Week 5. One ♀ in Group 5 had ↑ WBC, absolute PMN, platelet and reticulocyte counts and globulin and ↓ RBC, Ht, and albumin suggesting the possibilities of inflammation. Group 5 ♀ continued to have ↓ serum K^+, 10% lower than the values for controls during Week 7 (2 weeks of recovery post last dosing) analysis. However, the effect on serum glucose was reversed. The most notable clinical pathological findings for the ♀ sacrificed on Day 22 were ↓ absolute lymphocyte count, total protein, albumin and albumin to globulin ratio and ↑ BUN, creatinine, AST, ALP and inorganic phosphorus.

- Necropsy - Significantly ↑ relative and absolute kidney, liver and adrenal weights were seen in ♀ of Groups 4 & 5 and ♂ of Group 5. Similarly, ↑ relative and absolute kidney, liver and adrenal weights were seen in ♀ of Groups 5 with 2-week recovery. In addition, ♀ in Group 2 had ↑ relative kidney and adrenal weights. No notable macroscopic changes were identified as test article-related. Minimal centrilobular hepatocellular hypertrophy was seen in 3♀ and 2♂ in Group 5 and 1♂ in Group 1 at terminal scheduled necropsy. Similar incidence and severity of cardiomyopathy was characterized in some ♂ and ♀ in all group. Microscopic examination of recovery animals was limited to the liver and heart. Centrilobular hepatocellular hypertrophy was not seen in the recovery in Group 5 animals. Pathological examination of the ♀ that was sacrificed on Day 22 showed diffuse thickening of the jejunum and ileum and adhesions involving entire abdominal viscera and the diaphragm. Enlarged adrenal with dark red color was also identified. Transmural necrosis of the jejunum with chronic-active, fibrinous inflammation involving intestines and multiple abdominal tissues. Hemorrhagic necrosis of adrenal cortex was also characterized. The cause of death was intestinal perforation and septic peritonitis. Some minimal tubular degeneration, mineralization, basophilia and hyaline droplet was noted in the kidneys.
- Toxicokinetics - Mean PK parameters of SC-65872 and its active metabolite, SC-66905 on Days 1 and 25 are shown in the following table. Mean plasma concentrations of SC-65872 in ♀ rats were higher than in ♂ rats. Sex-difference in plasma concentrations of active metabolite, SC-66905 was not apparent. C_{max} values for SC-65872 in all dose groups on Day 25 were higher than those of the Day 1, indicating some accumulation of parent drug occurred. Higher systemic exposure to SC-65872 was found in the ♀ @ 25 mg/kg/day that was sacrificed at moribund on Day 22 by the evidence of higher plasma SC-65872 (17.6 μg/ml) levels as compared with other ♀ rats in the same dose group.

Day	Dose (mg/kg/day)	SC-65872 Parameters						SC-66905 Parameters					
		T_{max} (hr)		C_{max} (μg/ml)		$AUC_{0\text{-}12hr}$ (hr•μg/ml)		T_{max} (hr)		C_{max} (μg/ml)		$AUC_{0\text{-}12hr}$ (hr•μg/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	2.5	-	1.5	-	0.356	-	2.11	-	5.0	-	0.0392	-	0.312
	5	1.5	1.5	0.610	0.864	2.66	5.27	7.0	3.0	0.0949	0.0926	0.820	0.610
	10	1.5	1.5	1.29	1.97	5.68	11.3	1.5	7.0	0.261	0.192	1.79	1.49
	25	1.5	1.0	5.39	5.20	17.1	34.1	1.5	3.0	1.03	0.617	5.92	4.04
	50	1.5	-	6.98	-	32.9	-	5.0	-	2.52	-	16.5	-
25	2.5	-	0.5	-	0.560	-	3.04	-	7.0	-	0.0877	-	0.453
	5	1.5	1.5	0.696	1.19	2.50	7.48	1.5	0	0.130	0.233	0.904	1.19
	10	1.5	1.0	1.54	3.74	4.62	17.3	1.5	5.0	0.373	0.207	1.76	1.75
	25	1.5	1.0	4.53	8.35	14.1	54.2	1.5	5.0	1.28	0.646	8.00	6.00
	50	1.5	-	9.19	-	33.8	-	7.0	-	2.35	-	13.9	-

- Liver Microsome Enzyme and P-450 - The yield of liver microsomal protein (/g liver) were comparable in all groups. Livers from the ♂ rats had higher yield of microsomal protein per gram liver. However, a slight ↓ in mean cytochrome P-450 content (<30%) was obtained from the liver microsomes of SC-65872 treated group. The following table represents results for the tests to

determine microsomal enzyme activity and a list of predicted markers for cytochrome P-450 gene families.

Microsomal Enzymes Activities	Marker for Cytochrome P-450	Results
ECOD (7-Ethoxycoumarin O-Deethylase)	CYP1A1 or CYP2B1	↑ in both ♂ & ♀
MROD (7-Methoxyresorufin O-Demthylase)	CYP1A1	↔ in both ♂ & ♀
EROD (7-Ethoxyresorufin O-Deethylase)	CYP1A1	↔ in both ♂ & ♀
PROD (7-Pentoxyresorufin O-Dealkylase)	CYP1A1, CYP2B1, or CYP3A	↑ in both ♂ & ♀
BROD (7-Benzyloxyresorufin O-Dealkylase)	CYP1A1, CYP2B1, or CYP3A	↑ in both ♂ & ♀
6β-OH (6β-Hydroxylase)	CYP3A	↑ in both ♂ & ♀
16β-OH (16β-Hydroxylase)	CYP2B1	↑ in both ♂ & ♀
2α-OH (2α- Hydroxylase)	CYP2C11 (♂) and CYP2C12 (♀)	↓ in ♂; below limit of detection in ♀
16α-OH (16α- Hydroxylase)	CYP2C11 (♂) and CYP2C12 (♀)	↓ in ♂; ↑ in ♀
18-OH (18- Hydroxylase)	CYP3A	↑ in both ♂ & ♀

Western blot analysis using anti-rat CYP3A or CYP2B polyclonal antibodies also confirmed an increase in CYP3A and CYP2B in SC-65872 treated rats. Hence, treatment with SC-65872 resulted in ↑ CYP3A and CYP2B but not CYP1A1 in both ♂ and ♀ rats, ↓ CYP2C11 in ♂ and ↑ CYP2C12 in ♀ rats.

Therefore, the NOAEL for SC-65872 was 25 mg/kg/day for ♂ rats and 5 mg/kg/day for ♀ rats following 4 weeks of oral bid administration.

2.2.2.7. 13-Week Repeated Dose Oral Gavage Toxicity Study With a Four-Week Reversal with SC-65872 in Rats; Date: 04-Jun-1997, Document No. P30S4544. (Vol. 1.44-47)

Study Nº: SA4544/CHW 6127-311
Report Nº: P30S4544 & M3097059 (PK)
Study Aim: To assess the potential toxicity of SC-65872 following oral gavage administration to rats for ≥14-week with a 4-week reversal phase and to determine the PK profile of the test material relative to dose, duration of dosing and gender.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 1.25, 2.5, 5, 12.5, 25, 50 mg/5 ml/kg po bid (10-14 hr apart) by gavage
Animals: Sprague-Dawley Crl:CD®(SD)BR rats, ~8 weeks of age; weighing 269-324 g for ♂ and 176-214 g for ♀.
Study Location: [redacted]
GLP/QAU Compliance: Yes
Study Date: Dosing Initiation - 9/18/1996 (Day 1);
Terminal Sacrifice - 12/23/1996 (Group 5♀) and 12/23/1996 (Groups 1-6);
Recovery Sacrifice - 1/3/1997 (Groups 1 and 5 ♀) and 1/20/1997 (Groups 1 and 5 ♂)
Study Design: Rats were assigned randomly to 11 dose groups as shown in the following table.

Groups		Dose (mg/kg/day)		Dose (mg/kg/dose)		Nº of Animals			
						Toxicology		PK	
Toxicology	PK	♂	♀	♂	♀	♂	♀	♂	♀
1		0	0	0	0	25[a]	25[a]	-	-
2	7	5	2.5	2.5	1.25	15	15	12	12
3	8	10	5	5	2.5	15	15	12	12
4	9	25	10	12.5	5	15	15	12	12
5	10	50	25	25	12.5	25[a]	25[a]	12	12
6	11	100	-	50	-	15	-	12	12

[a] The rats designated for terminal sacrifice were necropsied at Week 12 post-dose for Group 5 ♀ and Week 14 post-dose for Groups 1-4, 5 (♂) and 6. The remaining rats in Groups 1 and 5 continued without treatment for an additional 4 weeks and were sacrificed.

The following observations were conducted:

- Mortality and Clinical Signs - 1x/day.
- Physical Examination - 1x/Pre-R on Day 1 and 1x/week thereafter.
- Body Weight and Food Consumption - 1x/Pre-R on Day 1 and 1x/week thereafter.
- Ophthalmoscopic Examinations - Pre-R and Week 12.
- Clinical Pathology - Weeks 6, 12 (Terminal Group 5 ♀), 14 (Terminal Groups 1-4, 5♂ and 6), 16 (recovery Group 5 ♀), and 18 (recovery Group 1 and Group 5♂). The following parameters were measured:

HEMATOLOGY				
aPTT	PT	WBC		Differential Leukocyte Count
Cell Morphology	RBC	MCV		Mean Platelet Volume
Corrected Leukocyte Count	Hb Ht	MCH	MCHC	Platelet Count
CLINICAL CHEMISTRY				
ALT	Calcium	Inorganic Phosphorus		Total Bile Acids
Albumin	Chloride	Potassium		Total Cholesterol
Albumin/Globulin Ratio	Creatinine	Sodium		Total Protein
Alkaline Phosphatase	Globulin	Sorbitol Dehydrogenase		Triglycerides
AST	Glucose	Total Bilirubin		Urea Nitrogen
URINE CHEMISTRY				
Osmolality	Urine Chloride	Urine Phosphorus		Urine Potassium
Urine Calcium Timed Excretion (Calculated)	Urine Chloride Timed Excretion (Calculated)	Urine Phosphorus Timed Excretion (Calculated)		Urine Potassium Timed Excretion (Calculated)
Urine Creatinine	Urine Volume (~ 20 hr)	Urine Sodium		Urine Calcium
Creatinine Clearance (Calculated)		Urine Sodium Timed Excretion (Calculated)		
URINALYSIS				
Appearance/Color	Glucose	Ketones	Occult Blood	Protein
Bilirubin	Microscopic Examination of Sediment		pH	Urobilinogen

- PK - Blood samples (3/sex/time point) were collected from Groups 7-11 on Days 1, 28, 80 (Group 10♀ only) and 90 at 0.5 1, 2, 4, 7, and 12 hr after dosing.
- Terminal and Recovery Sacrifice - terminal sacrifices: Weeks 12 (Group 5♀) and 14 (Groups 1-4, Group 5 ♂ and 6); recovery sacrifices: Weeks 16 (Group 5♀) and 18 (Groups 1 and 5 ♂). Necropsy was performed on all animals (unscheduled deaths + terminal sacrificed) in toxicology groups (Groups 1-6). Animals found dead or sacrificed in extremis in Groups 7-11 were subjected to a gross necropsy and discarded. The following organs (when present) were weighed:

Adrenals	Liver	Prostate	Testes with Epididymides
Brain (with Brainstem)	Lung	Spleen	Thymus
Heart	Femur with Articular Surface	Seminal Vesicles	Ovaries
Kidneys	Pituitary (Weighed Postfixation)	Stomach	Uterus
Cecum (Emptied, Rinsed, Weighed)	Colon (Emptied, Rinsed, Weighed)	Thyroid/Parathyroids (Weighed Postfixation)	

The following tissues (when present) were preserved in 10% neutral-buffered formalin. All tissues from all animals sacrificed at the end of the treatment period in Groups 1 and 5, Group 4 females, and Group 6 males and from all animals from Groups 1-6 that died or were sacrificed in extremis during the study examined microscopically. The kidney, stomach, duodenum, jejunum, ileum, colon, cecum, and rectum from all animals sacrificed at the end of the treatment period in Groups 2, 3 and 4 (♂) and from recovery animals in Groups 1 and 5 were examined microscopically. Gross lesions from all animals in Groups 1-6 were examined microscopically.

Adrenals (2)	Heart	Pancreas	Stomach
Aorta (Thoracic)	Kidneys (2)	Pituitary	Testes with Epididymides (2)
Bone (Femur)	Gross Lesions	Prostate	Thymus
Brain with Brainstem (Fore-, Mid-, Hind-)		Spinal Cord (Cervical, Mid-Thoracic, and Lumbar)	
Colon, Cecum, Rectum	Salivary Glands (Submandibular)		Thyroid with Parathyroids
Liver	Lung	Lesions	Tongue
Duodenum, Jejunum, Ileum	Mandibular Lymph Node	Sciatic Nerve	Trachea
Esophagus	Mammary Gland with Skin	Seminal Vesicles	Urinary Bladder
Eyes (with Optic Nerve)	Mesenteric Lymph Node	Skeletal Muscle	Uterus
Harderian Gland	Ovaries (2)	Spleen	Vagina

Results:

- Mortality and Clinical Signs - There were 22 deaths with clinical signs of cold to touch, hunched posture, pale body, distended abdomen, thin, hypoactivity, rough haircoat, and urine stains. The cause of all deaths except the one in control group was due to GI (most frequently in the jejunum and ileum) injury (ulceration/necrosis with abdominal inflammation). It appeared that ♀ rats had more severe, higher frequency and longer in duration in the observed clinical symptoms at the same dose level as compared to ♂. The incidence of deaths for each group is presented in the following table. One Group 5 ♀ had swollen abdomen during recovery phase (Days 93-120).

Group	Unscheduled Deaths		Terminal Sacrifice		Recovery Sacrifice	
	♂	♀	♂	♀	♂	♀
1	1	0	14	15	10	10
2	0	0	15	15	-	-
3	1	3	14	12	-	-
4	0	3	15	12	-	-
5	4	9	11	6	10	10
6	1	-	14	-		

- Body Weights and Food Consumption - Reduced mean body weights were observed in Group 6 ♂ at Weeks 3→14 (↓5.3-9.4%) and Group 5 ♀ at Weeks 9 (↓5.6%) and 11 (↓6.7%). Total mean body weight gain for ♂ in Groups 4, 5 and 6 following 13-week treatment were significantly lower than controls with values of ↓12.6%, ↓10.5% and ↓19% respectively. Similarly, reduced total body weight gain (↓15.5%) was seen in Group 5 ♀ at the terminal sacrifice. There were few sporadic significant changes in weekly food consumption [Group 6 ♂ - ↓7.6% at Week 2; Group 5 ♀ - ↓6.6% at Week 4, ↑14% at Week 13 (recovery phase)].
- PK/TK - SC-65872 was absorbed and systemically available. The mean PK parameters for SC-65872 and its metabolite, SC-66905 on Days 1, 28, 80 (Group 4♀ only), and 90 are shown in the following table. Accumulation of SC-65872 or SC-66905 had occurred after repeated oral dosing as higher AUC values were noted in both ♂ and ♀ @ ≥2.5 mg/kg on Days 28 and 80/90

than those on Day 1. In addition, C_{max} and AUC values for SC-65872 in female rats were greater than those for male rats.

Dose (mg/kg)	SC-65872						SC-66905					
	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-12} (μg•hr/ml)		T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-12} (μg•hr/ml)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
DAY 1												
1.25	-	2	-	0.595	-	3.94	-	7	-	0.0536	-	0.455
2.5	1	1	0.48	0.819	2.58	4.53	2	4	0.124	0.0703	0.862	0.541
5	2	2	0.908	1.46	5.71	9.45	2	2	0.237	0.14	1.65	1.28
12.5	2	2	3.35	5.42	17.7	36.1	4	2	0.769	0.431	6.18	3.78
25	2	-	5.92	-	37.5	-	2	-	1.67	-	14.1	-
50	4	-	10.7	-	71.1	-	4	-	3.89	-	34.3	-
DAY 28												
1.25	-	1	-	0.56	-	3.75	-	4	-	0.0351	-	0.333
2.5	1	2	0.714	1.09	3.18	8.27	4	4	0.151	0.0953	0.992	0.737
5	1	2	1.53	3.02	7.04	21.9	4	2	0.339	0.2	2.37	1.9
12.5	1	2	4.75	10.6	26	77.6	4	2	1.15	0.983	8.34	7.44
25	2	-	8.66	-	47.2	-	2	-	2.7	-	18.1	-
50	1	-	12	-	84.8	-	7	-	6.13	-	51.7	-
DAY 80/90												
1.25	-	2	-	0.58	-	4.15	-	7	-	0.0303	-	0.336
2.5	2	1	0.646	1.33	3.75	10.3	4	4	0.156	0.104	1.08	0.864
5	1	2	1.43	3.52	8.68	24.2	7	7	0.251	0.218	2.23	2.19
12.5	2	2	6.71	12.3	42.2	98.6	4	7	1.4	1.06	11.3	9.57
25	2	-	9.55	-	58.6	-	7	-	2.86	-	25.8	-
50	3	-	11.1	-	94.9	-	7	-	7.20	-	54.6	-

- Ophthalmoscopic Examinations - Low incidence of unilateral pathological findings were identified in some animals at Week 13 ophthalmological examinations. These alterations might not be treatment-related as they were not dose-dependent and not found in the high-dose group. The incidence of each ophthalmic lesion is presented in the following table.

