water Maze: Days 60 and 70 post partum
- Mating Procedure - On Day 85, 1♂ and 1♀ from the same dose group were placed together for a maximum of 14 days. Vaginal lavage was examined for spermatozoa and to identify pregnancy.
- Observation at parturition - 3x/day from Gestation Day 20 for signs of parturition and any sign of dystocia.

F_2 Generation:
- Pups - On Day 0 post partum, the pus were weighed and examined for malformations, sexed and the number of alive and dead recorded.
- Clinical Condition and Mortality - 1x/day.
- Body Weight - Days 0 and 4 post partum.

Terminal Sacrifice:

F_0 and F_1 Adult Generation - Necropsy and gross pathological examination were performed. F_1 males were sacrificed immediately after the end of mating period. F_1 females that failed to mate were sacrificed 26-28 days after the end of mating period. F_0 dams were sacrificed on Days 21-

23 post partum and the number of implantation sites were recorded. F_1 dams were sacrificed on Days 4 or 5 post partum and the number of implantation sites were recorded. The following were retained in 10% neutral buffered formalin for fixation and possible future histopathological examination: animal identification, seminal vesicles, epididymides[10], testes[10], mammary glands (thoracic and inguinal), uterus, vagina, ovaries, abnormal tissues, and prostate. All digestive tracts retained as abnormal tissues of all F_0 females who died preterminally or were sacrificed in a moribund condition, and selected tissues retained as abnormal for the F_1 females in the 30 and 100 mg/kg/day treated groups were prepared for histological examination.

F_1 and F_2 Pups - Pups dying or sacrificed as malformed on or before Day 7 post partum for the F_1 generation and Day 4 post partum for the F_2 generation were placed in Bouin's fluid for subsequent examination using a modified Barrow and Taylor[11] technique. A complete necropsy was performed on pups of the F_1 generation dying or sacrificed between Days 8 and 21 post partum and postweaning F_1 generation not selected for breeding or for the determination of plasma concentrations of SC-58635.

On Day 4 or 5 post partum, any externally abnormal F_2 generation pups were examined as described above for pups dying or malformed. Externally normal F_2 generation pups were euthanized and discarded without further examination.

PK/TK:

F_0 Generation: Plasma samples were obtained from 5 dams/group for the vehicle control, 10 and 30 mg/kg/day treated groups and 4 dams/group for the 100 mg/kg/day treated group.

F_1 Generation - Plasma samples were obtained from pups that were not selected for breeding for the determination of SC-58635 plasma concentrations at terminal sacrifice.

Results:

F_0 Generation:

- Clinical Signs and Mortality - Deaths or moribund were found in 1 ♀ @ 30 mg/kg/day and 8 ♀ @ 100 mg/kg/day group with clinical findings of fur staining of the muzzle and urogenital regions, thin body condition and prominent backbone, body condition dehydrated/weak, cold to touch, decreased muscle tone, decreased activity, pale skin, shallow respiration, discharges from eyes/vagina, and firm abdominal structure. Deaths were the result of peritonitis and/or gastrointestinal lesions.
- Body Weights and Food Consumption - Similar body weights and body weight gains during gestation and lactation were seen in the control and treated groups. A dose-related, transitory, decrease in food consumption was noted for all treated groups from Gestation Days 6 to 9 (78.3, 76.3, 75.0, and 71.4 grams/animal for the control 10, 30, and 100 mg/kg/day groups, respectively).
- F_0 Reproductive Performance - A slight ↓ in the gestation index was seen in ♀ at the 30 and 100 mg/kg/day groups (95.8 and 92.0 %, respectively vs. 100% in the control group) as a result of the deaths of one pregnant animal in the 30 mg/kg/day group and 2 pregnant animals in the 100 mg/kg/day group during gestation. A significant ↓ in the mean number of live pups was observed in mid- and high-dose ♀ (15.6, 14.5 and 14.1 live pups/litter in the control, 30 and 100 mg/kg/day groups, respectively). A significant ↑ in the incidence of litters with dead pups was also observed in mid dose (5 dead pups from 23 litters) and high dose (8 dead pups from 23 litters) groups.

F_1 Generation:

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[10] Fixed with Zenker's fluid for sacrificed rats only.

[11] Barrow, M.V. and Taylor, W.J., 1969. A rapid method for detecting malformations in rat fetuses. J. Morph. 127: 291-306.

- F_1 Pups - Pup viability, body weights, survival and lactation indices were comparable across all groups and there were no treatment-related clinical observations for the F_1 generation pups. Dilation of various gastrointestinal segments, digesta changes and/or urinary bladder changes were noted in pups born to dams that were found dead or at moribund in the 100 mg/kg/day group. These observations might be secondary to the deteriorating condition of the dams.
- Visual Function - Comparable results were seen in all groups for the visual placing and pupillary closure.
- Physical Development - Pups born to dams in mid and high dose groups showed significant delayed in the mean days of preputial separation. The mean day of development of tooth eruption and the values for righting reflex, negative geotaxis and auricular startle were similar between groups.
- Behavior Assessment - No remarkable findings were attributable to the treatment.
- Reproductive Performance - There were no significant differences in the parental and maternal performance parameters (mating and fertility index, conception rate, gestation index, length of gestation, implantation sites and live birth index).

F_2 Generation:

- Viability, Clinical Signs, Body Weights and Gross Pathological Findings - No differences were found.

PK/TK: SC-58635 was absorbed and systemically available to the F_0 dams and their offspring The following table shows the range of plasma concentrations of SC-58635 seen in the dams and pups.

DOSE (mg/kg/day)	Range of Plasma Concentrations of SC-58635 (μg/ml)	
	DAMS	PUPS
10	0.175 - 0.660	<0.0250 - 0.0484
30	0.422-1.20	<0.0250 - 0.435
100	<0.0250 - 2.44	<0.0250 - 7.15

Based on the results of this study the NOAEL for the survival, physical development, behavior and reproductive performance of the F_1 ♂ and ♀ was 100 mg/kg/day as only minor changes were seen in development. The NOAEL for F_0 toxicity was 10 mg/kg/day due to mortality at 30 and 100 mg/kg/day and an increase in dead pups at 30 and 100 mg/kg/day.

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2.5. GENETIC TOXICOLOGY

2.5.1. *IN VITRO TESTS*

2.5.1.1. An Evaluation Of The Mutagenic Potential Of SC-58635 In The Ames Salmonella/Microsome Assay, Document No.: PSA-94S-4242; Date: 18-Jul-1994 (Vol. 1.65, p. 1-23)

Study Nº: SA4242
Report Nº: PSA-94S-4242
Study Aim: To evaluate mutagenic potential of SC-58635 using Ames Salmonella/microsome assay
Compound: SC-58553 (Lot Nº C00025) dissolved in DMSO, 100 mg/ml
Dose: 10, 50, 100, 500, 1000, and 5000 μg/plate.
Vehicle Control: DMSO, 50 μl/plate
Indicator Cells: *Salmonella typhimurim* strains (histidine auxotrophs) TA97a, TA98, TA100, TA1535 and TA1538
S9 Mix: Aroclor 1254-induced rat-liver S9 homogenate
Positive Control:

Chemical	S9 Mix	Tester Strains	Conc. (μg/plate)
NaN_3 (sodium azide)	-	TA1535, TA100	1
2-Nitrofluorene	-	TA 1538, TA98	2.5
ICR-191 acridine	-	TA97a	0.5
2-Aminoanthracene	+	TA97a, TA98, TA100, TA1535, TA1538	1.0

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Test Article Exposure Time: 48 hr at 37°C
Study Location: Searle Research and Development, Skokie, IL
Study Date: 5/3/94 - 5/5/94
Compliance with GLP/QAU: Yes

Results: A precipitate was observed when *Salmonella typhimurim* (all tested strains) incubated with SC-58635 at concentrations 1000 and 5000 μg/plate and colony counts were not determined at these concentrations. SC-58635 was toxic at concentrations of ≥500 μg/plate as a reduction in the number of revertants and the presence of microcolonies. Therefore, SC-58635, at concentrations up to 500 μg/plate, was not mutagenic at any concentrations under current testing system.

2.5.1.2. An Evaluation Of The Mutagenic Potential Of SC-58635 In The CHO/HGPRT Mutation Assay, Document No.: PSA-94S-4299; Date: 05-Dec-1994 (Vol. 1.65, p. 24-52)

Study Nº: SA4299
Report Nº: PSA-94S-4299
Study Aim: To evaluate mutagenic potential of SC-58635 using CHO/HGRT mutation assay
Compound: SC-58553 (Lot Nº 94K014-A1B) dissolved in DMSO
Positive Controls: ICR-191 acridine, 1 μg/ml; 3-methylcholanthrene (MCA), 1 μg/ml
Dose:
Range-Finding: 0.08, 0.27, 0.80, 2.67, 8.0, 2.67, 8.0, 26.67, 80.0, 266.67, and 800.0 μg/ml
-S9: 4, 8, 12, and 16 μg/ml
+S9: 15, 30, 45, and 60 μg/ml
Indicator Cells: CHO cells (subline K1-BH4)

S9 Mix: The 9000 x g supernatant fraction of the liver homogenate from Aroclor 1254-treated rats (b)(4)(CC)

Exposure Time: -S9: 20-24 hr at 37°C; +S9: 4 hr at 37°C

Study Location: G.D. Searle, Skokie, IL

Study Date: 10/5/94 - 11/4/1994

Compliance with GLP/QAU: Yes

Study Design: Cells were treated with various concentrations of SC-58635 or positive control compounds, either for 20-24 hr without metabolic activation or approximately 4 hr with metabolic activation.

Results: Results of the dose range finding cytotoxicity test in the presence or absence of metabolic activation are shown in the following table.

Compounds	Concentration (μg/ml)	Relative Cell Survival (%)	
		-S9	+S9
DMSO	1% (v/v)	100	100
SC-58635	0.08	68	94
	0.27	88	81
	0.80	82	83
	2.67	65	78
	8.00	49	81
	26.67	NC	60
	80.00	NC	NC
	266.67	NC	NC
	800	NC	NC

NC = Not cloned due to insufficient cell numbers.

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Data from the mutation experiment with or without S9 mix are presented in the following table. Apparently, under the test condition without S9 mix, the concentrations of SC-58635 used did not reach maximum condition as 47% of cell survival were observed at 16 μg/ml, the highest concentration tested[12]. Therefore, celecoxib was not mutagenic at doses up to 16 μg/ml and 45 μg/ml in the absence and presence of S9 activation, respectively.

Compounds	-S9			+S9		
	Concentration (μg/ml)	Cell Survival on Day 1 (%)	Mutant Colonies/1x10^6 Clonable Cells	Concentration (μg/ml)	Cell Survival on Day 1 (%)	Mutant Colonies/1x10^6 Clonable Cells
DMSO	1%(v/v)	100	1.5	1% (v/v)	100	1.1
ICR-191 acridine	1	27	362.8**	-	-	-
MCA	-	-	-	1	53	166.1**
SC-58635	4	78	1.7	15	80	0.6
	8	68	1.0	30	69	1.7
	12	58	3.8	45	7	0.0
	16	47	0.6	60	NC	-

** significant at $p \leq 0.01$.

2.5.1.3. An Evaluation Of The Potential Of SC-58635 To Induce Chromosome Aberrations In Vitro In Chinese Hamster Ovary (CHO) Cells, Document No.: PSA-94S-4302; Date: 17-Nov-1994 (Vol. 1.65, p. 53-92)

Study Nº: SA4302

Report Nº: PSA94S-SA4302

Study Aim: To evaluate mutagenic ability of SC-58635 to induce chromosomal aberrations in CHO-WBL cells

Compound: SC-58553 (Lot Nº 94K014-A1B) dissolved in DMSO

[12] ICH S2A Document: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals, 19 July 1995.

Dose: 0.08, 0.27, 0.80, 2.67, 8.0, 2.67, 8.0, 26.67, 80.0, 266.67, and 800.0 μg/ml for range-finding study; 10, 20, and 40 μg/ml for assay condition -/+ S9 activation mixtures
Vehicle Control: DMSO, 200 μl
Positive Controls: Mitomycin C (MMC), 0.5 μg/ml; Cyclophosphamide (CP), 5 μg/ml
Indicator Cells: CHO cells (subclone WBL)
Exposure Time: -S9, 4 and 24 hr; +S9, 4 hr
Study Location: G.D. Searle, Skokie, IL
Study Date: 10/4/95 - 11/2/94
Compliance with GLP/QAU: Yes
Study Design: Cells with or without metabolic activation system (liver S9 homogenate) were treated with various concentrations of SC-58635 for 4 hr or 24 hr. Cells were washed and fresh complete culture medium was added. Twenty one to 22 hr from the beginning of dosing, colcemid (0.1 μg/ml) was added to cells for 1.5-2 hr. Cell were then collected and metaphase analysis were performed. The following parameters were calculations:

% Aberrant Cells = (Total number of cells with at least one aberration)/(Total number of cells examined per dose)x 100

Cell with >1 Aberration = (Total number of cells with two or more aberrations)/(Total number of cells examined per dose) x 100

Aberrations/cell = (Total number of aberrations)/(Total number of cells) x 100

Results: In the range finding cytotoxicity experiment, results showed that no viable cells could be found at the doses ≥80 μg/ml and precipitations occurred at doses ≥266.67 μg/ml in the presence or absence of S9. **An increase in cell endoreduplication was observed in cells treated with SC-58635 in the presence of activation mix. Higher frequency of endoreduplicated cells was noted at 30 and 40 μg/ml as shown in the following table.** The biological significance of this increasing incidence of cell abnormality is unknown.

Treatment	Dose	Cell Viability (%)			Endoreduplication (%)		
	(μg/ml)	Exp. 1	Exp. 2	Exp. 3	Exp. 1	Exp. 2	Exp. 3
DMSO	20 μl	100	100	100	0	1	0.5
SC-58635	20	100	100	116	4	-	0
	30	-	70	97	-	10	3
	40	41	46	45	14	9	17

No viable cells were noted in all experiments when cells were treated with 80 μg/ml of SC-58635. Data from the 4 hr aberration assays are shown in the following table.

Treatment	Dose	Nº Cells Scored		Abs/Cells		%Cells w/Abs		% Cells w/>1 Abs		% Cell Survival	
	μg/ml	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
DMSO	20 μl	200	200	0.010	0.000	1.0	0.0	0.0	0.0	100	100
MMC	0.5	66		≥0.667		45.5		13.6		72	
CP	5.0		71		≥0.704		43.7		18.3		55
SC-58635	10	200	200	0.000	0.010	0.0	1.0	0.0	0.0	101	107
	20	200	200	0.000	0.010	0.0	0.5	0.0	0.5	94	100
	40	200	200	0.020	0.030	2.0	1.0	0.0	0.5	49	41

2.5.2. *IN VIVO TEST*

2.5.2.1. An Evaluation Of The Potential Of SC-58635 To Induce Micronucleated Polychromatic Erythrocytes In The Bone Marrow Of Rats (Micronucleus Test), Document No.: PSA95S-30-SA4326; Date: 10-Mar-1995 (Vol. 1.65, p. 93-139)

Included as an appendix to this report were:

1. Final Report Amendment No. 1: An Evaluation Of The Potential Of SC-58635 To Induce Micronucleated Polychromatic Erythrocytes In The Bone Marrow Of Rats (Micronucleus Test), Document No.: PSA96S-31-SA4326; Date: 25-Mar-1996 (Vol. 1.65, p. 133-135)
2. Final Report Amendment No. 2: An Evaluation Of The Potential Of SC-58635 To Induce Micronucleated Polychromatic Erythrocytes In The Bone Marrow Of Rats (Micronucleus Test), Document No.: P31S4326; Date: 26-Feb-1997 (Vol. 1.65, p. 136-137)
3. Final Report Amendment No. 3: An Evaluation Of The Potential Of SC-58635_To Induce Micronucleated Polychromatic Erythrocytes In The Bone Marrow Of Rats (Micronucleus Test), Document No.: P33S4326; Date: 05-Mar-1997 (Vol. 1.65, p. 138-139)

Study Nº: SA4326
Report Nº: PSA95S-30-SA4326
Study Aim: To evaluate the potential of SC-58635 to induce micronuclei in the bone marrow polychromatic erythrocytes of 8 week old Sprague-Dawley rats
Compound: SC-58553 (Lot Nº 94K014-A1B) suspension in 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O; Cyclophosphamide (CP), 60 mg, served as positive control
Dose & Route: 150, 300, and 600 mg/kg/day for 3 days, 10 ml/kg, oral gavage
Control Vehicle: 0.5% methylcellulose (w/v) & 0.1% polysorbate 80 (v/v) in H_2O
Animals: 30♂ & 30♀ Sprague-Dawley rats, strain CD(SD)BR, ~8 weeks of age, weighing 239.6 - 262.5 g for % and 183.8 - 199.6 g for & rats
Study Location: G.D. Searle, Skokie, IL
Study Date: 12/6/1994 - 1/5/1995
Compliance with GLP/QAU: Yes
Study Design:

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Group	Dose	Nº Animals
Vehicle Control	10 ml	5/Sex
Cyclophosphamide	60 mg	5/Sex
SC-58635	150 mg	5/Sex
SC-58635	300 mg	5/Sex
SC-58635	600 mg	5/Sex

Animals were randomly assigned into 5 groups of 10 (5♂ & 5♀) and orally (by gavage) received either vehicle, cyclophosphamide (60 mg/kg) or SC-58635 (150, 300, or 600 mg/kg, 10 ml/kg) once daily for 3 days. Clinical sign and mortality were monitored. Animals were sacrificed on Day 4, approximately 24 hr post last dosing. Bone marrow from tibia of each animal was extracted; four smears were prepared and stained with acridine orange. Slides were evaluated for micronuclei in polychromatic (PCE) and erythrocytes.

Results: No overt clinical signs or mortality were observed. No SC-58635 induced micronucleus formation in any treatment group. In contrast, cyclophosphamide caused significant higher incidence ($p \leq 0.01$) of micronucleus formation compared to the vehicle control. Therefore, **SC-58635 did not cause micronucleated polychromatic erythrocytes in the bone marrow of rat was not a clastogen**.

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2.6. SPECIAL TOXICOLOGY STUDIES

2.6.1.1. Antigenicity Study Of SC-58635, Document No.: JBC-95-ZOAG-0276; Date: 03-Oct-1995 (Vol. 1.53, p. 40-106)

Study Nº: JBC-95-ZOAG-0276

Study Aims: To assess the antigenic potentials of SC-58635 by Active Systemic Anaphylaxis (ASA) Reaction with ♂ guinea pigs following oral or subcutaneous sensitization, by Homologous Passive Cutaneous Anaphylaxis (HmPCA) Reaction using sera of ASA animals and by Heterologous Passive Cutaneous Anaphylaxis (HtPCA) Reaction in rats using ♂ mice sera after oral or ip sensitization.

Compound: SC-58635 (Lot Nº 94K031-A2A) in methylcellulose (MC)-Tween 80 (5:1 w/w in H_2O) for sensitization use or in polyethylene glycol (PEG) 400- H_2O (2:1 v/v) for challenge use

Dose and Route:

- ASA Reaction - Test articles were prepared as followings:
  - Oral Sensitization Preparation - SC-58635, 5 or 25 mg/3ml methylcellulose-Tween 80
  - Subcutaneous Sensitization Preparation - 25 mg/3ml SC-58635 in MC-Tween 80 and Freund's Complete Adjuvant (FCA) (1:1 v/v)
  - Challenge Preparation - SC-58635, 5 mg/ml in PEG 400- H_2O; Bovine Serum Albumin (BSA), 3mg/ml in saline
- Homologous Passive Cutaneous Anaphylaxis (HmPCA) Reaction - Test articles were prepared as followings
  - Challenge Solution Preparation - SC-58635, 5 mg/ml in PEG 400- H_2O; Bovine Serum Albumin (BSA), 3mg/ml in saline; Evans Blue 10 mg/ml in saline
  - Sera from ASA animals for Intradermal Inoculation - 1/5, 1/15, and 1/45 dilutions for sera from SC-58635 sensitized animals; 1:100, 1/300 and 1/900 dilutions for sera from BSA sensitized animals.
- Heterologous Passive Cutaneous Anaphylaxis (HtPCA) Reaction -
  Oral Sensitization Preparation - SC-58635, 5 or 25 mg/20ml methylcellulose-Tween 80
  IP Sensitization Preparation - SC-58635, 25 mg/20 ml of MC and Alum in saline (1:1 v/v); BSA, 3 mg/20 ml of MC and Alum in saline (1:1 v/v)
  Challenge Solution Preparation - SC-58635, 5 mg/ml in PEG 400- H_2O; Bovine Serum Albumin (BSA), 3mg/ml in saline; Evans Blue 10 mg/ml in saline.

