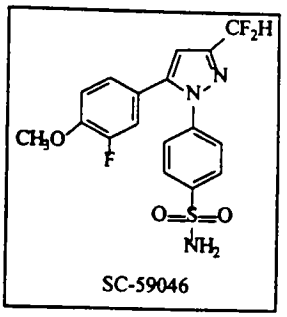
Study Nº SA4219
Report Nº PSA-95S-30-4219
Study Aim: To identify potential target organs or dose limiting toxicities and evaluate for tolerance following repeated dosing of SC-58635 and SC-59046 in rats
Compound: SC-58635 (Lot Nº GDS-2977-158) & SC-59046 (Lot Nº GDS-3196-095) in 1.5% methylcellulose and 0.1% Tween 80; 10, 20, 40 60, and 80 mg/ml
Dosage & Route: 100, 200, 400 600 and 800 mg/kg, 10 ml/kg oral (by gavage)
Control Vehicle: 1.5% methylcellulose + 0.1% Tween 80
Animals: 30♂ & 30♀ Sprague-Dawley rats, strain Crl:CD®(SD)BR, 5 wk of age, weighing from 104.9-135.1 g for Phase I study and 68.6 - 101.0 g for Phase II study, 5 sex/group
Study Location: G.D. Searle, Skokie, IL
Compliance with GLP/QAU: No



SC-59046

Study Design:

Phase I: SC-58635 and SC-59046 were given to rats (5 sex/group) orally by gavage using a dosing schedule, as shown in the following table, with 3 day escalation intervals at an initial dose level of 100 mg/kg, until a maximum dose level of 800 mg/kg reached.

Phase II: SC-58635 and SC-59046 at levels of 600 & 800 mg/kg were orally administered to rats (3/sex/group) by gavage daily for 3 days.

PHASE I (DOSE ESCALATION)				
Group	Treatment	Dose (mg/kg/day)	Treatment Days	Nº of Animals
1	Vehicle Control	-	1 - 15	5/sex
2	SC-58635	100	1 - 3	5/sex
		200	4 - 6	
		400	7 - 9	
		600	10 - 12	
		800	13 - 15	
3	SC-59046	100	1 - 3	5/sex
		200	4 - 6	
		400	7 - 9	
		600	10 - 12	
		800	13 - 15	
PHASE II				
Group	Treatment	Dose (mg/kg/day)	Treatment Days	Nº of Animals
1	Vehicle Control	-	1 - 3	3/sex
2	SC-58635	600	1 - 3	3/sex
3	SC-58635	800	1 - 3	3/sex
4	SC-59046	600	1 - 3	3/sex
5	SC-59046	800	1 - 3	3/sex

The animals were observed daily approximately 1-4 hr post dosing for clinical signs and mortality. Body weights were recorded once during pretreatment and daily during the treatment period; feed consumption was measured every 3 days. Hematological and clinical chemistry examinations, necropsy were performed on fasted animals (16 hr prior to scheduled necropsy) on Day 16 for Phase I and Day 4 for Phase II studies. The hematological and blood chemistry parameters analyzed and organs collected are shown in the following table. PK sampling were performed on Days 3, 6, 9, 12, 15, and 16 for Phase I and Days 3 and 4 for Phase II experiments. Macro- and micro-histological (only representative samples from Phase I study) examinations were also conducted.

HEMATOLOGY		SERUM CHEMISTRY			
*White Blood Cells	MCV	*ALT	*Chloride	Inorganic Phosphorus	*Total Bilirubin
*Differential WBC	MCH	*Albumin	Cholesterol	*Potassium	Total Protein
Red Blood Cells	MCHC	Alkaline Phosphatase	Creatinine	*Sodium	Triglycerides
Hemoglobin	Mean Platelet Volume	AST	Globulin	*Sorbitol Dehydrogenase (SDH)	
*Hematocrit	Platelets	Calcium	Glucose	Total Bile Acids (TBA)	*Urea

*If the sample size from an animal was insufficient to measure all of the parameters listed above, the parameters marked with an asterisk were measured first. Non-asterisk parameters were measured in the order listed as the sample size permitted.

ORGAN COLLECTED IN PHASE I STUDY		
*Brain	*Liver	*Stomach
*Heart	*Lungs	*Testes (Both)
Intestine, Small (Duodenum, Jejunum, Ileum)	Lymph Node (Submaxillary and Mesenteric)	*Thymus
Intestine, Large (Cecum, Colon)	Pancreas	*Thyroid Glands** (both)
*Kidneys (both)	*Spleen	Urinary Bladder

* Tissues designated with an asterisk were weighed. Paired organs were weighed together.