Parameters and Pathological Findings		Incidence										
		1		2		3		4		5		6
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
Nº of Animals Examined		14	15	15	15	15	13	15	12	14	6	14
Nº of Animals with No Visible Lesions		14	15	14	15	13	12	13	11	11	6	14
Chromodacryorrhea						1		1				
Opaque Eye (OD)										1		
Normal Eye Structure Not Visible				1		1				2		
Globe	Diffuse→Severe Phthisis (OD)			1		1				2		
	Severe Panophthalmitis (OD)			1						2		
Cornea	Central Corneal Neovascularization (OD)									1		
	Severe Keratitis (OD)									1		
	Focal Corneal Perforation (OD)			1						2		
Fudus	Diffused Retinopathy (OD)								1			
	Retinal Linear Atrophy (OS)						1					
Peripapillary Abnormal Shaped Optic Nerve (OD)									1			

- Clinical Pathology -
  - Hematology - A slight increase in WBC (1.1-1.3x) with ↑ segmented neutrophils (2.6-1.75x) was noted in the ♂ @ 100 mg/kg at Weeks 6 and 14. In addition, increased segmented neutrophils (2.0-1.69x) was identified in ♂ @ 25 mg/kg at Weeks 6 and 14.
  - Serum Chemistry - Slightly lower Cl^- and K^+ values but within normal biological ranges were noted in ♂ @100 mg/kg and ♀@ 10 and 25 mg/kg at Weeks 6 and 14. Elevated group mean values for the total bile

acids (1.5-2.5x) were noted in ♂ @ 50 and 100 mg/kg and ♀ @ 10 and 25 at Weeks 6 and 14. However, some animals in the control group also had highly elevated total bile acids

- Urine Chemistry - Higher mean urine volume values with lower urine sodium concentration were noted in ♂ @ 100 mg/kg and ♀ @ 25 mg/kg.
- Urinalysis - There were no significant changes in any of parameters analyzed.

- Organ Weights, Gross- and Microscopic-Pathology -

Organ Weights: There were moderate increases in absolute and relative spleen, kidney, liver, and colon weights in ♂ and ♀ @ mid- and high- doses as shown in the following table. Significant increases in absolute and relative adrenal weights were noted in ♂ @ 100 mg/kg/day and ♀ @ ≥25 mg/kg/day. There were no significant changes in absolute and relative organ weights of recovery animals.

Dose (mg/kg/day)		Organ	Organ Weight		Organ Wt/Body Wt		Organ Wt/Brain Wt	
♂	♀		♂	♀	♂	♀	♂	♀
25	10	Spleen	↑11%	↑17%	↑18%	↑20%	↑14%	↑20%
50	25		↑4%	↑33%	↑14%	↑44%	↑4%	↑40%
100	-		↑23%		↑38%		↑24%	
50	25	Uterus		↓24%		↓19%		↓22%
25	10	Kidney		↑17%		↑20%		↑20%
50	25		↑13%	↑30%	↑22%	↑42%	↑12%	↑34%
100	-		↑21%		↑35%		↑22%	
100	-	Prostate	↓29%		↓21%		↓27%	
50	25	Liver	↑5%	↑16%	↑14%	↑26%	↑4%	↑21%
100	-		↑13%		↑26%		↑14%	
25	10	Adrenal		↑39%		↑43%		↑43%
50	25		↑9%	↑77%	↑18%	↑92%	↑8%	↑84%
100	-		↑18%		↑29%		↑18%	
50	25	Colon	↑18%	↑43%	↑29%	↑56%	↑22%	↑48%
100	-		↑5%		↑18%		↑7%	
5		Seminal Vesicle	↓18%		↓15%		↓19%	
10			↓22%		↓20%		↓22%	
25	10		↓22%		↓18%		↓21%	
50	25		↓28%		↓22%		↓27%	
100	-		↓24%		↓15%		↓23%	

Gross Findings: The major gross findings identified in unscheduled deaths (♂ @ ≥10 mg/kg and ♀ @ ≥5 mg/kg) were limited to GI (perforation/necrosis/thicken/distended/adhesions in jejunum, ileum, and/or duodenum with or without secondary peritonitis), adrenal cortex (enlarged) and liver (interlobar adhesion). At scheduled terminal sacrifice, gross changes of enlarged adrenal cortex, mass in jejunum and adhesion in abdominal cavity were identified in one ♀ @ 25 mg/kg female and mass in the ileum were seen in one ♂ @ 25 mg/kg. There were no gross findings attributable to the treatment in the animals sacrificed following a 4-week recovery period.

Histopathology: Treatment-caused histopathological changes were limited to the GI (necrosis/perforation with peritonitis), adrenal glands (diffuse vacuolization/hypertrophy in zona fasciculata), liver (centrilobular to midzonal hepatocellular enlargement) and kidney (increased incidence of mineralized material in the renal pelvis with associated transitional cell hyperplasia). Necrosis of the intestinal wall was noted most frequently in the jejunum and ileum, with associated inflammation of the serosa. The incidences of these changes are listed in the following table. There were no treatment-related changes were identified in the recovery animals.

Pathological Findings	Incidence										
	1		2		3		4		5		6
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
Glandular Stomach - Erosion											
Terminal Sacrifices		2			1			1			
Non-Glandular Stomach - Necrosis											
Unscheduled Deaths						1		1			
Duodenum, Jejunum, Ileum, and Cecum - Necrosis with peritonitis											
Unscheduled Deaths					1	3		3	4	9	1
Terminal Sacrifices							1			1	1
Adrenal Cortex - Zona fasciculata, diffuse vacuolization (slight → moderate)											
Unscheduled Deaths									2	4	
Terminal Sacrifices								1	8	3	10
Adrenal Cortex - Zona fasciculata, diffuse hypertrophy (slight → moderate)											
Unscheduled Deaths								2		9	
Terminal Sacrifices										6	
Liver - Centrilobular to midzonal hepatocellular enlargement											
Terminal Sacrifices									8		11
Kidney - Mineralized material in pelvis/urothelium and/or transitional cell hyperplasia											
Unscheduled Deaths						1		1	2	1	
Terminal Sacrifices				2	1	1	1	1	4	4	4

Therefore, the NOAEL for SC-65872 when administered orally twice daily for 13 weeks was 5 mg/kg/day for ♂ and 2.5 mg/kg/day for ♀.

2.2.2.8. 26-Week Gavage Toxicity Study of SC-65872 in the Rat, SA4625; Date: 12-Apr-1999, Document No. P30S4625 (Vol. 1.56-59)

Study Nº: SA4625
Report Nº: P30S4625 & M3097397 (PK)
Study Aim: To evaluate the reversibility of any effects of the 26-week treatment after a 4 week reversal period; and to evaluate the pharmacokinetics profile of the test material relative to dosage, duration of dosing, and effect of gender.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: ♂: 0, 5, 12.5, 25 mg/10 ml/kg/day po by gavage
♀: 0, 2.5, 5.0, 10.0/7.5/5.0 mg/10 ml/kg/day po by gavage
Dosing Frequency: 1x/day for ≥182 days
Animals: CD rats [redacted] ~6 weeks of age, weighing 116.9-184.4 g.
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077; [redacted]
GLP/QAU Compliance: Yes
Study Date: 3/25/1997 to 9/23-25/1997 (Days 183-185, terminal sacrifice) and 10/21/1997 (Day 211, reversal sacrifice)
Study Design: Groups of rats were randomly assigned to one of the 7 dose groups as shown in the following table. Ten rats/sex from Groups 1 and 4 were allowed to have a 4-week recovery period.

Group		Dose (mg/kg/day)		Nº Rats/Sex	Nº Animals/Sex Sacrificed	
		♂	♀		Days 183/185[a]	Day 211[a]
Tox Study	1	0	0	25	15	10
	2	5.0	2.5	15	15	0
	3	12.5	5.0	15	15	0
	4	25.0	10.0/7.5/5.0[b]	25	15	10
PK Study	5	0	0	5	-	-
	6	5.0	2.5	15	-	-
	7	12.5	5.0	15	-	-
	8	25.0	10.0/7.5/5.0[b]	15	-	-

[a] PK animals that died or were sacrificed moribund were necropsied, tissues were not retained. All surviving PK animals were sacrificed and discarded without necropsy following the last blood sampling.

[b] The dosage was lowered to 7.5 mg/kg/day on Day 88 and then to 5 mg/kg/day on Day 107.

The following observations were conducted.

- Clinical Signs and Mortality - 2x/day during the treatment and 1x/day during the reversal period.
- Physical Examination - 1x/week (Groups 1-4)
- Ophthalmic Examination - Pre-R, Weeks 12 and 25.
- Body Weights - 2x/week during Weeks 1-4 and 1x/week thereafter.
- Food Consumption - 1x/week.
- Clinical Pathology - Weeks 13, 25 and 30 (Reversal). The following parameters were measured:

HEMATOLOGY/COAGULATION			
Cell Morphology	RBC	WBC	Differential Leukocyte Count
Corrected Leukocyte Count	Ht	MCV	aPTT
Large Unstained Cells (LUC)	MCHC	MCH	PT
Platelet Count	Mean Platelet Volume	Hb	Fibrinogen
CLINICAL CHEMISTRY			
ALT	Calcium	Inorganic Phosphorus	Total Bile Acids
Albumin	Chloride	Potassium	Total Cholesterol
Albumin/Globulin Ratio	Creatinine	Sodium	Total Protein
Alkaline Phosphatase	Globulin	Sorbitol Dehydrogenase	Triglycerides
AST	Glucose	Total Bilirubin	Urea Nitrogen
URINALYSIS			
Osmolality	Urine Chloride	Urine Phosphorus	Urine Potassium
Urine Creatinine	Urine Volume (~ 22 hr)	Urine Sodium	Urine Calcium
Occult Blood	Glucose	Ketones	Protein
Bilirubin	Microscopic Examination of Sediment	pH	Urobilinogen

- PK/TK - Weeks 1, 12, and 25. Blood samples were collected from Groups 5-8 (3 rats/sex/time point) at 0.5, 1, 2, 4, 7, 12, 16, and 24 hrs post dosing.
- Necropsy - Weeks 27 and 31 (Reversal). All animals were necropsied. Animals found dead or sacrificed in a moribund condition (Toxicology and PK) were necropsied. Organ weights were not collected from unscheduled deaths. The following listed tissues were collected from all Toxicology animals and preserved in 10% buffered formalin. Tissues denoted with * were weighed at scheduled sacrifice and paired organs were weighed together. Sections of tissues collected from Groups 1, 3, and 4 sacrificed during Week 27 and any Toxicology animals that died or sacrificed in a moribund condition were examined microscopically. In addition, histopathological examination was performed on sections of adrenal glands, GI, and grossly observed lesions from Group 2 and reversal animals.

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

Results:

- Clinical Signs and Mortality - The following table shows the mortality and treatment-related deaths for each group. Due to high incidence of treatment-caused deaths seen in the high dose ♀, the high dose was lowered from 10 to 7.5 mg/kg/day on Day 88 and then to 5 mg/kg/day on Day 107. After this dose adjustment, the dose for mid- and high-dose ♀ were merged into one group. Clinical observations of ventral staining, pale and/or thin appearance, hunched posture, rough coat, swollen abdomen, pale gums, discharge/crust (nose) were noted in animals that died of treatment-caused GI toxicity (perforation/peritonitis) or sacrificed in a moribund condition.

Group		Dose (mg/kg/day)		Total Deaths		SC-65872-Related		Other Cause[a]	
		♂	♀	♂	♀	♂	♀	♂	♀
Tox Study	1	0	0	1	1	0	0	1	1
	2	5.0	2.5	0	7	0	5	0	2
	3	12.5	5.0	0	3	0	3	0	0
	4	25.0	10.0/7.5/5.0	9	19	7	19	2	0
PK Study	5	0	0	1	0	0	0	1	0
	6	5.0	2.5	1	7	0	6	1	1
	7	12.5	5.0	2	11	1	10	1	1
	8	25.0	10.0/7.5/5.0	3	7	3	7	0	0

[a] Other cause of deaths included accidental (gavage or result of bleeding procedures), urinary calculosis, or no apparent cause.

- Ophthalmic Examination - There were no remarkable changes attributable to the treatment.
- Body Weights and Food Consumption - No significant changes in ♂ body weights body weight changes and food consumption were identified.
- Clinical Pathology - One each ♂ @ 0, and 25 mg/kg had highly elevated AST, ALT, SDH, and total bile acid values with microscopic liver changes (moderate multifocal necrosis in the control and slight portal fibrosis) at Week 26. These findings might not be treatment-related as only a single animal each in control and high dose group. A significant increase in absolute PMN was noted in mid- and high-dose ♀ at Week 13 (2.1-2.3x of control) and Week 26 (3.8-5.0x of control). In addition, mid- and high-dose ♀ had ↑ WBC (1.5-1.9x) with ↑ lymphocyte (1.2-1.5x) and ↑ large unstained cell counts (1.8-2.3x) and ↑ platelet counts (↑21-23%) at Week 26. The changes in leukogram (↑WBC, PMN, lymphocytes and large unstained cell values) in Group 3/4 ♀ were also noted at reversal Week 4. Elevated urinary Ca excretion (↑44-60%) was noted in high-dose ♂ Weeks 13 and 26 and high-dose ♀ at Week 13, and mid-/high-dose ♀ at Week 26.
- PK/TK - SC-65872 was absorbed and systemically available. Mean PK parameters for SC-65872 and its active metabolite SC-66905 in ♂ and ♀ On Days 1, 78 and 169 are listed in the following table. Plasma C_{max} and AUC_{0-24} values for SC-65872 and SC-66905 increased with dose. Generally, ♀ had higher C_{max} and AUC_{0-24} values for SC-65872 than those in ♂. On contrast, ♂ had higher C_{max} and AUC_{0-24} values for SC-66905 than those in ♀.

Day	Group	Dose[a] mg/kg/day		SC-65872						SC-66905					
				T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)		T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	6	5	2.5	0.5	1	1.21	0.627	6.07	3.92	2	4	0.305	0.0787	2.28	0.793
	7	12.5	5	1	1	3.31	1.44	18.6	9.45	4	4	0.928	0.187	7.36	1.63
	8	25	10	1	1	6.06	2.69	39.5	21.6	4	4	2.04	0.526	17.7	4.53
78	6	5	2.5	0.5	1	1.33	1.03	7.29	9.84	4	4	0.292	0.0994	2.33	0.774
	7	12.5	5	2	4	3.90	2.20	34.3	18.1	4	4	1.07	0.182	12.1	1.89
	8	25	10	2	2	6.01	4.42	51.3	42.1	7	4	2.37	0.500	22.3	5.42
169	6	5	2.5	1	0.5	1.54	1.17	8.71	12.1	4	7	0.275	0.0782	2.59	0.986
	7	12.5	5	2	2	7.99	2.89	39.0	25.8	2	2	1.30	0.161	15.0	2.31
	8	25	5[a]	2	2	7.33	2.86	55.7	23.7	7	2	1.86	0.207	17.6	2.46

[a] Dose was 10 mg/kg/day for Days 1 → 87; 7.5 mg/kg/day for Days 88 →106, and 5 mg/kg/day for Days 107 through termination.

The exposures of SC-65872 on Day 169 as measured by AUC in the low-, mid-, and high-dose ♂ were ~2x, 9x, and 13x of maximum recommended human dose (MRHD), 20 mg/day for chronic indication, respectively. The exposures of SC-65872 as measured by AUC for the low-, mid-, and high-dose ♀ were ~3x, 6x, and 6x of maximum recommended human dose (MRHD), 20 mg/day for chronic indication, respectively.

- Necropsy -

Organ Weights: There were increases in absolute and relative adrenal, kidney, and spleen weights in ♂ and ♀ @ mid- and high- doses as shown in the following table. A slight reduce in absolute and relative prostate weights was noted in mid- and high-dose ♂.

Dose (mg/kg/day)		Organ	Week 26				Reversal Week 4			
			Organ Weight		Organ Wt/Body Wt		Organ Weight		Organ Wt/Body Wt	
♂	♀		♂	♀	♂	♀	♂	♀	♂	♀
5.0	2.5	Spleen		↑35%		↑32%				
12.5	5.0		↑8%	↑154%	↑7%	↑163%		↑19%		↑25%
25			↑11%		↑21%		↓13%		↓7%	
-	5.0	Uterus		↓10%		↓11%		↓17%		↓10%
12.5	5.0	Kidney	↑9%	↑8%	↑8%	↑8%				
25			↑13%		↑20%		↑10%		↑17%	
12.5		Thyroid	↑16%		↑14%					
25			↑19%		↑22%					
	2.5	Pituitary		↓15%		↓11%				
	5.0			↓25%		↓22%		↓36%		↓32%
12.5	5.0	Adrenal	↑9%	↑17%	↑9%	↑20%				
25.0			↑17%		↑27%					
	5.0	Colon		↑13%		↑14%		↑5%		↑11%
12.5	-	Prostate	↓13%		↓13%					
25	-		↓14%		↓8%		↓26%		↓24%	

Unscheduled Deaths/Sacrifices: Treatment-caused mortality due to GI toxicity occurred in ♀ @ ≥2.5g/kg/day and ♂ @ ≥12.5 mg/kg. The incidence of treatment-related intestinal lesions in unscheduled dead animals is presented in the following table. GI lesions predominantly present in the distal small intestine (jejunum and ileum) were characterized by mucosal ulceration, perforation, and associated peritonitis (abdominal adhesions and accumulation of fluid) secondary to leakage of gastrointestinal (GI) contents into the abdominal cavity.

Group		♂		♀	
		Mortality	No. w/ GI Injury	Mortality	No. w/ GI injury
Tox Study	1	1	0	1	0
	2	0	0	7	5
	3	0	0	3	3
	4	9	7	19	19
PK Study	6	1	0	7	6
	7	2	1	11	10
	8	3	3	7	7

Scheduled Sacrifices: Treatment-caused gross morphologic evidence of GI injury was identified in one low-dose and three mid/high-dose ♀ at the terminal necropsy. No test article-related gross changes were observed at the recovery necropsy.

