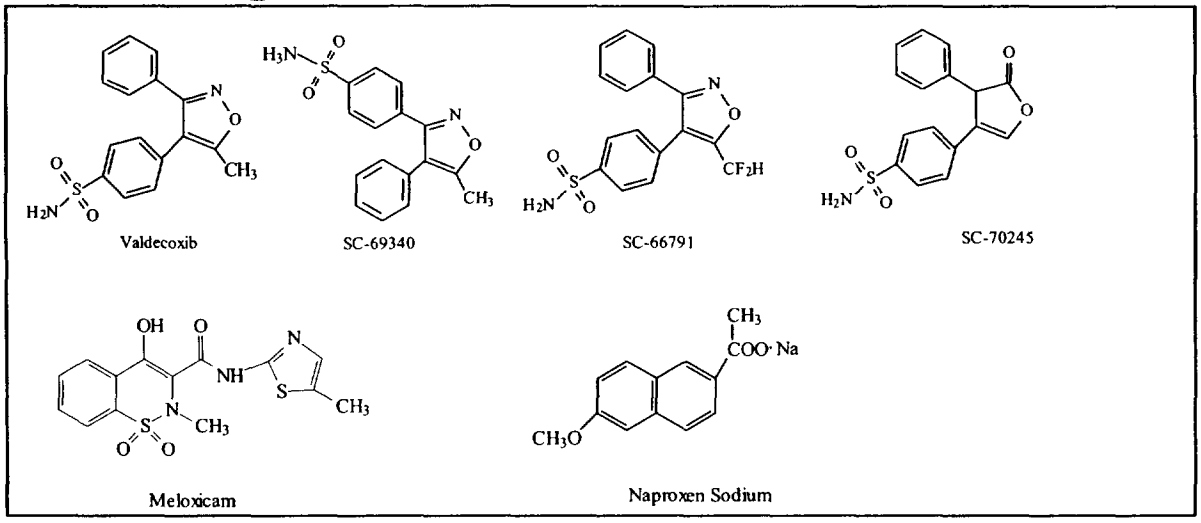
basal levels of COX-2 were observed in the dog epidermis. This observation was quite different from human in that basal levels of COX-2 were present in human epidermal keratinocytes[7].
No significant COX-2 immunoreactivity was detected in the epidermal keratinocytes of skin biopsies collected at 0 or 4 hours after infliction of wounds. In contrast, epidermal keratinocytes (basal layer) undergoing hyperplasia especially adjacent to the incision and inflammatory reaction showed mild →marked expression of COX-2 from Days 1 to Day 14. In addition, marked COX-2 immunoreactivity was seen in sloughed keratinocytes in the epidermal crust/ulcer. Small number of infiltrated neutrophils (approximately 2-5%) and numerous dermal macrophages exhibited COX-2 immunoreactivity. In comparison to epidermal keratinocytes and macrophages, COX-2 immunoreactivity in infiltrated neutrophils was very slight. The capillary endothelial cells and fibroblasts of granulation tissue present in wounds showed moderate COX-1 immunoreactivity. COX-1 immunoreactivity was also present in the hyperplastic epidermal keratinocytes similar to normal epidermis. No COX-2 immunoreactivity was determined in the capillaries and fibroblasts of granulation tissue.
At necropsy, skin wounds with characteristics of full-thickness loss of skin, rounded edges, dry, and partial scab formation were present at *Strep.* inoculation sites in all Group 4, SC-65872-treated, dogs but not in Group 3 control dogs. Microscopic evaluations of these wounds showed cellulitis, ulceration, and infiltration of neutrophils, lymphocytes, histiocytes, and plasma cells. Wound healing was in progress in all animals by the evidence of formation of epidermal hyperplasia with rete ridge and proliferation of granulation tissue (neovascularization and fibroplasia).
Immunohistochemical evaluations for COX-1 and COX-2 were performed on the skin wound and stomach of a Group 4 dog (2401) that was sacrificed on Day 17, wounds at *Strep.* inoculation sites of Group 4 dogs (2402, 2404, 2405 and 2406), and on the heart of the dog (2403) that was found dead on Day 28. In addition to normal distribution of COX-1 and COX-2 in the canine skin, moderate→marked COX-2 immunoreactivity was observed in the hyperplastic and sloughed epidermal keratinocytes and inflammatory cells (macrophages and rare neutrophils) and COX-1 immunoreactivity in the granulation tissue. In the stomach, COX-1 immunoreactivity was present in the gastric mucosa, blood vessels and ganglion cells. No COX-2 immunoreactivity was present in the unaffected part of the stomach. However, at the site of erosion/ulceration, moderate COX-2 immunoreactivity was observed in the sloughed mucosal cells (epithelial and lamina proprial cells) and in a few cells of lamina propria adjacent to the erosion. In the heart, COX-1 was observed in the cardiomyocytes, blood vessels and granulation tissue within the lesion. No COX-2 was observed in the unaffected regions of heart. Marked COX-2 immunoreactivity was present in the endothelial cells and sub-endocardial fibroblasts of endocardium and interventricular valves, blood vessels adjacent to the lesions, and in the inflammatory cells (macrophages and rare neutrophils).