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

Results:

- Clinical Observations and Mortality - Mild hair loss and skin abrasions were periodically identified and these findings might not be treatment related. No deaths occurred in either Phase I or II of this study.
- Body Weights and Food Consumption - There were no differences in body weights and mean body weight gains in Phase I study. In Phase II study, mean body weights of males receiving 800 mg/kg of SC-59046 and females receiving either 600 or 800 mg/kg of SC-59046 were 12-17% and 17-22% less than controls, respectively. Mean body weight gains of animals @ 600 or 800 mg/kg of SC-59046 were 84-137% less than controls. Significantly higher mean feed consumption was seen in Phase I females given SC-58635 during Days 1-7 (↑ 10.4%) and Days 10-15 (↑ 16%) as compared with controls. In the Phase II study, significantly reduced in mean feed consumption in ♂ & ♀ given 600 (♂: ↓ 21%; ♀: ↓ 69%) or 800 mg/kg (♂: ↓ 56%; ♀: ↓ 53%-69%) of SC-59046 was noteworthy.
- Clinical Laboratory Pathology - There were some statistical significant but biological insignificant changes (slightly ↓ RBC with slightly ↑ MCV and MCH) in hematology parameters identified in the treatment groups during Phase I study. Treatment related significant changes in clinical chemistry parameters are presented in the following table.

Group	TBA		Urea		Chol		ALT	
	♂	♀	♂	♀	♂	♀	♂	♀
Phase I Study								
SC-58635 (100→800 mg/kg)	↑ (1.5x)					↑ (1.3x)		
SC-59046 (100→800 mg/kg)	↑ (1.4x)	↑ (1.4x)				↑ (1.7x)		
Phase II Study								
SC-58635 (600 mg/kg)				↑ (2.0x)		↑ (2.0x)		
SC-58635 (800 mg/kg)						↑ (1.9x)		
SC-59046 (600 mg/kg)		↑ (2.2x)			↑ (1.6x)			↑ (1.5x)
SC-59046 (800 mg/kg)		↑ (1.2x)			↑ (1.5x)	↑ (2.0x)		↑ (1.5x)

- Necropsy (Organ Weights, Macro- and Microscopic Pathology) - Cytochrome P-450 content per mg protein was increased in the pooled liver samples from SC-58635 (↑1.8x) & SC-59046 (↑1.5-2.4x) treated animals. Increased mean liver weights (13-36%) and liver/body weight ratios (8-46%) were noted in both SC-58635 and SC-59046 treated animals. No treatment caused macroscopic findings were seen for male or female rats in Phase I study. Two ♀ receiving 800 mg/kg of SC-59046 appeared to be thin. One ♂ from both 600 mg/kg of SC-58635 & SC-59046 groups showed mild to moderate liver enlargement. Slight mild hypertrophy of centrilobular hepatocytes was common finding in Phase I animals receiving treatment.

- PK/TK - Mean plasma levels of SC-58635 & SC-59046 in ♂ & ♀ during the escalating dose phase and tolerance phase were shown in the following table.

Day	Dose	Time	Plasma SC-58635 (μg/ml)		Plasma SC-59046 (μg/ml)	
	(mg/kg)	(hr)	♂	♀	♂	♀
PHASE I						
3	100	3	5.84 ± 0.47	8.00 ± 0.53	8.69 ± 0.20	10.6 ± 0.6
6	200	3	6.62 ± 0.16	8.40 ± 0.49	9.44 ± 0.32	10.8 ± 0.9
9	400	3	7.38 ± 0.70	10.1 ± 0.60	12.3 ± 0.3	14.7 ± 0.3
12	600	3	8.62 ± 0.73	12.5 ± 0.80	12.3 ± 0.7	16.0 ± 1.4
15	800	3	7.10 ± 0.51	13.9 ± 0.90	13.9 ± 1.3	20.3 ± 2.7
16	800	24	5.18 ± 1.31	6.28 ± 1.34	9.38 ± 2.88	18.8 ± 3.7
PHASE II						
3	600	3	17.8 ± 1.50	31.4 ± 10.5	23.1 ± 2.1	37.1 ± 2.9
3	600	24	9.09 ± 2.48	27.0 ± 16.5	19.1 ± 10.0	4.64 ± 0.62
3	800	3	14.8 ± 0.70	32.4 ± 3.40	38.2 ± 2.4	40.7 ± 4.4
3	800	24	7.88 ± 0.97	55.0 ± 7.80	16.5 ± 7.4	51.8 ± 4.9

Plasma levels of SC-58635 & SC-59046 in female rats were much higher than those in male rats. Higher plasma concentrations were observed following administration of drugs to naive rats (Day 3, Phase II) compared to rats received lower dose in an escalating dose schedule (Days 12-15, Phase I) indicating that metabolic eliminations of both compounds were inducible.