Histopathology: Treatment-related microscopic changes included mucosal erosion, ulceration, and/or inflammation in the jejunum, ileum and cecum with secondary peritonitis and adrenal cortical hypertrophy. The incidence in animals with gross and/or histomorphologic evidence of GI lesions is presented in the following table.

Incidence of Treatment-Related Gross and/or Histopathologic GI Injury				
Sex	Group 1	Group 2	Group 3	Group 4
♂	0/25	0/15	1/15	7/25
♀	0/25	6/15	5/15	20/25

The histologic changes in the adrenal cortex were identified in 4 ♂ @ 25 mg/kg, 4♀ @ 2.5 mg/kg and 16 ♀ @ 10.0/7.5/5.0 mg/kg with characteristics of hypertrophy of endocrine cells in the zona fasciculata that was probably accountable for the increased adrenal weights observed in the study. Increased extramedullary hematopoiesis (EMH) in several high-dose ♂and low- and mid/high-dose ♀. This change was considered a compensatory hematopoietic response secondary to intestinal injury and associated peritonitis. There were no treatment-related microscopic changes were found in recovery animals.

Therefore, based on observed GI toxicity, the NOAEL of SC-65872 was 5 mg/kg/day for ♂ and could not be established for ♀.

2.2.2.9. Amendment: P31S4722: A Study of SC-65872 When Administered Via Gavage to the Rat for Twenty-Six Weeks, SA4722; Date: 16-Oct-2000, Document No.. (Vol. 1.60-63) Appendix:

Study Nº: SA4722
Report Nº: P30S4722 & M3098278 (PK)
Study Aim: To evaluate the toxicity of SC-65872 when administered to rats 1x/day by gavage for 26 weeks with a 4-week reversal period
Compound:
Vehicle Control:
Dose & Route: ♂ - 0.06, 0.2, 0.6, and 2.0 mg/5 ml/kg/day po
♀ - 0.03, 0.1, 0.3, and 1.0 mg/5 ml/kg/day po
Dosing Frequency: 1x/day for ≥182 days
Animals: ♂ + ♀ CD rats [redacted] 5-6 weeks of age, weighing 100-180 g
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: Yes.
Study Date: 11/4/1997 - 5/5-7/1998 (Week 27, Terminal Sacrifice) and 6/4/1998 (Week 31, Reversal Sacrifice).

Study Design: Groups of rats were randomly assigned to one of the 9 dose groups as shown in the following table. Ten rats/sex from Groups 1 and 5 were allowed to have a 4-week recovery period.

Group		Dose (mg/kg/day)		Nº Rats/Sex	Nº Animals/Sex Sacrificed	
		♂	♀		Days 183/185[a]	Day 213[a]
Tox	1	0	0	25	15	10
	2	0.06	0.03	15	15	0
	3	0.2	0.1	15	15	0
	4	0.6	0.3	15	15	
	5	2.0	1.0	25	15	10
PK	6	0.06	0.03	15	-	-
	7	0.2	0.1	15	-	-
	8	0.6	0.3	15		
	9	2.0	1.0	30	-	-

[a] PK animals that died or were sacrificed moribund were necropsied, tissues were not retained. All surviving PK animals were sacrificed and discarded without necropsy following the last blood sampling.

The following observations were conducted.

- Clinical Signs and Mortality - 2x/day during the treatment and 1x/day during the reversal period.
- Physical Examination - Pre-R and x/week (Groups 1-4)
- Body Weights - 2x/week during Weeks 1-4 and 1x/week thereafter.
- Food Consumption - Pre-R and 1x/week.
- Clinical Pathology - Weeks 13, 26 and 30 (Reversal). The following parameters were measured:

HEMATOLOGY/COAGULATION			
WBC	RBC	Platelet Count	Mean Platelet Volume
Large Unstained Cells (LUC)	Ht	MCV	Hb
Differential Leukocyte Count	MCHC	MCH	
CLINICAL CHEMISTRY			
ALT	Calcium	Inorganic Phosphorus	Total Bile Acids
Albumin	Chloride	Potassium	Total Cholesterol
Albumin/Globulin Ratio	Creatinine	Sodium	Total Protein
Alkaline Phosphatase	Globulin	Sorbitol Dehydrogenase	Triglycerides
AST	Glucose	Total Bilirubin	Urea Nitrogen

- PK/TK - Weeks 1, 4, 12, and 25. Blood samples were collected from Groups 6-9 (3 rats/sex/time point) at 0.5, 1, 2, 4, 7, 12, 16, and 24 hrs post dosing.
- Necropsy - Weeks 27 (Days 183-185) and 31 (Reversal). All animals were necropsied. Animals found dead or sacrificed in a moribund condition (Toxicology and PK) were necropsied. Organ weights were not collected from unscheduled deaths. The following listed tissues were collected from all Toxicology animals and preserved in 10% buffered formalin. Tissues denoted with * were weighed at scheduled sacrifice and paired organs were weighed together. Sections of tissues collected from Groups 1 and 5 and 3 Toxicology animals that died or sacrificed in a moribund condition and livers collected from Groups 1, 4, and 5 sacrificed during Week 27 and any were examined microscopically.

*Adrenal Glands (Both)	*Liver	Kidney
Intestine, Small (Duodenum, Jejunum, Ileum)	Rectum	Urinary Bladder
Intestine, Large (Cecum, Colon)	*Stomach	Lesions

Results:

- Mortality and Clinical Signs - There were 8 unscheduled deaths in Toxicology groups (♂: 5 @ 2 mg/kg; ♀ - 1 each @ 1, 0.1 and 0.03 mg/kg) with signs of ventral staining, rough coat, reduced feces, and reduced activity prior to death. The cause of death for Groups 1-5 animals is shown in the following table.

Animal No.	Group/Sex	Cause of death*
1502	5/M	Gastrointestinal hemorrhage
1510	5/M	Undetermined
1516	5/M	Undetermined
1519	5/M	Lymphoma
1523	5/M	Accidental
2203	2/F	Accidental
2414	4/F	Undetermined
2522	5/F	Intestinal injury
*Determined by clinical or pathological examinations.		

In addition, there were 7 unscheduled deaths in PK study Groups (1 each ♂ in Group 6, 7, and 9; 1 each ♀ in Groups 6 and 8 and 2♀ in Group 9). Four of these PK animals were necropsied and no treatment-related gross lesions were found.

- Body Weights and Food Consumption - No treatment-related changes in mean body weights, weight gains, and food consumption were recorded.
- Clinical Pathology - No treatment-related changes in hematology and clinical chemistry parameters were observed.
- PK/TK - SC-65872 was absorbed and systemically available. C_{max} and AUC values of SC-65872 and SC-66905 increased with dose. The mean PK parameters for SC-65872 and SC-66905 on Days 1, 28, 80, and 169 are presented in the following table. Accumulation of SC-65872 did occur after repeated dosing as C_{max} and AUC values increased with duration.

Dose (mg/kg)	Sex	SC-65872				SC-66905			
		Day 1	Day 28	Day 80	Day 169	Day 1	Day 28	Day 80	Day 169
		C_{max} (μg/ml)							
0.06	♂	0.0282	0.0185	0.0335	0.0345	0.00522	0.00484	0.00649	0.00837
0.2		0.105	0.0883	0.117	0.126	0.0257	0.0153	0.0191	0.0124
0.6		0.291	0.258	0.334	0.448	0.0491	0.0447	0.0603	0.0495
2		0.758	0.594	0.898	1.43	0.171	0.260	0.253	0.209
0.03	♀	0.00632	0.0180	0.0249	0.0284	0.0	0.00130	0.00349	0.00199
0.1		0.0693	0.0720	0.0818	0.103	0.00704	0.00516	0.00985	0.00573
0.3		0.184	0.160	0.266	0.400	0.0246	0.0160	0.0238	0.0258
1		0.414	0.518	0.963	1.11	0.0641	0.0468	0.0701	0.0547
		AUC_{0-24} (μg•hr/ml)							
0.06	♂	0.148	0.110	0.210	0.274	0.0420	0.0392	0.0689	0.0749
0.2		0.622	0.512	0.972	0.836	0.239	0.170	0.251	0.176
0.6		1.66	1.50	2.28	2.68	0.543	0.528	0.605	0.580
2		4.29	4.13	6.14	8.91	1.70	1.84	2.13	2.24
0.03	♀	0.0415	0.153	0.241	0.279	0.0	0.00963	0.0256	0.0212
0.1		0.421	0.441	0.674	0.740	0.0715	0.0641	0.0836	0.0800
0.3		1.34	1.56	2.42	3.02	0.232	0.211	0.285	0.325
1		3.42	3.97	7.21	6.83	0.728	0.684	0.880	0.742

- Necropsy -

  Organ Weights: No treatment-related effects on absolute or relative organ weights.

  Unscheduled Sacrifices: Treatment-related pathological changes were limited to GI. These changes included:

  - gross findings of jejunal ulceration (4 cm in length) with multiple adhesions involving the abdominal viscera in 1♀ @ 1.0 mg/kg/day with microscopic lesions of jejunal mucosal erosion/ulceration and chronic active inflamation of serosal surface of abdominal viscera;

- dark greenish discolored gastrointenstinal contents, a potential indication of gasgstrointestinal hemorrhage, without microscopic findings in 1♂ @ 2 mg/kg/day.

Terminal Sacrifices: No treatment-related gross or microscopic changes were characterized.

Therefore, based on observed GI toxicity, the NOAEL of SC-65872 was 2 mg/kg/day for ♂ and 0.3 mg/kg/day for ♀.

2.2.3. DOG STUDIES

2.2.3.1. Two-Week Oral Capsule Toxicity Study of SC-65872 in the Dog; Date: 08-May-1996, Document No. P30E4436. (Vol. 1.48)

Study Nº: EX4436
Report Nº: P30E4436/MRC95S-31-950306 & MRC95S-30-950306 (PK)
Study Aim: This is an exploratory study to evaluate the potential and target organ or dose-limiting toxic effects of SC-65872 in dogs following 2-week of repeated oral dosing.
Compound:
Vehicle Control:
Dose & Route: 0, 2.5, 7.5, and 15mg/kg/dose, bid (~10 hr apart) po for a total 29 times over 15 days.
Animals: ♂ & ♀ Beagle dogs, 8-12 months of age, weighing 10.9-13.7 kg, 2/sex/group
Study Location: G.D. Searle; 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: N/A
Study Date: Dosing Initiation - 10/26/95; Terminal Sacrifice - 11/10/95 (Day 16).
Study Design:

Group Nº	Compound	Dose (mg/kg/dose)	Dose (mg/kg/day)	Dosing Duration	Nº of Animals/Group
1	Control	-	-	15-Day	2/Sex
2	SC-65872	2.5	5		2/Sex
3	SC-65872	7.5	15		2/Sex
4	SC-65872	15	30		2/Sex

The following parameters were monitored during the study.

- Mortality and Clinical Observations - 1x/day (~1-3 hr post 1st daily dose).
- Physical Examination - Days -8 and 9.
- Body Weight and Food Consumption - Days -8, -1, 5 and 12.
- Clinical Pathology - Days -8 and 16.
- Toxicokinetics - Days 1 and 15 at 0.5, 1, 1.5, 2, 2.5, 3.5, 7, 10, and 24 hr post 1st dose.
- Necropsy - Day 16, only tissues from dogs in Groups 1 & 4 were prepared for microscopic examinations.

Results:

- Mortality and Clinical Observations - One ♂ @ 30 mg/kg/day was sacrificed on Day 14 with clinical signs of bloody stools. No any other remarkable clinical symptoms were seen.
- Body Weight and Food Consumption - Food consumption and body weight changes were not affected by the treatment.
- Clinical Pathology - Slight decreases in RBC, Ht, Hb concentrations were noted in Group 4 high-dose animals.
- Toxicokinetics - Micronized SC-65872 was absorbed and systemically available following repeated oral administration to the dog. Plasma SC-65872 levels increased with increasing dosage and these increases were not proportionally to the dose. Sex-difference in the drug metabolism

was apparent by the evidence of higher mean plasma drug levels in the ♀ than in the ♂. The following table presents a summary of PK parameters for SC-65872 and its active metabolite, SC-66905.

Day	Dose (mg/kg/day)	SC-65872 Parameters						SC-66905 Parameters					
		T_{max} (hr)		C_{max} (μg/ml)		$AUC_{0\text{-}12hr}$ (hr•μg/ml)		T_{max} (hr)		C_{max} (μg/ml)		$AUC_{0\text{-}12hr}$ (hr•μg/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	5	1.75	1.25	0.934	1.58	2.96	4.74	3.5	3.0	0.447	0.623	2.68	3.05
	15	2.25	1.25	1.42	2.09	4.14	6.57	2.5	2.5	0.690	1.26	3.42	7.03
	30	1.50	2.00	1.38	3.07	5.30	9.09	2.25	2.0	0.740	1.63	4.07	8.38
15	5	1.25	2.00	0.632	1.43	2.93	5.66	2.88	2.75	0.768	1.04	5.20	6.57
	15	3.25	2.25	2.70	1.91	16.7	8.89	2.0	1.75	2.87	2.90	22.1	20.0
	30	1.00	2.30	2.59	3.08	16.0	19.5	1.0	1.75	3.34	3.70	22.9	28.5

- Necropsy - Organ weights (absolute and relative) of treated animals were comparable to those in control group. A small ulcer (3 mm) in the proximal duodenum and numerous large ulcers (0.25-2.0 x 0.25-1.0 cm) in the jejunum and ileum, and moderate hemorrhage in the sclera and/or bulbar conjunctiva were observed macroscopically in the ♂ that was sacrificed on Day 14. Microscopic evaluation confirmed the presence of chronic ulcers in the duodenum, jejunum, and ileum. Mild unilateral hemorrhage in the bulbar conjunctiva was also identified microscopically. For the animals sacrificed at terminal necropsy, no drug-related gross lesions could be identified. Histological examination revealed changes associated with drug treatment in the kidneys with characteristics of degeneration/necrosis of the renal papilla in both ♀ @ 15 mg/kg/day.

Therefore, the NOAEL for 2-week oral administration of SC-65872 to the dog was 5 mg/kg/day.

2.2.3.2. Two-Week Investigative Oral Capsule Toxicity Study to Evaluate the Effects of SC-65872 on the Rectum of the Male Dog, EX4493; Date: 19-Nov-1996, Document No. P30E4493. (Vol. 1.48)

Study Nº: EX4493
Report Nº: P30E4493 & M3096142 (PK)
Study Aim: To establish the repeatability of rectal injury observed in a previous study (SA4467).
Compound: [redacted]
Vehicle Control:
Dose & Route: 0, 2.5 mg/kg/dose, bid po
Animals: ♂ Beagle dogs, 6-18 months of age, weighing 7.6-13.9 kg, 4 or 8/group.
Study Location: G.D. Searle, 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: N/A
Study Date: Dosing Initiation - 3/28/96; Terminal Sacrifice - 04/12/96.
Study Design: This was an exploratory study. Animal grouping and treatment schedule are shown in the following table.

Group	SC-65872 Lot Nº	Dose (mg/kg/dose)	Dose (mg/kg/day)	Dosing Duration	Nº Animals/Group
1	Control	0	0	2-Week	4
2	GDS-6050-031	2.5	5.0		8
3	GDS-6111-137	2.5	5.0		8

All animals were treated orally twice daily from days 1-15 for a total of 30 doses. The following parameters were monitored during the study.

- Mortality and Clinical Signs - 2x/day;

- Physical Examination - Days -3, 5, and 8;
- Body Weight - Days -3, 5, and 8;
- Feces Collection - Days 6-7 and 13-14 from 4/group over a 24-hr period;
- Toxicokinetics - Days 1-2 and 14-15 at 0.5, 1, 2, 3, 5, 7, 12, 16, and 24 hr post 1st dose; the 12 hr samples were collected on Days 1 and 14 before the 2nd dose administration.
- Necropsy - Day 16.

Results: No remarkable treatment-related clinical signs were noted. Body weight and body weight change were not affected. There were no remarkable gross findings at necropsy. No drug-related histopathological changes were seen in kidneys or GI tract. The data from PK analysis of plasma and fecal excretion of SC-65872 are presented in the following table. The corresponding $AUC_{0\text{-}12hr}$ values of active metabolite SC-66905 for GDS-6111-137 and GDS-6050-031 lots were 4.02 and 6.63 hr•μg/ml on Day 1 and 7.28 and 17.7 hr•μg/ml on Day 14, respectively. The plasma AUC values on Day 14 were 17x and 36x exposure exaggerations for Lot GDS-6111-137 and Lot GDS-6050-031, respectively relative to the $AUC_{0\text{-}24hr}$ (0.422 hr•μg/ml) at the ED_{80} for anti-inflammatory activity in a rat adjuvant arthritis model.
The mean rectal tissue SC-65872 concentrations for dogs receiving either GDS-6111-137 lot or GDS-6050-031 lot were 0.183 and 0.247 μg/g tissue, respectively.