2.6.2.2. Amendment: P31E4700: Two Week Oral Capsule Toxicity Study to Compare the Potential of SC-65872 and Other Related Compounds to Cause Skin Lesions in the Dog (EX 4700); Date: 07-May-1999, Document No. P30E4700. (Vol. 1.113-114)

Study Nº:	EX 4700
Report Nº:	P30E4700 & M3098122 (PK)
Study Aim:	To compare the potential of SC-65872 with SC-65872, SC-69340, SC-66791, and SC-70245 and marketed NSAIDs, naproxen sodium and meloxicam to induce skin lesions in beagle dogs.
Compound:	[redacted]

[7] Leong J, et al, 1996. Expt Cell Res 224:79-87.

[redacted]



Dose: Daily dose for each test compound were listed in the below table.
Route: Oral
Dosing Frequency: bid (~12 hr apart)
Bacterial Stocks: *Streptococcus* Group G, 1.9×10^9 cells/ml
Animals: ♂ and ♀ beagle dogs [redacted] ~6-9 months of age, weighing 5.7-8.5 kg; 3/sex/group.
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077; [redacted]

GLP/QAU Compliance: No.
Study Date: 2/3/1998 (Day 1) - 2/17-19/1998 (Days 15-17).
Study Design: Groups of 3/sex dogs were given either control or test compounds at dosages as shown in the following table 2x/day at approximately 12 hr apart. The dose of SC-65872 was selected to obtain the similar exposure as in the chronic dog study (SA4615). The positional isomer of SC-65872 but without an active metabolite, SC-69340, was dosed to achieve an exposure equivalent to SC-65872. The selection of dosages for SC-66791 and SC-70245 were based on the exposure exaggeration calculated for SC-65872 using ED_{80} in a rat adjuvant-induced arthritis model. Meloxicam was dosed at ~7x the estimated therapeutic exposure. Naproxen sodium was dosed to achieve 3-10x the therapeutic exposure. Omeprazole was used to reduce the incidence and severity of the upper gastrointestinal toxicity of naproxen sodium and meloxicam. Omeprazole (10 mg/day) was administered (Groups 6, 7 & 8) 1x/day in conjunction with the 1st daily dosing. Dogs were inoculated subcutaneously with pure cultures of *Streptococcus* Group G on the right side of the neck on Day 4. The inoculation sites were monitored for the development of swelling and open sores. Skin specimens (either the site of abscess or injection site if abscess did not form) were collected at necropsy for histopathological examinations.

Group	Compound	Dose (mg/kg/dose)	Daily Dose (mg/kg/day)	Dosing Frequency.	Dosing Duration	Nº dogs/group
1	Control (Gelatin Capsule)	0	0	bid	14-16 Days	3/sex
2	SC-65872 (Valdecoxib)[c]	7	14			
3	SC-66791[c]	20[b]	40			
4	SC-69340[c]	20[b]	40			
5	SC-70245[c]	20[b]	40			
6	Naproxen Sodium + Omeprazole[a]	5	10			
7	Naproxen Sodium + Omeprazole[a]	25	50			
8	Meloxicam + Omeprazole[a]	1.5	3			

[a] Omeprazole was administered with the morning dose, at 10 mg/day to reduce the incidence and severity of gastrointestinal toxicity.

[b] Each dose was approximately divided into two gelatin capsules.

[c] The IC_{50} against human recombinant COX-1 and COX-2 are listed as follows:

	Valdecoxib	SC-66791	SC-69340	SC-70245
hCOX-1	170 μM	146 μM	>1000 μM	>100 μM
hCOC-2	0.05 μM	0.07 μM	0.2 μM	70 μM

The following observations were conducted.

- Clinical Signs and Mortality - 1x/day at 1-5 hr post 1st daily dose.
- Physical Examination - Pre-R (Day -7) and Week 2.
- Body Weights - Days -6, -1, 3, and 11.
- Food Consumption - Not Recorded.
- Clinical Pathology - Days -6, 7, and 14. The following parameters as shown in the below table were analyzed.

Hematology					
RBC	WBC/Total/Differential		MCH	MCV	
Ht	Platelet Count & Volume		Hb	MCHC (Calculated)	
Blood Chemistry					
AST	ALT	ALP	Urea Nitrogen	Total Bilirubin	Cholesterol
Glucose	Albumin	Globulin	Total Protein	Creatinine	Na
Ca	Phosphate	A/G Ratio	Triglyceride	Total Bile Acid	K / Cl
Urine Chemistry					
Ca	Cl	Creatinine	Phosphorous	PGE_2/6-keto-PGF-1α	
K	Na	Protein	Urine Excretion	Creatinine Clearance	

- Plasma Renin Activity - Days 1, 7, and 14 at 2 hr post dosing.
- Plasma Angiotensin II Determination - Days 7 and 14 at 2 hr post dosing.
- PK/TK - Blood samples were collected from all animals at 0.5, 1, 2, 3, 5, 7, and 12 hr (prior to 2nd daily dose) after the 1st daily dose on Days 1, 7, and 14.
- Necropsy - Days 15-17. There were three unscheduled deaths (Group 4, Day 17 and Day 28) during the study. The following listed tissues or representative samples were collected and preserved in 10% buffered formalin. Organ weights were not recorded. Section from all collected tissues were examined microscopically.