2.2.1.4. 4-Week Oral Toxicity Study With SC-58635 In Rats, Document No.: PSA-95C-4261; Date:18-Jan-1995 (Vol. 1.13 -1.14)

Included as an appendix to this report were:

1. Evaluation Of The SC-58635 Plasma Concentration Data From The Four Week Oral Gavage Toxicity Study With SC-58635 In Rats, SA4261 Document No.: MRC-94S-0184; Date: 31-Oct-1994
2. Final Report Amendment No. 1: Evaluation Of The SC-58635 Plasma Concentration Data From The Four Week Oral Gavage Toxicity Study With SC-58635 In Rats, SA4261 (MRC-94S-0184), Document No.: M3194184; Date: 29-Sep-1997
3. Final Report Amendment No. 1: 4-Week Oral Toxicity Study With SC-58635 In Rats Document No.: PSA95C-31-SA4261; Date: 16-May 1995
4. Final Report Amendment No. 2: 4 Week Oral Toxicity Study With SC-58635 In Rats Document No.: PSA95C-32-SA4261; Date: 06-Oct-1997
5. Final Report Amendment No. 3: 4-Week Toxicity Study With SC-58635 In Rats (SA4261), Document No.: P33S4261; Date: 11-Nov-1997

Study Nº: SA4261
Report Nº: PSA-94C-SA4261
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♀ rats, strain Crl:CD®(SD)BR VAF/Plus®, 5 wk of age, weighing 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:
Compliance with GLP/QAU: Yes
Study Design: Animal grouping and dosage assignments were listed as following:

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

Clinical signs and mortality were monitored twice daily. Body weight measurements (measured 2x before dosing, on the 1st day of treatment and weekly thereafter), food consumption (recorded weekly) estimation, ophthalmological examination, clinical pathology (hematology, clinical chemistries & urinalysis) parameters, and histopathological (macro- and microscopic) examinations were included in the present study. On Day 31 blood samples were collected from animals in groups 6 and 7, prior to dosing and at 2 and 3 hr post dosing.

Results:

- Clinical Observations and Mortality - On Day 10, one female in group 5 (600 mg/kg) was found to be moribund and sacrificed. Peritonitis and perforation of jejunum was revealed during the post-mortem pathological examination. On Day 29, one male in group 4 (400 mg/kg) was scarified in a moribund condition and was found to have pyelonephritis at necropsy. One control female was observed to be pale and lethargic, with rough haircoat and labored breath, and subsequently died on Day 31.
- Body Weights, Food Consumption & Ophthalmology - There were no differences in weight gains and food consumption. No noticeable changes could be found during ophthalmology inspection.
- Ophthalmological Examination - No treatment-related changes were noted.
- Clinical Pathology Findings - Lower urine pH, lower Cl^-, higher cholesterol, lower albumin and higher globulin were observed for ♀ given 400 or 600 mg/kg during Week 5. But these changes were within normal value ranges.
- Post-mortem Pathology -

  Week 5 Terminal Sacrifice: Slight higher absolute liver weights (11%) for female rats receiving 400 mg/kg and higher liver/body weight ratios for females given 400 or 600 mg/kg were found; but there were no corresponding microscopic findings. There were no test material associated microscopic findings.

  Week 9 Recovery Sacrifice: There were no treatment related changes in terminal body weights. Statistically significant higher absolute thymus and kidney weights, and thymus/body weight and kidney/body weight ratios for female receiving 400 mg/kg and higher absolute epidimides weights for male rate given 400 mg/kg of SC-58635 were noted. No significant macro- and microscopic findings were attributable to the treatment at terminal sacrifice.
- PK Analysis - Mean plasma concentrations (± SEM) of SC-58635 on Day 31 are shown in the following table. Plasma SC-58635 levels were higher in female rats than male rats in dose groups (400 & 600 mg/kg/day). Similar findings were noted in other studies in rats.