Lot Nº	T_{max} (hr)		C_{max} (μg/ml)		$AUC_{(0\text{-}12hr)}$ (hr•μg/ml)		Fecal Excretion (mg/kg)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14	Day 7	Day 14
GDS-6111-137	2.0	2.0	1.59	1.78	5.76	7.69	0.0988	1.028
GDS-6050-031	2.0	2.0	1.06	0.97	3.49	3.59	0.1641	1.060

2.2.3.3. Two-Week Oral Capsule Toxicity Study Of Lot# GDS-6111-163 of SC-65872 in the Dog, EX 4497; Date: 20-Aug-1996, Document No. P30E4497. (Vol. 1.49)

Study Nº: EX 4497
Report Nº: P30E4497/M3096115 (PK)
Study Aim: This is an exploratory study to evaluate the toxic effects and PK of SC-65872 lot Nº GDS-6111-163 in dogs following 2-week of repeated oral dosing.
Compound:
Vehicle Control:
Dose & Route: 0, 1.25, and 2.5 mg/kg/dose, bid (~10 hr apart) po for a total 28 times over 14 days.
Dosing Frequency: bid
Animals: ♂ & ♀ Beagle dogs, 6-9 months of age, weighing 17.0-11.8 kg, 4/sex/group
Study Location: G.D. Searle; 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: N/A
Study Date: Dosing Initiation - 4/9/96;
Terminal Sacrifice - 4/25-26/96 (Day 17/18)
Study Design:

Group Nº	Compound	Dose (mg/kg/dose)	Dose (mg/kg/day, bid)	Dosing Duration	Nº of Animals/Group
1	Control	-	-	14-Day	4/Sex
2	SC-65872	1.25	2.5		4/Sex
3	SC-65872	2.5	5.0		4/Sex

Due to dosing error, on Day 1, repeated dosing started on Day 3 and lasted for ≥14 days.
The following parameters were monitored during the study.
- Mortality and Clinical Observations - 1x/day (~1-3 hr post 1st daily dose).
- Physical Examination - 1x on Days -4, 7 and 14.

- Body Weight and Food Consumption - 1x on Days -4, 7 and 14.
- Feces Collection - Days 6-7 and 13-14 over an ~24 hr period.
- Clinical Pathology - Days -6 and 17/18 prior to sacrifice.
- Toxicokinetics - Days 3 and 116 at 0.5, 1, 2, 3, 5, 7, 12, 16, and 24 hr post 1st dose.
- Necropsy - Day 17/18, only tissues from dogs in Groups 1 & 3 were prepared for microscopic examinations.

Results:

- Mortality, Clinical Observations, and Physical Examination - A ♂ @ 5.0 mg/kg was removed from the study and sacrificed on Day 14 due to extensive bleeding in the penis and prepuce. Red penile discharge was observed in this animal on Days 7, 8, and 14. No remarkable clinical or physical signs were observed in any other animals during physical examination.
- Body Weight and Food Consumption - Normal.
- Clinical Pathology - A slight increase in blood urea value was noted for the ♂ @ 5.0 mg/kg that was removed from the study on Day 14.
- Necropsy - Statistical significant increases in the absolute and relative thymus weights (~133-140% of controls) were detected in ♂ @ 2.5 & 5.0 mg/kg/day. No significant macro- and micro-scopic changes were seen in all animals necropsied at terminal sacrifice.
- Toxicokinetics - Following oral administration of SC-65872 to the dogs, plasma levels of SC-65872 were detectable at both doses. Therefore, SC-65872 was absorbed and systemic available. Mean PK parameters for SC65872 and is active metabolite, SC-66905 are shown in the succeeding table.

Day	Dose (mg/kg/day)	C_{max} (μg/ml)		C_{max} Exp Multiples		T_{max} (hr)		$AUC_{0\text{-}12hr}$ (μg•hr/ml)		AUC Exp Multiples	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
PK Parameters for SC-65872											
3	2.50	0.945	0.792	29.3	24.4	2.0	2.0	3.01	2.21	14.3	10.5
	5.0	2.45	2.00	75.6	61.7	2.0	2.0	8.24	6.78	39.1	32.1
16	2.50	0.917	0.920	28.3	28.4	2.0	2.0	3.39	2.65	16.1	12.6
	5.0	2.12	1.65	65.4	50.9	2.0	2.0	9.53	6.84	45.2	32.4
PK Parameters for SC-66905											
3	2.50	0.521	0.584	-	-	3.0	3.0	2.70	2.64	-	-
	5.0	1.22	1.11	-	-	3.0	3.0	6.72	5.93	-	-
16	2.50	0.840	0.935	-	-	3.0	2.0	5.23	5.52	-	-
	5.0	2.08	1.76	-	-	16.0	3.0	15.2	12.9	-	-

Therefore, it can be concluded from the present study that NOAEL was 5.0 mg/kg/day for SC-65872 in dogs.

2.2.3.4. Four-Week Oral Capsule Toxicity Study Of SC-65872 in the Dog, SA 4491; Date: 20-Aug-1996, Document No. P30S4491. (Vol. 1.50-51); Metabolic Profiling of [phenyl-^{14}C(U)]SC-65872 in the 4-Week Dog Toxicity Study, SA4491; Date: 01-Nov-1996, Document No. M3096342. (Vol. 1.22); Excretion of [phenyl-^{14}C(U)]SC-65872 in the 4 Week Toxicity Study, SA4491; Date: 30-Oct-1996, Document No. M3096340. (Vol. 1.22)

Study Nº: SA 4491

Report Nº: P30S4491/M3096129, M2096189, M3096254, M3096340, and M3096342 (PK)

Study Aim: To evaluate the potential toxic effects, reversibility of these effects and PK of SC-65872 in dogs during and after 4-week of repeated oral dosing.

Compound: [redacted]

Vehicle Control: [redacted]
Dose & Route: 0, 0.5, 1.25, and 2.5 mg/kg/dose, bid po for 4-week
Dosing Frequency: bid
Animals: Beagle dogs, 7-20 months of age, weighing 7.0-11.3 kg, 3-6/group.
Study Location: G.D. Searle; 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: Yes
Study Date: 5/7/1996 - 6/19/1996
Study Design: Animal grouping and dosage assignment are presented in the table as follows. All animals in Groups 2-6 were treated orally twice daily from days 1-29 for a total of ≥58 doses. Group one dogs received empty gelatin capsule. Two/sex dogs in Groups 1 & 4 were allowed to have a 2-week recovery period after the last dose.

Group Nº	Compound	Dose (mg/kg/dose)	Dose (mg/kg/day)	Dosing Duration	Nº of Animals/Group
1	Control	-	-	4-Week	6/sex (2/sex)[a]
2	SC-65872	0.5	1.0		4/sex
3	SC-65872	1.25	2.5		4/sex
4	SC-65872	2.5	5.0		6/sex (2/sex)[a]
5	SC-65872[b]	0.5	1.0		3/sex
6	SC-65872[b]	1.25	2.5		3/sex

[a] The number in parentheses indicated the number of animals that had in 2-week reversal period.
[B] Animals in Groups 5 & 6 were used for the PK experiment and were dosed with [^{14}C] SC-65872 as 1st daily dose on Days 1 & 28.

The following parameters were monitored during the study.

- Mortality and Clinical Signs - 2x/day;
- Physical Examination - Days -5, 10, 28, and 38;
- Body Weight and Food Consumption - Days -11 and -4; 1x/week during treatment and recovery period for Groups 1-4 and days 8, 15, and 22 for Groups 5 & 6.
- ECG - Days -14 or -13 and 22, 23, or 24;
- Ophthalmic Examination - Days -7 and 23;
- Buccal Mucosa Bleed Time - Days 30, 31 or 44 prior to scheduled necropsy;
- Clinical Pathology - Days -7/-6, 23/24 and 44.
- Urine Collection - Days -6/-5 and 24/25.
- Toxicokinetics - Days 1 and 29 at 0.5, 1, 2, 3, 5, 7, 12, 16, and 24 hr post 1st dose; the 12 hr samples were collected on Days 1 and 29 before the 2nd dose administration.
- Necropsy - Days 29 and 44.
- Cytochrome P-450 Analysis - ~40 g liver samples were collected from all animals in terminal sacrifice groups at necropsy.

Results:

- Mortality and Clinical Signs - No deaths occurred. No treatment-related clinical symptoms were noted.
- Body Weight and Food Consumption - No remarkable changes were attributable to the treatment.
- Ophthalmic Examination - Normal.
- ECG - Normal.
- Clinical Pathology - Increased urine osmolality was noted in ♀ @ 1, 2.5, and 5 mg/kg/day on Days 24-25. Serum chemistry analysis on Days 23/24 showed that one ♂ @ 5 mg/kg/day had a slight ↑ in blood urea (28.0 mg/dl), one ♀ @ 5 mg/kg had a slightly elevated AST value and one ♀ @ control and one ♂ @ 5 mg/kg/day had ↑ ALT values.
- Gross Pathology and Histology - No notable drug-treatment related gross changes were seen at necropsy. Microscopic examination revealed lesions in the kidney of one ♂ @ 2.5 mg/kg/day and one ♀ @ 5.0 mg/kg/day reversal group with characteristics of slight to mild unilateral focal

degeneration of the interstitium in the renal papilla. No other remarkable microscopic findings were attributable to the treatment.

- PK - Plasma SC-65782 and its active metabolite, SC-66905 levels were analyzed and summaries of PK parameters for both SC-65782 and SC-66905 are shown in the following table. Similar C_{max} and $AUC_{0\text{-}12hr}$ values for SC-65872 were obtained on Day 1 and Day 29, indicating little or no accumulation of SC-65872 occurred. On contrast, C_{max} and $AUC_{0\text{-}12hr}$ values for SC-66905 on Day 29 were ~1.25 to 1.8x higher than Day 1 in animals @ 1.25/2.50 mg/kg/day suggesting some accumulation of the active metabolite, SC-66905, in the plasma.

Day	Dose (mg/kg/day)	C_{max} (μg/ml)		C_{max}/Dose		T_{max} (hr)		$AUC_{0\text{-}12hr}$ (μg•hr/ml)		$AUC_{0\text{-}12hr}$/Dose	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
PK PARAMETERS FOR SC-65872											
1	0.50	0.405	0.444	0.811	0.888	2.00	1.00	1.20	1.26	2.41	2.53
	1.25	1.360	1.120	1.090	0.899	1.00	1.00	4.67	3.41	3.73	2.73
	2.50	1.980	1.580	0.791	0.634	2.00	1.00	7.36	5.58	2.94	2.23
29	0.50	0.384	0.291	0.767	0.582	2.00	1.00	1.13	0.85	2.26	1.69
	1.25	1.020	0.787	0.816	0.629	2.00	2.00	3.76	2.94	3.01	2.35
	2.50	2.180	1.420	0.871	0.574	2.00	2.00	9.64	5.83	3.85	2.33
PK PARAMETERS FOR SC-66905											
1	0.50	0.262	0.361	0.524	0.722	3.00	3.00	1.27	1.69	2.54	3.38
	1.25	0.595	0.706	0.476	0.565	3.00	2.00	3.33	3.47	2.67	2.78
	2.50	1.550	1.310	0.621	0.523	12.0	3.00	5.71	6.15	2.28	2.46
29	0.50	0.382	0.420	0.764	0.841	2.00	2.00	1.99	2.06	3.98	4.12
	1.25	0.734	1.000	0.587	0.802	2.00	3.00	4.45	5.54	3.56	4.43
	2.50	1.950	1.720	0.779	0.687	2.00	3.00	12.6	10.7	5.06	4.27

Plasma elimination half-life of total radioactivity on Day s1 and 28 are shown in the following table. Plasma sample profiles from 2, 5, and 24 hr post dosing with radiolabeled SC-65872 did not show sex-, dose- or duration-difference.

Dose		$T_{½}$ (hr) (Mean±SE)			
		Day 1		Day 28	
mg/kg/dose	mg/kg/day	♂	♀	♂	♀
0.5	1.0	50.1 ± 2.1	48.5 ± 3.6	53.7 ± 7.5	49.5 ± 6.4
1.25	2.5	64.2 ± 3.6	47.9 ± 6.0	58.9 ± 6.0	51.7 ± 5.0

The total radioactivity collected in feces and urine within 0-168 hr period was 93-104% of dose. The majority of radioactivity was eliminate through biliary excretion and/or intestinal secretion. Urinary excretion was the minor route. The excretion of radioactivity in the ♀ was comparable to the ♂. There no difference in excretion of total radioactivity in urine and feces between Day 1 and Day 28. The HPLRC radioactivity profiles of urine and feces showed that elimination of [phenyl-^{14}C(U)]SC-65872 occurred after metabolism on Day 1. Significant ↑ in the amount of parent compound in the fecal samples on Day 28 was detected indicating that a ↓ in absorption or an ↑ in biliary excretion of SC-65872 might have occurred.

Day	Dose mg/kg/day	% of Dose Excreted in Urine						% of Dose Excreted in Feces					
		SC-67817		SC-66905		SC-65872		SC-67817		SC-66905		SC-65872	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	1	0.764	0.714	3.40	4.20	0.0303	0.00	8.47	9.01	1.62	0.41	5.83	17.5
	2.5	1.25	1.23	3.67	5.11	0.0658	0.00	8.86	14.3	0.00	0.697	2.63	5.67
28	1	0.143	0.0347	2.78	4.62	0.00	0.00	1.66	5.27	5.26	6.61	53.3	51.7
	2.5	0.132	0.148	3.33	5.47	0.00	0.00	1.95	2.99	5.66	2.40	28.2	27.6

- Liver Microsome Enzyme and P-450 - The yield of liver microsomal protein (16.5-29.3 g/g liver) and total microsomal cytochrome P-450 (0.350-0.667 nmole/mg protein) were comparable in all

groups for both sexes.. The following table represents results for the tests to determine microsomal enzyme activity and a list of predicted markers for cytochrome P-450 gene families.

Microsomal Enzymes Activities	Cytochrome P-450 Marker	Results
ECOD (7-Ethoxycoumarin O-Deethylase)	CYP2B11	↑ : ♂ (5 mg/kg/day) & ♀ (≥1 mg/kg/day)
MROD (7-Methoxyresorufin O-Demthylase)	CYP1A1	↔ in both ♂ & ♀
EROD (7-Ethoxyresorufin O-Deethylase)	CYP1A1	↔ in both ♂ & ♀
PROD (7-Pentoxyresorufin O-Dealkylase)	CYP2B	↑ in both ♂ & ♀ (@ 1 & 2.5 mg/kg/day)
BROD (7-Benzyloxyresorufin O-Dealkylase)	CYP2B11	↔
6β-OH (6β-Hydroxylase)	CYP3A	↔ in ♂ ; ↑ in ♀
2β-OH (2β-Hydroxylase)	CYP3A	↑: ♂ (5 mg/kg/day) & ♀ (≥1 mg/kg/day)
16β-OH (16β-Hydroxylase)	CYP2B	↑ in both ♂ & ♀
16α-OH (16α- Hydroxylase)	?	↔ in ♂; ↑ in ♀
Testosterone 18-OH (18- Hydroxylase)	CYP3A	↑ in both ♂ & ♀ (≥2.5 mg/kg/day)

Western blot analysis using polyclonal anti-rat CYP2B or CYP3A antibodies showed an increase in CYP3A protein in ♂ @ 2.5 mg/kg/day and ♀ @ ≥1 mg/kg/day. Unequivocal results were obtained for CYP2B protein.

Based upon reported findings, the NOAEL of SC-65872 in the present study was 1.0 mg/kg/day.

2.2.3.5. 13-Week Repeated Dose Oral (capsule) Toxicity Study with a 4-Week Reversal with SC-65872 In Dogs, SA 4545; Date: 20-Jun-1997, Document No. P30S4545. (Vol. 1. 52-53)

Study Nº: SA4545/CHW 6127-312
Report Nº: P30S4545, M3097121 (PK), P3000105 (Special Kidney Evaluations Report)
Study Aims: To evaluate (1) the subchronic toxicity of SC-65872 when administered daily by gelatin capsule to dogs for at least 13 weeks; (2) the reversibility of any effects of 13-week treatment after a 4-week recovery period; and (3) the PK and metabolic profiles of SC-65872.
Compound: [redacted]
Dose/Route: 0.5,1 and 2 mg/kg/dose bid (10-14 hr apart) po
Duration: 2x/day for ≥13 weeks
Vehicle Control: [redacted]
Animal: Beagle dogs, 6-7 months of age, weighing 6.0-9.1 kg for the ♂ and 4.6-7.2 kg for the ♀.
Study Site: [redacted]
Study Date: 10/22/96 to 1/22-24/97
GLP/QAC Compliance: Yes
Study Design: Groups of dogs were orally given SC-65872 (0, 0.5, 1, or 2 mg/kg/dose) in gelatin capsule twice daily for 13 weeks. After at least 13 weeks of treatment, the 1st four dogs/sex in Groups 1 and 4 and all animals in Groups 2 and 3 were sacrificed. Surviving animals in Groups 1 and 4 were sacrificed following a 4-week recovery period. The following observations were performed.

Group	Dose level		Nº of Animals[a]
	mg/kg/dose	mg/kg/day	
1	-	-	7/sex
2	0.5	1	4/sex
3	1	2	4/sex
4	2	4	7/sex

- Clinical Observation and mortality - 2x/day.

- Physical Examination - Weeks 4, 13 and 17.
- Body Weights and Food Consumption - 1x/week.
- ECG - pretest and Week 13 at 1-4 hr post the 1st daily dose.
- Ophthalmoscopic Examination - pretreatment and Week 13.
- Clinical Pathology - pretest, Week 13s and 17.
- Necropsy - The terminal (4 dogs/sex/group in Groups 1-4) and recovery sacrifices (3 dogs/sex/group in Groups 1 and 4) were performed during Weeks 14 and 18, respectively. At each scheduled sacrifice, the following organs were weighed (paired organs were weighed together) after careful dissection and trimming of fat and other contiguous tissue:

Adrenals	Brain (with Brainstem)	Heart
Kidneys	Liver with Drained Gallbladder	Large Intestine (Cecum and Colon)[a]
Lung	Ovaries	Pituitary
Prostate	Small Intestine (Duodenum, Jejunum, Ileum)[a]	Stomach
Testes With Epididymides	Thyroids with Parathyroids	Uterus with Cervix

[a] Rinsed with saline to remove ingesta/feces.