Kidneys	Stomach	Skin (Including Bacterial Inoculation Sites)
GI Tract	Adrenals	Skin Lesions

- Special Stains - COX-1 and COX-2 and apoptosis staining were performed on the right kidneys of all animals.

Results:

- Clinical Signs and Mortality - Three unscheduled sacrifices (2♂ @ 3 mg/kg/day of Meloxicam on Days 10 and 13, respectively; 1♂ @ 40 mg/kg/day of SC-70245 on Day 15) took place due to the

presence of severe skin lesions (cellulitis/ulcerations) and/or GI toxicity. Melena and/or red discoloration of feces was observed in Groups 6, 7, and 8. These findings correlated with gross and/or histological evidence of GI injuries (erosions/ulceration).

- Clinical Observation of Bacterial Inoculation Sites - The skin reaction to subcutaneous bacterial inoculation was evaluated by the development of swelling and ulceration. The incidence of skin ulceration and mean area of ulceration (>1 cm^2) are presented in the following table. Three dogs in control group (3/6) and 5/6 Group 4 (SC-69340) developed slight transient abrasions/ulceration (size ≤1 cm^2) at the Streptococcus inoculation sites between Days 8 and 12. Dogs treated with either SC-65872, SC-66791, SC-70245, naproxen sodium, or meloxicam developed slight transient swellings at the *Streptococcus* inoculation sites on Day 5 (one day post inoculation). These swelling progressed into ulcerations in size of 1.5-75 cm^2 with serosanguinous to yellow creamy exudation (pus) within 4-7 days of inoculations (Days 8→ 11).

Group	Test article	Dose (mg/kg/day)	Incidence (n=6/group)	Size of Skin Ulcer (cm^2)[a]	Stat. Analyses vs Group 1	Stat. Analyses vs Group 2
1	Control	0	0	-	-	**
2	SC-65872	14	5	5.1 ± 4.4	**	-
3	SC-66791	40	5	10.4 ± 8.3	**	NS
4	SC-69340	40	0	-[b]	NS	NS
5	SC-70245	40	4	3.4 ± 1.5	**	NS
6	Naproxen	10	5	7.0 ± 4.0	*	NS
7	Naproxen	50	5	8.7 ± 9.6	*	NS
8	Meloxicam	3	5	19.0 ± 31.6	*	NS

[a] Mean ±SD of area of skin ulceration (the largest area of ulceration noted on any given day for an animal was included in this calculation);

[b] One animal in this group had skin ulcer of 1 cm^2.

** $p \leq 0.01$; * $p \leq 0.05$.

- Body Weight - No significant changes were attributable to the treatment.
- Clinical Pathology -
  - Hematology: Increased WBC (↑1.5-2.5x) with increased neutrophil (↑1.7-3.4x) and monocyte (↑1.5-3.2x) counts on Day 7 was noted in all groups as a consequence of subcutaneous inoculation of Group G *Streptococcus*. The changes in leukogram were not observed in control, SC-65872, SC-69340 and SC-70245 groups on Day 14, correlating with complete or partial resolution of skin lesions. The WBC (↑2.0-2.5x), neutrophil (↑1.6-4.4x) and monocyte (1.3-5.3x) counts remained elevated in ♂+♀ dogs @ 40 mg/kg/day of SC-66791, 3 mg/kg/day of meloxicam, or 10 or 50 mg/kg/day of naproxen on Day 14. In addition, reduced RBC by 40-46% with reduced Hb and Ht by 28-44% and 29-41%, respectively was noted in ♂+♀ dogs @ 50 mg/kg/day of naproxen or 3 mg/kg/day of meloxicam on Day 14. These changes in leukogram and hemagram were secondary response to treatment-induced GI injury.
  - Clinical Chemistry: Increased BUN values were noted in 1♂ (↑~2x) + 2♀ (↑2-3x) and 1♂ (↑2x) + 3♀ (↑2.6-11x) @ 50 mg/kg/day of Naproxen on Day 7 and 14, respectively.
  - Urinalysis: Marked decreases in urinary excretion of PGE_2 and 6-keto-PGF-1α were noted in animals treated with SC-65872, naproxen sodium (50 mg/kg/day), and meloxicam on Days 7 and 14. Total urine PGE_2 and 6-keto-PGF-1α excretions (mean ± SD) on Day 7 for Groups 1, 2, 7, and 8 on Days 7 and 14 are shown in the below table.

Group	Test Article	Daily Dose (mg/kg/day)	PGE_2 (ng/ml)		6-keto-PGF-1α (ng/ml)	
			Day 7	Day 14	Day 7	Day 14
1	Control	0	2.35 ± 1.22	1.13 ± 0.64	2.77 ± 3.19	1.02 ± 0.30
2	SC-65872	7	0.28 ± 0.27*** (↓88%)	0.27 ± 0.11** (↓76%)	0.39 ± 0.33*** (↓86%)	0.45 ± 0.06 (↓56%)
7	Naproxen Sodium	50	0.33 ± 0.33*** (↓86%)	0.30 ± 0.18** (↓73%)	0.37 ± 0.21*** (↓87%)	0.86 ± 0.57 (↓16%)
8	Meloxicam	3	0.15 ± 0.05*** (↓94%)	0.20 ± 0.14*** (↓82%)	0.41 ± 0.14** (↓85%)	0.49 ± 0.41 (↓52%)

* p≤ 0.05; ** p≤0.01; *** p≤0.001

Other noticeable changes in urinalysis were reduced urine K and Cl excretions on Day 7 and/or 14 in Groups 7 and 8 as shown in the following table.