Animals: 5-7 weeks old ♂ Crj:Hartley guinea pigs, weighing 351-388 g for ASA reaction and 477-511 g for HmPCA reaction; 9 weeks old C3H/HeNCrj ♂ mice used in HtPCA sensitization, weighing 27-29 g; and 9 weeks old ♂ Crj:CD (SD) rats used in HtPCA challenge, weighing 332-366 g.

Study Date: 4-25-95 to 10-3-95

Study Site: (b)(4)(CC)

GLP/AUC: Yes

Study Design:

- ASA Reaction -

Sensitization Phase						Challenge (iv) Phase		Nº Animals
Compound	Dose (mg/kg)	FCA	Route	Dosing Frequency	Total Nº of Dose	Compound	Dose (mg/kg)	
SC-58635	5	-	po	7x/week	15	SC-58635	5	5
SC-58635	25	-	po	7x/week	15	SC-58635	5	5
SC-58635	25	+	sc	2x/week	5	SC-58635	5	5
BSA	3	+	sc	2x/week	5	BSA	5	5
MC	-	+	sc	2x/week	5	MC	5	5

- HmPCA Reaction (4 hr) - Sera used for challenge were obtained from guinea pigs sensitized for ASA reaction on Day 29.

Sensitization Phase						Challenge (iv) Phase		
Compound	Dose (mg/kg)	FCA	Route	Dosing Frequency	Total Nº of Dose	Compound	Dose (mg/kg)	Nº Animals Challenged
SC-58635	5	-	po	7x/week	15	SC-58635	5	2
SC-58635	25	-	po	7x/week	15	SC-58635	5	2
SC-58635	25	+	sc	2x/week	5	SC-58635	5	2
BSA	3	+	sc	2x/week	5	BSA	5	2
MC	-	+	sc	2x/week	5	SC-58635	5	2

- HtPCA Reaction - Sera used for challenge were obtained from mice on Day 29 after 1st sensitization.

Sensitization Phase - Mice							Challenge (iv) Phase - Rat		
Compound	Dose (mg/kg)	FCA	Route	Dosing Frequency	Total Nº of Dose	Nº Animals Sensitized	Compound	Dose (mg/kg)	Nº Animals Challenged
SC-58635	5	-	po	7x/week	15	5	SC-58635	5	2
SC-58635	25	-	po	7x/week	15	5	SC-58635	5	2
SC-58635	25	+	ip	1x/week	3	5	SC-58635	5	2
BSA	3	+	ip	1x/week	3	5	BSA	3	2
MC	-	+	ip	1x/week	3	5	SC-58635	5	2

Results:

- ASA Reaction - No death occurred. Staggering gate, convulsion, rubbing nose, coughing, lacrimation, dyspnea, and lying on side position were observed in BSA positive control animals. In BSA and SC-58635 sensitized animals had signs of restlessness, trembling, rubbing nose, urination and defecation following receiving iv challenge injection of SC-58635. These responses may not be related to antibody-antigen (SC-58635), since it was also noted in the MC control animals. Results suggested that intravenous injection of SC-58635 cause noteworthy adverse reactions in the guinea pigs.
- HmPCA Reaction - Sera from SC-58635 and MC sensitized guinea pig did not cause vascular leakage lesions around inoculated sites. Contrarily, sera from BSA-sensitized animals induced cause vascular leakage lesions around inoculated sites with titers of ≥900.
- HtPCA Reaction - Sera from 2/5 mice ip sensitized with BSA caused positive leakage lesions around inoculation sites.

In conclusion, SC-58635 did not pose antigenic properties.

2.6.1.2. Dermal Sensitization Study Of SC-58635 In Guinea Pigs-Maximization Test (SA 4515), Document No.: P30S4515; Date: 06-Dec-1996 (Vol. 1.54, p.1-90).

Study Nº: SA4515/CHW 6053997
Document Nº: P30S4515
Study Aims: To assess the contact sensitization potential of SC-58635 when administered by intradermal injection and topical application in guinea pigs.
Compound: SC-58635 (Lot Nº GDS4695-042)
Dose & Route: 5% in FCA/H_2O intradermal injection for sensitization; 25% in Petrolatum dermal topical for induction and challenge
Positive Control: Hexyclcinnamaldehyde; **the positive control was not performed concurrently but within 6 months of the conduct of this study (Study Nº: CHW51104719, 1/8/96 to 2/5/96).**
Animals: Young adult albino guinea pigs, Crl:(HA)BR, weighing 400-508 g, 4-8 weeks of age, 20 for the test group and 10 for the control group
Dosing Date: 6/6/96 - 7/8/96

Study Site: Corning Hazleton Inc., 3301 Kinsman Blvd., Madison, WI 53704
GLP/AUC: Yes
Study Design: The below table depicts the detailed treatment schedules for the control and test groups.

Day	Treatment Schedule	Skin Induction Site (4 cm x 6 cm area)		
		Anterior Site	Medial Site	Posterior Site
CONTROL GROUP (10 ANIMALS)				
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml Propylene Glycol	0.1 ml Propylene Glycol in FCA(1:1)
7	Topical Pre-treatment	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	Petrolatum secured by an overwrap with tape for 48 hr.		
22	Challenge	Petrolatum secured by an overwrap with tape for 24 hr.		
TEST GROUP (20 ANIMALS)				
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml of 5% SC-58635 in Propylene Glycol	0.1 ml of 5% SC-58635 in FCA/H_2O (1:1)
7	Topical Pre-treatment	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	25% w/w SC-58635 in Petrolatum secured by an overwrap with tape for 48 hr.		
22	Challenge	25% w/w SC-58635 in Petrolatum secured by an overwrap with tape for 24 hr.		

The following observations were made during the study:

- Clinical Signs - 1x/day.
- Body Weight - 1x before test material application and 1x at termination of in-life phase.
- Skin Reaction - The challenge sites were examined at 24 and 48 hr following challenge application patch removal. The reactions were scored according 4-point scale: 0 = no reaction; 1 = scatter mild redness; 2 = moderate and diffuse redness; 3 = intense redness and swelling.

The test and control materials were classified according to the following scheme.

MAXIMIZATION RATINGS	
Sensitization Rate (%)*	Classification
0	Non-Sensitizer
>0-8	Weak Sensitizer
9-28	Mild Sensitizer
29-64	Moderate Sensitizer
65-80	Strong Sensitizer
81-100	Extreme Sensitizer

*Percentage of animals exhibiting a dermal reaction at challenge.

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Results:

- Clinical Observations and Body Weights - One animal each in the test (Days 16 and 17) and control (Day 22) groups had soft stool.
- Dermal Reaction to SC-58635 at Challenge - No animals had reaction to the challenge application of control material or SC-58635.

The sponsor stated that based on the results, SC-58635 might not be a dermal sensitizer in guinea pigs maximization test. However, the review pharmacologist do not concur with the conclusion drawn by the sponsor as positive controls were not conducted simultaneously. Therefore, the study it self may not be valid and no conclusion can be drawn from the present study.

2.6.1.3. Primary Dermal Irritation Study Of SC-58635 In Rabbits (EPA-TSCA Guidelines) (HWI 41200179), Document No.: PSA95C-30-SA4318; Date: 26-Apr-1995 (Vol. 1.54, 91-128)

Study Nº: SA4318
Report Nº PSA-95C-30-SA4318
Study Aim: To assess the relative level of primary skin irritation of SC-58635 on rabbits under semi-occluded conditions
Compound: SC-58553 (Lot m 94K014-A2B), white powder
Dose & Route: 0.5 g (≈1.0 ml dose); skin topical application

Animals: 6♂ healthy adult New Zealand White Rabbits; Strain: Hra:(NZW)SPF; Weight: 2806 - 3487 g

Study Location: (b)(4)(CC)

Study Date (In-Life): 12/12/1994 - 12/15/1994

Compliance with GLP/QAU: Yes

Study Design: Each rabbit received a 0.5 g dose of SC-58635 moisturized with H2O as a single dermal application. The area of application was covered with a 2.5 cm x 2.5 cm gauge patch, loosely overwrapped with Saran Wrap7 and secured with Elastoplast7 tape to ensure the drug in contact with the skin. At the end of 4 hr exposure, the dressing was then removed and the remaining SC-58635 was wiped from the skin. The test sites were examined and scored for dermal irritation at 4, 24, 48 and 72 hr following patch removal.

Results: There was no dermal irritation. The average of the individual animal index scores was 0.

2.6.1.4. Primary Eye Irritation Study Of SC-58635 In Rabbits (EPA-TSCA Guidelines) (HWI 41200180), Document No.: PSA95C-30-SA4319; Date: 27-Apr-1995 (Vol. 1.54, p.129-171)

Study Nº: SA4319

Report Nº: PSA95C-30-SA4319

Study Aim: To assess the relative level of irritation produced following a single exposure of a test material to one eye of albino rabbits

Compound: SC-58553 (Lot Nº 94K014-A2B) powder

Dose & Route: 0.011 g (≈1.0 ml dose); intraocular

Animals: 6♂ Adult New Zealand White Rabbits, 3/group; Strain: Hra:(NZW)SPF; Weight: 2.0 - 3.5 kg

Study Location: (b)(4)(CC) , WI 53704

Study Date (In-Life): 12/14/94 - 12/17/1994

Compliance with GLP/QAU: Yes

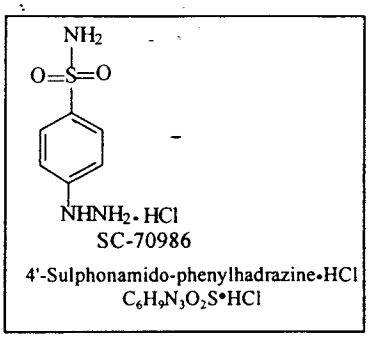
Study Design: Each rabbit received 0.011 g (0.1 ml wt equivalent) of the drug placed into the everted lower lid of the right eye, with the left eye serving as the untreated control. The upper and upper eyelids were held gently together for 1 sec and then released. The eyes of rabbits in group I remained unflushed immediately after treatment while the treated eyes of the rabbits in group II were flushed with lukewarm tap water for 1 min starting 30 sec after the drug applied. the treated eyes were examined for ocular irritation at 1, 24, 48, and 72 hr post treatment. Irritation was graded and recorded according to the Draize method. Sodium fluorescein was used to aid in revealing possible corneal damage at 72 post dose.

Results: Redness and swelling (slight to moderate conjunctivitis, scored 4.0) were observed in all tested eyes in group I animals at 1 hr post exposure to the drug. The conjunctival irritation disappeared and resolved completely in all animals in group I by 48 hr post treatment. Only redness (scored 3.3) were seen in all tested eyes of group II animals and the conjunctival irritation completely resolved by 24 hr post treatment. Sodium fluorescein examinations were negative for all animals 72 hr post dosing. Therefore, SC-58635 could be considered as minimally irritating according to the Kay & Calandra[13] classification criteria.

ON ORIGINAL

[13] Kay, J. H. and Calandra, J. C., "Interpretation of Eye Irritation Tests," Journal of the Society of Cosmetic Chemists, 1962. 13(6) :281-289.

2.7. TOXICITY OF STARTING MATERIAL IN THE SYNTHESIS OF SC-58635



2.7.1.1. Acute Oral Toxicity Study Of 4-Sulfonamidophenyl Hydrazine Hydrochloride In Rats (EX4503), Document No.: P30E4503; Date: 24-Feb-1997 (Vol. 1.66, p.1-50)

Study Nº: EX4503
Study Report Nº: CHW 60401961
Study Aims: To evaluate the acute toxicity of 4-sulfonamidophenyl hydrazine hydrochloride (SC-70986), a raw material for the product of SC-58635 by oral gavage to rats.
Compound: 4-sulfonamidophenyl hydrazine (Lot Nº N00106) in dist. H_2O
Vehicle: dist. H_2O
Dose and Route: 250, 500, 1000, and 2000 mg/kg/10 ml po by gavage
Animals: Sprague-Dawley rats, Crl:CD®(SD)BR, ~7-19 weeks of age, weighing 212-289 g, 5/sex/group
Study Site: (b)(4)(CC)
Study Date: 4/29/96 - 6/10/96
GLP/AUC: N/A
Study Design: Rats were given a single dose of 4-sulfonamidophenyl hydrazine hydrochloride at doses of 250, 500, 1000, or 2000 mg/kg. Animals were observed for clinical signs of toxicity at 1, 2.5, and 4 hr post dosing and daily thereafter for 14 days. Mortality was checked 2x/day. Body weights were recorded on Days 0, 7 and 14. All animals were subjected to gross pathological examination. No tissues were preserved.

Results:

- Mortality - The mortality for each group and calculated LD_{50} for each sex and combined sex are listed in the below table.

Dose mg/kg	Mortality ♂	Mortality ♀	LD_{50} (95% Confidence Limit) mg/kg ♂	LD_{50} (95% Confidence Limit) mg/kg ♀
250	0/5	0/5		
500	1/5 (Day 0)	0/5		
1000	2/5 (Day 0)	5/5 (Days 0 &1)	1000 (558-1792)	707 (483-1036)
2000	5/5 (Day 0)	5/5 (Day0)	785 (556-1108)	

- Clinical Signs - Hyporeactivity, staggered gait, absence of gasping/righting reflex, prostration, clonic convulsions, thin appearance, hunched posture, red-stained face, excessive salivation, lacrimation, mydriasis, dyspnea, soft stool, wet and/or yellow-stained urogenital area were major observations. All surviving animals but 2♀ @ 500 mg/kg that had clinical signs of toxicity returned to the normal state by Day 3 post treatment.
- Body Weights - Surviving animals in each group showed similar body weight gains except one ♀ @ 250 mg/kg exhibit a weight loss of 6 g during the 2nd week of the study.
- Gross Pathology - No gross lesions were noted in the rats @ 250 mg/kg. The most apparent findings in rats that died during the study were coloration changes (brown, dark brown or dark red) of the lungs, GI tract, the nasal/oral discharge, and content of the GI tract.

2.7.1.2. Primary Eye Irritation Study Of 4-Sulfonamidophenyl Hydrazine Hydrochloride In Rabbits (EX4504), Document No.: P30E4504; Date: 08-Oct-1996 (Vol. 1.66, p. 51-90)

Study Nº: EX4504/CHW 60401963
Report Nº: P30E4504
Study Aims: To examine primary eye irritation study of 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) in rabbits.
Compound: 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) (Lot Nº: N00106)
Dosage & Route: 73 mg powder, ocular instillation
Animals: Adult albino rabbits Hra:(NZW) SPF, 14-18 weeks of age, 2395-2744 g, 3/group
Study Date: 5/1/96 - 5/22/96
Study Site: (b)(4)(CC)
GLP/AUC: N/A
Study Design: Test material, 73 mg 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986), was placed into the lower eyelid of the right eye on rabbits (2 groups of 3). The left eye served as untreated control. The treated eyes of Group 2 rabbits were flushed with water 30 sec after drug administration. Eye irritation were scored according the Draize technique at 1, 24, 48, 72, and 96 hr and 7, 14, and 24 days post instillation.

Results: Corneal and iridal involvement and moderate conjunctival irritation were noted in Group 1 animals. In contrast, only corneal involvement and slight conjunctival irritation were seen in the Group 2 rabbits (eyes were washed 30 sec after instillation of test compound). The average primary eye irritation scores are shown in the following table.

Time	Group 1 (Unflushed)	Group (H_2O Flushed)
1 hr	25.7	13.0
24 hr	23.7	11.0
48 hr	21.3	6.0
72 hr	20	4.7
96 hr	16.3	2.7
Day 07	6.3	0
Day 14	2.0	0
Day 21	0	0

2.7.1.3. Primary Dermal Irritation Study Of 4-Sulfonamidophyenyl Hydrazine Hydrochloride In Rabbits (EX4505), Document No.: P30E4505; Date: 13-Sep-1996 ((Vol. 1.66, p. 91-110)

Study Nº: EX4505/CHW 60401962
Report Nº: P30E4505
Study Aims: To examine primary skin irritation study of 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) in rabbits.
Compound: 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) (Lot Nº: N00106)
Dosage & Route: 0.5 g in 0.4 ml dist. H_2O applied to skin directly
Animals: 3♂ & 3♀ adult albino rabbits Hra:(NZW) SPF, 14-18 weeks of age, 2418-2569 g.
Study Date: 4/30/96 - 5/14/96
Study Site: (b)(4)(CC)
GLP/AUC: N/A
Study Design: Test material, 0.5 g of 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986), was moistened with approximately 0.4 ml of dist. H_2O and was applied to the rabbit skin area that had been clipped. The area of application was cover with an 2.5 cm x2.5 cm gauze patches secured with paper tape, overwrapped with Sara Wrap and secured with Elasplast tape. The

patches were removed after 4 hr exposure to the test article. The degree of erythema and edema was recorded 30 min, 24 hr, 48 hr, 7, and 96 hr and 7 and 14 days after removal of the test material.

Results: Based on the results presented in the following table, 4-Sulfonamidophenyl hydrazine hydrochloride was considered to be a slight skin irritant under the present testing condition.

Time	Average Score
4 hr	25.7
24 hr	23.7
48 hr	21.3
72 hr	20
96 hr	16.3
Day 07	6.3
Day 14	2.0

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2.7.1.4. Dermal Sensitization Study Of 4-Sulfonamidophenyl Hydrazine Hydrochloride In Guinea Pigs-Maximization Test, Document No.: P30E4506; Date: 24-Feb-1997 (Vol. 1.66, p. 111-198)

APPEARS THIS WAY ON ORIGINAL

Study Nº: EX4506/CHW 60401964
Report Nº: P30E4506
Study Aims: To determine the contact sensitization potential of 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986) in guinea pigs.
Compound: 4-Sulfonamidophenyl hydrazine hydrochloride (SC-70986)(Lot Nº: N00106)
Dosage & Route: 0.1 ml of 5% SC-70986 in sterile H_2O or FCA/H_2O (1:1) intradermal injection for sensitization and 25% w/w SC-70986 in Petrolatum directly applied to skin for induction and challenge.
Animals: adult albino guinea pigs Crl:(HA)BR, 4-8 weeks of age, 357-494 g, 20 for the test group and 10 for the control group.
Study Date: 5/3/96 - 6/8/96
Study Site: (b)(4)(CC)
GLP/AUC: N/A

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Study Design:

Day	Treatment Schedule	Skin Induction Site (2 cm x 4 cm area)		
		Anterior Site	Medial Site	Posterior Site
		CONTROL GROUP (10 ANIMALS)		
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml Sterile H_2O	0.1 ml H_2O in FCA(1:1)
7	Topical Pre-treatment	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	Petrolatum secured by an overwrap with tape for 48 hr.		
22	Challenge	Petrolatum secured by an overwrap with tape for 24 hr.		
		TEST GROUP (20 ANIMALS)		
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml of 5% SC-70986 in Sterile H_2O	0.1 ml of 5% SC-70986 in FCA/H_2O (1:1)
7	Topical Pre-treatment	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	25% w/w SC-70986 in Petrolatum secured by an overwrap with tape for 48 hr.		
22	Challenge	25% w/w SC-70986 in Petrolatum secured by an overwrap with tape for 24 hr.		

FCA = Freund's Complete Adjuvant

The following observations were made during the study:

- Clinical Signs - 1x/day.
- Body Weight - 1x before test material application and 1x at termination of in-life phase.
- Skin Reaction - The challenge sites were examined at 24 and 48 hr following challenge application patch removal. The reactions were scored according 4-point scale: 0 = no reaction; 1 = scatter mild redness; 2 = moderate and diffuse redness; 3 = intense redness and swelling.

The test and control materials were classified according to the following scheme.

MAXIMIZATION RATINGS	
Sensitization Rate (%)[a]	Classification
0	Non-Sensitizer
>0-8	Week Sensitizer
9-28	Mild Sensitizer
29-64	Moderate Sensitizer
65-80	Strong Sensitizer
81-100	Extreme Sensitizer

[a]Percentage of animals exhibiting a dermal reaction at challenge.