The following tissues (when present) from each animal were preserved in 10% neutral buffered formalin. All tissues from animals in Groups 1 and 4 sacrificed after 13 weeks of treatment were embedded in paraffin, sectioned, stained with haematoxylin and eosin, and examined microscopically. In addition, the kidneys, stomach, and small and large intestines from all animals in Groups 2 and 3, and from all recovery animals were examined microscopically.

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

[a] Preserved In Bouin's Fixative.

- PK/TK - Blood samples were obtained from the 4sex/group on Days 1, 28, 39, and 91 at 0.5, 1, 2, 3, 5, 7, and 12 hr post dose.

Results:

- Clinical Observation and mortality - All dogs survived to their scheduled sacrifice. Swollen feet and/or limbs were common findings in Group 4 dogs (3/7 ♂ & 5/7 ♀).
- Body Weights and Food Consumption - There were no treatment-related changes in mean body weights, body weight gains and food consumption were noted..
- ECG - No abnormalities were detected.
- Ophthalmoscopic Examination - The bilateral moderate optic nerve hypoplasia was noted in one Group 4 ♀ and it considered to be a nonchanging congenital condition as stated by the sponsor..
- Clinical Pathology - No test article-related changes in the hematology or coagulation parameters, serum chemistry, urine chemistry, and urinalysis were noted.
- Necropsy -
  Organ Weights: Comparable organ weights were recorded for each group at the terminal sacrifice animals. Significant ↑ the absolute and relative uterus and ovary weights were noted in Group 4 ♀ at the recovery sacrifice as results of normal menstrual cyclic activity in all three dogs.

Gross and Histopathology: No treatment-related gross or microscopic pathological findings were characterized at the terminal or recovery sacrifice.

- PK/TK - SC-65872 was absorbed and systemically available. The plasma C_{max} and $AUC_{0-12\ hr}$ values of SC-65872 and its active metabolite, SC-66905, increased with dose on Days 1, 28, 49, and 91. There was no gender differences in observed PK parameters for both SC-65872 and SC-66905. Higher AUC_{0-12} values for SC-66905 but not SC-65872 were noted on Days 28, 49, and 91. The mean plasma PK parameters for SC-65872 and SC-66905 are summarized in the below table.

Dose mg/kg/dose bid	N	SC-65872						SC-66905					
		T_{max} (hr)		C_{max} (μg/ml)		$AUC_{0-\infty}$ (μg•hr/ml)		T_{max} (hr)		C_{max} (μg/ml)		$AUC_{0-\infty}$ (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
DAY 1													
0.5	4	2	1	0.193	0.151	0.380	0.357	2	2	0.119	0.099	0.567	0.631
1	4	2	2	0.433	0.410	0.938	0.911	2	3	0.279	0.293	1.45	1.71
2	4	1	1	0.729	0.470	2.37	1.47	2	2	0.597	0.416	2.55	2. 5
DAY 28													
0.5	4	1	1	0.127	0.194	0.335	0.350	1	1	0.108	0.142	0.896	0.959
1	4	1	2	0.334	0.278	0.946	0.938	2	3	0.353	0.335	2.79	2.28
2	4	1	2	0.457	0.472	2.19	1.89	1	3	0.591	0.760	5.04	7.19
DAY 49													
0.5	4	1	0.5	0.153	0.159	0.377	0.338	2	2	0.138	0.141	1.02	0.773
1	4	1	2	0.340	0.311	1.01	0.825	3	2	0.370	0.335	2.93	2.32
2	4	2	1	0.518	0.640	2.81	1.95	5	2	0.593	0.750	5.88	7.25
DAY 91													
0.5	4	1	1	0.200	0.145	0.507	0.333	2	2	0.206	0.175	1.01	0.800
1	4	2	2	0.441	0.253	1.25	0.773	2	2	0.523	0.304	3.21	2.32
2	4	2	2	0.573	0.571	2.64	2.20	2	2	0.535	0.941	4.36	7.01

Therefore, MTD was not achieved in this study as no treatment-related effects on mortality, clinical observations, body weights, food consumption, clinical pathology or histomorphology were noted in the high-dose groups (4 mg/kg/day). NOAEL for SC-65872 was not established in this study.

2.2.3.6. Combined 26-Week and 52-Week Capsule Toxicity Study with a 4-Week Reversal with SC-65872 in Dogs (SA 4615); Date: 02-Feb-1998, Document No. P20S4615. (Vol. 1.64-67)

Study Nº: SA4615/6127-361
Report Nº: P20S4615 and M3097358 (PK)
Study Aims: To determine the chronic toxicity of SC-65872 when administered orally to dogs for 26 or 52 weeks and the reversibility of any effect following a 4-week recovery period.
Compound: [redacted]
Dose & Route: 0, 1.5, 3, and 7 mg/kg/dose bid po (~11 hr apart) for 26 or 52 weeks
Animals: 104 (52/sex) beagle dogs [redacted]
5-7 months of age, weighing 5.5-8.2 kg for ♂ and 4.8-7.6 mg/kg for ♀, 8-14/sex/group
Study Location: [redacted]
Study Date: 3/18/1997 (Start Dosing); 9/18/1997 (Interim Sacrifice); 10/17/1997 (Recovery Sacrifice)
GLP/QAU Compliance: Yes

Study Design: Neat SC-65872 was administered orally to dogs in a gelatin capsule at dosages of 0, 1.5, 3, and 7 mg/kg bid for 26 weeks with a 4-week recovery phase. The group assignments are presented in the following table.

Group	Dose		Nº of Dogs/Group[a]	
	mg/kg/dose	mg/kg/day	♂	♀
1 (Control)[b]	0	0	14	14
2 (Low)	1.5	3	8	8
3 (Mid)	3	6	8	8
4 (High)	7	14	14	14

[a] After ≥26 weeks of dosing, 4/sex/group in Groups 1-4 were sacrificed; an additional 3/sex/group in Groups 1 and 4 were sacrificed following a 4-week recovery period.

[b] The control group received the same number and size of capsules as the Group 4 (high dose) animals.

The following observations were conducted.

- Clinical Signs and Mortality - 2x/day.
- Physical Examination - Pre-R (Day 1), Weeks 13 and 26.
- Body Weights - Pre-R (Day 1), 1x/week for Weeks 1-14 and 1x/4 weeks thereafter; Weeks 27 and 31 (recovery animals) and at scheduled termination.
- Food Consumption - Pre-R (Day 1), 1x/week for Weeks 1-14 and 1x/4 weeks thereafter; Weeks 26 and 30 (recovery animals.
- EEG - Pre-R and Weeks 4, 13, and 26 1-4 hr post 1st daily dose. Leads I, II, III, aVR, aVL, aVF, rV_2, V_2, V_4, and V_{10} were recorded on non-sedated animals.
- Ophthalmoscopic Examinations - Pre-R and Week 26.
- Clinical Pathology - Pre-R and Weeks 7 (hematology only), 13, 26, and 30 (Groups 1 and 4 recovery animals; hematology and serum chemistry only). The following parameters as shown in the below table were analyzed.

Hematology						
aPTT	PT	Reticulocyte Count (Slides was prepared but not read)			RBC	Platelet Count
Ht	Hb	MCH	MCV	MCHC (Calculated)	WBC/Differential	Mean Platelet Volume

Blood Chemistry						
ALT	Albumin	A/G Ratio	ALP	AST	Calcium	Chloride
Creatinine	γ-GT	Globulin	Glucose	Inorganic Phosphorus	Potassium	Sodium
Total Bile Acids	Total Bilirubin	Total Cholesterol	Total Protein	Triglyceride	Urea Nitrogen	

Urinalysis				
Appearance	Bilirubin	Glucose	Ketones	Microscopic Examination of
Occult Blood	pH	Protein	Urobilinogen	Sediment

Urine Chemistry				
Osmality	Urine Creatinine	Creatinine Clearance	Urine Cl	Urine Cl Timed Excretion
Volume (~20 hr)	Urine Phosphorus	Urine Na	Urine K	Urine K Timed Excretion
Urine Phosphorus Timed Excretion		Urine Na Timed Excretion	Urine Ca	Urine Ca Timed Excretion

- PK/TK - Blood samples were collected on Days 1, 14, 30 and 182 at 0.5, 1, 2, 3, 5, 7, and 12 (prior to 2nd daily dose) hr post dosing. Plasma levels of SC-65872 and its active metabolite, SC-66905 were determined [redacted] The sensitivity of detection for an undiluted 300 μl plasma aliquot was 0.0100 μg for both SC-65872 and SC-66905.
- Necropsy - Weeks 27 (Groups 1-4, 4/sex/group) and 31 (recovery phase; Groups 1 and 4, 3/sex/group). Necropsy was performed on all terminal sacrifices and unscheduled deaths. The following organs as shown in the table were weighed and paired organs were weighed together.

Adrenals	Liver with Drained Gallbladder	Prostate	Thymus
Brain (with Brainstem)	Lung	Spleen	Thyroids with Parathyroids
Heart	Ovaries	Stomach[a]	Uterus with Cervix
Kidneys	Pituitary	Testes with Epididymides	

[a] Rinsed with saline to remove ingesta/feces.

The following tissues (when present) or representative samples from each animal were preserved in 10% phosphate-buffered formalin, unless otherwise specified. All tissues from Groups 1 and 4 scheduled sacrificed animals and from each unscheduled sacrificed animal were examined microscopically. In addition, the kidneys from all Groups 2 and 3 animals that were sacrificed at Week 27 were examined microscopically.

Adrenals	Gallbladder	Pancreas	Lesions
Aorta	Heart	Pituitary	Testes with Epididymides[b]
Bone Marrow (Sternum)	Kidneys	Prostate	Thymus
Brain with Brainstem	Salivary Glands (Mandibular)		Thyroid with Parathyroids
Colon, Cecum, Rectum	Liver	Sciatic Nerve	Tongue
Duodenum, Jejunum, Ileum	Lungs	Skeletal Muscle	Trachea
Esophagus	Stomach (Pyloric and Fundic Regions)		Urinary Bladder
Lymph Nodes (Mesenteric and Retropharyngeal)		Spinal Cord (Cervical, Mid-Thoracic, and Lumbar)	
Eyes[a]	Mammary Gland (♀)	Skin	Uterus with Cervix
Femur with Bone Marrow	Ovaries	Spleen	Vagina

[a] Preserved in Davidson's fixative; [b] Preserved in Bouin's fixative.

- Electron Microscopy - Specimens from the outer cortex of the left kidney of 4 Group 1 and 3 Group 4 animals at the week 53 sacrifice were subjected to electronic microscopic evaluations.
- Special Stains - Renal cortical lesions in 3/sex Group 4 and kidneys from 1/sex Group 1 animals were evaluated by histochemical and immunohistochemical stains. Histochemical stains included: [redacted] stains to identify potential intralesional bacteria; [redacted] stains for interstitial and vascular connective tissue proliferation; periodic acid methenamine silver (PAMS) for outlining basement membranes, and Congo red for identification of amyloid deposition. Immunohistochemical stains included COX-1 and COX-2 for identification of cyclooxygenase isoforms, Smooth Muscle Actin (SMA) and Factor-VIII (F-VIII) for evaluation of blood vessels, and Proliferating Cell Nuclear Antigen (PCNA) to assess proliferation of tubular epithelial cells.
- Urinary Prostaglandin Analysis - Urine samples collected at Weeks 52 and 56 were analyzed for PGE_2, 6-keto-prostaglandin F1α (6-keto-PGF-1α), and 2, 3 diphosphoglycerol (2,3 DPG) by [redacted] and 11-dehydro-thromboxane B_2 [redacted]

Results:

- Clinical Signs and Mortality - Two dogs (1 each ♀ @ 6 and 14 mg/kg/day) were sacrificed in a moribund condition on Day 45 due to large, ulcerated skin sores with abscesses in the muscular tissue. Red or black discolored feces were identified in dogs @ 6 and 14 mg/kg/day. One high dose ♂ had melena on Day 40, was removed from treatment on Day 41 and was subsequently sacrificed followed by a 10-week recovery period. Higher incidences of pale gums and diarrhea were seen in SC-65872 treated dogs. Male dogs @ 6 and 14 mg/kg/day had higher incidence of swollen gums and feet. A dose-dependent increase in skin sores (particularly noted on the feet/limbs and/or the ventral surface of the body) was observed in the SC-65872 treated dogs and some of these observations required prescribed treatment. Aggressive topical treatment included cleansing the affected areas with soap and water and/or a betadine surgical scrub solution, rinsing with tap water and drying with paper towels, followed by spraying the area with betadine or hydrogen peroxide. In some of the more severe cases required topical (Bacitracin® [redacted] 2-3x/day) or systemic (Penicillin G Procaine® or [redacted] im bid for 4-7 days) antibiotic

interventions. Only dogs (2♂ & 2♀) @ 14 mg/kg/day had received systemic antibiotics. The incidence of clinical observations of swollen areas and skin sores for each group is summarized in the following table.

Skin Appearance	Dose (mg/kg/day)							
	0		3		6		14	
	♂	♀	♂	♀	♂	♀	♂	♀
Swollen Skin/Pelage	0	2	0	3	2	4	5	4
Sore(s)	5	5	4	5	8	7	13	13

- Cytological Evaluation and Bacterial Isolation - Cytological evaluations of the aspirate (neck area) from a ♂ @ 14 mg/kg/day revealed elevated leukocytes, mostly neutrophils, an indicative of an infectious process. Culture swabs were also taken from affected skin areas. The following table shows bacterial isolates identified in some dogs @ 6 and 14 mg/kg/day.

Dose Group (mg/kg/day)	Animal ID	Sampling Day	Location of Swab Sampling	Bacterial Isolates
14	G34062 (♂)	45	Chest	*Lactobacillus spp.* and *Staphylococcus intermedius*
			Neck	*Staphylococcus aureus*
14	G34115 (♀)		Chest	No Growth.
			Neck	No Growth.
6	G34100 (♀)		Neck	No Growth.
			Shoulder	*Proteus mirabilis* and *Streptococcus bovis*
14	G34104 (♀)	55	Mandibular	*Pseudomonas putida, Enterococcus faecalis*, and *Enterococcus casseliflavus.*

- Body Weights and Food Consumption - Comparable mean body weights were recorded during the study. However, significant lower body weight changes were noted in high-dose ♂ during Weeks 1-4 and 7 (38%-100%) and high dose ♀ during Week 2 (↓200%). Increased weight change by 37.5% was observed in Group 2 ♀ during Week 7. Sporadic changes in mean food consumption values were seen, such as ↑ mean values by 20% in ♂ of Groups 1 and 4 during Week 9 and ↓ mean values by 19% in Group 3 ♀.
- EEG - No anomalies were identified.
- Ophthalmoscopic Examinations - There were no treatment-associated findings. Some changes with characteristics of unilateral focal anterior subcapsular cataract in the lens (OS), unilateral focal persistent papillary membrane in the iris/anterior chamber (OS), and unilateral focal persistent hyaloid remnant in the vitreous (OS) were identified in three control dogs on Day 177 (Week 26) during ophthalmoscopic evaluations.
- Clinical Pathology - Dose dependent ↓ (5-17%) in RBC, HB, and Ht with slightly ↑ (1-3%) MCH values were identified in SC-65872 treated dogs at Weeks 7, 13, 26, 39, and 52. There were some minor but not biological meaning changes in the leukogram. Groups 3 (1.6x for both ♂ & ♀) and 4 (~3x for ♂ and ~2x for ♀) dogs had significant higher BUN values at Weeks 13, 26, 39 and 52. Slightly elevated creatinine values (1.1-1.2 vs 0.8-0.9 in the controls) were noted in ♂ dogs @ 14 mg/kg at Weeks 13, 26, 39 and 52.
- PK/TK - SC-65872 was absorbed and systemically. It appeared that the plasma SC-65872 and SC-66905 $AUC_{0\text{-}12hr}$ and C_{max} values were linear and dose proportional. The plasma $AUC_{0\text{-}12hr}$ values for SC-65872 and SC-66905 were higher on Day 182 than on Days 1, 14 and 30, an indicative of accumulation. The following table shows mean PK parameters for SC-65872 and SC-66905 on Days on Days 1, 14, 30 and 182.

Dose (mg/kg)	N		SC-58672						SC-66905					
			T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-12} (μg•hr/ml)		T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-12} (μg•hr/ml)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
DAY 1														
1.5	8	8	2	2	0.643	0.667	1.47	1.37	2	2	0.526	0.609	1.96	1.79
3.0	8	8	2	2	1.36	1.13	3.42	2.99	2	2	0.888	0.726	3.68	4.17
7.0	14	14	2	2	2.02	1.41	5.92	4.02	2	2	1.47	1.15	8.00	5.91
DAY 14														
1.5	3	3	1	2	0.588	0.378	1.55	1.02	2	2	0.633	0.431	3.10	2.79
3.0	3	3	2	2	1.77	1.45	5.01	6.47	2	2	1.48	1.68	9.08	13.5
7.0	3	3	2	2	2.42	1.79	13.5	8.17	1	2	4.20	2.66	35.8	20.3
DAY 30														
1.5	4	4	1	2	0.516	0.388	1.48	1.06	4	4	0.531	0.312	3.34	2.65
3.0	4	4	2	2	1.16	1.07	4.35	4.79	4	4	1.26	1.00	9.33	9.79
7.0	7	7	2	2	1.94	2.10	11.4	10.9	2	2	2.99	2.77	29.6	21.4
DAY 182														
1.5	4	4	1	2	0.717	0.584	2.39	1.69	2	2	0.622	0.506	3.77	4.17
3.0	4	4	2	2	1.42	1.22	6.05	5.58	2	2	1.27	1.43	9.81	12.5
7.0	7	7	2	2	3.56	2.71	20.9	16.6	2	2	3.60	3.31	28.5	28.5

- Gross and Histopathology -

  Organ Weights: There were no treatment-related changes in absolute and relative organ weights.