Group	Test Article	Daily Dose (mg/kg/day)	K Excretion (mmole/17 hr)				Cl Excretion (mmole/17 hr)			
			Day 7		Day 14		Day 7		Day 14	
			♂	♀	♂	♀	♂	♀	♂	♀
1	Control	0	13.1	17.6	15.6	14.4	10.6	10.7	16.1	16.4
2	SC-65872	7	13.0	12.8	15.0	14.5	7.9* (↓25%)	14.2	14.6	13.6
7	Naproxen Sodium	50	5.1** (↓61%)	8.8 (↓50%)	4.8 (↓69%)	9.4 (↓35%)	1.8** (↓83%)	6.6 (↓38%)	1.9 (↓88%)	14.9
8	Meloxicam	3	11.8 (↓10%)	8.7 (↓51%)	17.3	17.3	4.8** (↓55%)	6.6 (↓38%)	8.6 (↓47%)	17.3

Plasma Renin activity and Angiotensin II Levels - Mean plasma renin activity and angiotensin II levels for each group are presented in the following table. Elevated plasma renin activity and angiotensin II levels were noted in dogs @ 50 mg/kg/day of Naproxen and 3 mg/kg/day of Meloxicam.

Group	Test Article	Daily Dose (mg/kg/day)	Renin Activity (ng/ml)			Angiotensin II (pg/ml)	
			Day 1	Day 7	Day 14	Day 7	Day 14
1	Control	0	5.38	6.81	5.79	39.1	50.7
2	SC-65872	7	7.48 ↑1.4x	6.13	1.24 ↓79%	12.3 ↓69%	42.4
3	SC-66791	20	10.76* ↑2.0x	3.19 ↓53%	4.96	10.5 ↓73%	53.1
4	SC-69340	20	8.39 ↑1.6x	7.65	5.28	28.9 ↓26%	48.0
5	SC-70245	20	8.06 ↑1.5x	3.89 ↓43%	0.89* ↓99.8%	11.2 ↓71.3%	29.1 ↓43%
6	Naproxen Sodium	10	3.61 ↓33%	4.28 ↓37%	5.04	28.6 ↓27%	125.1** ↑2.5x
7	Naproxen Sodium	50	11.02* ↑2.0x	20.28*** ↑3.0x	11.39* ↑3.0x	118.3*** ↑3.0x	270.0*** ↑5.3x
8	Meloxicam	3	7.04 ↑1.3x	10.06 ↑1.5x	8.26 ↑1.5x	49.6 ↑1.3x	373.6*** ↑7.4x

* p≤ 0.05; ** p≤0.01; *** p≤0.001

- Immunohistochemical Stains - The assessment of apoptosis and expression of cyclooxygenase (COX-1 and COX-2) with the special immunochemical staining technique was performed on one kidney from each dog. There were no differences in the incidence or severity of apoptosis between control and treatment groups. Treatment with specific COX-2 inhibitors and with marketed NSAIDs caused a mild to marked increase in renal COX-2 immunoreactivity (above control). Dogs treated with specific COX-2 inhibitors or 50 mg/kg/day of Naproxen showed increased COX-2 immunoreactivity in the macula densa and thick ascending limb of loop of Henle (TAL). In contrast, dogs treated with 10 mg/kg/day of Naproxen or 3 mg/kg/day of

Meloxicam showed increased COX-2 immunoreactivity in papillary interstitial cells, macula densa and TAL. No remarkable differences in renal COX-1 expression between treatment and control groups.

- Determination of PGE_2 and 6-keto-PGF-1α Levels in Exudate - The following table showed PGE_2 levels (mean ± SD) in exudate fluid collected from *Streptococcus* inoculation sites. It appeared that SC-65872, SC-66791, Naproxen and Meloxicam caused a significant reduction in PGE_2 levels as compared to control or SC-69340, the mirror image of SC-65872.

Group	Test Article	Daily Dose (mg/kg/day)	PGE_2 (ng/ml)	6-keto-PGF-1α (ng/ml)
1	Control	0	158.0 ± 114.6	3.42 ± 5.11
2	SC-65872	7	10.8 ± 8.2* (↓93%)	0.28 ± 0.06 (↓92%)
3	SC-66791	20	2.2 ± 0.5*** (↓97%)	0.24 ± 0.04 (↓93%)
4	SC-69340	20	97.7 ± 93.1 (↓38%)	0.58 ± 0.13 (↓82%)
5	SC-70245	20	85.9 ± 68.8 (↓46%)	0.61 ± 0.39 (↓82%)
6	Naproxen Sodium	10	4.3 ± 1.9** (97%)	0.43 ± 0.33 (↓87%)
7	Naproxen Sodium	50	3.9± 0.3** (↓98%)	0.11 ± 0.04 (↓97%)
8	Meloxicam	3	3.6 ± 4.3*** (↓98%)	0.85 ± 1.29 (↓74%)

* p≤ 0.05; ** p≤0.01; *** p≤0.001

- PK/TK - All tested compounds were absorbed and systemically available following oral administration. The PK parameters for each tested compound on Day s 1, 7, and 14 are listed in the following table.