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Results:

- Clinical Observations and Body Weights - The test group had reduced stool (8/20) and thin appearance (3/20). The test group had less body weight gains than the control group.
- Dermal Reactions - Mild to intense skin reactions were noted in all animals in the test group after challenge. Some animals (12/20) in the test group showed subcutaneous hemorrhaging, necrosis, and desquamation in the test sites following challenge. None of control animals had response to the challenge.

Based on the findings from this study, 4-sulfonamidophenyl hydrazine hydrochloride (SC-70986) was considered as an extreme dermal sensitizer in guinea pigs.

2.7.1.5. An Evaluation Of The Mutagenic Potential Of SC-70986 In the Ames Salmonella/Microsome Assay (EX4641), Document No.: P30E4641; Date: 14-May-1997 (Vol. 1.66, p. 199-228)

Study Nº: EX4641
Report Nº: P30E4341
Study Aims: To evaluate SC-70986, a raw material for the product of SC-58635, for potential mutagenic activity in the *Salmonella*/microsomal Ames assay.
Compound: SC-70986, 4-sulfonamidophenyl hydrazine HCl, (Lot Nº N00106) in H_2O, 100 mg/ml
Dose: 10, 50, 100, 500, 1000, and 5000 μg/plate
Vehicle Control: H_2O
Test Cells: *Salmonella typhimurium*: histidine auxotrophs TA97a, TA98, TA100, TA102, and TA1535.
Positive Control:

Chemical	S9 Mix	Tester Strains	Conc. (μg/plate)
NaN_3 (sodium azide)	-	TA1535 and TA100	1
2-aminoanthracene	-	TA98	2.5
	+	TA97a, TA98, TA100, and TA1535	1.0
ICR-191 acridine	-	TA97a	0.5
Cumen Hydroperoxide	-	TA102	100
Danthron	+	TA102	50

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Test Article Exposure Time: 48 hr at 37°C
Study Site: Searle Research and Development, Skokie, IL.
Study Date: 4/9 - 4/11/97
GLP/QAC Compliance: No

Results: SC-70986, up to 5000 μg/plate, was not toxic to *Salmonella typhimurium* (all tested strains). Significant increases in the number of revertant colonies were observed in all tested strains except TA1535. The concentrations of SC-70986 that caused significant increases the number of

revertant colonies are presented in the following table. Based on these data, it can be concluded that SC-70986 is mutagenic with all strains except TA1535 under the current testing condition.

Test Strain	S9 Mix	Concentration (μg/plate)
TA97a and TA102	-	≥50
TA97a	+	≥100
TA98 and TA100	+/-	5000

3. ADME

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3.1. ABSORPTION PHARMACOKINETICS, SERUM $T_{½}$

3.1.1. RAT

3.1.1.1. The Pharmacokinetics And Metabolism Of [^{14}C]SC-58635 Following Single Intravenous Dose Administration To The Rat (HWI 6127-220), Document No.: MRC-94S-0145; Date: 28-Nov-1994 (Vol. 1.67, p. 1-101)

Report Nº: MRC-94S-0145
Study Aim: To evaluate pharmacokinetics and metabolism of [^{14}C]SC-58635 following a single intravenous dose administration to the rat
Compound: [^{14}C]SC-58635 dissolved in PEG-400:H_2O, 2:1, v/v
Dosage & Route: 1 mg/kg, 2 ml/kg iv bolus via the tail vein over 1 min
Animals: 15♂ & 15♀ Sprague Dawley [Hla®(SD)CVF®] rats, weighing 225 - 350 g, age 7-14 weeks
Study Location: (b)(4)(CC) [redacted]
Compliance with GLP/QAU: N/A
Study design: Animal group allocation, dose levels and sampling schedules are as follows.

Group (Animal Nº)	Dose (mg/kg)	Route	Sample Type	Sampling Time
I (12♂ &12♀)	1	IV	Plasma	5 , 15, 30, and 60 min, 2, 4, 8, and 24 hr post dosing
II (3♂ & 3♀)	1	IV	Urine, Feces	predose (-24-0 hr), 0-24, 24-48, 48-72, 72-96, 96-120 hr post dosing

Animals were fasted overnight prior to dosing until approximately 4 hours post administration. Animals in group I and II were sacrificed at 48 hr and 120 hr post dosing, respectively. Blood samples were collected from jugular vein into heparinized tubes. Urine and fecal samples were collected by free-catch in containers surrounded by dry ice. Plasma concentrations of SC-58635 were determined by the (b)(4)(C analysis.

Results: The mean pharmacokinetic parameters are summarized in the following table. The clearance of SC-58635 in the female rats was much slower than that in the male rats (1.90 vs 7.76 ml/min•kg).

	$T_{½}$ (hr)	Clp (ml/min•kg)	VC (l/kg)	$AUC_{0-\infty}$ (μg•hr/ml)
♂	3.73	7.76	2.51	2.15
♀	14	1.9	2.42	8.38

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The excretions of SC-58635 and its metabolites in the urine and feces are shown in the following table. Very small percentage of SC-58635 was excreted following IV administration indicating that SC-58635 was eliminated by hepatic metabolism.

Sample	Time (hr)	% SC-58635		% SC-60613		% SC-62807	
		♂	♀	♂	♀	♂	♀
Urine	0 - 24	0.50	0.40	0.70	0.79	98.6	97.2
Feces	0 - 24	0.79	0.00	3.62	3.38	94.0	94.4
	24 - 48	2.69	1.77	0.69	8.59	86.2	88.9

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48 - 72	-	1.88	-	8.26	-	84.0

3.1.1.2. Pharmacokinetics And Metabolism Of SC-58635 In Rat, Document No.: MRC-94S-0226; Date: 19-Jan-1995 (Vol. 1.67, p. 102-143)

Report Nº: MRC-94S-0226
Study Aim: To evaluate pharmacokinetics of SC-58635, a potent and highly selective cyclooxgenase-2 (COX-2) inhibitor in rats
Compound: SC-58635 dissolved in PEG-400:H_2O, 2:1
Dosage & Route: 2 mg/ml for iv bolus and oral solution; 0.4 mg/ml for [^{14}C]SC-58635 po solution
Animals: ♂ Sprague Dawley rats, weighing ~0.3 kg, 3/group
Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP/QAU: N/A

Results: SC-58635 was given to rats, 3/group, by tail vein injection or gavage. Blood samples were collected from each rat by retroorbital bleed into heparinized tubes. [^{14}C]SC-58635 was administrated by gavage at 2 mg/kg in the same vehicle. Feces and urine samples were collected in some cases. Results showed that the peak plasma concentration (C_{max}) following the 10 mg/kg oral dose to the rat was 2.01 µg/ml and was reached at 3 hr (T_{max}). The AUC was 18.5 µg•hr/ml and systemic availability of SC-58635 following oral solution doses was 64.5%. Plasma elimination half-life and total plasma clearance rate of SC-58635 were 3.49 hr and 5.81 ml/min/kg, respectively. At two hr following a 2 mg/kg oral dose, [^{14}C]SC-58635 could be detected in liver (9.98%), skin (8.15%), muscle (23.7%) and fat (15.9%). Little or no radioactivity remained in tissues or plasma 7 days post dosing. After 48 hr, plasma radioactivity was less than twice background. $T_{½}$ was 3.72 hr. Total excretion time seemed to be 120 hr. The recovery from urine and feces (0-168 hr) was 7.22% and 93.4%, respectively. The pharmacokinetic parameters of SC-58635 in male rats are presented in the following table.

Route	Dose mg/kg	C_{max} µg/ml	T_{max} hr	$AUC_{0-\infty}$ (µg•hr/ml)	Clp ml/min•kg	V_D ml/kg	BA %	$T_{½}$ hr
Oral	10	2.01	3	18.5	NA	NA	64.5	3.67
Oral*	2	0.599	3	NA	NA	NA	NA	3.72
IV	10	4.87	NA	28.7	5.81	1860	NA	3.49

*Radioactive Dose
NA = Not Applicable

Two metabolites of SC-58635 were identified based on (b)(4)(CC analysis, the benzylic hydroxylated (SC-60613) and corresponding carboxylic acid (SC-62807) analogues. Following oral intake of [^{14}C]SC-58635, the majority of metabolites in the plasma appeared to be SC-60613; whereas, SC-62807 was found to be the major metabolites in the urine and feces. Rat liver microsome metabolized [^{14}C]SC-58635 in vitro quicker than human hepatic microsomes, and in both cases SC-60613 was the major metabolite. Pharmacokinetic-pharmacodynamic correlation was performed in the Lewis rat adjuvant arthritis model. The approximate SC-58635 C_{max} (3 hr) at the ED_{80} dose (1.43 mg/kg/day, measured on Day 10) was 0.453 µg/ml. Approximate C_{max} (on Day 10) in the adjuvant arthritis model during bid dosing of 0.3, 1, 3, 10, 30 and 100 mg/kg were 0.144, 0.317, 0.509, 1.94, 3.73 and 7.44 µg/ml, respectively.

3.1.1.3. The Plasma Concentrations Of SC-58635 At The ED_{80} For Adjuvant Arthritis In The Rat, Document No.: M3096294; Date: 06-Jun-1997 (Vol. 1.67, p. 144-169)

Report Nº: M3096294

Study Aim: To determine the AUC of SC-58635 at the ED_{80} in the rat adjuvant arthritis model
Compound: SC-58635 (Lot Nº: E90077) in 0.5% methylcellulose, 0.1% polysorbate 80
Dose & Route: 0.7 mg/kg bid po (by gavage) with 12 hr apart for 7 days , and a single dose on Day 8.
Animals: 12♂ healthy Charles River rats, 12♂ healthy Lewis rats, and 8♂ Lewis rats with adjuvant-induced arthritis, weighing ~165-393 g
Study Site: Searle Research and Development, Skokie, IL.
Compliance with GLP/QAU: N/A
Blood Collection: Blood was collected at 0.5, 1, 2, 3, 4, 8, 12 and 24 hr post dose on Day 8. Analysis of Plasma SC-58635 was Performed by Corporation, Austin, TX.

Result: Mean concentration of SC-58635 in plasma and PK parameters after oral administration of SC-58635 to male Charles river rats, Lewis rats and Lewis rats with adjuvant-induced arthritis are shown in the following table.

Time (hr)	PLASMA CONCENTRATION (SC-58635 μg/ml)		
	Charles River Rats	Lewis Rats	Arthritis Lewis Rats
0.5	0.0852	0.104	0.086
1	0.0968	0.133	0.118
2	0.0922	0.118	0.162
3	0.115	0.108	0.156
4	0.0948	0.128	0.152
8	0.0249	0.0342	0.0565
12	0.0162	BDL	0.0406
24	BDL	BDL	0.0393
PK PARAMETERS			
T_{max} (hr)	3	1	2
C_{max} (μg/ml)	0.115	0.133	0.162
AUC_{0-24} (μg•hr/ml)	1.38	1.67	2.29

BDL = Below Detection Limit (0.01 μg/ml)

3.1.1.4. Evaluation Of The SC-58635 Plasma Concentration Data Following Multiple Dose Administration To The Rat, MRC-94S-0230, Document No.: MRC-94S-0230; Date: 16-Nov-1994 (Vol. 1.67, p. 170-213)

Study Nº: SA4261
Report Nº: MRC-94S-0230
Study Aim: To assess the short term toxicity of SC-58635 administered daily by oral gavage to rats for 4 weeks and the reversibility of effects after 4 weeks without treatment
Compound: SC-58635 (Lot Nº GDS-2977-158) in 0.5% methylcellulose and 0.1% Tween 80
Dosage & Route: 20, 40, 80, 400 and 600 mg/kg, 10 ml/kg by oral gavage
Control Vehicle: 0.5% methylcellulose and 0.1% Tween 80
Animals: 66♂ & 66♀ Sprague-Dawley rats, strain Crl:CD®(SD)BR VAF/Plus®, 5 wk of age, weighing from 126.7-175.4 g for ♂ and 111.8-143.2 g for ♀; 10-15/sex/group for toxicity study and 3/sex/group for PK assessment.
Study Location: (b)(4)(CC)
Compliance with GLP/QAU: Yes
Study Design: Animal grouping and dosage assignments were listed as followings:

Group		SC-58635 (mg/kg)	Nº of Animals
TOXICITY STUDY			
1	Control	0	15/sex

2	Low	20	10/sex
3	Mid	80	10/sex
4	Mid-high	400	15/sex
5	High	600	10/sex
PK ASSESSMENT			
6	Mid-high	400	3/sex
7	High	600	3/sex

On Days 1 and 26 of dosing the rats were dosed with [^{14}C]SC-58635. The rats were dosed with unlabelled SC-58635 on the intervening doses. Blood was collected from all dose groups at 0.5, 1, 2, 3, 4, 6, 8 and 24 hr on Day 1 and Day 26 of dosing. The concentration of SC-58635 in plasma was determined using a validated high performance liquid chromatography (HPLC). The analysis for plasma SC-58635 levels was conducted at G.D. Searle, Skokie, IL.

Results: SC-58635 was absorbed and systemically available. In male rats, systemic exposure to SC-58635 increased with dose over the dose range of 20 to 600 mg/kg except at the 600 mg/kg dose group. It appeared that maximal exposure to SC-58635 was achieved between 400 and 600 mg/kg in the male rats. The systemic exposure to SC-58635 increased with dose over the dose range of 20 to 600 mg/kg in the female rats. However, this increase was not dose proportional. The C_{max} and AUC values for female and male rats on Day 26 were on average lower than those on Day 1, indicating that induction of SC-58635 metabolism had occurred after repetitive dosing. A gender differences in the metabolism was noted as higher C_{max} and AUC values were observed in the females. The mean PK parameters on Days 1 and 26 are listed in the following table.

PK Parameters	Sample Day	Dose (mg/kg/day)											
		20			80			400			600		
		♂	♀	♂+♀	♂	♀	♂+♀	♂	♀	♂+♀	♂	♀	♂+♀
T_{max} (hr)	Day 1	3.00	3.00	3.00	8.00	8.00	8.00	3.00	8.00	8.00	6.00	8.00	8.00
	Day 26	2.00	6.00	2.00	2.00	2.00	2.00	4.00	4.00	4.00	4.00	8.00	3.00
C_{max} (μg/ml)	Day 1	2.597	3.437	3.017	5.193	7.643	6.418	10.283	12.3	10.697	6.713	13.9	10.06
	Day 26	1.573	2.63	1.973	3.087	5.55	4.318	5.853	9.6	7.727	5.533	16.2	9.825
AUC_{0-24} (μg•hr/ml)	Day 1	30.261	41.845	36.053	73.214	117.542	95.378	195.925	244.789	220.357	97.591	275.885	186.738
	Day 26	19.173	35.997	27.585	29.737	82.002	55.87	60.718	158.938	109.828	58.188	314.51	186.349

3.1.1.5. Evaluation Of Plasma Concentration Data In A Pharmacokinetic Study In Female Rats During Pre-Mating And Early Pregnancy With SC-58635 (M2097202), Document No.: M3097339; Date: 02-Dec-1997 (Vol. 1.67, p. 214-360)

Report Nº: M3096294

Study Aim: To determine the AUC of SC-58635 at the ED_{80} in the rat adjuvant arthritis model

Compound: SC-58635 (Lot Nº: 95K010-A1A) in 0.5% methylcellulose (w/v) and 0.1% polysorbate 80 (w/v)

Dose & Route: 5, 15, 30 and 50 mg/kg, po for at least fourteen days prior to mating, throughout the mating period and through Gestation Day 7.

Animals: ♀ Charles River CrlCD®BR,

Study Site: Covance Laboratories, Inc., Vienna, VA.

Compliance with GLP/QAU: N/A

Blood Collection: Blood was collected from 3 rats/dose at 0.5, 1, 2, 4, 8, and 24 hr post dose on Days 1 and 23 (Gestation Day 7). Analysis of Plasma SC-58635 was Performed by (b)(4)(CC) [redacted] (b)(4)(CC) [redacted] assay. Assay sensitivity was 0.0250 μg SC-58635/mL for a 0.300 ml sample without dilution.

Result: Following oral gavage administration to CrlCD®BR female rats, SC-58635 was absorbed and systemically available. The mean PK parameters (n=3) are shown in the following table. The plasma SC-58635 C_{max} and AUC values were similar on Days 1 and 23, indicating that repetitive dose administration at 5, 15, 30 and 50 mg/kg/day do not alter the pharmacokinetics of SC-58635.

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Day of Dosing	Dose (mg/kg/day)	Tmax (hr)	C_{max} (μg/ml)	C_{max}/Dose	AUC_{0-24} (μg•hr/ml)	AUC/Dose
1	5	2	1.84	0.368	25.6	5.11
	15	8	3.59	0.239	57.6	3.84
	30	8	3.96	0.132	70.6	2.35
	50	8	5.93	0.119	95.7	1.91
23 (Gestation Day 7)	5	2	1.63	0.327	23.3	4.66
	15	2	3.35	0.224	47.2	3.15
	30	4	5.17	0.172	63.3	2.11
	50	8	5.25	0.105	90.9	1.82

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3.1.2. *GUINEA PIG*

3.1.2.1. Pharmacokinetics And Metabolism Of SC-58635 In Dog And Guinea Pig, Document No.: MRC-94S-0227; Date: 19-Jan-1995 (Vol. 1.67, p. 361-377)

Report Nº MRC-94S-0227
Study Aim: To evaluate pharmacokinetics and metabolism of SC-58635 following intravenous infusion and oral administration of solution and capsule
Compound: SC-58635 dissolved in PEG-400:H_2O, 2:1, v/v
Dosage & Route: 0.5 & 5 mg/kg with 0.5 & 5 mg/ml iv and 5 mg/kg oral for used in dog
0.6 & 6 mg/kg with 0.12 & 1.2 mg/ml iv for used in guinea pig
Animals: ♀ Beagle dogs, weighing 9 -13 kg and ♂ Hartley guinea pigs, weighing 0.4 -0.5 kg.
Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP/QAU: N/A
Experimental Design: Female dogs and male guinea pigs, two animals per group, were intravenously infused with two different dosages (0.5 & 5 mg/kg for dogs and 0.6 & 6 mg/kg for guinea pigs) of SC-58635 over a period of 15 min with a 15-30 min interval between two infusions. Female dogs were also given SC-58635 with doses of 5 mg/kg oral solution and oral capsule with neat chemical inside. Multiple blood sampling were performed and concentrations of SC-58635 and it's metabolites were determined by the (b)(4)(CC method.

Results: The peak plasma levels and systemic availability of SC-58635 in female dogs and male guinea pigs as well as other pharmacokinetic parameters are summarized in the following table.

Species	Dose mg/kg	Route	C_{max} µg/ml	T_{max} µg/ml	AUC (0-∞) µg•hr/ml	C_L ml/min•kg	V_D ml/kg	BA %	$T_{½}$ hr
Dog	5	oral[a]	2.19	0.5	16.2	5.14	N/A	57.1	9.15
Dog	5	oral[b]	0.517	3.0	4.80	17.4	N/A	16.9	11.8
Dog	0.5, 5	iv	6.95	N/A	31.2	3.08	2420	N/A	8.84
G. pig	0.6, 6	iv	5.02	N/A	5.49	20.5	1983	N/A	1.16

[a] Solution in PEG-400:H_2O (2:1); [b] Neat chemical in capsule; N/A = Not applicable.

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Elimination rate of SC-58635 in guinea pig appeared to be more rapid compared to the dog and rat. The order plasma $T_{½}$ of SC-58635, pyrazole-type COX-2 inhibitor, in dog, rat and guinea pig was dog>rat>guinea pig indicating differences in rate or type of metabolism in these species. The systemic bioavailability of SC-58635 following oral administration to the dog with neat chemical in gelatin capsule was significantly lower compared to the oral solution (16.9% vs 57.1%).