  Unscheduled Death/Sacrifice: There were 3 unscheduled sacrifices. One each ♀ @ 6 and 14 mg/kg/day were sacrificed on Day 45 due to ulcerated skin lesions with characteristics of acute suppurative inflammation and edema. No drug-caused GI toxicity was observed in these two ♀. One ♂ @ 14 mg/kg/day had signs of melena on Day 41 and was removed from the treatment. This dog was subsequently sacrificed after a 10-week recovery period. Morphological changes of moderately severe chronic inflammation and tubular atrophy with fibrosis in the left kidney without treatment-related GI lesions were characterized in this dog.

  Interim Sacrifice (Week 27, 4/sex/group) and Interim Recovery Sacrifice (Week 31, 3/sex from Groups 1 and 4):: Treatment-related histopathological changes were limited to the kidney (minimal→moderate tubular atrophy with necrosis). The incidence and severity of renal lesions for each group is presented in the following table. The observed lesions were primarily located in the outer cortex (subcapsular) and, in the more severe cases, were accompanied by glomerular atrophy, fluid in [redacted] tubule dilatation, and slight thickening of vessel walls in small cortical blood vessels in areas of moderate tubular atrophy with fibrosis. Generally, <5% of the renal parenchyma was involved.

Tubular Atrophy with Fibrosis	Week	0		3 mg/kg/day		6 mg/kg/day		14 mg/kg/day	
		♂	♀	♂	♀	♂	♀	♂	♀
Unremarkable	27	4	4	4	4	0	1	0	0
Minimal		0	0	0	0	1	3	1	2
Slight		0	0	0	0	3	0	2	1
Moderate		0	0	0	0	0	0	1	1
Mean Severity Grade		0.0	0.0	0.0	0.0	1.8	0.8	2.0	1.8
Unremarkable	31	3	3					0	0
Minimal		0	0					1	2
Slight		0	0					1	1
Moderate		0	0					1	0
Mean Severity Grade		0.0	0.0					2.0	1.3

  Terminal and Recovery Sacrifice: No gross lesions were observed. Treatment-related microscopic changes of renal tubular atrophy and necrosis were identified in dogs @ 6 and 14 mg/kg/day.

These findings were also identified in the interim sacrificed dogs. The incidence and severity of renal lesions for each group is presented in the following table.

Tubular Atrophy with Fibrosis	Week	0		3 mg/kg/day		6 mg/kg/day		14 mg/kg/day	
		♂	♀	♂	♀	♂	♀	♂	♀
Unremarkable	53	4	4	4	4	0	1	0	0
Minimal		0	0	0	0	3	2	0	0
Slight		0	0	0	0	1	0	2	3
Moderate		0	0	0	0	0	0	1	0
Mean Severity Grade		0.0	0.0	0.0	0.0	1.3	0.7	2.3	2.0
Unremarkable	57	3	3					0	0
Minimal		0	0					0	2
Slight		0	0					1	1
Moderate		0	0					2	0
Mean Severity Grade		0.0	0.0					2.7	1.3

- Electron Microscopy - No test article-related ultrastructural changes were observed in the electron micrographs.
- Special Stains -

  Histochemical Stains: Results from various histochemical stains revealed absence of bacteria [redacted] or amyloid deposition [redacted] in the renal cortical lesions. A slight increase in interstitial fibrous connective tissue and outlined small blood vessels within the lesions was identified.

  Immunohistochemical Stains: COX-2 expression was markedly increased in the macula densa and thick ascending limbs of loop of [redacted] in all SC-65872-treated animals (sacrificed at or before 26 weeks of dosing) as compared with the control. The COX-2 immunoreactivity in SC-65872-treated animals returned to approximately normal levels following a 4-week recovery period. No change in COX-1 immunoreactivity was observed in SC-65872 treated or control animals. PCNA positive tubular epithelial cells were present in both control and SC-65872-treated animals. However, a slight ↑ in the number of PCNA positive cells was noted in SC-65872-treated animals.
- Urinary Prostaglandin Analyses - No test treatment-related changes in urinary excretion of 11-dehydrothromboxane B_2 were observed. However, treatment of SC-65872 caused a decrease in urinary excretion of PGE_2 and 6-keto-PGF-1α by 26 to 71% as shown in the following table. The suppression of urinary excretion of 6-keto-PGF-1α and PGE_2 was nearly reversible in ♂ following a 4-week recovery period (Week 56).

Dose (mg/kg/day)	Sampling Time	6-keto PGF-1α (pg/ml)		PGE_2 (pg/ml)	
		♂	♀	♂	♀
0	Week 52	170.00 ± 95.79	281.19 ± 121.16	2077.00 ± 871.97	2467.14 ± 1522.51
1.5		126.58 ± 114.85 (↓26%)	81.48 ± 31.24 (↓71%)	1030.50 ± 267.83 (↓50%)	1672.50 ± 442.07 (↓32%)
3.0		59.53 ± 25.82 (↓65%)	86.73 ± 80.06 (↓69%)	1302.00 ± 740.39 (↓37%)	942.67 ± 261.33 (↓62%)
7.0		96.62 ± 121.27 (↓43%)	89.28 ± 78.75 (↓68%)	802.50 ± 352.25 (↓61%)	927.67 ± 261.33 (↓62%)
0	Week 56	232.37 ± 233.52	402.00 ± 292.72	1846.67 ± 2196.12	3160.00 ± 1353.37
7.0		260.00 ± 50.27 (↑12%)	101.50 ± 70.34 (↓75%)	1427.33 ± 453.79 (↓23%)	1840.00 ± 1401.82 (↓42%)

Therefore, the NOAEL was 3.0 mg/kg/day for SC-65872 as treatment-related lesions of skin sores, discolored feces, and renal tubular atrophy with fibrosis were noted in dogs @ 6 and 14 mg/kg/day. The overall incidence of SC-65872-treatment related findings is summarized in the following table.

Findings	0 mg/kg/day	3 mg/kg/day	6 mg/kg/day	14 mg/kg/day
Skin Sores	10	9	15	26
Discolored feces (red/black)	0	0	3	3
Renal tubular atrophy with fibrosis	0	0	14	27

2.2.4. MONKEY STUDIES

2.2.4.1. Two-Week Oral Range-Finding Toxicity Study of SC-65872 in Cynomolgus Monkeys, SA4901; Date: 10-Aug-2000, Document No. P20S4901. (Vol. 1.54)

Study Nº: SA4901/Sbi 0757-26
Report Nº: P20S4901/M3099100 & M2099403 (PK)
Study Aim: To determine the potential toxicity of SC-65872 when orally administered twice daily to cynomolgus monkeys for 14 days.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 30, 60, and 120 mg/24 ml/kg bid po
Dosing Frequency: bid (1-14 hr apart) for 14-day
Animals: 10♂ + 10♀ naive cynomolgus monkeys, 2-6 years of age, weighing 2.2-4.1 kg for ♂ and 1.7-2.4 kg for ♀.
Study Location: [redacted]
GLP/QAU Compliance: Yes.
Study Date: 3/8-9/1999 - 3/23/1999
Study Design: Animals were assigned to treatment groups as shown in the table below and given either vehicle control or SC-65872 by oral gavage 2x/day for 14 days.

Group	Dosage (mg/kg/dose)	Dose (mg/kg/day)	Dose Vol. (ml/kg)	Doing/Frequency/ Duration	Nº/Sex/Group
1	0	0	24	bid for 2-week	2/2
2	30	60			4/4
3	60	120			2/2
4	120	240			2/2

The following parameters were monitored.

- Mortality and Clinical Signs - 2x/day.
- Body Weights - Pre-Rx and Days 1, 4, 7, and 14.
- Food Consumption - 1/day, visual assessment.
- Clinical Pathology - Pre-Rx and Days 6 and 14. The following parameters were analyzed.

SERUM CHEMISTRY			
Sodium	Indirect Bilirubin	Calcium	Total Protein
Potassium	Alkaline Phosphatase (AP)	Phosphorus	Albumin
Chloride	Lactate Dehydrogenase (LDH)	Glucose	Globulin
Carbon Dioxide (CO_2)	Aspartate Aminotransferase (AST)	Urea Nitrogen (BUN)	Albumin/Globulin Ratio
Total Bilirubin	Alanine Aminotransferase (ALT)	Creatinine	Cholesterol
Direct Bilirubin	Gamma-Glutamyltransferase (γGT)	Uric Acid	Triglycerides
HEMATOLOGY/COAGULATION			
RBC	WBCs/Differential	Hematocrit (Ht) MCV	MCH MCHC
Reticulocyte Counts	Hemoglobin (Hb)	Blood Cell Morphology	Platelet Counts
Fibrinogen	Activated Partial Thromboplastin Time (aPTT)		Prothrombin Time (PT)
URINALYSIS			
Color/Character	Urobilinogen	Glucose	Sodium Chloride
pH/Specific Gravity	Creatinine	Ketones	Occult Blood
Nitrite	Potassium	Bilirubin	Quantitative Protein
Leukocyte Esterase	Phosphorus	Protein	Microscopics*

* Microscopic examination was not performed if the specimen was clear and negative for protein, blood, nitrite and leukocyte esterase

Creatinine clearance was determined prestudy and in Week 2. Serum and urine creatinine values were used for the creatinine clearance calculations.

- PK/TK - Days 1 and 14. Blood was collected at 0.5, 1, 2, 3, 5, 8, and 12 hr post dosing.
- Necropsy - Day 15. The following organs when present were weighed before fixation. Paired organs were weighed together unless gross abnormalities were present, in which case they were weighed separately. The pituitary was weighed post fixation.

Adrenals	Brain	Heart	Kidneys	Ovaries	
Testes	Thymus	Liver	Thyroid w/ Parathyroids	Pituitary (Post Fixation)	

The following tissues and organs (or portions of) when present, from all animals sacrificed were collected and preserved in neutral buffered 10% formalin (except for the eyes, which were preserved in 3% glutaraldehyde solution for optimum fixation). A bone marrow smear was collected from the seventh rib at all necropsies. The tissues listed in the below table (except tattoos) from each groups were examined microscopically. A bone marrow smear was collected from the seventh rib of all animals and was not examined.

Tissues and Organs Collected and Preserved						
Aorta	Heart		Testes		Urinary Bladder	
Salivary Gland (Mandibular)	Trachea	Lung	Seminal Vesicles		Bone - Femoral Head, 7th Rib	
Tongue	Kidney		Ovaries	Uterus	Skeletal Muscle (Thigh)	
Esophagus	Bone Marrow (Sternum)		Cervix	Vagina	Eyes w/ Optic Nerve	
Stomach	Lymph Nodes - Mandibular, Mesenteric				Sciatic Nerve	
Small Intestine - Duodenum, Jejunum, Ileum			Adrenals		Brain	
Large Intestine - Cecum, Colon, Rectum			Pituitary		Spinal Cord (Thoracic)	
Pancreas	Spleen	Thymus	Thyroid/Parathyroids		Gross Lesions	
Liver Gallbladder	Epididymis	Prostate	Skin/Mammary Gland		Animal Number Tattoo	

- Liver Enzymes - A portion (~40 g) of the liver was collected from a similar location in each animal and flash frozen in liquid nitrogen. The samples were analyzed for cytochrome P450 and total protein content by [redacted] Post-mitochondrial supernatant and microsomal fractions were prepared . The post-mitochondrial supernatants were analyzed for total protein concentration. The microsomal fractions were analyzed for the following parameters:
  - Total Protein and Total Cytochrome P450;
  - Ethoxycoumarin O-Deethylase (ECOD);
  - Ethoxyresorufin O-Deethylase (EROD, CYP1A);
  - Testosterone 6β-Hydroxylase (6β-OH, CYP3A);

- Testosterone 16 β-Hydroxylase (16β-OH, CYP2B);
- Coumarin 7-Hydroxylase (COH, CYP2A); and
- p-Nitrophenol Hydroxylase (PNP, CYP2E).

Results:

- Mortality and Clinical Signs - No deaths occurred. Clinical signs of emesis, decreased activity, hunched appearance, tremor, lethargy, and/or decreased skin turgor were noted in animals @ 60, 120, or 240 mg/kg/day.
- Food Consumption - Reduced (low) food consumption was observed in Groups 1-4 with incidence of 2, 11, 15, and 18, respectively.
- Body Weights - Body weight loss (0.1-0.3 kg) was noted in 2 each @ 120 and 240 mg/kg. The decreases in body weights were likely due to reduced food consumption and emesis.
- Clinical Pathology - One ♂ @ 120 mg/kg had elevated ALT (5.5x of pre-study value). Slightly elevated BUN values (↑1.5-4.8x) with increased creatinine (~1.5x) were noted in some animals @ ≥120 mg/kg. A slight but dose-dependent decrease in RBC (↓15-25%) with decreases in hemoglobin and hematocrit (↓14-25%) and reduced platelet count (↓15-58%) were observed in animals @ 60, 120, and 240 mg/kg. These changes were secondary to GI blood loss.
- PK/TK - SC-65872 was absorbed and systemically available. Accumulation of SC65872 occurred following repeated dosing as higher mean C_{max} and AUC_{0-12} values for SC-65872 on Day 14 than those on Day 1 were observed.

Dose (mg/kg/dose) bid		SC-65872						SC-66905					
		T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-12} (μg•hr/ml)		T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-12} (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Day 1	30	2	1	8.94	6.22	44.9	28.8	1	1	0.983	0.592	3.26	2.22
	60	2	2	10.2	15.1	78.6	81.9	2	2	0.465	1.16	2.74	4.17
	120	2	2	9.87	20.9	77.1	177	2	2	1.87	1.53	7.63	8.86
Day 14	30	2	2	14.9	13.7	118	107	3	2	0.508	0.471	3.10	2.80
	60	3	2	29.9	23.4	308	230	3	3	0.892	1.40	6.83	8.28
	120	2	1	44.4	44.2	479	437	2	2	2.01	1.41	20.3	13.4

- Macro- and Histological Findings - Treatment-related pathological changes were limited to GI with characteristics of focal areas of mucosal erosion or ulceration, inflammation, fibrosis, and hemorrhage. The incidence of these findings is presented in the following table. Enlarged lymph nodes with microscopic findings of lymphohistiocytic hyperplasia in the lymph nodes and spleen were noted in Groups 3 and 4.

Histological Findings of GI Lesions		Control (N=2/sex)	60 mg/kg (N=4/sex)	120 mg/kg (N=2/sex)	240 mg/kg (N=2/sex)
Stomach	- *minimal→mild erosion*	1♂	-	1♀	1♀
	- mild→moderate ulceration	-	-	-	2♀
Jejunum	- moderate erosion			1♂	
Duodenum	- moderate ulceration			2♀	1♂+1♀

- Effects on Hepatic Enzyme, P450 - The presented data were inconclusive due to the small sample size and high variability among animals.

Therefore, the NOAEL was 60 mg/kg/day for this study based on treatment-related GI pathological findings.

2.2.4.2. Four-Week Toxicity Study of SC-65872 Administered Orally to Cynomolgus Monkeys, EX4809; Date: 06-Oct-1999, Document No. P20E4809. (Vol. 1.55)

Study Nº: EX4809

Report Nº: P20E4809/M3098370 (PK)
Study Aim: To determine the potential toxicity of SC-65872 when administered twice daily by the oral route to cynomolgus monkeys for 28 days.
Compound:
Vehicle Control:
Dose & Route: 0, 3, 7, and 14 mg/5 ml/kg po bid (~10-14 hr apart).
Dosing Frequency: bid for 28-day
Animals: Cynomolgus monkeys ~3-7 years of age, weighing 2.4-3.7 kg for ♂ and 2.1-3.0 kg for ♀; 2/sex/group
Study Location:
GLP/QAU Compliance: Yes
Study Date: 5/28/1998 - 6/26/1998
Study Design: Groups of 2 monkeys/sex were randomly assigned to receive either vehicle or SC-65872 at dose levels of 3, 7, or 14 mg/kg 2x/day via nasogastric gavage for 28 days as shown in the following table.

Group	Dose Level (mg/kg/day)	Dose (mg/kg/dose)	Dose Vol. (ml/kg/day)	Route/Duration	Nº/Group
1	0	0	10	po for 28-day	2/sex
2	6	3	10		2/sex
3	14	7	10		2/sex
4	28	14	10		2/sex

The following parameters were monitored.