Tested Compound	Daily Dose mg/kg	T_{max} (hr)						C_{max} (μg/ml)						AUC_{0-12} (μg•hr/ml)					
		Day 1		Day 7		Day 14		Day 1		Day 7		Day 14		Day 1		Day 7		Day 14	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
SC-65872	14	2	2	2	3	3	3	3.49	2.69	3.56	6.96	4.17	4.46	14.3	8.37	22.0	44.3	25.1	21.5
SC-66791	40	2	2	2.5	3	3	2	1.19	1.34	11.5	15.6	5.01	7.10	4.35	6.49	106	136.7	40.6	50.6
SC-69340	40	2	2	2	2	2	2	1.62	2.92	2.69	3.76	1.53	2.28	6.42	9.23	13.5	15.4	5.20	7.25
SC-70245	40	2	2	2	2	2	3	1.12	1.53	1.47	2.36	1.31	1.57	7.45	7.49	9.49	14.9	6.09	7.09
Naproxen	10	3	2	1	5	2	1	34.6	36.1	50.0	44.6	40.0	45.0	352	375	526	489	422	475
	50	1	1	0.5	1	1	1.3	95.2	93.8	58.1	45.2	45.3	45.0	859	815	401	444	367	395
Meloxicam	3	3	5	2	3	3	2	2.35	2.10	12.2	14.8	10.5	12.5	23.4	22.0	126	138	68.4	119

- Macro- and Histo-pathology - Gross and histologic examination of the inoculation sites in the above groups exhibited moderate to severe cellulitis with skin ulceration in most of the animals. Thickening of the subcutaneous region due to granulation tissue proliferation (fibrosis) at the injection sites was found in one Group 5, three Group 7, and one Group 8 animals. Lesions of kidney toxicity, renal papillary necrosis (RPN) with microscopic characteristics of slight to moderate focal necrosis of all elements of the papilla (including collecting ducts, vasa recta, loops of Henle, and interstitial cells) and tubular atrophy and fibrosis (TAF) with characteristics of slight to moderate tubular atrophy, degeneration/necrosis and regeneration of tubular epithelium, tubular dilatation, slight interstitial fibrosis and infiltration of lymphocytes, plasma cells, neutrophils and histiocytes were identified in dogs treated with 50 mg/kg/day of Naproxen or 3 mg/kg/day of Meloxicam. RPN was present in one or both kidneys as consequence of treatment-induced loss of vasodilatory renal prostaglandins leading to development of ischemia and TAF lesions were usually bilateral and were primarily present in the outer cortex as a result

of treatment-associated marked reduction in renal blood flow leading to reduced blood flow to the distant regions of the cortex. The incidence of gross and microscopic cellulitis/skin ulceration, GI and kidney lesions in each group is listed in the following table.

Group	Compound	Dose mg/kg/day	Skin Lesions[a]		GI Injury		RPN[b]		TAF[c]	
			♂	♀	♂	♀	♂	♀	♂	♀
1	Control	0	0	0	0	0	0	0	0	0
2	SC-65872	14	3	2	0	1	0	0	0	0
3	SC-66791	40	3	2	2	1	0	0	0	0
4	SC-69340	40	0	0	0	0	0	0	0	0
5	SC-70245	40	2	3	0	2	0	0	0	0
6	Naproxen	10	3	3	3	3	0	0	0	0
7	Naproxen	50	1	2	3	3	1	2	1	3
8	Meloxicam	3	3	2	3	3	2	2	0	0

[a] Cellulitis with Skin Ulceration
[b] RPN = Renal Papillary Necrosis
[c] TAF = Tubular Atrophy and Fibrosis

2.6.2.3. 20-Day Exploratory Oral Capsule Study in the Dog to Determine the Effects of SC-65872 on Susceptibility to Bacterial Infections (EX 4733); Date: 19-Jan-2000, Document No. P30E4733. (Vol. 1.116)

Study Nº: EX 4733
Report Nº: P30E4733
Study Aims: To determine whether self mutilation play a role in the induction or severity of skin lesion following oral administration of SC-65872.
Compound: [redacted]
Dose & Route: 0 and 7 mg/kg bid po (10-14 hr apart) for 20 days
Animals: ♂ & ♀ beagle dogs [redacted] ~6 months of age, weighing 7.3-8.8 kg, 3/sex/group
Bacterial Stocks: *Streptococcus* Group G, 10^8-10^9 cells/ml
Study Location: G.D. Searle & Co., Skokie, IL
Study Date: 11/12/1997 (Day 1) - 12/2/1997 (Terminal Sacrifice, Day 21)
GLP/QAU Compliance: N/A
Study Design: Neat SC-65872 was administered orally in a gelatin capsule at dosages of 0 and 7 mg/kg twice a day for 20 days. On Day 2, all dogs were inoculated with *Streptococcus* Group G ($2x10^6$ cells/ml normal saline) on the back in the dorsal mid-thoracic region and no lesions were noted. Therefore, on Day 7, all dogs were inoculated subcutaneously with 1.0 ml of *Streptococcus* Group G (3x107 cells/ml) on the neck. The inoculation sites were monitored for swelling and abscess formation.