3.1.3. DOG

3.1.3.1. The Pharmacokinetics And Metabolism Of SC-58635 After Intravenous And Oral Administration To The Male And Female Beagle Dog (An Exploratory Study), Document No.: MRC-94S-0133; Date: 18-Nov-1994 (Vol. 1.68, p. 1-114)

Report Nº MRC-94S-0133
Study Aim: To evaluate pharmacokinetics and metabolism of [^{14}C]SC-58635 following intravenous bolus (1 & 15 mg/kg) and oral administration in a nonrandomized cross-over design to ♂ & ♀ beagle dogs
Compound: [^{14}C]SC-58635 dissolved in PEG-400:H_2O, 2:1, v/v
Dosage & Route: 1 & 15 mg/kg, 1 ml/kg iv and 1 mg/kg po
Animals: 3♂ & 3♀ Beagle dogs, weighing 9 -14 kg, 6 (3♂ & 3♀)/group
Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP/QAU: N/A
Study Design: The study design (a nonrandomized cross over), dose levels and sampling schedules were presented in the following table. Animals were fasted 15 to 20 hr prior to dosing until approximately 4 hours post administration. Each dose was given once to each animal as a solution in PEG-400:H_2O (2:1, v/v) with a washout period of at least 3 weeks between administration of each dosage form. Blood samples were collected by venipuncture according to the schedules listed in the above table. Urine and fecal samples were collected by free-catch in containers surrounded by dry ice. Plasma concentrations of SC-58635 were determined by the HPLC analysis.

Group	Dose (mg/kg)	Route	Sample Type & Sampling Time	
			Plasma	Urine & feces
I[a] (3♂ & 3♀)	1	IV	2, 5 , 15, 30, and 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10, 24 and 48 hr	-18 - 0, 0 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120, 120 - 144, and 144 - 168 hr
II[a] (3♂ & 3♀)	15	IV		
III (3♂ & 3♀)	1	oral	15 and 30 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 24 and 24 hr	

* Only plasma samples were collected during this period of study.
[a] This is a non-randomized study and same animals were used in Group I, II & III.

Results: The results of this PK study were summarized as following:

- Considerable variations were seen in the K_m and V_{max} estimated in these study with the K_m ranging from 2.13 - 47.5 µg/ml and V_{max} ranging from 1.27 - 15.2 mg/kg/hr.
- The absolute biovailabilities of SC-58635 in both male and female dogs were 85.9 ± 20.7 and 74.4 ± 5.6, respectively.
- The pattern and route of eliminations were similar in male and female dogs following either oral or iv administration of SC-58635.
- SC-58635 was eliminated by metabolism followed by excretion of the metabolites in bile and urine. The majority metabolites of SC-58635 were excreted in urine and feces. The radioactivity in the metabolites excreted in urine and feces following 1 mg/kg either oral or iv administration were shown in the table listed below.

Sample	Route	[^{14}C] (%)	SC-58635 (%)	SC-60613 (%)	SC-62807 (%)
Urine	iv	4.22	0.00741	0	2.67
	Oral	3.05	0.0134	0.0271	2.07
Feces	iv	90.5	0	0	60
	Oral	91.4	0	1.33	84.1

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The mean plasma levels ± SEM of SC-58635 in male and female dogs and pharmacokinetic parameters following iv and oral administration at a dose of 1 mg/kg are summarized in the following two tables.

IV Administration (1 mg/kg)			Oral Administration (1 mg/kg)		
PK Parameters	♂	♀	PK Parameters	♂	♀
α (hr^{-1})	13.3 ± 12.1	7.87 ± 5.19	T_{max} (hr)	0.667 ± 0.167	1.00 ± 0.59
$\alpha_{1/2}$ (hr)	0.288 ± 0.26	0.334 ± 0.244	C_{max} (μg/ml)	0.553 ± 0.070	0.309 ± 0.015
β (hr^{-1})	0.203 ± 0.073	0.246 ± 0.083	$AUC_{0-\infty}$ (μg•hr/ml)	2.118 ± 0.465	1.565 ± 0.321
$\beta_{1/2}$ (hr)	3.92 ± 1.41	4.09 ± 1.92	BA (%)	85.9 ± 20.7	74.4 ± 5.6
C_L (ml/min/kg)	10.0 ± 2.90	7.98 ± 2.00			
V_D (l/kg)	2.30 ± 0.32	2.30 ± 0.59			

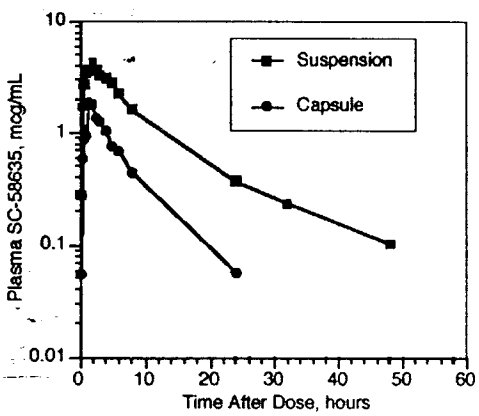
3.1.3.2. The Systemic Availability And Excretion Of SC-58635 Following Oral Administration Of Test Article In Capsule And Suspension Forms To The Female Dog (A Pilot Study), Document No.: M3094124; Date: 02-May-1996 (Vol. 1.68, p. 115-140)

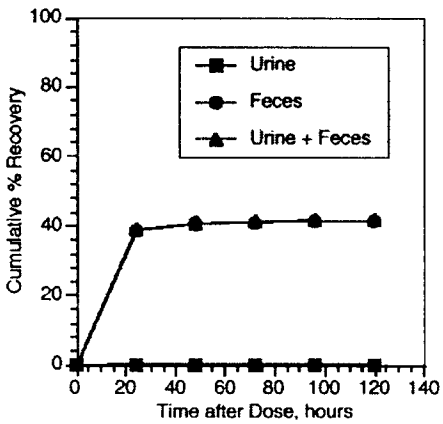
Report Nº M3094124
Study Aim: To determine the systemic availability of SC-58635 following administration of the drug to the dogs as a suspension and in capsule form.
Compound: SC-58635 (Lot Nº C00025) in capsule and [^{14}C]SC-58635 (Lot Nº GDS3168-171) suspension in 0.5% methylcellulose/1% polysorbate 80/H_2O
Dosage Route: 20 mg/kg po
Animals: 2 female beagle dogs, weighing 9.2 and 11.3 kg, respectively.
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
Compliance with QAU: N/A
Sample Collection:

- Blood - 0, 15, 30 and 45 min, 1, , 1.5, 2, 2.5, 3, 4, 5, 6, 8, 24, and 48 hr post dosing.
- Urine and Feces - Urine and fecal samples were collected for consecutive 24 hr periods: -18-0, 0-24, 24-48, 48-72, 72-96, and 96-120 hr.

Results:

Plasma SC-58635 concentrations in a ♀ dog following a single oral dose of 90 mg/kg SC-58635 as neat chemical in a gelatin capsule or as suspension are depicted in the following figure (left panel). Cumulative of radioactivity in urine and feces in a female dog following oral administration of [14C]SC-58635 suspension 0.5% methylcellulose/1% polysorbate 80/H_2O are presented in the following figure (right panel).



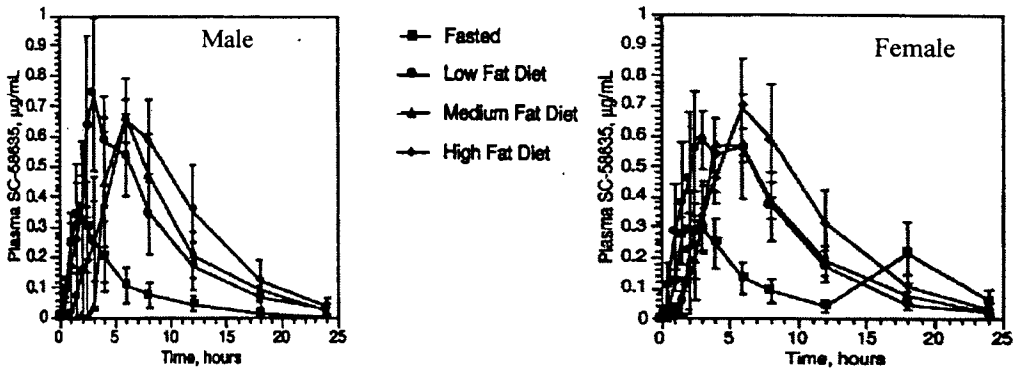


3.1.3.3. Plasma Concentrations Of SC-58635 In Dogs After Oral Administration Of SC-58635 With And Without Food, Document No.: MRC-95S-0047; Date: 13-Oct-1995 (Vol. 1.68, p. 141-188)

Report Nº MRC95S-0047 (HWI 6127-234)
Study Aim: To determine the plasma concentrations and PK following a single capsule administration of SC-58635 when administered with varying amount of dietary fat to beagles.
Compound: SC-58635 in gelatin capsule
Dosage Route: 5 mg/kg po
Animals: Beagle dogs (3♂ & 3♀), ~ 9-10 months of age, weighing 7-12 kg
Study Location: (b)(4)(CC)
Compliance with QAU: Yes
Experimental Design:

Study Phase	Dose (mg/kg)	Diet	Nº of Dogs
1	5	Fasted	3♂ & 3♀
2	5	Low Fat	3♂ & 3♀
3	5	Medium Fat	3♂ & 3♀
4	5	High Fat	3♂ & 3♀

Results: Mean plasma SC-58635 in ♂ and ♀ dogs following a single oral dose, 5 mg/kg, administration under various diet condition are depicted in the following figure.



T_{max} and C_{max} were increased when SC-58635 was administered with food despite of the fat contents. The mean PK parameters following oral administration of 5 mg/kg to the dogs were enlisted in the following table.

Diet	C_{max} (µg/ml)		T_{max} (hr)		AUC_{0-24} (µg•hr/ml)	
	♂	♀	♂	♀	♂	♀
Fasted	0.356	0.364	1.5	7.5	1.89	3.22
Low Fat	0.712	0.775	3.0	3.67	5.63	5.58
Medium Fat	0.706	0.631	5.33	4.67	5.07	5.07
High Fat	0.737	0.808	6	5.33	6.64	6.66

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3.1.3.4. The Bioavailability Of SC-58635 Following Oral Administration In Different Dosage Forms To The Female Dog (A Pilot Study), Document No.: M3094152; Date:07-May-1996 (Vol. 1.68, p. 189-219)

Report Nº M3094152
Study Aim: To determine plasma concentrations of SC-58635 following administration of the compound to dog in several different capsule formulation.

Compound: SC-58635 in different formulated gelatin capsules
Formulation 1: (b)(4)(TS)
Formulation 2:
Formulation 3:
Formulation 4:
Dosage & Route: Single dose of 5 mg/kg po
Animals: Healthy ♀ dogs, 8.5-11.9 kg, 3/group
Study Location: G.D. Searle, Skokie, IL
Compliance with QAU: Not Indicated.
Study Design: This was a nonrandomized crossover study. There was a 7-day washout between two dosage forms of administrations.

Group	Dose (mg/kg)	Formulation Capsule	Nº of Animals
1	5	1	3
	5	3	
2	5	2	3
	5	4	

Blood samples were collected at 0 and 30 min, and 1, 1.5, 2, 2.5, 3.5, 7, and 24 hr post each dosing. Plasma SC-58635 levels were determined using an (b)(4)(C method.

Results: Plasma SC-58635 levels of dogs receiving different formulations of SC-58635 capsules are presented in the following table. It appeared that SC-58635 was systemically absorbed following oral administration of SC-58635 in the four different capsule formulations. High degree of variability in the plasma concentrations were seen among animals within each dose group.

Sampling	Plasma SC-58635 Concentration (Mean ± SEM), μg/ml			
Time (hr)	Formulation 1	Formulation 2	Formulation 3	Formulation 4
0	0.0012 ± 0.0012	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
0.5	0.149 ± 0.078	0.393 ± 0.300	0.104 ± 0.053	0.393 ± 0.178
1	0.531 ± 0.370	0.587 ± 0.196	0.352 ± 0.219	0.689 ± 0.178
1.5	0.633 ± 0.390	0.687 ± 0.123	0.487 ± 0.317	0.970 ± 0.148
2	0.652 ± 0.368	0.656 ± 0.052	0.541 ± 0.276	0.953 ± 0.062
2.5	0.596 ± 0.332	0.825 ± 0.178	0.460 ± 0.214	0.845 ± 0.076
3.5	0.675 ± 0.308	0.704 ± 0.144	0.489 ± 0.212	0.783 ± 0.164
5	0.465 ± 0.212	0.462 ± 0.101	0.324 ± 0.126	0.510 ± 0.165
7	0.335 ± 0.166	0.313 ± 0.090	0.278 ± 0.121	0.443 ± 0.155
24	0.0939 ± 0.0574	0.112 ± 0.045	0.136 ± 0.107	0.176 ± 0.083

3.1.3.5. Single IV Dose Pharmacokinetic Study In Dogs With SC-58635, Document No.: M2095295; Date: 10-Sep-1996 (Vol. 1.68, p. 220-264)

Report Nº: MRC-95C-100-950295 and M2195295 (Plasma Concentrations)
Study Nº: CHV 700-341
Study Aim: To evaluate the *in vivo* clearance of SC-58635 when administered in a single dose iv to dogs.
Compound: SC-58635
Dose & Route: 5 mg/kg, 1 ml/kg iv
Animals: 2♂ & 2♀ beagle dogs
Study Site: (b)(4)(CC)
Compliance with GLP/QAU: N/A
Study Date: 12/01/95 - 02/28/96
Study Design: Two ♂ and 2♀ beagle dogs previous characterized as fast metabolizer of SC-58635 were sacrificed. Liver and salivary glands were collected from each animal. Liver microsomes and postmitochonrial supernatants were prepared from approximately ¼ of liver for

total P450 content and protein analyses. Blood samples were collected at 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, ,6, 8, 12, 24, and 48 hr post dose.

Results: The yields of total protein and microsomal protein were similar in both sexes, ranging from 96.8 mg to 102 mg/g and 21.6 to 23.6 mg/g of liver, respectively. Similar amounts of total microsomal P450 (0.405 - 0.606 nmol/mg protein) were obtained from both sexes. Plasma SC-58635 concentrations and PK parameters for each animal are shown in the following table. Tremendous individual variations in PK parameters were noted. Female dogs had higher AUC values and slower clearance rate.

Time (hr)	Plasma SC-58635 Concentrations (μg/ml)			
	Animal Nº			
	32630 (♂)	32631 (♂)	32632 (♀)	32633 (♀)
0.083	2.42	2.53	2.2	3.54
0.167	2.87	NSR	2.19	3.35
0.25	1.61	2	2.26	2.74
0.5	1.37	1.75	2.4	2.88
0.75	1.06	1.76	1.86	2.73
1	0.748	1.37	1.62	2.29
1.5	0.43	1.26	0.982	1.72
2	0.408	0.751	1.11	1.45
3	0.138	0.547	0.736	1.15
4	0.0415	0.324	0.526	0.976
6	0.0215	0.13	0.684	0.235
8	ND	0.0483	0.0792	0.565
12	ND	ND	ND	0.35
24	ND	ND	ND	0.0986
48	0.0143	0.435	1.54	0.888
$\beta_{1/2}$ (hr)	0.818	1.41	1.94	7.58
Cl (ml/min•kg)	34.00	17.2	11.9	5.69
Vd_{area} (l/kg)	2.41	2.11	1.99	3.74
Vdss (l/kg)	2.23	2.08	2.06	2.72
$AUC_{0-\infty}$ (μg•hr/ml)	2.45	4.86	7.03	14.6

ND - below limit of detection o f assay (0.0 25μg/ml)
NSR - no sample received; vial empty
Note: 48 hour data was not used in calculations

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3.1.3.6. Effect Of Growth On The Pharmacokinetics Of SC-58635 After Intravenous Administration To Dogs, Document No.: M3095183; Date: 06-Jun-1997 (Vol. 1.68, p. 265-318)

Study Nº: HWI 6127-256 or MRC-95C-10-950183
Report Nº: M3095183
Study Aim: To determine the effect growth on plasma SC-58635 concentrations and PK following iv administration of SC-58635 to the same dogs at age 14 and 19 months.
Compound: SC-58635 (Lot Nº: 94K031-A1A for Phase 1 study and 95K010-A1A for Phase 2 study) in PEG 400:H_2O (2:1, v/v)
Dose & Route: 5 mg/ml/kg iv single dose at age 14.3-14.8 months and at age 18.7-19.2 months.
Animals: 4♂ and 4♀ beagle dogs previous used for Study MRC-94S-0196, fast clearance 2/sex and slow clearance 2/sex

Study Phase	Study Day	Dose (mg/kg)	Nº of Animals
1	1	5	4♂, 4♀
2	133	5	4♂, 4♀

Study Site: (b)(4)(CC) [redacted]
Compliance with GLP/QAU: N/A

Study Date: Phase 1, 7/19 - 7/21/95 and Phase 2, 11/28 - 12/01/95

Blood Collection: Blood was collected at 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hr post dose. Analysis of Plasma SC-58635 was Performed by (b)(4)(CC) (b)(4)(CC)

Results: Mean plasma (±SEM) SC-58635 and PK parameters after iv administration to fast or slow clearance dogs at age of 14.3-14.8 months old and 18.7-19.2 months old are listed in the following table. Data showed that maturation did not alter metabolism and PK profiles of SC-58635.

Time (hr)	PLASMA SC-58635 CONCENTRATIONS (μg/ml)			
	Fast Clearance		Slow Clearance	
	14.3-14.8 Months Old	18.7 -19.2 Months Old	14.3-14.8 Months Old	18.7 -19.2 Months Old
0.083	3.17 ± 0.13	2.79 ± 0.17	3.31 ± 0.37	3.44 ± 0.37
0.167	2.75 ± 0.22	2.56 ± 0.28	3.23 ± 0.21	3.05 ± 0.18
0.25	2.5 ± 0.21	2.49 ± 0.25	2.93 ± 0.21	2.77 ± 0.21
0.5	2.11 ± 0.25	2.08 ± 0.24	2.61 ± 0.08	2.82 ± 0.27
0.75	1.65 ± 0.2	1.79 ± 0.3	2.36 ± 0.06	2.56 ± 0.19
1	1.44 ± 0.17	1.43 ± 0.21	2.22 ± 0.06	2.03 ± 0.06
1.5	1.06 ± 0.16	1.11 ± 0.17	1.9 ± 0.12	1.94 ± 0.01
2	0.927 ± 0.141	0.892 ± 0.126	1.78 ± 0.06	1.7 ± 0.04
3	0.504 ± 0.13	0.444 ± 0.109	1.21 ± 0.09	1.24 ± 0.08
4	0.344 ± 0.118	0.292 ± 0.086	1.06 ± 0.07	1.02 ± 0.07
6	0.149 ± 0.062	0.115 ± 0.041	0.739 ± 0.066	0.711 ± 0.036
8	0.0771 ± 0.0397	0.0874 ± 0.051	0.507 ± 0.056	0.586 ± 0.013
12	0.0303 ± 0.0243	0.0176 ± 0.0141	0.31 ± 0.062	0.368 ± 0.059
24	BLD	BLD	0.0969 ± 0.0358	0.131 ± 0.045
48	BLD	BLD	BLD	BLD
PK PARAMETERS				
$\beta_{1/2}$ (hr)	1.77 ± 0.39	2.28 ± 0.9	6.08 ± 1.18	7.22 ± 1.61
Cl (ml/min•kg)	16.7 ± 3.0	17.6 ± 3.0	5.59 ± 0.63	5.08 ± 0.45
V_{area} (l/kg)	2.3 ± 0.17	2.85 ± 0.47	2.8 ± 0.33	3.00 ±0.4
Vdss (l/kg)	1.96 ± 0.09	2.12 ± 0.1	2.3 ± 0.25	2.54 ± 0.25
$AUC_{0-\infty}$ (μg•hr/ml)	5.53 ± 1.07	5.29 ± 1.11	15.4 ± 1.5	16.8 ± 1.7

BDL = Below Detection Limit (0.01μg/ml).

3.1.3.7. The Statistical Analysis Of The SC-58635 IV Pharmacokinetic Data In The Dog, Document No.: M3097234; Date: 25-Sep-1997 (Vol. 1.68, p. 319-344)

Report Nº: M3097234

Study Aim: Using the cluster analysis method to evaluate plasma SC-58635 concentration data from 38 dogs in three separate studies (see 3.1.3.5: Report Nº M3095295; 3.1.3.12: Report Nº M3097238; and 3.1.3.13: Report Nº MRC-94S-0196) and to determine whether the two populations could be distinguished by statistical methods.