Dose (mg/kg)	Sampling Time (hr)	SC-58635 Concentration (μg/ml)	
		♂	♀
400	0	1.372 ± 0.400	5.833 ± 2.576
	2	7.147 ± 1.089	12.847 ± 2.926
	3	9.057 ± 1.455	17.400 ± 3.523
600	0	1.751 ± 0.426	10.643 ± 1.010
	2	8.353 ± 0.554	17.833 ± 0.953
	3	10.550 ± 0.477	21.900 ± 0.458

2.2.1.5. 13-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635 Document No.: PSA95C-30-SA4346; Date: 11-Jan-1996 (Vol. 1.19-1.21)

Included as an appendix to this report was:
Pharmacokinetics And Metabolism Support For A 13-Week Oral Toxicity Study Of SC-58635 In The Rat, SA4346, Document No.: MRC95S-30-950283; Date: 29-Nov-1995

Report Nº: 700-332, PSA95C-30-SA4346; MRC95C-30-950232 (Radioanalysis); MRC95S-30-950283 (PK & Metabolism)
Study Nº: CHV 700-332/CHW 6157-183, SA4346
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:
Study Date: March 16, 1995 - July 14, 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 was comprised of 10/sex/group.

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. Animal and dose group assignments are presented in the above table. The following observations were conducted:

- Mortality and Clinical Signs - 2x/day.
- Body Weight - Day 1, 2x/week for the first 4 weeks of treatment, and 1x/week thereafter.
- Food Consumption - Day -4, and 1x/week thereafter.
- Ophthalmoscopic Examination - pretest and week 13.
- Clinical Laboratory Evaluation - week 6 (5/sex/group) and on the day of sacrifice.
- PK/TK - Blood (12/sex/group, 1 or 2/sex/time point) samples were collected at 0.5, 1, 2, 3, 4, 6, 8, and 24 hr following the ingestion of radiolabeled [^{14}C]SC-58635. Each rat was sampled 1x

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 C_{max} 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	6.66	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 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 radioactive 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

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.

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.

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 ileum) 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.

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					1	1		2	1	
Interstitial Suppurative Nephritis/Fibrosis					1					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

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 incidences of interdigital pyoderma/subcutis abscess, and papillary necrosis/pyelitis and/or interstitial suppurative nephritis/fibrosis were 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:

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-R and once ~1-4 hr postdose during weeks 4, 8, and 13; and once during week 17 for the recovery animals.
- Ophthalmoscopic Examination - pre-R and during Weeks 8 and 12, and 17 (recovery animals).
- Clinical Laboratory Evaluation - pre-R 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 at an approximately 24-hr interval.
- 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 with 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 ($31x10^3/\mu l$) and absolute PMN counts ($27.5x10^3/\mu l$) 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 -

Absorption: 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 parent drug and SC-62807 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 (mg/kg/day)	% SC-60613				% SC-58635			
	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)
(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

The following observations were conducted. The concentrations of SC-58635 in plasma were determined using a validated HPLC procedure.

- Physical Examinations - Day 1 pre-R.
- Mortality & Clinical Signs - 2x/day; pre-R and ~1-3 hr after dosing.
- Body Weights - 2x pre-R 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-R 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.

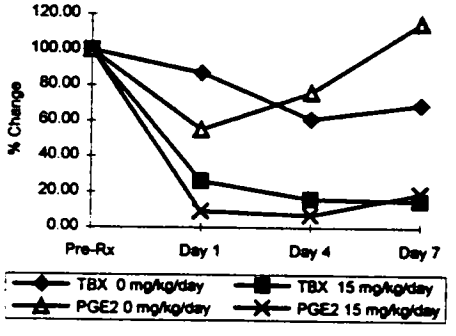
Results:

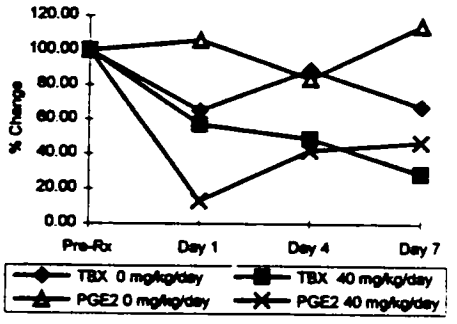
- Clinical Signs and Mortality - No deaths occurred. Swelling of the forelimbs was seen in dogs receiving test article. This forelimb swelling was more extensive in Phase 2 animals. Moreover, in one animal, the swelling extended from the forelimbs to involve the chest, ventral thorax, and neck.
- Body 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 $x10^3/\mu l$) and total WBC (11.1 vs 20.5 $x10^3/\mu l$) 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-R	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:	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:	

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		Group	Dose (mg/kg/day)	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-R, 2x/week up to Week 4, and 1x/week thereafter.
- Food Consumption - 1x/week.
- Ophthalmoscopic Examinations - Pre-R 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

- 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 [^{14}C]SC-58635 as 1st daily dose on Day1 and Weeks 26 and 52.			

Study Location:

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

Compliance with GLP/QAU: Yes

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-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 Pre-R 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.

  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	