Group	Compound	Dose (mg/kg/dose)	Dose (mg/kg/day)	Dosing Frequency/Duration	Nº Animals	Bacterial Inoculation Day
1	Control	0	0	bid/20-day	3/sex	2 & 7
2	SC-65872	7	14		3/sex	2 & 7

The following observations were conducted.

- Clinical Signs and Mortality - 1x/day at 1.5-2.5 hr post 1st daily dose.
- Physical Examination - Pre-R (Day -2), Days 7 and 13 at ~1.5-2.5 hr post 1st daily dose.
- Body Weights - Days -5, -1, 6, 13, and 21.
- Food Consumption - Not Recorded.
- Clinical Pathology - Days -7 and 20. The following parameters as shown in the below table were analyzed.

HEMATOLOGY				
RBC	WBC (Total/Differential)		Platelet Count	Mean Platelet Volume
Ht	Hb	MCH	MCV	MCHC (Calculated)
BLOOD CHEMISTRY				
Total Protein	Albumin		Globulin	A/G Ratio

- PK/TK - Blood samples were collected on Days 1, 4, and 20. The samples were stored at approximately -20°C but not analyzed.
- Blood Cultures - Blood was collected with a Opticult Blood Collection tube from one Group 2 ♀ that were sacrificed at moribund on Day 15.
- Necropsy - Day 21. Skin samples including inoculation sites and all lesions were collected and processed for histopathological examination..
- Immunocytochemical and Flow Cytometric Evaluation of Leukocyte Adhesion Molecules (CD11/CD18) and Leukocyte Myeloperoxidase Activity - Days -1, 10, and 14.
- Exudate Collection - Exudate samples were collected from bacteria inoculation sites of 5 animals (1♂+2♀ @ 0 and 1♂+1♀ @ 14 mg/kg/day) 4-8 days post-inoculation.

Results:

- Clinical Signs and Mortality - One Group 2 ♀ (47332202) was sacrificed on Day 15 for humane reasons due to the presence of a large swelling (16x10x5 cm) in the right axilla adjacent to the bacterial inoculation site. Signs of thin ventral staining pale gums reduced activity swollen neck, limb, axilla, and chest and no feces were observed in this dog.
- Clinical Observation of Bacterial Inoculation Sites - Several dogs had skin lesions around the sites inoculated on Day 7 but not Day 2. The incidence and duration of skin lesion persisted is shown in the following table. There was no evidence of self biting or scratching of subcutaneous inoculation sites. Higher incidence of dogs in the SC-65872 treated group develop skin ulceration and more severe skin lesions than the control.

Treatment	Animal Nº	Onset of Ulceration	Days of Ulceration Persisted	Largest Ulceration Observed	Area (cm^2) of Largest Ulceration
Control	47331101	Day 13	6	Day 13	0.25
	47332101	Day 11	1	Day 11	0.06
	47332102	Day 12	1	Day 12	0.06
SC-65872	47331201	Day 12	2	Day 12	0.25
	47331202	Day 11	8	Day 12	1.0
	47331203	Day 13	8	Day 15	6.0
	47332201	Day 13	6	Day 15	0.5
	47332203	Day 14	7	Day 17	16.0

- Body Weights - No significant changes were attributable to the treatment.
- Clinical Pathology - A mild increase in total WBC (1.4-2.8x) with an increase in neutrophils (1.4-3.3x) and monocytes (1.3-2.9x) on Day 20 was noted in some Group 2 dogs. These changes were considered a biological response to bacterial infection and skin ulceration.
- Expression of CD11 and CD18 - There were no significant differences in the expression of CD11a, CD11b, CD11c, and CD18 on peripheral blood neutrophils (PMN) or lipopolysaccharide (*E. coli* strain 055:B5) and calcium ionophore A23187 stimulated PMN from SC-65872 treated dogs. Similarly, no remarkable differences in the expression of CD11b or CD18 on exudate fluid derived neutrophils and the staining pattern for myeloperoxidase in the bone marrow myeloid cells.
- Blood Cultures - The blood cultures taken from the dog that was sacrificed on Day 15 were positive for *Staphylococcus epidermis, Pseudomonas aeruginosa, Staphylococcus aureus* (common skin and oral microflora).
- Necropsy -

Unscheduled Sacrifice - Gross findings of severe disseminated cellulitis with ~200 ml of pus involving right rib cage, axilla, and forelimb, moderate hydroperitoneum and erosion/ulceration at the gastro-duodenal junction (pylorus) were identified in the dog that was sacrificed on Day 15.
Terminal Sacrifice - Skin ulceration at neck and/or thoracic region (back) subcutaneous inoculation sites were noted in SC-65872 treated but not control dogs. Microscopic examination of these lesions revealed the characteristic of cellulitis, skin ulceration and infiltration of neutrophils, lymphocytes, histiocytes, and plasma cells. The incidence of cellulitis and skin ulceration at bacterial inoculation sites at terminal sacrifice is presented in the following table. Slight alopecia (n=3) and/or slight epidermal crust (n=1) at the subcutaneous inoculation sites with histologic changes of mild dermal and subcutaneous fibrosis and accumulation of epidermal crust were observed in the control group.