Compound: SC-58635 in PEG 400:H_2O (2:1, v/v)

Dose & Route: 5 mg/1 ml/kg iv single dose

Animals: 38 beagle dogs

Study Site: (b)(4)(CC)

Sample Collection: Blood was collected 5, 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hours after dose administration and concentrations of SC-58635 in plasma were determined using a validated (b)(4)(CC) assay (b)(4)(CC)

Sample Analysis Site: (b)(4)(CC)

Study Design: In the present study, the cluster analysis method was used to evaluate the plasma SC-58635 concentration data obtained from three separate iv pharmacokinetic studies 3.1.3.5: Report Nº M3095295; 3.1.3.12: Report Nº M3097238; and 3.1.3.13: Report Nº MRC-94S-0196) to

determine whether this phenomena could be distinguished using statistical methods. The pharmacokinetic parameters were summarized across the three studies by population.

Results: Cluster analysis revealed that there are two populations of dogs: those that eliminate SC-58635 from plasma at a fast and those that eliminate SC-58635 at a slow rate. There is no sex-related difference in the distribution of these two populations. A summary of mean (±SEM) PK parameters is presented in the following table.

PK Parameters	Fast			Slow		
	♂ (N=11)	♀ (N=8)	♂ + ♀	♂ (N=8)	♀ (N=11)	♂ + ♀
$T_{½}$ (hr)	1.77 ± 0.25	1.66 ± 0.16	1.72 ± 0.25	4.69 ± 0.44	5.54 ± 0.36	5.18 ± 0.29
Clp (ml/hr•kg)	19.2 ± 2.2	16.9 ± 1.2	18.2 ± 1.5	7.43 ± 0.44	6.95 ± 0.45	7.15 ± 0.32
Vd (l/kg)	2.63 ± 0.43	2.32 ± 0.15	2.5 ± 0.24	2.95 ± 0.21	3.27 ± 0.21	3.14 ± 0.15
Vdss (l/kg)	2.18 ± 0.20	1.98 ± 0.05	2.10 ± 0.11	2.26 ± 0.09	2.45 ± 0.09	2.37 ± 0.07
$AUC_{0-\infty}$ (μg•hr/ml)	4.95 ± 0.47	5.20 ± 0.47	5.05 ± 0.36	11.5 ± 0.7	12.5 ± 0.7	12.1 ± 0.5

3.1.3.8. The Bioavailability Of SC-58635 Following Oral Administration In Different Dosage Forms To Dogs, Document No.: M3095231; Date: 05-Dec-1997 (Vol. 1.68, p. 345-410)

Report Nº M3095231

Study Aim: To determine the plasma SC-58635 concentrations following IV administration of SC-58635 and oral administration of SC-58635 in a solution, in two capsule formulations and in two tablet formulations.

Compound: SC-58635 (lot Nº GDS4695-042)

IV Solution: 5 mg/ml in PEG 400:H_2O (2:1, v/v)

Oral Solution: 2 mg/ml in PEG 400:H_2O (2:1, v/v)

Capsule A: (b)(4)(TS)

Capsule B:

Tablet C:

Tablet D:

Dosage & Route: Single dose of 5 mg/kg iv or po

Animals: 4♂ and 4♀ dogs, 7.77-11.78 kg, 6-13 months old

Study Location: (b)(4)(CC)

Compliance with QAU: Not Indicated.

Study Design: This was a nonrandomized crossover study and the sequences of dosing were shown in the following table. There was a 7-day (Phases 1, 2, 3, and 4) or a 14-day (Phases 5 and 6) washout between two dosage forms of administrations. Blood samples were collected over 24 (oral dose - at 15 and 30 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8 12 and 24 hr) or 48 hr (iv dose - at 5, 10, 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hr) post dose.

Phase	Dose (mg/kg)	Route	Formulation	Nº of Dogs
1	5	iv	Solution	4/sex
2	5	Oral	Solution	
3	5	Oral	Capsule A	
4	5	Oral	Capsule B	
5	5	Oral	Tablet C	
6	5	Oral	Tablet B	

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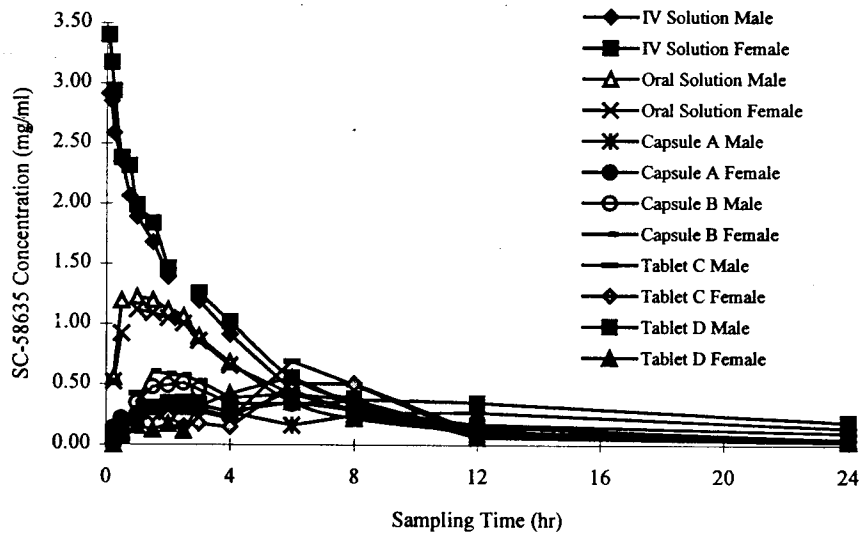
Results: SC-58635 was absorbed and systemically available following administration in five different dosage forms. Mean plasma SC-58635 levels at various time point following iv and oral

administration in the different dosage forms are presented in the following table. As depicted in the figure, there was no apparent sex-related difference in absorption of test compound.

Sample Time (hr)	Plasma SC-58635 Concentration (µg/ml)											
	IV Solution		Oral Solution		Capsule A		Capsule B		Tablet C		Tablet D	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0.0833	2.915	3.405	-	-	-	-	-	-	-	-	-	-
0.167	2.853	3.175	-	-	-	-	-	-	-	-	-	-
0.25	2.588	2.940	0.560	0.524	0.078	0.141	NM	0.011	NM	0.106	0.057+	NM
0.5	2.350	2.383	1.195	0.923	0.098	0.220	0.126	0.022	0.075	0.195	0.151	0.122
0.75	2.065	2.318	-	-	-	-	-	-	-	-	-	-
1	1.890	1.990	1.225	1.121	0.221	0.254	0.349	0.349	0.425	0.245	0.214	0.156
1.5	1.680	1.838	1.198	1.091	0.268	0.290	0.482	0.607	0.316	0.247	0.308	0.126
2	1.392	1.467	1.118	1.051	0.321	0.321	0.495	0.585	0.285	0.231	0.348	0.173
2.5	-	-	1.063	1.005	0.345	0.327	0.514	0.575	0.262	0.155	0.355	0.116
3	1.195	1.257	0.900	0.861	0.336	0.296	0.458	0.527	0.275	0.176	0.323	0.320
4	0.914	1.022	0.686	0.658	0.267	0.234	0.344	0.392	0.216	0.150	0.280	0.427
6	0.456	0.560	0.357	0.421	0.165	0.449	0.344	0.423	0.693	0.509	0.353	0.562
8	0.268	0.386	0.222	0.296	0.247	0.269	0.362	0.373	0.501	0.508	0.286	0.335
12	0.272	0.352	0.124	0.153	0.091	0.114	0.083	0.109	0.073	0.115	0.172	0.065
24	0.145	0.192	0.031	0.048	0.036	0.040	0.031	0.049	0.045	0.041	0.103	0.028

NM = Below lower limit of quantitation, 0.0100 µg/ml.



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3.1.3.9. The Bioavailability Of SC-58635 Following Oral Administration In Different Dosage Forms To Dogs, Document No.: M3095301; Date: 09-Dec-1997 (Vol. 1.69, p. 1-92)

Report Nº M3095301

Study Aim: To determine the plasma SC-58635 concentrations following iv administration of SC-58635 and oral administration of SC-58635 in a solution, in two immediate release capsule formulations, in two immediate release tablet formulations, in one controlled-release capsule formulation and in three controlled-release tablet formulations.

Compound: SC-58635 (lot Nº GDS4695-042)

IV Solution: 5 mg/ml in PEG 400:H_2O (2:1, v/v)

Oral Solution: 2 mg/ml in PEG 400:H_2O (2:1, v/v)

Tablet A: (b)(4)(TS) [redacted]

Tablet C:

Capsule B:
Phase II Caps
Capsule D:
Tablet E
Tablet F:
Tablet G:

(b)(4)(TS) [redacted] formulations as stated by the sponsor and detailed ingredients were not disclosed; used for Phases 7, 8, 9 and 10 studies at doses of 5 mg/kg.

Dosage & Route: Single dose of 5 mg/kg iv or po
Animals: 4♂ and 4♀ dogs, 7.77-11.78 kg, 6-13 months old
Study Location: (b)(4)(CC) [redacted]

Compliance with QAU: Not Indicated.

Study Design: Group of 4/sex Beagle dogs were administered SC-58635 IV in a solution, orally in a solution, in two immediate release tablet formulations, in two immediate release capsule formulations, in one controlled-release capsule formulation and in three controlled-release tablet formulations of SC-58635 in a nonrandomized crossover design as shown in the following table. There was a 7- day washout period between Phases 1, 2 and 3. There was a 28-day washout period between Phases 3 and 4. There was a 40-day washout period between Phases 4 and 5. There was a 14-day washout period between Phases 5, 6 and 7. There was a 28-day washout period between Phase 7 and 8. There was a 7-day washout period between phases 8, 9 and 10. Blood samples were collected over 24 (oral dose - at 15 and 30 minutes and 1, 1.5, 2, 2.5, 3, 4, 6, 8 12 and 24 hr) or 48 hr (iv dose - at 5, 10, 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24 and 48 hr) post dose. Plasma concentrations of SC-58635 were determined using a validated (b)(4)(CC) [redacted] (b)(4)(CC) [redacted] assay.

Phase	Dose (mg/kg)	Route	Formulation	Nº of Animals	
				♂	♀
1	5	IV	Solution	4	4
2	5	Oral	Tablet C		
3	5	Oral	Tablet A		
4	5	Oral	Capsule B		
5	5	Oral	Solution		
6	5	Oral	Phase II Capsule		
7	5	Oral	Capsule D		
8	5	Oral	Tablet E		
9	5	Oral	Tablet F		
10	5	Oral	Tablet G		

APPEARS THIS WAY ON ORIGINAL

Results: Data showed that SC-58635 was absorbed and systemically available following administration. Mean plasma SC-58635 levels at various time point following iv and oral administration in the different dosage forms are presented in the following table. High degree of variability in the plasma concentrations were seen among animals within each dose group.

Time (hr)	IV Solution	Tablet C	Tablet A	Capsule B	Oral Solution	Phase II Capsule	Capsule D	Tablet E	Tablet F	Tablet G
0.0833	3.178	-	-	-	-	-	-	-	-	-
0.167	2.941	-	-	-	-	-	-	-	-	-
0.25	2.825	0.071	1.346	0.389	0.874	0.068	0.154	0.190	0.022	0.021
0.50	2.571	0.240	0.813	0.672	1.323	0.246	0.297	0.412	0.028	0.072
0.75	2.421	-	-	-	-	-	-	-	-	-
1	2.111	0.396	0.507	0.742	0.916	0.258	0.368	0.185	0.056	0.202
1.5	1.833	0.521	0.576	0.690	1.091	0.376	0.389	0.191	0.127	0.347
2	1.665	0.626	0.439	0.666	0.954	0.443	0.399	0.210	0.183	0.505
2.5	-	0.598	0.289	0.628	0.979	0.404	0.371	0.202	0.185	0.583
3	1.476	0.441	0.266	0.530	0.878	0.574	0.364	0.171	0.177	0.538
4	1.322	0.537	0.354	0.460	1.258	0.533	0.320	0.155	0.156	0.509
6	0.887	0.379	0.470	0.328	0.977	0.354	0.229	0.109	0.106	0.366
8	0.699	0.332	0.375	0.251	0.811	0.321	0.209	0.086	0.091	0.316
12	0.496	0.234	0.126	0.185	0.564	0.311	0.187	0.064	0.067	0.284
24	0.324	0.192	0.101	0.134	0.332	0.147	0.141	0.142	0.079	0.368
48	0.141	-	-	-	-	-	-	-	-	-

3.1.3.10. Systemic Availability Of The Cyclooxygenase-2 Inhibitor, SC-58635, In Female Beagle Dogs After Administration Of SC-58635 Intragastrically (IG) Or Directly Through A Chronic Intestinal Access Port (CIAP) Into The Duodenum, Jejunum, Or Colon, Document No.: M3095195; Date: 11-Jun-1997 (Vol. 1.69 p. 93-125)

Report Nº: M3095195
Study Aims: To determine the primary site(s) of absorption of SC-58635 in the dog GI tract.
Compound: SC-58635 (Lot Nº 94L013-A1A) in PEG 400/saline (2:1)
Vehicle: PEG 400/saline (2:1)
Dose and Route: 10 mg/kg intragastrical injection or injected directly through CIAP in to the duodenum, jejunum or colon
Animals: 4 CIAP ♀ dogs, 6.8-10.3 kg
Study Site: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/AUC: N/A
Study Design: Four ♀ surgical prepared and 3 Chronic Intestinal Access Ports (CIAP) directly accessible to the upper duodenum, jejunum and colon were permanently implanted. SC-58635, 10 mg/kg, were injected intragastrically or directly through CIAP in to the duodenum, jejunum or colon. Blood samples were collected at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, 12, and 24 hr post dosing.
Results: Mean (±SM) plasma concentrations (μg/ml) of SC-58635 and pharmacokinetic parameters after administration of 10 mg SC-58635/kg intragastrically (ig) or directly through a CIAP into the duodenum, jejunum or colon of female beagle dogs are listed in the following table.

Time (hr)	IG	Duodenum	Jejunum	Colon
0	0	0	0.0113 ± 0.0113	0.007 ± 0.004
0.25	1.40 ± 0.42	1.17 ± 0.22	0.908 ± 0.246	0.109 ± 0.018
0.5	1.49 ± 0.38	1.23 ±0.25	0.902 ± 0.288	0.140 ± 0.028
0.75	1.39 ± 0.34	1.20 ± 0.21	0.858 ± 0.255	0.188 ± 0.045
1	1.39 ± 0.33	1.13±0.16	0.847 ± 0.252	0.223 ± 0.060
1.5	1.31 ± 0.28	1.12 ± 0.15	0.782 ± 0.165	0.301 ± 0.084
2	1.15 ± 0.24	1.03 t 0.20	0.717 ± 0.125	0.363 ± 0.111
3	0.945 ± 0.182	0.969 ± 0.204	0.595 ± 0.081	0.473 ± 0.164
5	0.633 ± 0.135	0.911 ± 0.350	0.487 ± 0.07	0.675 ± 0.161
8	0.391 ± 0.078	0.391 ± 0.075	0.464 ± 0.084	0.620 ± 0.074
12	0.287 ± 0.057	0.208 ± 0.043	0.333 ±0.076	0.534 ± 0.093
24	0.0901 ± 0.0257	0.0433 ± 0.0228	0.177 ± 0.084	0.098 ± 0.030
C_{max} (μg/ml)	1.62 ± 0.36	1.46 ± 0.20	1.06 ± 0.21	0.789 ± 0.118
T_{max} (hr)	0.688 ± 0.277	1.13 ± 0.63	2.25 ± 1.92	8.50 ± 2.02
AUC_{0-24} (μg•hr/ml)	10.3 ± 2.0	9.69 ± 1.57	9.37 ± 0.97	10.00 ± 0.9

3.1.3.11. The Bioavailability of SC-58635 Following Oral Administration In Different Dosage Forms To Dogs, Document No.: M3095048; Date: 14-May-1996 (Vol. 1.69, p. 126-179)

Study Nº MRC-95S-0048/HWI6127-235
Report Nº M3095048
Study Aim: To determine plasma concentrations of SC-58635 following administration of the compound to dog in several different capsule formulations.
Compound: SC-58635
Solution: in PEG 400 : H_2O (2:1, v/v)
Formulation A: (b)(4)(TS)
Formulation B:
Formulation C:
Formulation D:
Dosage & Route: Single dose of 5 mg/kg po
Animals: Healthy 3♂ & 3♀ dogs, 9-10 months of age, weighing 7-12 kg, 3/sex/group
Study Location: (b)(4)(CG)
Compliance with QAU: Not Indicated.
Study Design: This was a nonrandomized crossover study. There was a 7-day washout between two dosage forms of administrations. Blood samples were collected at 0 and 30 min, and 1, 1.5, 2, 2.5, 3.5, 7, and 24 hr post each dosing. Plasma SC-58635 levels were determined using an HPLC method.

Group	Dose (mg/kg)	Formulation	Route	Nº of Animals	
				♂	♀
1	5	Solution	po (gavage)	3	3
	5	A (Gelatin Capsule)	po		
	5	B (Gelatin Capsule)	po		
2	5	C (Gelatin Capsule)	po	3	3
	5	D (suspension)	po (gavage)		

APPEARS THIS WAY ON ORIGINAL

Results: Plasma SC-58635 levels and mean PK parameter (n=3) of dogs receiving different formulations of SC-58635 are presented in the following table. It appeared that SC-58635 was systemically absorbed following oral administration of SC-58635 in the five different formulations. High degree of variability in the plasma concentrations were seen among animals within each dose group. The bioavailability (BA) for SC-58635 was superior in the solution or suspension form.

Sampling Time (hr)	Plasma SC-58635 Concentration (Mean ± SEM), μg/ml									
	Solution		Formulation A		Formulation B		Formulation C		Formulation D	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0.25	0.975	0.509	0.006	0	0.022	0.115	0	0	0.138	0.081
0.5	1.52	0.824	0.093	0.005	0.094	0.247	0.072	0.064	0.334	0.453
1	1.37	0.820	0.215	0.244	0.271	0.228	0.200	0.443	0.608	0.826
1.5	1.23	0.762	0.353	0.357	0.355	0.189	0.529	0.672	0.762	0.936
2	1.08	0.604	0.421	0.318	0.381	0.138	0.586	0.717	0.729	0.865
2.5	0.853	0.594	0.362	0.243	0.282	0.101	0.537	0.586	0.643	0.800
3	0.780	0.517	0.315	0.189	0.265	0.086	0.437	0.492	0.539	0.741
4	0.628	0.413	0.228	0.145	0.234	0.071	0.332	0.384	0.447	0.576
6	0.436	0.286	0.167	0.107	0.278	0.066	0.213	0.233	0.304	0.354
8	0.303	0.187	0.157	0.083	0.210	0.062	0.160	0.160	0.234	0.234
12	0.163	0.080	0.219	0.094	0.190	0.043	0.105	0.087	0.183	0.142
24	0.004	0.016	0.083	0	0.103	0.040	0.033	0.041	0.058	0.039
C_{max} (μg/ml)	1.52	0.839	0.524	0.36	0.453	0.250	0.639	0.785	0.826	1.01
T_{max} (hr)	0.5	0.667	5.33	1.33	3.33	0.667	1.5	1.5	5.17	1.67
AUC_{0-24} (μg•hr/ml)	7.93	4.7	4.34	1.89	4.56	1.53	3.72	4.06	5.72	6.11
BA (%)	89.4	62.4	49.4	31.2	52.2	24.9	42.9	46.3	87.5	69.5

3.1.3.12. The Bioavailability Of SC-58635 Following Oral Administration In Different Dosage Forms To Dogs, Document No.: M3097238; Date: 06-Aug-1997 (Vol. 1.69, p. 180-297)

Report Nº: M3097238

Study Aims: To determine the plasma SC-58635 concentrations and PK following iv administration and oral administration in different capsule and tablet formulation.

Compound: iv formulation - SC-58635 (Lot Nº: 96K001-A3A) in PEG400/sterile H_2O (2:1, v/v)
oral tablet formulation - A (GDS-6115-051A), B (GDS6115-051B) and C (GDS6115-051F)
oral capsule formulation - D, E, F, and H (PT-128-96 and PT121-96)

Dose and Route: 5 mg/kg iv with a 29-day washout period;
40, 40 and 60 mg/kg for oral tablet formulation A, B, and C, respectively with a 7-day washout period;
50 mg/kg for capsule formulation D, E, F, and H (crossover with a 7-day washout period)

Animals: beagle dog

Study Site: (b)(4)(CC)

Study Design: Five ♂ and five ♀ beagle dogs were administered intravenously (iv) SC-58635 in polyethylene glycol (PEG) 400:sterile water (2: 1, v/v) at a single dose of 5 mg/kg. One male and three female dogs were selected from the original ten animals and were orally administered three different tablet formulations of SC-58635 (formulations A, B, & C) at single doses of 40, 40 and 60 mg/kg and four different capsule formulations of SC-58635 (formulations D, E, F & H) at single doses of 50 mg/kg in a nonrandomized crossover design.