- Mortality and Clinical Signs - 2x/day.
- Body Weights - 1x/week.
- Clinical Pathology and Renal Clearance Determination - Weeks 1, 2, and 4. Creatinine (absolute and relative to body weight) and inulin and p-aminohippuric acid (PAH) clearances were determined. Serum and urine creatinine values were used for the creatinine clearance calculations[1]. For inulin and PAH clearance, blood and urine samples were taken at various timepoints o.5, 1.5, 2.5, 3.5, and 4.5 hr) during a constant infusion of inulin and PAH. Inulin and PAH samples were analyzed. The following parameters were analyzed. Analysis of N-acetyl-β-glucosaminidase (NAG) and β2-microglobulin were performed

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[1] CLcreatinine = [(Urine Creatinine) X (Urine Volume)/1440 minutes]/Serum Creatinine

Serum Chemistry				
Sodium	Indirect Bilirubin	Calcium	Total Protein	
Potassium	Alkaline Phosphatase (AP)	Phosphorus	Albumin	
Chloride	Lactate Dehydrogenase (LDH)	Glucose	Globulin	
Carbon Dioxide (CO_2)	Aspartate Aminotransferase (AST)	Urea Nitrogen (BUN)	Albumin/Globulin Ratio	
Total bilirubin	Alanine Aminotransferase (ALT)	Creatinine	Cholesterol	
Direct bilirubin	Gamma-Glutamyltransferase (γGT)	Uric Acid	Triglycerides	
Hematology/Coagulation				
RBC	WBCs/Differential	MCV	MCHC	
Reticulocyte Counts	Hemoglobin	MCH	Platelet Counts	
Hematocrit	Blood Cell Morphology	aPTT	PT	
Urinalysis				
Color/Character	Urobilinogen	Glucose	Sodium	Chloride
pH/Specific Gravity	Creatinine	Ketones	Occult Blood	
Nitrite	Potassium	Bilirubin	Quantitative Protein	
Leukocyte Esterase	Phosphorus	Protein	Microscopics*	
11-Dehydro-TXB_2	N-Acetyl-β-glucosaminidase (NAG)	β2-Microglobulin	PGE_2	6-keto-$PGF_1\alpha$

* Microscopic examination was not performed if the specimen was clear and negative for protein, blood, nitrite and leukocyte esterase.

- PK/TK - Days 1 and 28. Blood samples were collected at 0.5, 1, 2, 3, 5, 8, and 12 hr after the 1st daily dose (prior to the next dose).
- Necropsy - Day 29. The following organs when present were weighed before fixation. Paired organs were weighed together unless gross abnormalities were present, in which case they were weighed separately. The pituitary was weighed post fixation.

Adrenals	Brain	Lungs	Kidneys	Ovaries
Epididymides	Heart	Pituitary (Post Fixation)	Liver	
Testes	Thymus	Thyroid w/ Parathyroids	Spleen	

The following tissues and organs (or portions of) when present, from all animals sacrificed were collected and preserved in neutral buffered 10% formalin (except for the eyes, which were preserved in 3% glutaraldehyde solution for optimum fixation). A bone marrow smear was prepared from the 7th rib of each animal. The tissues listed in the below table (except tattoos) from control and high-dose groups were examined microscopically. One half of each kidney was preserved for histopathology (and subsequent immunohistochemistry). For the remaining half of the left kidney, the cortex, medulla and papilla were removed and frozen separately. The remaining half of the right kidney was used for *in situ* hybridization to determine COX-1 and COX-2 mRNA expression.

Tissues and Organs Collected and Preserved						
Aorta	Heart		Testes		Urinary Bladder	
Salivary Gland (mandibular)	Trachea	Lung	Seminal Vesicles		Bone - Femoral Head, 7th Rib	
Tongue	Kidney		Ovaries	Uterus	Skeletal Muscle (Thigh)	
Esophagus	Bone Marrow (Sternum)		Cervix	Vagina	Eyes w/ Optic Nerve	
Stomach	Lymph Nodes - Mandibular, Mesenteric				Sciatic Nerve	
Small Intestine - Duodenum, Jejunum, Ileum			Adrenals		Brain	
Large Intestine - Cecum, Colon, Rectum			Pituitary		Spinal Cord (Thoracic)	
Pancreas	Spleen	Thymus	Thyroid/Parathyroids		Gross Lesions	
Liver	Gallbladder	Epididymis	Prostate	Skin/Mammary Gland		Animal Number Tattoo

Results:

- Mortality and Clinical Signs - No mortality occurred. No remarkable clinical signs were recorded.
- Body Weights and Food Consumption - No treatment-related changes were noted.
- Clinical Pathology - A slight increase in BUN (~1.5x of the pre-study value) was noted in Group 4 animals.

- PK/TK - SC-65872 was absorbed and systemically available. C_{max} and AUC values of SC-65872 and SC-66905 increased with doses. Higher C_{max} and AUC values of SC-65872 were noted on Day 28 as compared with those obtained on Day 1, an indication of accumulation after repeated dosing with SC-65872 as shown in the following table.

Day	Dose (mg/kg/day) bid	SC-65872						SC-66905					
		T_{max} (hr)		C_{max} (µg/ml)		AUC_{0-12} (µg•hr/ml)		T_{max} (hr)		C_{max} (µg/ml)		AUC_{0-12} (µg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	6	1	1	1.13	1.48	4.21	4.42	1	1	0.0630	0.0965	0.242	0.356
	14	2	2	1.45	2.75	5.82	10.7	2	2	0.107	0.309	0.477	1.37
	28	3	2	3.91	3.80	21.3	15.2	5	2	0.350	0.469	2.44	2.02
28	6	2	1	1.14	1.51	6.06	5.03	2	1	0.0495	0.212	0.230	1.06
	14	0.5	3	3.24	3.25	11.8	16.2	0.5	2	0.144	0.249	0.705	1.35
	28	2	2	8.03	12.0	49.2	81.0	3	3	0.366	0.461	2.60	3.04

Both SC-65872 and SC-66905 were detectable in the renal cortex, medulla and papilla. The levels of SC-66905 were generally lower those of SC-65872.

- Macro- and Micro-scopic Findings - There were no remarkable changes in organ weights. No treatment-related gross or histologic findings were identified.
- COX-1 and COX-2 mRNA Expression in Kidney - There were no significant effects on renal COX-1 immunoreactivity in all dose groups or COX-2 immunoreactivity in Group 2 animals following SC-65872 treatment. A positive COX-2 immunoreactivity was observed in the macula densa and thick ascending limb (TAL) of loop of Henle in two Group 3 and all Group 4 animals and in papillary interstitial cells in three Group 4 animals. Similarly, results from the in-situ hybridization assay for COX-2 revealed the presence of COX-2 mRNA in the macula densa of several SC-65872-treated animals and none in the control animals. COX-1 mRNA was detected in the papillary collecting ducts with similar intensity between control and SC-65872 treated animals. The findings of COX-2 mRNA expression in the macula densa and TAL indicated a slight induction of COX-2 in non-human primate kidneys following animals treated with SC-65872 @ doses ≥14 mg/kg. The biological significance of induction of COX-2 mRNA expression following treatment with SC-65872 is not clear.

Therefore, the MTD was not achieved as no remarkable changes in body weight, clinical pathology parameters, and macro/micro pathology were found in all SC-65872 treated groups.

2.2.4.3. A 12-Month Oral Toxicity Study of SC-65872 in Cynomolgus Monkey with a One-Month Recover Period; Date: 26-Oct-2000, Document No. P20S4900. (Vol. 1.68-70) Appendix: M3099241

Study Nº: SA4900/SBI 0763-26
Report Nº: P20S4900/M3099241 (PK/TK)
Study Aim: To characterize the potential toxicity of SC-65872 after 3 or 12 months of twice daily administration by nasogastric gavage to Cynomolgus monkeys (*Macaca fascicularis*)
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 5, 15, or 45 mg/3 ml/kg/day (2.5, 7.5, or 22.5 mg/kg, bid) administered twice daily (10-14 hours apart) po
Dosing Frequency: 2x/day
Animals: Cynomolgus monkeys (*Macaca fascicularis*) [redacted] 2-5 years of age, weighing 2.3-3.7 kg for ♂ and 2.2-3.3 kg for ♀; 6-10 sex/group.

Study Location: [redacted]
GLP/QAU Compliance: Yes
Study Date: 4/15/1999 - 5/11/2000
Study Design: Dosages were selected based on a two-week range-finding study in the cynomolgus monkey, in which GI toxicity was noted at ≥120 mg/kg/day. Groups of monkeys were given control or SC-65872 at various dosages as shown in the following table 2x/day via nasogastric gavage for 90 or 360 consecutive days.

Group	Dose (mg/kg/day)	Dose (mg/kg/dose)	N°/Sex/Group	Sacrificed (Day)			
				91	121[a]	361	391[a]
1	0	0	10	3/sex	2/sex	3/sex	2/sex
2	5	2.5	6		-		-
3	15	7.5	6		-		-
4	45	22.5	10		2/sex		2/sex

[a] Sacrificed after a 4-week recovery period.

The following observations were conducted.

- Mortality and Clinical Signs - 2x/day.
- Body Weights - Pre-R (Day -1) and 1x/week.
- Food Consumption - Qualitatively assessed.
- ECGs (Leads I, II, III, aVR, aVL, aVF) - Day 1, Weeks 12, 17, 51, and 56. ECG recordings were evaluated by a consulting cardiologist, [redacted]
- Ophthalmic Examinations - Day 1, Weeks 12, 17, 51, and 56.
- Clinical Pathology and Creatinine Clearance - Weeks 4, 8, 13, 17, 26, 39, 51, and 56. The following parameters were analyzed. Creatinine clearance (absolute and relative to body weight) was determined. Serum and urine creatinine values were used for the creatinine clearance calculations.

Serum Chemistry			
Sodium	Indirect bilirubin	Calcium	Total protein
Potassium	Alkaline Phosphatase (AP)	Phosphorus	Albumin
Chloride	Lactate Dehydrogenase (LDH)	Glucose	Globulin
Carbon Dioxide (CO_2)	Aspartate Aminotransferase (AST)	Urea nitrogen (BUN)	Albumin/globulin ratio
Total bilirubin	Alanine Aminotransferase (ALT)	Creatinine	Cholesterol
Direct bilirubin	Gamma-Glutamyltransferase (γGT)	Uric acid	Triglycerides
Hematology/Coagulation			
RBC	WBCs/Differential	MCV	MCHC
Reticulocyte Counts	Hemoglobin	MCH	Platelet counts
Hematocrit	Blood Cell Morphology	aPTT / PT	Fibrinogen
Urinalysis			
Color/Character	Urobilinogen	Glucose	Sodium / Chloride
pH/Specific Gravity	Creatinine	Ketones	Occult Blood
Nitrite	Potassium	Bilirubin	Quantitative Protein
Leukocyte Esterase	Phosphorus	Protein	Microscopics*

* Microscopic examination was not performed if the specimen was clear and negative for protein, blood, nitrite and leukocyte esterase.

- PK/TK - Days 1, 90, 180, and 360. Blood was collected at 0.5, 1, 2, 3, 5, 8, and 12 hr after the 1st daily dose (prior to the next dose).
- Necropsy - Days 91 (Groups 1-4: 3/sex), 161 (Recovery Sacrifice; Groups 1 and 4: 2/sex), 361 (Groups 1-4: 3/sex), and 391 (Recovery Sacrifice; Groups 1 and 4: 2/sex). The following organs when present were weighed before fixation. Paired organs were weighed together unless gross abnormalities were present, in which case they were weighed separately. The pituitary was weighed post fixation.

Adrenals	Brain	Lungs	Kidneys	Ovaries
Epididymides	Heart	Pituitary (Post Fixation)	Liver	
Testes	Thymus	Thyroid w/ Parathyroids	Spleen	

The following tissues and organs (or portions of) when present, from all animals sacrificed were collected and preserved in neutral buffered 10% formalin (except for the eyes, which were preserved in 3% glutaraldehyde solution for optimum fixation). A bone marrow smear was collected from the seventh rib at all necropsies. For all animals necropsied, the tissues listed in the below table (except tattoos) were examined microscopically.

Tissues and Organs Collected and Preserved						
Aorta		Heart		Testes		Urinary Bladder
Salivary Gland (Mandibular)		Trachea	Lung	Seminal Vesicles		Bone - Femoral Head, 7th Rib
Tongue		Kidney		Ovaries	Uterus	Skeletal Muscle (Thigh)
Esophagus		Bone Marrow (Sternum)		Cervix	Vagina	Eyes w/ Optic Nerve
Stomach		Lymph Nodes - Mandibular, Mesenteric				Sciatic Nerve
Small Intestine - Duodenum, Jejunum, Ileum				Adrenals		Brain
Large Intestine - Cecum, Colon, Rectum				Pituitary		Spinal Cord (Thoracic)
Pancreas		Spleen	Thymus	Thyroid/Parathyroids		Gross Lesions
Liver	Gallbladder	Epididymis	Prostate	Skin/Mammary Gland		Animal Number Tattoo

For unscheduled necropsies after Day 116, and for the Day 361 and Day 391 necropsies, a portion (~40 g) of the liver was collected from a similar location in each animal and sliced into approximately 0.5 cm thick slices. The liver samples were flash frozen for possible analysis of cytochrome P450 and total protein conten[redacted]

Results:

- Mortality and Clinical Signs - There were 6 (2 @ 0, 1 @ 5, 1 @ 15, and 2 @ 45 mg/kg/day) non-treatment related unscheduled deaths (died or sacrificed moribund) as the consequence of underlying disorders including severe watery-liquid stool and dehydration of unknown causes. Unformed stool was noted in all groups. However, the high-dose group had slightly higher incidence of watery-liquid stool relative to the control. A slightly higher incidence of skin lesions (laceration or sores on the tail/digits) was observed in the high dose animals. The following table shows the incidence of observed skin lesions in each group. The digit sores were approximately 3 to 5 mm in diameter and the severity of the sores was not different between control and SC-65872-treated animals. The onset of these lesions generally occurred after 3 to 4 months of dosing.

Skin Lesions	Control	5 mg/kg/day	15 mg/kg/day	45 mg/kg/day
Tail Lesion	1/20	0/12	1/12	5/20
Digit Lesion	2/20	6/12	6/12	8/20

- Body Weights and Food Consumption - No remarkable changes were attributable to the treatment.
- ECGs and Ophthalmic Evaluations - No significant changes were noted.
- Clinical Pathology - A slight increase in BUN (↑~1.8x of pre-treatment value) was noted in the high dose group on Weeks 4, 6, 13, 26, 39, and 51 and these changes in BUN were reversible. Data from creatinine clearance measurements were highly variable and equivocal.
- PK/TK - SC-65872 was absorbed and systemically available. Plasma concentrations of SC-65872 and its active metabolite, SC-66905, increased with dose. Mean PK parameters for SC-65872 and its active metabolite, SC-66905, on Days 1, 90, 180, and 360 are shown in the following table. The mean C_{max} and AUC values for SC-65872 in the mid-and high-dose groups (15 and 45 mg/kg/day) were slightly higher on Days 90, 180 and 360 than on Day 1, and indication of accumulation after repeated dosing. A reduction in AUC values for SC-65872 was observed on

Day 360 compared to Day 180 as a result of dose preparation error, in which the high dose group was given approximately 75% of targeted dose during Week 52.

Day	Dose (mg/kg/day) bid	SC-65872						SC-66905					
		T_{max} (hr)		C_{max} (µg/ml)		AUC_{0-12} (µg•hr/ml)		T_{max} (hr)		C_{max} (µg/ml)		AUC_{0-12} (µg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
1	5	1.67	1.42	0.535	0.846	1.86	2.78	1.83	1.83	0.0398	0.0492	0.140	0.126
	15	1.50	2.00	1.99	2.57	6.42	8.66	2.00	2.83	0.254	0.211	0.778	0.744
	45	2.00	2.60	4.55	4.60	22.0	22.1	2.10	2.40	0.355	0.480	1.36	1.89
90	5	1.08	0.80	0.740	1.06	2.50	2.83	1.67	1.40	0.0604	0.0612	0.216	0.131
	15	1.25	1.83	2.15	2.89	9.68	15.2	2.00	1.92	0.121	0.177	0.493	0.927
	45	2.70	3.50	11.1	10.0	78.9	78.2	2.60	4.40	0.392	0.254	2.56	1.94
180	5	1.83	1.50	1.15	1.22	3.57	3.60	1.83	1.83	0.0773	0.0683	0.203	0.198
	15	2.33	3.00	4.63	3.30	19.0	22.5	2.67	3.50	0.233	0.165	0.928	0.999
	45	2.25	2.40	10.6	11.9	85.0	101	2.50	2.40	0.223	0.191	1.29	1.40
360	5	0.83	1.00	0.767	0.758	2.84	2.39	0.50	1.33	0.0221	0.0242	0.0441	0.0901
	15	1.83	2.00	2.93	3.24	15.7	17.1	1.83	1.25	0.122	0.230	0.619	1.26
	45[a]	3.00	2.60	7.30	5.74	45.7	43.8	2.00	1.50	0.162	0.135	0.819	0.838

[a] The actual dose of this high dose group in Week 52 was estimated to be approximately 75% of targeted dose.

- Macro- and Micro-scopic Findings - Histological alterations in adrenal cortex with characteristics of diffuse hypertrophy/hyperplasia in the zona fasciculata, cellular degeneration, and depletion of cells in the zona reticularis were noted in monkeys @ 15 and 45 mg/kg/day at both the13-week and 52-week sacrifices. These changes were reversible.

Therefore, the NOAEL was 60 mg/kg/day for this study based on findings of treatment-related increased incidence of skin sores (laceration or sores on the tail/digits) and histopathological changes in adrenal cortex in monkeys @ ≥15 mg/kg/day

2.3. REPRODUCTIVE TOXICOLOGY

2.3.1. FERTILITY AND EARLY EMBRYONIC DEVELOPMENT STUDIES

2.3.1.1. An Oral Administration Study of Male and Female Fertility and Early Embryonic Development Through Implantation With SC-65872 Accompanied by Reversal in the Female Rat by Oral Administration in the Rat, SA4578; Date: 12-Dec-1998, Document No. P20S4578. (Vol.1.71-73)

Study Nº: SA4578/96222
Report Nº: P20S4578/M3097120 (PK)
Study Aim: To evaluate the effects of orally administered SC-65872 on male and female fertility and early embryonic development through implantation accompanied by reversal in the female rat.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: ♂ - 0.3, 3.0 and 9.0 mg/10 ml/kg/day po bid (~12 hr apart)
♀ - 0.2, 2.0 and 6.0 mg/10 ml/kg/day po bid (~12 hr apart)
Dosing Duration: ♂ - 4 weeks prior to mating continuing for a total of ≥7 weeks
♀ - 2 weeks prior to mating through Gestation Day (GD) 7.
Animals: [redacted] Crl:CD(SD)®BR rats [redacted]
Toxicology and PK/TK Study - 12 weeks of age for ♂ and 10 weeks of age for ♀, 391-442 g for ♂ and 214-260 g for ♀.