Group	Incidence at Inoculation Site		
	Back	Neck	Neck or Back
Control	0/6	0/6	0/6
SC-65872	2/6	4/6	6/6

2.6.2.4. Four Week Exploratory Range Finding Oral Capsule Study in the Dog to Determine the Effects of SC-65872 on Susceptibility to Bacterial Infections (EX 4723); Date: 26-Aug-1999, Document No. P30E4723. (Vol. 1.116)

Study Nº: EX 4723
Report Nº: P30E4723/M3098002 (PK)
Study Aim: To determine the effects of increasing dosages of SC-65872, time of bacterial inoculation in relation to dosing, and concentration of bacterial inoculum in the development of skin lesions using the previously developed experimental model of subcutaneous streptococcal infection.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0.15, 0.5, 1.5, 3, and 7 mg/kg/dose po bid(10-14 hr apart)
Animals: ♂ & ♀ beagle dogs ([redacted] 5-10 months of age, weighing 6.0-12.8 kg; 3 sex/group.
Study Site: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077 [redacted]
GLP/QAU Compliance: Not Indicated.
Study Date: 10/9-11/26/1997
Study Design: Dogs were randomized allotted into 6 groups and were treated with either placebo control or SC-65872 at doses shown in the following table. *Streptococcus* Group G at a concentration of 6×10^8 or 2×10^2 cells in 1.0 ml were inoculated into in the right and left side of the neck of Groups 1-5 dogs, respectively on Day 15. Group 6 dogs were inoculated on Day 1 with 1.0 ml of *Streptococcus* Group G containing approximately 1×10^9 or 2×10^7 cells on the right and left side of the neck, respectively.

Group	Compound	Dosage (mg/kg/dose)	Dose (mg/kg/day)	Dosing Duration	Bacterial Inoculation	Nº Dog/Group
1	Control	0	0	28-Day	Day 15	3/Sex
2	SC-65872	0.15	0.3			
3	SC-65872	0.5	1.0			
4	SC-65872	1.5	3.0			
5	SC-65872	3.0	6.0			
6*	SC-65872	7.0	14.0	7-Day	Day 1	

* Animals were treated for 7 days with a 3-week recovery phase.

The following observations were conducted.

- Clinical Signs and Mortality - 1x/day at 1.5-2.5 hr post 1st daily dose.
- Physical Examination - Pre-R and 1x/week thereafter.
- Body Weights - Days 7, 14, 21, and 28.
- Food Consumption - Not Recorded.
- Clinical Pathology - Days -24 (Pre-R), 8 (Group 6 only), 14, and 28. The following parameters as shown in the below table were analyzed.

Hematology				
RBC	WBC (Total/Differential)	Platelet Count		Mean Platelet Volume
Ht	Hb	MCH	MCV	MCHC (Calculated)
BLOOD CHEMISTRY				
Total Protein	Albumin	Globulin		A/G Ratio

- PK/TK - Blood samples were collected on Days 1, 4, and 28 (Groups 1-5). The samples from Group 1 were not analyzed.
- Necropsy - Day 28. Skin samples including inoculation sites and all lesions were collected and processed for histopathological examination.

Results:

- Clinical Signs and Mortality - One Group 5 ♂ was sacrificed on Day 19 due to the presence of large (2 x 2 cm and 3 x 3 cm) ulcers with on the left hind limb.
- Clinical Observation of Bacterial Inoculation Sites - Skin ulcerations developed in most (33 of 36) dogs at sites inoculated with $\geq 2 \times 10^7$ bacteria on Day 1 or 15. No swelling or skin ulceration was noted at sites inoculated with 2×10^2 bacteria. The severity of swelling and skin ulceration was dose-dependent as shown in the following table. Skin lesions were generally mild and healed in dogs @ ≤1.0 mg/kg/day by the end of the study. All Group 6 animals treated with SC-65872 at 14 mg/kg/day and inoculated with Group G Streptococcus on Day 1 of the study developed skin lesions (transient swellings progressing to cellulitis/skin ulceration). Skin lesions in all Group 6 dogs healed during the recovery period (Weeks 2-4) by the evidence of re-epithelialization and formation of granulation tissue.

Group	Test article	Dose (mg/kg/day)	Incidence[a]	Size of Skin Ulcer[b] (cm^2)
1	Control	0	0/6	0.5 ± 0.3
2	SC-65872	0.3	3/6	2.3 ± 2.7*
3	SC-65872	1.0	3/6	3.9 ± 3.0*
4	SC-65872	3.0	4/6	6.3 ± 8.5**
5	SC-65872	6.0	4/6	13.2 ± 19.1***

[a] Incidence of skin ulcers >1.0 cm^2.

[b] Mean ± SD of area of skin ulceration (U_{max}, the largest area of ulceration noted on any given day for an animal, was used in this calculation).

* p≤0.05; ** p≤0.01; *** p≤0.001.

- PGE_2 Levels in Exudate - Exudate samples from bacterial inoculation sites were collected from some dogs in Groups 1 (n=2), 2 (n=3), 3 (n=1), and 6 (n=3). Data presented in the following table showed that a marked decrease in PGE_2 levels were observed in Group 6 animals but no remarkable changes in PGE_2 were noted in samples from Groups 2 and 3. These results are similar to previous observations with selective COX-2 inhibitors and marketed NSAIDs (EX4700).