Blood Collection: 5, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 hr post iv administration;
15 and 30 min and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hr post oral dosing.

Results: The plasma $T_{½}$ and clearance of SC-58635 for ♂ and ♀ dogs after iv administration of 5 mg/kg SC-58635 and the $T_{½}$, C_{max}, and $AUC_{0-\infty}$ values of SC-58635 after oral administration of 50 mg/kg SC-58635 in capsule formulation H are shown in the following table. SC-58635 was absorbed and systemically available following oral administration of formulations A, B, C, D, E, F and H.

Dose (mg/kg)	Route	Sex	$T_{½}$ (hr)	Clp (ml/min•kg)	Vd_{ss} (l/kg)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg•hr/ml)
5	iv	♂	1.56 to 3.83	5.85 to 21.0	1.66 to 3.91	-	-
		♀	1.52 to 5.63	5.38 to 18.6	1.78 to 2.23	-	-
50 (Capsule H)	po	♂ & ♀	1.00 to 3.00	-	-	0.793 to 6.74	9.80 to 75.1

3.1.3.13. The Pharmacokinetics Of SC-58635 Following Single Intravenous And Oral Multiple Dose Administration to Dogs, Document No.: MRC-94S-0196; Date: 07-Dec-1995 (Vol. 1.69, p.298-409)

Report Nº MRC-94S-0196

Study Nº HWI 6127-229

Study Aim: To determine the PK of SC-58635 following administration of SC-58635 as a neat compound or as a formulated mixture to the dogs with or without meal feeding.

Compound: SC-58635 (Lot Nº 94K014-A2B) in gelatin capsule or PEG:H_2O (2:1, v/v)for Phase I, III and IV studies; formulated SC-58635 in 5 mg capsule (RTC 9673) for Phase II study.

Dosage: Phase I & II - 5 or 15 mg/kg po for 14 days for; Phase III - 5 mg/kg iv for; Phase IV- 25 mg/kg po for 14 days
Animals: 12♂ and 12♀ beagle Dogs
Study Site: (b)(4)(CC)
Compliance with QAU: N/A
Experimental Design:

- Phase I (Days 1-14 of the study): Dogs were administered orally SC-58635 as a neat chemical in a gelatin capsule at 5 or 15 mg/kg/day for 14 days.
- Phase II (Days 21-35 of the study): Dogs were administered orally SC-58635 in **formulated capsules** at 5 or 15 mg/kg for 14 days.
- Phase III (Day 51 of the study): SC-58635 was administered to the dogs in Groups 1 and 2 intravenous (IV) at a dose of 5 mg/kg.
- Phase IV (Days 78-92 of the study): Dogs were administered orally SC-58635 as neat compound in gelatin capsules at 25 mg/kg for 14 days with or without food.

Results: There are two distinct populations in both male and female dogs that eliminate SC-58635 from plasma at either a fast or slow rate. The pharmacokinetics following IV administration of SC-58635 were not different between male and female dogs. Fast SC-58635 clearance animals had higher exposure to SC-58635 (as measured by C_{max} and AUC). T_{max} of SC-58635 was prolonged when the compound was coadministered to dogs with food. Mean PK parameters either analyzed by the sex or by the rate of clearance from each phase (except Phase III) study are summarized in the following tables.

Phase I:

- Mean (±SEM) (Analyzed by sex) Pharmacokinetic Parameters of SC-58635 for Phase I of the Study

Day	Dose mg/kg/day	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
		♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)
1	5	3.33 ± 1.74	1.5 ± 0.18	0.287 ± 0.046	0.525 ± 0.168	2.49 ± 0.84	2.9 ± 1.12
	15	2.42 ± 0.42	2.92 ± 0.64	0.853 ± 0.097	1.92 ± 0.47	4.91 ± 0.71	14.2 ± 3.4
14	5	1.67 ± 0.17	1.42 ± 0.08	0.281 ± 0.07	0.357 ± 0.039	2.15 ± 0.62	1.62 ± 0.88
	15	3.17 ± 1.77	3.5 ± 1.17	0.439 ± 0.79	1.2 ± 0.23	3.27 ± 1.11	9.8 ± 2.36

- Mean (±SEM) SC-58635 Pharmacokinetic Parameters (Analyzed by the Rate of Clearance) for Phase I of the Study

Day of Dosing	Dose mg/kg	Clearance Rate	N	T_{max} (hr)	C_{max} (μg/ml)	AUC (μg•hr/ml)
1	5	F	6	1.50 ± 0.22	0.229 ± 0.046	0.950 ± 0.333
1		S	6	3.33 ± 1.74	0.583 ± 0.146	4.44 ± 0.80
14		F	6	1.50 ± 0.13	0.250 ± 0.055	0.818 ± 0.221
14		S	6	1.58 ± 0.15	0.389 ± 0.044	2.95 ± 0.18
1	15	F	3	2.17 ± 0.67	0.870 ± 0.077	3.80 ± 0.75
1		S	9	2.83 ± 0.45	1.56 ± 0.36	11.5 ± 2.6
14		F	3.	1.67 ± 0.33	0.384 ± 0.117	1.38 ± 0.46
14		S	9	3.89 ± 1.54	0.965 ± 0.192	8.25 ± 1.76

Phase II:

- Mean (±SEM) (Analyzed by sex) Pharmacokinetic Parameters of SC-58635 for Phase II of the Study

Day	Dose mg/kg/day	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
		♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)
1	5	1.33 ± 0.11	1.25 ± 0.11	0.306 ± 0.042	0.297 ± 0.018	2.56 ± 0.57	1.44 ± 0.30
	15	3.25 ± 1.76	3.00 ± 1.06	0.615 ± 0.107	1.03 ± 0.26	4.24 ± 0.88	7.64 ± 2.71
14	5	1.17 ± 0.11	1.67 ± 0.38	0.347 ± 0.057	0.547 ± 0.085	2.73 ± 0.74	2.47 ± 0.65
	15	1.25 ± 0.17	1.83 ± 0.36	0.681 ± 0.134	0.998 ± 0.250	4.22 ± 1.14	8.55 ± 2.92

- Mean (± SEM) Pharmacokinetic Parameters of SC-58635 for Phase II of the Study : Compound Administered as Neat Chemical in Gelatin Capsule

Day of Dosing	Dose mg/kg	Clearance Rate	N	T_{max} (hr)	C_{max} (μg/ml)	AUC (μg•hr/ml)
1	5	F	6	1.33 ± 0.11	0.279 ± 0.016	0.972 ± 0.132
1		S	6	1.25 ± 0.11	0.324 ± 0.040	3.03 ± 0.32
14		F	6	1.17 ± 0.11	0.453 ± 0.110	1.17 ± 0.31
14		S	6	1.67 ± 0.38	0.441 ± 0.048	4.02 ± 0.27
1	15	F	3	1.67 ± 0.44	0.841 ± 0.210	3.43 ± 1.33
1		S	9	3.61 ± 1.28	0.815 ± 0.188	6.77 ± 1.83
14		F	3.	1.33 ± 0.17	0.451 ± 0.127	1.52 ± 0.06
14		S	9	1.61 ± 0.27	0.968 ± 0.166	8.01 ± 1.89

APPEARS THIS WAY ON ORIGINAL

Phase III: No data were presented.

Phase IV:

- Mean (±SEM) (Analyzed by sex) Pharmacokinetic Parameters of SC-58635 for Phase IV of the Study

Day of Dosing	Dose mg/kg	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
		♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)
COMPOUND ADMINISTERED WITH FOOD							
1	25	9.67 ± 1.09	8.92 ± 1.96	2.41 ± 0.40	1.52 ± 0.41	25.9 ± 6.4	11.7 ± 3.1
14	25	7.83 ± 2.33	8.67 ± 2.11	2.34 ± 0.70	1.29 ± 0.28	27.8 ± 10.8	9.62 ± 2.28
COMPOUND ADMINISTERED WITHOUT FOOD							
1	25	3.67 ± 1.68	6.58 ± 1.93	1.18 ± 0.35	3.16 ± 0.79	7.57 ± 2.74	38.1 ± 11.5
14	25	4.00 ± 1.62	3.67 ± 0.53	1.69 ± 0.74	4.56 ± 1.00	12.3 ± 6.25	52.5 ± 17.5

- Mean (± SEM) (by Clearance) Pharmacokinetic Parameters of SC-58635, 25 mg/kg iv, for the Phase IV Study

Day of Dosing	Clearance Rate	N	T_{max} (hr)	C_{max} (μg/ml)	AUC (μg•hr/ml)
COMPOUND ADMINISTERED WITH FOOD					
1	F	6	9.00 ± 1.61	1.38 ± 0.33	8.42 ± 1.82
1	S	6	9.58 ± 1.56	2.55 ± 0.41	29.10 ± 5.0
14	F	6	8.25 ± 1.86	1.35 ± 0.28	7.78 ± 2.31
14	S	6	8.25 ± 2.54	2.29 ± 0.72	29.60 ± 10.1
COMPOUND ADMINISTERED WITHOUT FOOD					
1	F	3	5.67 ± 3.17	1.18 ± 0.25	7.51 ± 3.97
1	S	9	4.94 ± 1.49	2.50 ± 0.65	28.00 ± 9.1
14	F	3	3.17 ± 0.33	1.84 ± 0.53	11.90 ± 6.4
14	S	9	4.06 ± 1.09	3.55 ± 0.94	39.30 ± 13.6

APPEARS THIS WAY ON ORIGINAL

3.1.3.14. The Pharmacokinetics Of SC-58635 Following Multiple Dose (Q.D. And B.I.D.) Administration To Dogs, Document No.: MRC-95S-0050; Date: 02-Feb-1996 (Vol. 1.69, p. 410-457)

Report Nº MRC95S-005 (HWI 6127-237)

Study Aims: To determine the plasma levels of SC-58635 following oral administration of the drug in a gelatin capsule for 7 days.
Compound: SC-58635 (Lot Nº 94K014-A2B)
Dose and Route: 7.5 and 12.5 mg/kg/day (bid, po) and 20 mg/kg/day (qd, po) for 7 days
Animals: 6♂ & 6♀ beagle dogs, ~9-10 months of age, weighing 7-12 kg.
Study Location: (b)(4)(CC)
Compliance with GLP: N/A
Study Design

Group	Dose (mg/kg)	Dosing Frequency	Nº of Animals
1	7.5	bid	2/sex
2	12.5	bid	2/sex
3	20	qd	2/sex

Blood Collection:

- Group 1 & 2 - 0.5, 1, 2, 3, 4, 8, 12, 12.5, 13, 14, 15, 16, 20 and 24 hr post 1st daily dose on Day1 and 0.5, 1, 2, 3, 4, 8, 12, 12.5, 13, 14, 15, 16, 20, 24, 36, 48 hr post 1st daily dose on Day 7.
- Group 3 - 0.5, 1, 2, 2.5, 3.4, 6, 8, 12, 20 and 24 hr post dose on Day 1.

Results: Individual and mean PK parameters are presented in the following table.

Dose	Time	AUC_{0-12} (μg•hr/ml)			C_{max} (μg/ml)			T_{max} (hr)		
(mg/kg)	(Day)	♂	♀	Mean	♂	♀	Mean	♂	♀	Mean
7.5	7	5.23/5.71	7.06/5.43	5.86	0.773/1.03	0.872/0.732	0.852	2.0/2.0	2.0/2.0	3.5
12.5	7	7.58/9.87	24.5/8.03	12.5	1.13/1.75	2.80/1.32	1.75	1.0/0.5	3.0/2.0	1.63
20[a]	1	8.93/4.68	21.9/5.3	10.2	0.763/0.304	1.69/1.03	0.947	24.0/12.0	12.0/1.5	12.4

[a] AUC was calculated from 0-12 hr.

3.1.4. CYNOMOLGUS MONKEY

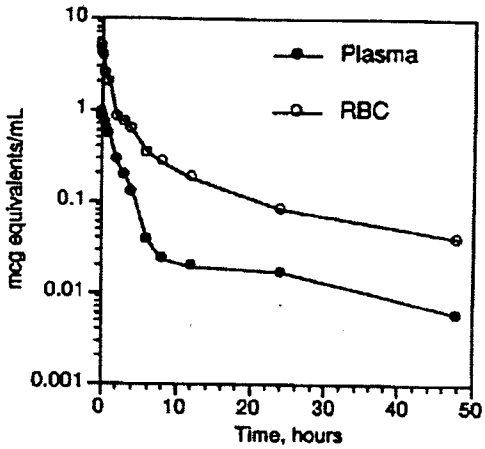
3.1.4.1. The Pharmacokinetics And Metabolism Of SC-58635 After Intravenous Administration To The Female Cynomolgus Monkey (An Exploratory Study), Document No.: MRC-94S-0210; Date: 17-May-1995 (Vol. 1.70, p. 1-68)

Report Nº MRC-94S-0210
Study Aim: To evaluate pharmacokinetics and metabolism of [^{14}C]SC-58635 following intravenous bolus (1 & 15 mg/kg) ♀ cynomolgus monkey in a non-randomized crossover design
Compound: [^{14}C]SC-58635 dissolved in PEG-400:H_2O, 2:1, v/v
Dosage & Route: 15 & 1 mg/kg, 1 ml/kg iv; each dose level was given once to each animal
Animals: 3♀ Cynomolgus monkey, weighed 3.4 - 3.8 kg
Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP/QAU: N/A
Study Design: Each animal was given once with each dose level through the left jugular vein and the 15 mg/kg dose was given prior to 1 mg/kg dose. There was a washout period of ≥1 wk. Blood samples were collected at 0, 2, 5, 15, 30, and 45 min, and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hr post dose administration. Urine and fecal samples were collected by free-catch in containers surrounded by dry ice at -18-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-160 hr. Plasma concentrations of SC-58635 were determined by the (b)(4)(CC) analysis.

Results: The plasmas concentrations of SC-58635 and PK parameter after iv administration at dose of 1 and 15 mg/kg to ♀ cynomolgus monkey are listed as follows:

Time (min)	Plasma Concentration (ng/ml) 1 mg/kg	15 mg/kg	Time (hr)	Plasma Concentration (ng/ml) 1 mg/kg	15 mg/kg	PK PARAMETERS (1 mg/kg)	
2	0.636 ± 0.156	10.6 ± 3.26	2	0.106 ± 0.006	2.77 ± 0.627	Clp (ml/min•kg)	22.7 ± 1.0
5	0.489 ± 0.122	8.75 ± 2.98	3	0.07 ± 0.10	1.49 ± 0.353	$T_{½}$ (hr)	1.66 ± 0.50
15	0.312 ± 0.035	6.68 ± 2.49	4	-[a]	0.785 ± 0.205	Vd (l/kg)	3.58 ± 1.02
30	0.278 ± 0.019	5.77 ± 1.39	6	-	0.233 ± 0.041	Vdss (l/ml)	3.22 ± 0.88
45	0.210 ± 0.029	4.76 ± 1.77	8	-	0.244 ± 0.086	[a] Value below sensitivity limit of the	
60	0.176 ± 0.029	4.17 ± 1.25	12	-	0.93 ± 0.042	assay.	

The volume of distribution was greater than total body water (≈0.7 l/kg), suggesting that SC-58635 was distributed into intracellular space and/or was bond to specific tissue sites. The major metabolite (SC-628078) of SC-58635 was eliminated through feces and urine and no parent drug was present in the excretions.



The concentrations of total ^{14}C in plasma and red blood cells of a female monkey following iv administration of 1 mg/kg of [^{14}C]SC-58635 are shown in the right figure. Radioactivity partitioned into red blood cells with RBC/plasma ratio ranging from 2.94 to 11.5.

Metabolic Profile -

Plasma: The mean percentages of total radioactivity present as [^{14}C]SC-58635, [^{14}C]SC-60613 and [^{14}C]SC-62807 in are shown in following table. [^{14}C]SC-62807 was the major circulating component in the plasma following the iv administration of a 1 mg/kg dose of [^{14}C]SC-58635.

Time (hr)	% SC-58635	% SC-60613	% SC-62807
0.083	72.6	0	27.4
0.25	34.4	1.57	64.0
0.5	28.6	1.31	70.1
2	34.2	0.624	64.8
3	20.5	0	79.5
4	24.7	0	75.3
6	9.92	0	90.1

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Urine and Feces: The percentage of the dose excreted in the urine as [^{14}C]SC-58635, [^{14}C]SC-60613 and [^{14}C]SC-62807 were 0, 0, and 18.7%, respectively. No parent drug was excreted in the feces. The following table shows cumulative % of the dose excreted as total carbon in urine and feces, and % of dose in feces profiles present as [^{14}C]SC-58635, [^{14}C]SC-60613 and [^{14}C]SC-62807 from one female cynomolgus monkey following iv administration of 1 mg/kg [^{14}C]SC-58635.

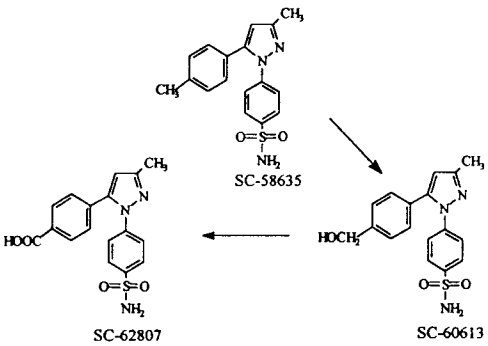
	% Dose Excreted as Total Carbon				% Dose in Feces		
Time (hr)	Urine	Feces	Urine + Feces	Time (hr)	SC-58635	SC-60613	SC-62807
0 – 24	18.9	0.0215	18.9	0– 24	0	0	0.0214
0 – 48	27.0	6.38	33.4	24– 48	0	0	6.27
0 – 72	27.0	40.6	67.6	48– 72	0	0	33.8
0 – 96	27.6	53.6	81.2	72– 96	0	0	12.6
0 – 120	27.7	61.5	89.1	0– 96	0	0	52.7
0 – 144	27.8	63.3	91.1				
0 – 168	27.9	63.5	91.4				

Therefore, SC-58635 was extensively metabolized and no parent drug was excreted in urine or feces. The major metabolite of SC-58635 excreted in urine and feces was SC-62807. The major circulating metabolite of SC-58635 was SC-62807. SC-58635 was eliminated by metabolism followed by excretion of the metabolites in feces and urine.

3.1.4.2. The Pharmacokinetics And Metabolism Of SC-58635 After Intravenous Administration To The Female Rhesus Monkey (An Exploratory Study), Document No.: MRC95S-30-950167; Date: 14-Sep-1995 (Vol. 1.70, p. 69-139)

Report Nº MRC95S-30-950167
Study Aims: To determine the PK and metabolism of SC-58635 after iv administration of 1 and 15 mg/kg of SC-58635 to the female rhesus monkey in a non-randomized crossover design.
Compound: [^{14}C]SC-58635 (143 μCi/mg) and SC-58635, 1 mg/ml
Vehicle: polyethylene glycol 400 (PEG): H_2O (2:1, v/v)
Dosage and Route: [^{14}C]SC-58635 - 1 mg/kg iv; SC-58635 - 1 or 15 mg/kg iv
Animals: 3 ♀ Rhesus monkey, weighing 6.45-6.75 kg
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP: N/A
Study Design

Monkey ID	Compound	Dose (mg/kg)	Route	Sample Collected
581	SC-58635	15	iv	Plasma
587	SC-58635	15	iv	Plasma
588	SC-58635	15	iv	Plasma
581	[^{14}C]SC-58635	1	iv	Plasma, Urine, RBC, Feces
587	SC-58635	1	iv	Plasma
588	SC-58635	1	iv	Plasma



Sample Collection:
- Blood - 0, 2, 5, 15, 30 and 45 min, 1, 2, 3, 4, 6, 8, 12, 24, and 24 hr post dosing.
- Urine and Feces - Urine and fecal samples were collected for consecutive 24 hr periods: -18-0, 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hr.