Reversal Phase Study (♀ only) - ~8 weeks of age, weighting 175-217 g.

Study Location: [redacted]

GLP/QAU Compliance: Yes

Study Date: 12/17/1996 - 2/21/1997

Study Design: Animals were randomly assigned into the groups as shown in the following table.

Group	Dose (mg/kg/day)		Dosing Frequency	Dosing Duration		Nº Treated ♂ + Nº untreated ♀	Nº Treated ♀ Paired with Non-treated ♀
	♂	♀		♂	♀		
Toxicology Study							
1 Control	0	0	bid	4-wk prior to mating → necropsy	2-wk prior to mating → GD 7	25 + 25	25
2	0.3	0.2				25 + 25	25
3	3.0	2.0				25 + 24	26
4	9.0	6.0				24 + 24	26
Reversal Phase Study (♀ only)							
5		0	bid		2-wk + 2-wk reversal prior to mating		25
6		6					25
PK/TK Study (♀ only)							
1 Control	0	0	bid	4-wk prior to mating → necropsy	2-wk prior to mating → GD 7		2
2	0.3	0.2					9
3	3.0	2.0					9
4	9.0	6.0					9

The following parameters were monitored:

- Mortality and Clinical Signs - 2x/day.
- Body Weights - 1x/week and GD 0, 3, 7, 10, and 13 for mated ♀.
- Food Consumption - 1x/week for ♂ and ♀ prior to mating and GD 0, 3, 7, 10, and 13 for mated ♀.
- Estrous Cycle Determination - All ♀ (treated and untreated) were determined by examination of the vaginal lavage for 10 days prior to mating.
- PK/TK - GD 7. Blood samples were collected (3♀/time point) at 0.5, 1, 2, 4, 7, and 12 hr post 1st daily dosing.
- Necropsy -
  ♂ - All were sacrificed at 2-3 weeks after mating. Sperm counts, motility, and morphology were evaluated. The following tissues and organs were preserved in 10% neutral formalin: epididymis (right), seminal vesicles, testes, prostate, and lesions any abnormalities.
  ♀ - All surviving and presumed pregnant females were sacrificed on GD 13 or if mating was not detected, at the end of mating. The uterus from each gravid ♀ was excised, weighed, and examined for the number and placement of implantation sites, live and dead fetuses, early resorptions, and any abnormalities of the placenta or amniotic sac. The ovaries of gravid females were examined for the number of corpora lutea. The uterus of apparently non-pregnant rats was stained with ammonium sulfide for verification. The following tissues and organs were preserved in 10% neutral formalin: mammary glands (cervical and inguinal), ovaries, vagina, uterus, and lesions or any abnormalities.

Results:

- Mortality and Clinical Signs - Treatment-related deaths or unscheduled sacrifices in moribund condition due to GI toxicity (ulceration/perforation/peritonitis) were noted in the high dose group (2♂ @ 9.0 mg/kg/day, 12♀ @ 6.0 mg/kg/day, and 3 reversal ♀ @ 6.0 mg/kg). These animals had clinical signs of firm, internal structure within the abdomen, skitieyes pale, dehydrated, hunched posture, backbone prominent, thin, weak, decreased muscle tone and piloerection, abdominal distension, fur staining, wet fur in the urogenital/abdominal region and decreased activity prior to

death. One ♂ @ 3.0 mg/kg/day died of unknown cause on Day 16. One ♀ @ 0.2 mg/kg/day died on GD 7 due to blood sampling error.

- Body Weights and Food Consumption - No significant treatment-related changes in mean body weight, body weight gains or food consumption for SC-65872 treated ♂ and ♀ in Groups 2-4. Slightly reduced body weights by ~5% with ↓ body weight gains by ~15-30% were observed in Group 6 reversal ♀ (6.0 mg/kg/day) during the premating period, Weeks 2→4. However, there were no differences in mean body weights and body weight gains during GD 0→13 between Groups 5 and 6.
- Estrous Cycle Determination - No treatment-related effects were noted.
- Male Reproductive Performance - No treatment-related effects on the percent motile sperm, spermatozoa counts and morphology were observed.
- Reproductive Parameters - No significant changes in the mating and fertility indices, conception rates and mean day of mating were noted in SC-65872 treated groups including Group 6 ♀ and data are presented in the following table. A significant reduction in numbers of corpora lutea, significant ↑ in pre- and post-implantation losses with significant ↓ in the numbers of implantation sites, a slight ↑ in the numbers of early resorption, and a significant ↓ in the live fetuses were noted in Group 3 and 4 ♀ (2.0 and 6.0 mg/kg/day, respectively). A slight ↑ in the numbers of early resorption and an ↑ in post-implantation loss with a slight ↓ in the live fetuses were noted in Group 6 reversal ♀. It appears that with a 2-week reversal phase prior to mating the SC-65872 treatment related effects on numbers of corpora lutea, numbers of live fetuses and the pre-implantation loss could be reduced.

Parameters for Treated ♀	Group 1 Control	Group 2 0.2 mg/kg/day	Group 3 2 mg/kg/day	Group 4 6 mg/kg/day	Group 5 Control	Group 6 6 mg/kg/day
Nº of animals (♂/♀) paired	27	35	35	33	25	22
Nº Mated	27	34	35	32	25	22
Nº of Pregnant	25	31	32	25	25	22
Nº Found Dead/Killed in Moribund	0	1	0	12	0	3
Mating Index (%)	100.0	97.5	100.0	97.0	100.0	100.0
Fertility Index (%)	92.6	88.6	91.4	89.3	100.0	100.0
Mean (±SD) Day of Mating	3.9±3.67	4.4±4.36	4.5±4.76	3.6±3.51	2.4±1.29	2.3±1.08
Corpora Lutea	17.6±2.04	17.5±1.68	15.9±2.82[a]	13.5±2.63[c]	18.4±2.34	17.3±2.01
Implantation Sites	16.3±1.84	16.0±1.91	12.9±4.18[b]	11.0±3.85[c]	16.6±2.57	15.7±1.70[a]
Preimplantation Loss (%)	7.2±6.10	8.5±8.88	21.0±18.45[c]	20.1±18.63[a]	9.5±11.34	9.1±8.28
Postimplantation Loss (%)	5.2±5.68	6.9±6.38	11.9±9.60[a]	18.7±21.02[a]	5.9±6.23	11.1±12.23
Early Resorptions (%)	0.8±0.90	1.0±0.71	1.5±1.18	2.1±2.56	1.0±1.10	1.6±1.87
Dead Fetuses	0.0±0.21	0.2±0.65	0.2±0.51	0±0.0	0.0±0.00	0.0±0.21
Live Fetuses	15.4±2.09	14.9±1.87	11.2±3.68[c]	8.9±4.03[c]	15.5±2.37	14.0±2.73[a]

[a] P≤0.05; [b] P≤0.01; [c] P≤0.001

- PK/TK - SC-65872 was absorbed and systemically available following oral administration. Mean PK parameters for SC-65872 and its active metabolite, SC-66905, on GD 7 are summarized in the following table. The C_{max} and AUC values increased with dose.

Dose (mg/kg/day) bid	SC-65872			SC-66905		
	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12} (μg•hr/ml)	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12} (μg•hr/ml)
0.2	7	0.0274	0.260	0	0	0
2	1	0.369	3.07	7	0.0333	0.226
6	1	1.38	10.8	7	0.0886	0.829

- Necropsy - Treatment-related GI toxicity were identified in the following groups:
  - ♂ @ 9 mg/kg (Group 4) - 2 unscheduled sacrificed ♂ with gross lesions of jejunal perforation and thickening of jejunal wall with adhesion to other abdominal organ/tissues and 1 terminal sacrificed ♂ with

lesions of as raised areas in the jejunal mucosa and a depressed area in the ileal mucosa associated with wide-spread intra-abdominal adhesions.

- ♀ @ 6 mg/kg (Group 4) - 10/12 unscheduled sacrificed ♀ with gross lesions of perforation and/or depressed area(s) primmily in the distal portion of the jejunum and thickening of jejunal wall with peroitonitis, 1 ♀ that was found dead on Study Day 12 with evidence of peritonitis without recognizable ulcerative intestinal lesions, and 2 terminal sacrificed ♀ with gross findings of perforation and/or pale, depressed area(s) in the distal portion of the jejunum and peritonitis.
- ♀ @ 2 mg/kg (Group 2) - 1 terminal sacrificed ♀ with gross findings of pale depressed and/or raised areas in the distal portion of the jejunum with adhesion to abdominal fat.
- Reversal ♀ @ 6 mg/kg (Group 6) - 3 unscheduled sacrificed ♀ with gross observations of perforation of the mid or distal portion of the jejunum with thickening of the jejunal wall and/or dilatation and adhesion to other abdominal organs.

2.3.2. EMBRYO-FETAL AND PERINATAL TOXICITY STUDIES

2.3.2.1. A Range-Finding Toxicity Study of SC-65872 in Pregnant Rats, EX4586; Date: 02-Dec-1997, Document No. P30E4586. (Vol. 1.74)

Study Nº: EX4586/M3097061
Report Nº: P30E4586
Study Aims: To provide information for a subsequent embryo-fetal development study in rats.
Compound: [redacted]
Dose/Route: 0, 0.1, 1, 3, 6.25, and 12.5 mg/5ml/kg/dose bid (12±2 hr apart) by oral gavage
Duration: 12-Day (Gestation Days 6-17).
Vehicle Control: [redacted]
Animal: ♀ [redacted] rats, (VAF)CD, ~7-8 weeks of age, weighing 179-249 g, 8/group for the toxicology study and 6/group for the PK study.
Study Site: G.D. Searle and Company, 4901 Searle Parkway, Skokie, IL 60077.
Study Date: 12/2/96 to 12/17/96
GLP/QAC Compliance: N/A
Study Design: Groups of mated ♀ rats were randomly assigned to the following dose groups.

Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Dosing Volume	Dosing Duration	Nº of Animals/Group	
					Toxicology	PK
1 (Control)	0		5 ml/kg/dose	GD 6→17	8	6
2	0.1	0.2				
3	1	2				
4	3	6				
5	6.25	12				
6	12.5	25				

The following parameters were monitored.

- Clinical Observation and mortality - 2x/day on Gestation Days 4 and 6-20.
- Body Weights and Food Consumption - Gestation Days 4, 6, 8, 10, 13, 16, 18, and 20.
- Necropsy - Gestation Day 20.
- No tissues were collected on this study. The reproductive tract was exposed and the numbers of corpora lutea, implantations, resorptions, and live or dead fetuses were recorded. Fetuses were weighed, given a detailed external examination, euthanized and discarded. The uterus from any non-pregnant animal was stained with 10% (aq) v/v ammonium sulfide solution and examined for implantation sites.
- PK/TK - Blood samples were collected from 3 rats/time point on Gestation Days 6 and 17 at 1, 2, 4, and 12 hr post dosing.

Results:

- Clinical Observation and mortality - There were 4 treatment-related deaths with clinical signs of nasal and vaginal discharge, piloerection and/or reduced activity, and macroscopic lesions of perforations of the ileum, jejunum or duodenum (1 @ 12.5 mg/kg/day and 3 @ 25 mg/kg/day). All died animals were confirmed pregnant.
- Body Weights and Food Consumption - A slight reduction in food intake (~5-19%) was observed in animals receiving 25 mg/kg/day during the whole period of study.
- PK/TK - Mean plasma PK parameters for SC-65872 and SC-66905 on Gestation Days 6 and 17 are shown in the following table.

Sampling Day	Dose[a] (mg/kg/dose)	N	SC-65872			SC-66905		
			T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12} (μg•hr/ml)	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12} (μg•hr/ml)
GD 6	0.1	3	2	0.0209	0.107	12	0.00977	0.0391
	1	3	4	0.216	1.81	2	0.0148	0.0867
	3	3	4	0.825	6.67	4	0.084	0.677
	6.25	3	2	1 1.96	13.4	4	0.227	1.72
	12.5	3	2	4.27	35.6	4	0.462	3.60
GD 17	0.1	3	1	0.0229	0.112	2	0.0147	0.0306
	1	3	2	0.332	2.14	2	0.0377	0.226
	3	3	1	1.45	11.5	4	0.154	1.32
	6.25	2	2	3.24	28.2	4	0.368	3.06
	12.5	3	2	7.49	61.0	4	0.957	8.75

[a] bid. dosing regimen 0.2, 2, 6, 12.5 and 25 mg SC-65872/kg/day.

- Necropsy - The following parameters were not affected: pregnancy rate, mean corpora lutea counts, implantations or pre-implantation loss. Increased numbers in resorptions and post-implantation losses and a slight ↓ in the numbers of live fetuses were noted in the groups @ 12.5 and 25 mg/kg/day.

In conclusion, the NOAEL for SC-65872 was 6 mg/kg/day (3 mg/kg/dose bid) in the present study as embryo-fetal toxicity was observed at dose levels ≥12.5 mg/kg/day by the evidence of ↑ in resorptions and a subsequent ↑ in post-implantation loss, and ↓ in the numbers of live fetuses.

2.3.2.2. An Oral Study of Embryo-Fetal Development in the Rat Administered SC-65872, SA4487; Date: 29-Jun-1998, Document No. P20S4487. (Vol. 1.75)

Study Nº: SA4487[redacted]
Report Nº: P P20S4487 and M3097198 (PK)
Study Aims: To evaluate the maternal and embryo/fetal toxicity and teratogenic potential of SC-65872 when administered iv to pregnant rats.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 1, 3, and 5 mg/5 ml/kg/dose bid (12±2 hr apart) by oral gavage for 12 days (Gestation Days 6→17)
Animals: [redacted] Crl:CD®BR rats, ~14 weeks of age, weighing 211-254 g for Toxicology study and 203-237 g for PK study on GD 0, 24/group for Toxicology study 2-9/group for PK study.
Study Location: [redacted]
Study Date: 3/3/97 - 3/22/1997
GLP/QAU Compliance: Yes
Study Design: Groups of 24 mated ♀ rats were randomly assigned to 4 dose groups as shown in the following table.

Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Dosing Volume	Dosing Duration	N° of Animals	
					Toxicology	PK
1 (Control)	0	0	5 ml/kg/dose	GD 6→17	24	2
2	1	2			24	9
3	3	6			24	9
4	5	10			24	9

The following parameters were monitored:

- Mortality and Clinical Signs - 1x/day.
- Body Weights and Food Consumption - Gestation Days 0, 6, 8, 10, 12, 14, 16, 18 and 20.
- PK/TK - Blood was collected (3/dose/time point) approximately 0.5, 1, 2, 4, 7, and 12 hr post-dose on Gestation Days 6 and 17. Control group blood samples were taken from both females at 1 and 4 hr postdose on Days 6 and 17. Plasma samples were shipped to the [redacted] for analysis of SC-65872 and SC-66905 levels by a validated [redacted]
- Necropsy and Uterine Examination - Gestation Day 20. The uterus from each gravid ♀ was excised, weighed, and examined for the number and placement of implantation sites, live and dead fetuses, early and late resorptions, and any abnormalities of the placenta or amniotic sac. The ovaries of gravid females were examined for the number of corpora lutea. The uterus of apparently non-pregnant rats was stained with ammonium sulfide for verification. The following formulations were used to calculate female reproductive performance parameters.
  - Pre-implantation Loss (%) = [(N° of corpora lutea - N° of implants)/N° of corpora lutea] x 100
  - Postimplantation Loss (%) = [(dead fetuses per litter + resorptions per litter)/N° of implantation sites per litter] x 100
  - Live Fetuses (Fetal Viability) (%) = (N° of live fetuses per litter/N° of implants per litter) x 100
  - Early Resorptions (%) = (early resorptions per litter/N° of implants per litter) x 100
  - Late Resorptions (%) = (late resorptions per litter/N° of implants per litter) x 100
  - Total Resorptions (%) = [(early + late resorptions per litter)/N° of implants per litter] x 100
- Fetal Examinations - Each fetus was sexed, weighed, examined for external abnormalities. Approximately ½ of all the fetuses from each litter were randomly selected and processed for visceral examination by the Wilson Technique for assessing soft tissue development. The remaining fetuses were eviscerated and processed for skeletal examination using the [redacted] staining method. All fetuses were retained in Bouin's fixative (fetuses examined for visceral abnormalities) or glycerin (fetuses examined for skeletal abnormalities).

Results:

- Clinical Signs and Mortality - No deaths occurred. No treatment-related clinical symptoms were observed.
- Body Weight and Food Consumption - There were no significant changes in the mean body weights and food consumption. A slight but not statistically significant reduction (↓7.7%) in mean body weight changes was noted in high dose group during Gestation Days 6→20. A slight but statistical significant increase (↑6.5%) in mean body weight changes was noted in animals @ 6 mg/kg/day during Gestation Days 6→20.
- Necropsy - Hydrometra was noted in one non-pregnant ♀ @ 2 mg/kg/day. There were no significant differences in the mean gravid uterine weights.
- Female Reproductive Parameters and Fetal Parameters - There were no increased incidences in fetal external, skeletal or soft tissue malformations/variations. Slight but not statistical significant increases in pre- and post-implantation loss and total soft tissue variations (dilatation of lateral ventricles and increased renal pelvic cavitation) were noted in the high dose group. Findings in the maternal reproductive and fetal parameters (Mean ± SD) are shown in the following table.