Results:
- Concentrations of total radioactivity in plasma and RBC following iv injection of 1 mg/kg of [^{14}C]SC-58635 -

Time (min)	Concentration (μg eq/ml)			Time (hr)	Concentration (μg eq/ml)		
	Plasma	RBC	RBC/Plasma Ratio		Plasma	RBC	RBC/Plasma Ratio
2	0.743	3.73	5.02	1	0.601	2.34	3.89
5	0.735	3.51	4.78	2	0.334	1.10	3.29
15	0.792	2.85	3.60	3	0.191	0.778	4.07
30	0.740	2.90	3.92	4	0.118	0.463	3.92
45	0.662	2.67	4.03	6	0.0396	0.196	4.95
				8	0.0229	0.0948	4.14
				12	0.0021	0.0299	14.3
				24	-	0.0234	-
				48	-	0.0013	-

- Concentration of SC-58635 in the plasma and PK parameters following iv injection of 1 and 15 mg/kg of SC-58635 -

Time (min)	Plasma Concentration (μg/ml) 1 mg/kg	15 mg/kg	Time (hr)	Plasma Concentration (μg/ml) 1 mg/kg	15 mg/kg
2	0.702	14.4	1	0.245	5.54
5	0.507	9.9	2	0.154	3.98
15	0.446	8.49	3	0.097	2.92
30	0.375	7.29	4	0.067	1.63
45	0.287	7.09	6	-[a]	0.515
PK Parameters			8	-	0.294
Clp (ml/min•kg)	17.8		12	-	0.093
$T_{½}$ (hr)	1.5		24	-	-
Vd (l/kg)	2.73		48	-	-
Vd_{ss} (l/kg)	2.34				

[a] value < 0.025 μg/ml (limit of detection)

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- Metabolic profiles of SC-58635 following iv injection of 1 mg/kg of SC-58635

Sample	Time (hr)	% SC-58635	% SC-60613	% SC-62807
Plasma	3	36.7	0	59.1
	4	30.2	0	69.8
Urine	0-24	0	0	21.1
Feces	0.24	0	0	18.4
	24-48	0	0	56.7

APPEARS THIS WAY ON ORIGINAL

3.2. PROTEIN BINDING

3.2.1. RAT, MOUSE, DOG AND HUMAN

3.2.1.1. Rat And Human Plasma Protein Binding Of [^{14}C]SC-58635 (A Pilot Study), Document No.: MRC-94S-0136; Date: 17-May-1995 (Vol. 1.70, p. 140-157)

Report Nº: MRC-94S-0136
Study Aim: To determine the extent of SC-58635 binding to protein in rat and human plasma.
Compound: [^{14}C]SC-58635 (Lot Nº GDS-4095-25, 146 μCi/mg)
Blood Samples: Rat and Human
Study Location: G.D. Searle & Co., 800 N. Lindbergh Blvd., St. Louis, MO 63167
Compliance with QAU: N/A
Study Design: Plasma protein binding of [^{14}C]SC-58635 was performed *in vitro* at concentrations ranging from 0.3 to 3.0 μg/ml, using rat and human plasma by using a dextran-coated charcoal method.

Results: The percentages of [^{14}C]SC-58635 bound to plasma *in vitro* are listed as follows. The binding of [^{14}C]SC-58635 to plasma protein appeared to be concentration-dependent.

[^{14}C]SC-58635 (μg/ml)	% [^{14}C]SC-58635 bound to plasma Rat	Human
0.3	95.6	97.3
1.0	85.3	-
3.0	88.3	90.6

APPEARS THIS WAY ON ORIGINAL

3.2.1.2. The Binding Of SC-58635 To Mouse, Rat, Dog And Human Plasma Proteins, Document No.: M3097065; Date: 16-Feb-1998 (Vol. 1.70, p. 158-216)

Report Nº: M3097065
Study Aim: To determine the extent of SC-58635 binding to plasma protein in vitro for mouse, rat, dog and human, as well as for human serum albumin and human α_1

acid glycoprotein and to evaluate the plasma concentrations of free and total SC-58635 in mouse, rat and dog after oral administration of SC-58635.

Compound: SC-58635 (Lot Nº 94K031-A2A); [^{14}C]SC-58635 (Lot Nº GDS-4671-84, 141 μCi/mg) in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) suspension or in gelatin capsule.

Animals: ♂ CD-1 mice, 20-40 g; ♂ & ♀ Sprague Dawley rats, 250-350 g; ♀ Beagle dogs, 8-12 kg.

Dose: Mouse, 10 or 300 mg/kg po; Rat, 1 or 400 mg/kg po; Dog, 1 or 100 mg/kg po.

Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.

Compliance with QAU: N/A

Study Design: The binding of [^{14}C]SC-58635 to plasma protein was evaluated *in vivo* for mouse, rat and dog. Male Charles River CD-1 mice (n=36/dose) were administered a single dose of 10 and 300 mg SC-58635/kg in of 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) suspension. Female SD rats (n=24/dose) were administered a single oral dose of 1 or 400 mg/kg SC-58635 in of 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) suspension. Female beagle dogs (n=3) were administered single doses of SC-58635 at 1 mg/kg of suspension in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) and 100 mg/kg capsule. Blood samples were collected from all animals after dose administration and plasma was prepared by centrifugation of blood. Plasma concentrations of total SC-58635 were determined by the (b)(4)(CC method. Plasma concentrations of free SC-58635 were determined using (b)(4)(CC)

The binding of [^{14}C]SC-58635 to plasma protein was evaluated *in vitro* using plasma prepared from mouse, rat, dog, and human blood and also in solutions of human serum albumin and α_1 acid glycoprotein. Blood was obtained from ♂ CD-1 mice, ♂ Sprague Dawley rats, a ♂ beagle dog, and a healthy ♂ human subject. Plasma samples for each species and the 0.067M KH_2PO_4-Na_2HPO_4 buffered (pH 7.4) solutions of human serum albumin (40 mg/ml) and human α_1 acid glycoprotein (1.80 mg/ml) were split into five equivalent aliquots that were fortified with to concentrations of 0. 1. 0.3. 1.0, 3.0 and 10 μg/ml. The protein binding of [^{14}C]SC-58635 to plasma proteins was evaluated for each concentration using an ultracentrifugation method.

Results: SC-58635 was highly bound to plasma protein in the mouse, rat, dog and human. Data from *in vitro* plasma protein binding experiment are listed in the below table.

Species	*In Vitro* % Plasma Protein Binding				
	[^{14}C]SC-58635 Concentrations (μg/ml)				
	0.1	0.3	1.0	3.0	10
Mouse	94.4	-	-	-	93.5
Rat	98.4	94.3	91.4	95.9	84.2
Dog	98.2	96.7	97.0	97.0	97.1
Human	98.2	97.9	96.5	96.7	96.3
human α_1 acid glycoprotein	92.4	91.6	91.0	88.4	78.6
human albumin	100	100	99.8	99.9	99.8

APPEARS THIS WAY ON ORIGINAL

Plasma C_{max} values for SC-58635 and % SC-58635 bound to protein at C_{max} following single oral administration of SC-58635 to the mouse, rat, and dog are presented in the following table.

SC-58635	Mouse		Rat		Dog	
Dose (mg/kg)	10	300	1	400	1	100
C_{max} (μg/ml)	2.57	12.7	0.198	6.74	0.275	3.62
% Plasma Protein Binding	98.1	99.2	98.8	99.1	98.9	99.5

APPEARS THIS WAY ON ORIGINAL

3.3. TISSUE DISTRIBUTION AND ACCUMULATION

3.3.1. RAT

3.3.1.1. Tissue Distribution And Excretion Of Radioactivity Following A Single Oral Dose Of [^{14}C] SC-58635 In Male Rats, Document No.: MRC-94S-0182; Date: 21-Jul-1995 (Vol. 1.70, p. 217-363)

Report Nº: MRC94S-0182
Study Nº HWI-6127-226
Study Aim: To assess the tissue distribution and excretion of [^{14}C]SC-58635 in Male Rats following a single oral dose
Compound: [^{14}C]SC-58635 in PEG 400/H_2O
Dosage: 2 mg/kg po
Animals: 31 ♂ Long-Evans rats, weighting 196-230 g, ~51 days old.
Study Location: (b)(4)(CC)
Compliance with QAU: Yes
Study Design: One animal served as control and was sacrificed for the blood and tissue collection. Total 30 animals were dosed with 2 mg/kg [^{14}C]SC-58635. The mean radioactive dose administered to each rat was 18.4 ± 0.81 μCi. Animals were sacrificed (3/time point) at 0.5, 1, 3, 8, 24, 72, 96, 144, and 168 hr postdose. Tissues and blood were collected following each sacrifice. Urine, feces and expired air were collected at selected intervals from the rats sacrificed for tissue collection at 168 hr postdose. The radioactivity in the blood, urine and feces samples and tissues distribution of radioactivity were determined.

Results: The absorption of [^{14}C]SC-58635 was rapid; the T_{max} for the blood and plasma was 1 hr postdose with C_{max} of 4.18 and 0.966 μg equivalents/g, respectively. The highest mean C_{max} values in various tissues were liver, RBCs, blood, adrenal glands, lacrimal glands, and bone marrow, with levels of 6.28, 5.70, 4.18, 3.31, 3.24 and 2.99 μg equivalents/g, respectively. By 72 hr postdose, concentrations in the most tissues were below the limit of detection. The mean & cumulative (n=3) percent of radioactive dose in urine, and feces was presented in the following table. At 168 hr post administration, 0.71%, 14.9%, and 6.71% of radioactivity was recovered in the feces, urine and cage wash, respectively indicating that the major route of excretion was through the faces.

Collection Time (hr)	Mean % of Radioactive Dose		Collection Time (hr)	Cumulative % of Radioactive Dose	
	Urine	Feces		Urine	Feces
0-6	5.08	12.1	0-6	5.08	12.1
6-24	5.71		0-24	10.8	
24-48	1.99	50.8	0-48	12.8	46.0
48-72	0.94	13.7	0-76	13.7	59.7
72-96	0.38	9.84	0-96	14.1	69.6
96-120	0.24	0.72	0-120	14.3	70.3
120-144	0.24	0.40	0-144	14.6	70.7
144-168	0.30	0.17	0-168	14.9	70.9

APPEARS THIS WAY ON ORIGINAL

3.3.1.2. The Pharmacokinetics And Metabolism Of [^{14}C] SC-58635 After Oral Administration To the Pregnant Rat, Document No.: M3097235; Date: 22-Sep-1997 (Vol. 1.71, p. 1-81)

Study Nº: Covance 6127-328
Study Report Nº: M3097235

Study Aims: To obtain information on the PK and metabolism of [^{14}C]SC-58635 after a single oral administration to pregnant rats and to determine whether drug-associated radioactivity reached the fetuses or the amniotic fluid.

Compound: [^{14}C]SC-58635 (Lot Nº: GDS 4671-84, 97.5% purity with 141 μCi/mg of specific activity) in PEG400/H_2O (2:1), 0.5 mg/ml and 30 μCi/mg

Vehicle: PEG400/H_2O (2:1)

Dose and Route: 5 mg/10 ml/kg

Animals: 19 timed-pregnant ♀ Sprague-Dawley rats, Crl:CD®(SD)BR, weighing 303-346 g

Study Site: Covance Laboratories Inc., 3301 Kinsman Blvd., Madison, WI 53704

Study Date: 11/20-11-21/96

GLP/AUC: N/A

Study Design: Pregnant rats were given a single oral dose of [^{14}C]SC-58635, 5mg/kg, by gavage on Day 18 of gestation. Maternal blood, amniotic fluid and all fetuses from each animal were collected at different time as shown in the following table.

Group	Nº of Pregnant ♀	Compound	Dose (mg/ml/kg)	Sampling Time (hr)
1	1	-	-	Pre-dose
2	3	[^{14}C]SC-58635	5/10	0.5
3	3	[^{14}C]SC-58635	5/10	1
4	3	[^{14}C]SC-58635	5/10	2
5	3	[^{14}C]SC-58635	5/10	4
6	3	[^{14}C]SC-58635	5/10	8
7	3	[^{14}C]SC-58635	5/10	24

APPEARS THIS WAY ON ORIGINAL

Results:

- TISSUE DISTRIBUTION OF RADIOACTIVITY - Mean (±SE) % radioactive dose and PK parameters in plasma, amniotic fluid and fetuses following a single oral dose of [^{14}C]SC-58635 (5 mg/kg) are shown in the below table.

Sampling	μg Equivalent [^{14}C]SC-58635/g		
Time (hr)	Plasma	Amniotic Fluid	Fetuses
0.5	0.728 ± 0.074	0.057 ± 0.018	0.444 ± 0.055
1	0.837 ± 0.143	0.052 ± 0.008	0.666 ± 0.046
2	0.814 ± 0.034	0.089 ± 0.010	0.772 ± 0.055
4	1.07 ± 0.103	0.130 ± 0.022	0.984 ± 0.104
8	2.28 ± 0.225	0.192 ± 0.012	1.51 ± 0.061
24	0.557 ± 0.04	0.066 ± 0.009	0.594 ± 0.043
PK PARAMETERS			
T_{max} (hr)	8	8	8
C_{max} (μg eq/ml)	2.28	0.192	1.51
$AUC_{0-\infty}$ (μg eq•hr/g)	37.8	3.7	30.6

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- DISTRIBUTION OF RADIOACTIVITY IN EXTRACTS - The following table illustrates the distribution of radioactivity in extracts of samples of plasma, amniotic fluid, and fetus collected at specified times postdose for pregnant female rats following a single oral dose of [^{14}C]SC-58635 (5 mg/kg) and HPLC analysis of extracts.

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Hours Postdose	Composite Conc.[b]	% TR[c]	Extract Conc.	(b)(4)(C Analysis of Aqueous Extracts					
				SC-62807		SC-60613		SC-58635	
				% TR	Conc.	% TR	Conc.	% TR	Conc.
PLASMA									
Control[a]	NA	98.1	NA	ND	NA	0.3	NA	92	NA
1	0.8335	92.8	0.774	0.9	0.007	3.8	0.032	84.9	0.708
8	2.281	92.7	2.115	0.6	0.013	4.7	0.106	87.2	1.988
24	0.5566	93.8	0.522	1 0.8	0.004	4.5	0.025	8 6.6	0.483
AMNIOTIC FLUID									
Control[a]	NA	97.2	NA	ND	NA	0.3	NA	94.9	NA
1	0.0523	130.6	0.068	12.3	0.006	17.6	0.009	94.4	0.049
8	0.1921	93.6	0.18	6.7	0.013	12.1	0.023	70	0.134
24	0.0661	76.8	0.051	ND	ND	8.2	0.005	63.4	0.042
FETUS									
Control[a]	NA	93.8	NA	ND	NA	0.2	NA	89.7	NA
1	0.2635	97.2	0.256	ND	ND	1.8	0.005	92.5	0.243
8	0.5733	96.9	0.556	ND	ND	3.2	0.018	92.8	0.532
24	0.2176	98.2	0.214	ND	ND	4.7	0.01	88	0.192

[a]Fortified control; [b]Concentration: μg eq/g; [c]TR = Total radioactivity

3.3.1.3. Milk Secretion Of [^{14}C] SC-58635 In The Rat, Document No.: M3097236; Date: 02-Sep-1997 (Vol. 1.71, p. 82-163)

Included as an appendix To This Report were:
Milk Secretion Of [^{14}C] SC- 58635 In The Rat, Document No.: M2096302; Date: 29-Aug-1997 (Vol. 1.71, p. 103- 159)
Final Report Amendment No. 1: Milk Secretion Of [^{14}C]SC-58635 In The Rat, Document No.: M3197236; Date: 24- Sep- 1997 (Vol. 1.71, p. 160- 163)

Study Nº: Covance 6127-329
Report Nº: M3097236/M2096302
Study Aims: (1) To determine the extent of transfer of [^{14}C]SC-58635 from maternal blood to milk in the rat and to assess the nature of the radioactive residues in plasma and milk.
(2) To determine tissue distribution of [^{14}C]SC-58635 in rats using whole body autoradiography (WBA) and microautoradiography (MAR).
Compound: [^{14}C]SC-58635 (Lot Nº: GDS 4671-84, 97.5% purity with 141 μCi/mg of specific activity) in PEG400/H_2O (2:1)
Dose and Route: 5 mg/kg po by gavage
Animals: 24 adult Sprague-Dawley lactating rats, Crl:CD®(SD)BR, weighing 262-358 g.
Study Site: (b)(4)(CC)
GLP Compliance: N/A
Study Date (In-Life): 11/13-15/1996,
Study Design: Lactating rats (4-20 days postpartum) were treated with [^{14}C]SC-58635, 5 mg/kg, by oral gavage. Blood and milk were collected at 0.5, 1, 2, 3, 5, 8, 24 and 48 hours postdose (3/time point). Plasma and milk were assayed for total radioactivity by liquid scintillation counting (LSC). Plasma samples were also analyzed for SC-58635 using a validated (b)(4)(CC) (b)(4)(CC) Samples were analyzed at (b)(4)(CC) (b)(4)(CC)

Results: The concentrations of SC-58635 in plasma and milk following a single oral administration of [^{14}C]SC-58635 were similar. The distribution of radioactivity in extracts of plasma and milk samples collected at specified times postdose following a single oral dose of

]SC-58635 (5 mg/kg) to female lactating rats and (b)(4)(CC) nalysis of extracts are presented in the following two tables.

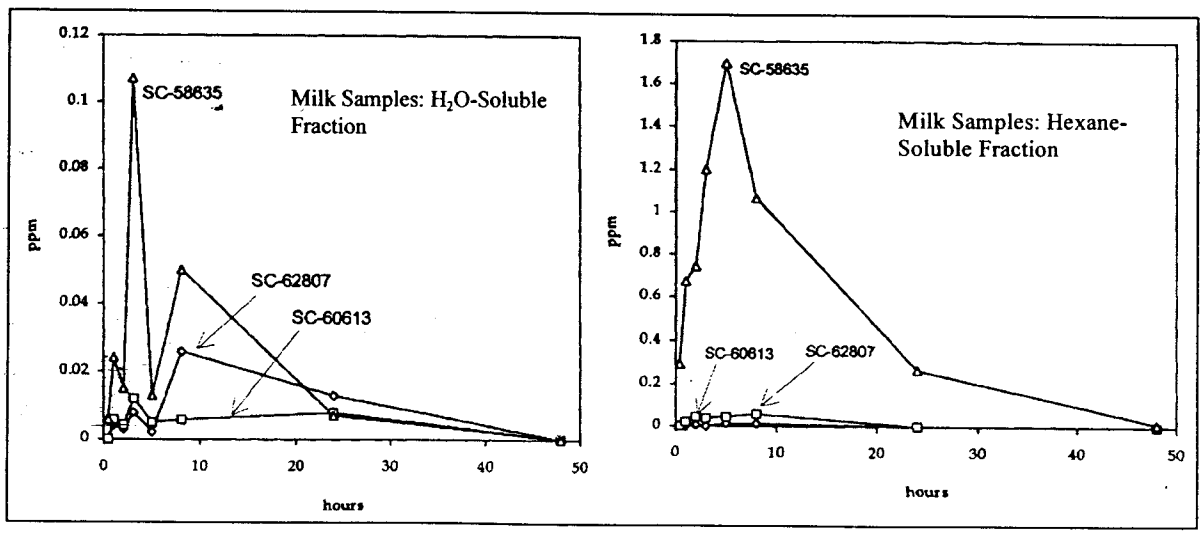
PLASMA SAMPLES		Collection Time (hr)		
		Control	5	24
Pooled Sample Conc.		NA	1.266	0.279
ACN/ACN: H_2O Extract %TR		98.1	94.3	95.7
Extracted Conc.		NA	1.193	0.267
(b)(4)(C Analysis of Aqueous Extracts				
SC- 62807	%TR	ND	1.2	1.7
	Conc.	ND	0.015	0.005
SC- 606 13	%TR	0.3	3.7	4.8
	Conc.	NA	0.047	0.013
SC- 58635	%TR	92.0	86.6	85.2
	Conc.	NA	1.096	0.238

MILK SAMPLES		Collection Time (hr)								
		Control	0.5	1	2	3	5	8	24	48
Pooled Sample Conc.		NA	0.398	1.114	1.391	1.520	1.891	1.694	0.303	0.024
Acetone: H_2O Extract		86.8	79.6	72.0	66.2	97.8	106.4	79.3	99.9	92.3
Extracted Conc.		NA	0.317	0.802	0.874	1.487	2.012	1.342	0.303	0.022
%TR Aqueous 1		1.2	1.6	2.8	1.4	8.4	1.7	5.3	11,9	7.7
%TR Aqueous 2		NA	0.6	0.5	0.6	0.6	NA	0.3	NA	0.2
(b)(4)(C Analysis of Aqueous Extract of Pooled Samples										
SC- 62807	%TR	0.1	ND	0.4	0.2	0.5	0.1	1.5	4.4	2.8
	Conc.	NA	ND	0.004	0.003	0.008	0.002	0.026	0.013	<0.001
SC- 606 13	%TR	0.1	0.2	0.5	0.3	0.8	0.2	0.3	2.5	ND
	Conc.	NA	<0:001	0.006	0.004	0.012	0.005	0.006	0.008	ND
SC- 58635	%TR	0.6	1.4	2.1	1.1	7.0	0,7	3.0	2.3	ND
	Conc.	NA	0.006	0.024	0.015	0.107	0.013	0.050	0.007	ND

Percentages are reported to one decimal place; concentration values are reported to three decimal places.
Conc. = Concentration, μg equivalents/g; TR = Total radioactivity; NA = Not applicable; ND = Not detected.

The PK parameters for SC-58635 in plasma and milk following a single oral administration of [^{14}C]SC-58635 are summarized as followings.

Sample	C_{max} (μg eq/g)	T_{max} (hr)	AUC_{0-24} (μg eq•hr/ml)	$AUC_{0-\infty}$ (μg eq•hr/ml)	$T_{½}$ (hr)
Plasma	1.22	5	22.2	23.5	5.38
Milk	1.90	5	30.7	30.9	5.93



3.3.1.4. Tissue Distribution Of [^{14}C] Celecoxib In Sprague-Dawley Rats Using Whole-Body Autoradiography And Microautoradiography, Document No.: M2096278; Date: 24-Jun-1997 (Vol. 1.71, p. 164-210)

Study Report Nº: M2096278/EHL 96130 & M2196278

Study Aims: To determine tissue distribution of [^{14}C]SC-58635 in rats using whole body autoradiography (WBA) and microautoradiography (MAR)

Compound: [^{14}C]SC-58635 (Lot Nº: GDS 4671-84, 97.5% purity with 141 μCi/mg of specific activity) in PEG400/H_2O (2:1), 2 mg/ml for the bolus dose and 1 mg/ml for the infusion dose.

Vehicle: PEG400/H_2O (2:1)

Dose and Route: 2 mg/kg iv bolus or iv infusion at 0.4 mg/kg/hr for 5 hr

Animals: 9♂ Sprague-Dawley rats, Crl:CD®(SD)BR, ~9 weeks of age, weighing 308 g, 3/group

Study Site: (b)(4)(CC) [redacted]

Study Date: **8/27/96-4/2/96(?) (How could the study was finished long before it was even started?)**

GLP/AUC: No

Study Design: Three groups of rats were given an iv bolus loading dose of [^{14}C]SC-58635, 2 mg/kg, followed by an iv infusion at 0.4 mg/kg/hr for 5 hr.

Group 1 - used for whole body autoradiography;

Group 2 - Tissues were processed for microautoradiography;

Group 3 - Brain was dissected, frozen and processed for metabolic profile determination. The following samples were collected for SC-58635 or radioactivity determinations.

- Blood Sampling - Blood was collected from the carotid artery (Groups 1 & 2 rats) at 1 and 4 hr after iv infusion initiated.
- Organ and Tissues - Aliquots of the liver, heart, blood, lung, brain, testes, muscle, and gut content were obtained after whole-body sectioning of frozen animals for the analysis of radioactivity.

Results: Levels of radioactivity in whole blood, plasma, and cellular fraction, and analysis of tissue radioactivity are shown in the following two tables.

Time Point	Whole Blood		Plasma		Cell Fraction		Ratios		
	Mean dpm/g	μg eq/g	Mean dpm/g	μg eq/g	Mean dpm/g	μg eq/g	Plasma/Cell Fraction	Plasma/Blood	Cell Fraction/Blood
1 hr	430518	4.88	59040	0.67	815867	9.24	0.08	0.13	2.06
4 hr	412013	4.67	68448	0.78	759310	8.60	0.09	0.18	1.90
5 hr	328975	3.72	79257	0.90	557489	6.31	0.14	0.24	1.69

Tissue	Mean dpm/g[a]	Average μg eq/g[a]	Tissue/Blood Ratio
Liver	666643	7.54	1.61
Blood	409361	4.63	1.00
Lung[b]	452950	5.13	1.15
Testes	122037	1.38	0.29
Brain	164708	1.86	0.40
Muscle	255940	2.90	0.59
Gut Content[c]	11136949	126.05	30.80
Salivary Gland	215715	2.44	0.52
Kidney'	279661	3.17	0.75

[a]Mean of 3 animals except where noted; [b] Value from one animal; [c]Mean of two animals.

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The liver, heart, lungs, kidney, and intestinal contents had the highest radioactivity. The Microradiogaphy study showed that the epithelium of the cecum and hepatocyes had specific

localization of [^{14}C]SC-58635. The radioactivity recovered from the brain was 97.1-98.7% and was determined to be 100% unchanged drug [^{14}C]SC-58635.

3.4. METABOLISM CHARACTERISTICS AND METABOLITES

3.4.1. *RAT*

3.4.1.1. The Isolation And Identification Of In Vivo Metabolites Of [^{14}C] SC-58635 In Rats, Document No.: M3094211; Date: 11-Apr-1996 (Vol. 1.71, p. 211-243)

Report Nº: M3094211

Study Aim: To determine PK and metabolism profiles and identify metabolites eliminated in bile from 3♂ rats dosed orally with 5 mg/kg of [^{14}C]SC-58635.

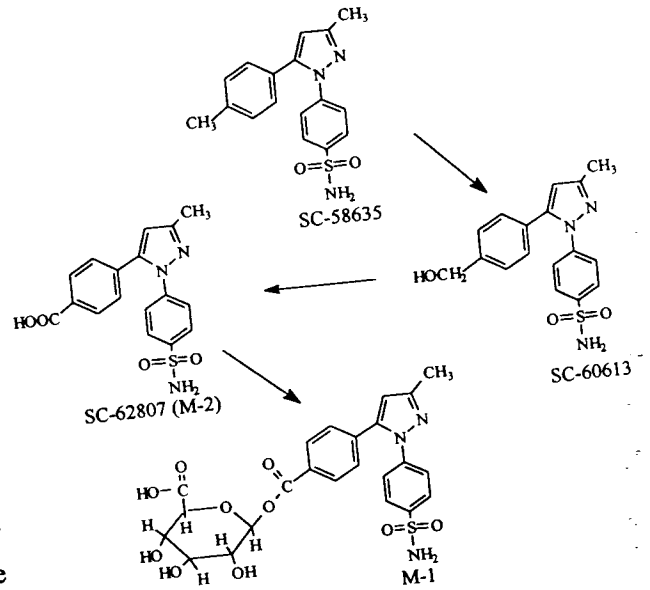
Compound: [^{14}C]SC-58635 in PEG 400 : H_2O (2:1, v/v)

Dose & Route: 5 mg/kg, 10 ml/kg intragastrically

Animals: 3♂ rats, weighing 297-328 g.

Study Location: G.D. Searle, Skokie, IL

Compliance with QAU: Not Indicated.



Results: Two major metabolites, SC63807 (carboxyl metabolite) and the glucuronide conjugate of SC-60613, were identified in bile. The structures of SC63807 and the glucuronide conjugate of SC-60613 are illustrated in the right figure.

3.4.1.2. Enterohepatic Circulation of [^{14}C]SC-58635 Following Oral Administration To The Male Rat, Document No.: M3096267; Date: 01-Dec-1997 (Vol. 1.71, p. 244-290)

Report Nº: M3096267

Study Aim: To determine the potential for enterohepatic circulation of SC-58635 in the rat

Compound: [^{14}C]SC-58635 (Lot Nº: GDS 4671-84, 97.5% purity with 141 μCi/mg of specific activity) in PEG 400 : H_2O (2:1, v/v), 2mg/ml, 5 μCi/mg; SC-58635 (Lot Nº: E90077 and 94K-031-A2A)

Dose & Route: 5 mg/kg, 10 ml/kg intragastrically

Animals: 6♂ Sprague-Dawley rats, weighing 254 - 262 g for donor rats and 249 - 261 g for recipient rats, 3/group

Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.

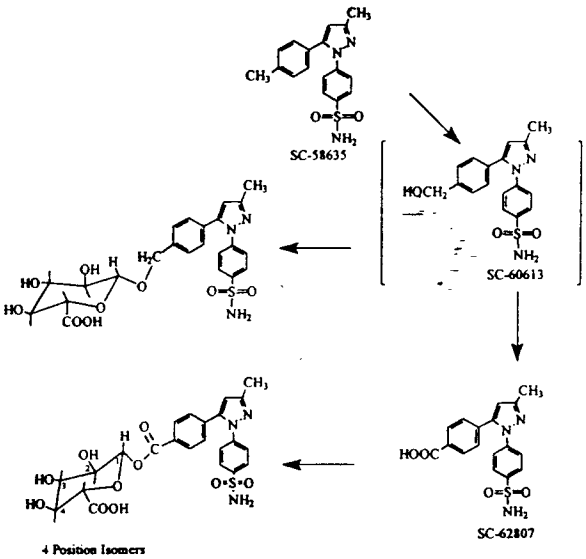
Compliance with QAU: Not Indicated.

Study Design: Six Sprague-Dawley male rats were surgically altered to allow bile to flow from a donor rat (n=3) into the duodenum of a recipient rat (n=3). [^{14}C]SC-58635 was administered orally at a dose of approximately 20 mg/kg to three donor rats. Blood was collected from the recipient rats (n=3) at 1, 2, 4 and 6 hr after oral dose administration to the donor rats. The donor rats were sacrificed at 6.5 hr post dose and bile was collected from the donor rats for 30 minutes immediately

prior to sacrifice. Plasma was frozen immediately on dry ice and selected samples shipped frozen to (b)(4)(CC) . Plasma samples were analyzed for concentrations of SC-58635 and total radioactivity. The bile was analyzed for total radioactivity and profiled by (b)(4)(CC)

The major metabolites in the bile extracts were identified by (b)(4)(CC)

Results: Concentrations of SC-58635 in the plasma collected from the three donor rats at sacrifice were 1.56, 1.93 and 0.446 μg/ml indicating that SC-58635 was systemically absorbed. There were no measurable levels (assay sensitivity limit, 0.025 μg/ml) of SC-58635 in plasma from the recipient rats, indicating that enterohepatic circulation of SC-58635 does not occur in rats administered 20 mg/kg SC-58635. Six metabolites of SC-58635 were identified in rat bile by (b)(4)(CC) They were SC-62807, a glucuronide conjugate of SC-60613 and four glucuronide conjugates of SC-62807. The glucuronic acid moiety of the SC-60613 glucuronide conjugate was incorporated on the hydroxyl of SC-60613. The position of the glucuronide on two of the four glucuronide conjugates of SC-62807 was determined to be on the carboxyl moiety of SC-62807. One of the SC-62807 acyl-glucuronides was a 1-O-glucuronide conjugate. The position of the glucuronide on SC-62807 was not established for the other two SC-62807 glucuronides. The sponsor stated that "It is possible that the other three glucuronide conjugates of SC-62807 are positional isomers formed as the result of acyl migration".



Proposed Metabolic Pathway of SC-58634 in Rat Bile

3.4.1.3. The Pharmacokinetics And Metabolism Of [^{14}C]SC-58635 Following Multiple Dose Administration To The Rat, Document No.: MRC-94S-0132; Date: 07-Dec-1994 (Vol. 1.72, p. 1-256)

Report Nº MRC-94S-0132
Study Aim: To evaluate pharmacokinetics and metabolism of [^{14}C]SC-58635 following oral administration for 4 weeks
Compound: SC-58635 (Lot Nº 94L013-A1A) & [^{14}C]SC-58635 (used on Days 1 & 26) suspension in 0.5% methylcellulose and 0.1% Tween 80
Dosage & Route: 20, 80, 400 & 600 mg/kg, 10 ml/kg, for 4 week by oral gavage
Control Vehicle: 0.5% methylcellulose and 0.1% Tween 80
Animals: 96♂ & 96♀ Sprague-Dawley rats, strain Crl:CD®(SD)BR, weighing 100 - 220 g, 3, 6 or 15/sex/ group
Study Location: (b)(4)(CC)
Compliance with GLP/QAU: N/A
Study Design: Group designation & dose levels were listed as followings:

Group	Nº of Animals	Dose levels (mg/kg)
1[a]	15♂ & 15♀	20
2[a]	15♂ & 15♀	80
3[a]	15♂ & 15♀	400
4[a]	15♂ & 15♀	600
5[b]	6♂ & 6♀	20
6[b]	6♂ & 6♀	80
7[b]	6♂ & 6♀	400
8[b]	6♂ & 6♀	600
9[c]	3♂ & 3♀	20
10[c]	3♂ & 3♀	80
11[c]	3♂ & 3♀	400
12[c]	3♂ & 3♀	600

[a] Each animal received [^{14}C]SC-58635 on Days 1 & 26, and SC-58635 on Days 2 - 25. Blood samples were taken on Days 1 & 26 at specific time (0.5, 1, 2, 3, 4, 6, 8, and 24 hr) post dosing from 12 animals of each group. Liver was collected from 3/sex/group on Day 26.

[b] Three/sex/group received a single dose of [^{14}C]SC-58635 on Day 1, and 3/sex/group received SC-58635 on Days 1 - 25, and a dose of [^{14}C]SC-58635 on Day 26; urine and fecal samples were collected at specific time intervals (-24-0, 0-24, 24-48, 48-72, 72-96, 96-120 hr) after dosing with [^{14}C]SC-58635. All animals were sacrificed following the last excreta collection.

[c] Each rat received a dose of SC-58635 from Day 1 to 26 and liver was collected from each one following dosing on Day 26.

Animals were checked 2x daily for moribundity and mortality. animals were weighed on Days 1, 8, 15, 22, and 26. PK analysis was performed on blood, urine and fecal samples. Liver samples from the animals received SC-58635 were used to prepare post-mitochondrial supernatant for cytochrome P-450 analysis.

Results: The observations from the present study were summarized as following:

The PK parameters for concentrations of total 14C in plasma following oral administration of SC-58635 on Days 1 & 26 are presented in the following table

Dose (mg/kg/day)	C_{max} (µg eq/g)		T_{max} (hr)		$T_{½}$ (hr)		K (hr^{-1})		AUC_{0-t} (µg eq•hr/g)		$AUC_{0-\infty}$ (µg eq•hr/g)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Day 1												
20	4.44	4.98	2	2	3.25	7.07	0.1954	0.0981	42.8	59.6	43.1	66.2
80	14.1	19.7	3	2	3.60	6.18	0.1925	0.1121	153.7	260.8	155.2	279.5
400	55.4	61.8	3	2	8.69	10.3	0.0798	0.0674	694.3	1015	813.9	1261
600	69.6	102	2	6	4.32	8.02	0.1604	0.0864	782.1	1721	795	2138
Day 26												
20	4.25	4.66	1	2	3.88	7.48	0.1785	0.0927	33.6	54.8	34.0	61.5
80	13.1	15.2	2	2	3.90	7.41	0.1776	0.0936	93.7	188.6	94.9	209.4
400	39.0	58.7	2	4	4.16	7.05	0.1667	0.0983	307.3	680.9	313.0	745.7
600	63.1	93.8	2	4	4.34	13.6	0.1596	0.0509	475.4	1471	484.6	2068

The PK parameters for concentrations of total 14C in RBC following oral administration of SC-58635 on Days 1 & 26 are shown in the following table.

Dose (mg/kg/day)	C_{max} (µg eq/g)		T_{max} (hr)		$T_{½}$ (hr)		K (hr^{-1})		AUC_{0-t} (µg eq•hr/g)		$AUC_{0-\infty}$ (µg eq•hr/g)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Day 1												
20	19.8	23.0	2	2	5.62	14.6	0.1233	0.0474	230.4	341.3	241.2	494.1
80	56.1	53.5	0.5	0.5	4.97	9.53	0.1395	0.0727	531.1	757.2	554.3	937.3
400	98.1	102	3	3	9.93	9.21	0.0698	0.0752	1379	1824	1703	2368
600	153	185	1	0.5	7.08	8.31	0.0979	0.0834	1884	2971	2064	3785
Day 26												
20	32.1	31.2	1	0.5	5.30	14.4	0.1308	0.0482	293.0	434.2	304.1	628.6
80	62.8	62.7	1	0.5	5.30	6.93	0.1309	0.1000	564.5	829.1	587.7	961.1
400	108	111	1	4	4.38	14.6	0.1584	0.0473	1153	1628	1195	2421
600	137	149	1	4	6.64	19.8	0.1044	0.0351	1396	2393	1507	4105

Following oral dose administration, radioactivity was rapidly absorbed. The Cmax of radioactivity in plasma and RBC occurred around 2 and 3 hr post dosing.

The $T_{½}$ of plasma [14C]SC-58635 was 3.55 - 8.69 hr for ♂ animals and 6.18 - 13.6 hr for ♀ rats. The hepatic cytochrome P-450 content did not change with dose, but liver radioactivity increase proportionally with dose.

The main route of excretion was through feces and the radioactive dose was extensively abolished; approximately 86.6 % - 94.9% of radioactivity was eliminated over a period of 120 hr in both ♂ and ♀ rats at all dose levels. Elimination via urinary tract was 7.0% to 10.9%. Total radioactivity recovered was 95.1 - 105%. The rate, route and patter of excretion following multiple dose administration was similar to the single dose administration.

3.4.1.4. Evaluation Of The Total Radioactivity Data In a 13-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635 (SA4346), Results Of Radioanalysis, Document No.: MRC95C-30-950232; Date: 09-Nov-1995 (Vol. 1.72, p. 257-369)

Report Nº: MRC95C-30-950232
Study Nº: SA4346/CHV 700-332 and CHW 6157-183
Study Aim: To identify toxic effects of SC-58635 when administered orally by gavage to rats for at least 13 weeks.
Compound: SC-58635 (Lot Nº 94K014-A4A), [^{14}C]SC-58635 (Lot Nº GDS 4404-145, 7.68 μCi/mg)
Vehicle: 0.5% methylcellulose (w/v) + 0.1% Polysorbate 80 (Tween® 80) (w/v) in dist. H_2O
Dosage: 0, 20, 80, 400 mg/kg/day, 10 ml/kg po for ≥ 13 weeks
Animals: 388 (194/sex) Sprague-Dawley Crl:CD®BR rats, ~6 wk old
Study Location: (b)(4)(CC)
Study Date: March 16, 1995 - July 14, 1995
Radioanalysis: 22 March 1995 - 26 July 1995
Compliance with GLP/QAU: Yes

Main and Recovery[a] Study				Satellite PK Study			
Group	Dose (mg/kg/day)	Nº of Animals		Group	Dose (mg/kg/day)	Nº of Animals	
		♂	♀			♂	♀
1	0 (MC)	25	25				
2	20 (Low)	25	25	5	20 (Low)	18	18
3	80 (Mid)	25	25	6	80 (Mid)	18	18
4	400 (High)	25	25	7	400 (High)	18	18

[a] The recovery group comprised of 10/sex/group.

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Experimental Design: Rats were given SC-58635, 0, 20, 80 or 400 mg/kg/day via oral gavage once daily for at least 13 weeks; dosing continued through the day prior to terminal sacrifice (Days 93/94). Recovery animals were kept without treatment for an additional 4 weeks. Rats in the satellite PK study group received [^{14}C]SC-58635 on Days 1, 37, 86 and received nonradiolabeled SC-58635 on other days during the study. Blood were collected at 0.5, 1, 2, 4, 6, 8, and 24 hr following dosing with radiolabeled SC-58635. Urine and feces were collected at 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hr after radiolabeled dose administration. Plasma, red blood cells, urine, and feces were analyzed for content of radioactivity by liquid scintillation counting.

Results:

- Radioactivity in Plasma and RBC - The following table shows C_{max} and T_{max} values for radioactivity in plasma and RBC following oral administration of [^{14}C] SC-58635 on Days 1, 37 and 86. Concentrations of radioactivity in the cellular fraction of blood were much higher than in plasma. The C_{max} values were higher in ♀ than ♂.