Group	Animal Number	Study Day	PGE_2 (ng/ml)
1	47231101-♂	18	122
	47231102-♂	18	52.2
2	47232201-♀	18	68.3
	47232202-♀	18	104
	47231202-♂	20	35.8
3	47232303-♀	20	51.1
6	47231603-♂	2	0.65
		4	1.33
	47231601-♂	4	1.62
	47231602-♂	4	1.01

- Body Weights - No significant changes were attributable to the treatment.
- Clinical Pathology - No treatment-related changes were identified in Groups 2-5. A mild increase in WBC (♂: 2.0x; ♀: 1.3x) with an increase in neutrophils (♂: 2.7x; ♀: 1.4x) and monocytes (♂: 2.7x; ♀: 2.0x) as a consequence of bacterial infection and skin ulceration was noted in Group 6 dogs on Day 8. These changes returned to prestudy levels during the recovery period.
- Necropsy - Dog @ 3 or 6 mg/kg/day displayed mild to severe skin ulcerations (1→10 cm in diameter) with microscopic characteristics of cellulitis, skin ulceration and infiltration of neutrophils, lymphocytes, histiocytes, and plasma cells at the subcutaneous inoculation sites (right side of neck only). The skin lesions in the 14 mg/kg/day animals healed with scar tissue formation. No gross lesions were identified in the control, 0.3, and 1 mg/kg/day dose groups. Wound healing as evidenced by epidermal hyperplasia with rete ridge formation and proliferation of granulation tissue (neovascularization and fibroplasia) was in progress in most animals. Incidence of cellulitis and skin ulceration at bacteria inoculation sites at terminal sacrifice was summarized in the following table.

Group	Test article	Dose (mg/kg/day)	Incidence
1	Control	0	0
2	SC-65872	0.3	0
3	SC-65872	1.0	0
4	SC-65872	3.0	3/6
5	SC-65872	6.0	5/6
6[a]	SC-65872	14.0	0

[a] Animals were treated with SC-65872 for 7 days and placed on a 3-week of reversal phase on Day 8.

- PK/TK - SC-65872 was systemically available following oral administration. Mean plasma SC-65872 and SC-66905 levels for each dosing group on Days 1, 4, and 28 are shown in the following table.

Day	Dose (mg/kg/day)	Time (hr)	SC-65872		SC-66905	
			♂	♀	♂	♀
1	0.3	2	0.0942	0.0774	0.0976	0.0795
		12	0.00520	0.00493	0.0347	0.0294
	1.0	2	0.248	0.298	0.366	0.306
		12	0	0.0119	0.0857	0.155
	3.0	2	0.738	0.797	0.479	0.826
		12	0.0497	0.0289	0.271	0.459
	6	2	1.74	2.05	1.22	2.17
		12	0.246	0.355	0.739	0.896
	14	2	5.73	4.13	6.38	4.43
		12	3.66	3.94	5.60	4.70
4	0.3	2	0.117	0.109	0.0504	0.0537
		12	0.00420	0.00443	0.0384	0.0582
	1.0	2	0.296	0.403	0.154	0.191
		12	0.00937	0.00713	0.0896	0.134
	3.0	2	0.763	0.673	0.349	0.335
		12	0.0351	0.00870	0.276	0.284
	6	2	1.27	1.56	0.662	0.603
		12	0.0597	0.122	0.512	0.952
	14	2	2.07	2.36	1.16	0.999
		12	0.227	0.729	1.67	2.01
28	0.3	2	0.0751	0.0546	0.0571	0.0564
		12	0	0.00613	0.0293	0.0510
	1.0	2	0.201	0.258	0.180	0.252
		12	0.00353	0.00380	0.0725	0.131
	3.0	2	0.952	0.618	0.413	0.572
		12	0.0207	0.0218	0.214	0.362
	6	2	1.92	1.08	1.19	0.884
		12	0.253	0.0940	0.858	0.636
	14	2	-	-	-	-
		12	-	-	-	-

Therefore, SC-65872 caused a dose-dependent increase in incidence and severity of cellulitis/skin ulceration following experimental subcutaneous inoculation of $\geq 2x10^7$ streptococcal bacteria. Skin lesions can develop as early as Day 1 following SC-65872 dosing and bacterial inoculation.

2.6.3. EFFECTS ON RENAL FUNCTION

2.6.3.1. Six-Week Oral Capsule Exploratory Study to Determine the Potential Effects of SC-65872 on Renal Function in the Male Beagle Dog, EX4800; Date: 07-Sep-2000, Document No. P30E4800. (Vol. 1.117-118)

Study Nº: EX4800
Report Nº: P30E4800 & M3098365 (PK)
Study Aim: To determine the possible effects of SC-65872 and reduction in dietary sodium on selected parameters of renal and cardiovascular function in ♂ beagle dogs.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 14 mg/kg/day po
Dosing Frequency: bid (10-14 hr apart) for 42 days
Animals: ♂ beagle dogs [redacted] 7-8 months of age, weighing 8.2-9.5 kg; 6/group
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077 [redacted]

GLP/QAU Compliance:
Study Date: 6/19/1998 - 7/31/1998
Study Design: Dogs (♂) were randomly assigned to 2 dose groups as shown in the following table and orally dosed with vehicle or SC-65872 2x/day for 42 days. All dogs were switched from their standard diet (~0.45% elemental sodium) to a low salt diet (~0.05% elemental sodium) on Day 15.

Group	Compound	Dose (mg/kg/dose)	Dosage (mg/kg/day)	Dosing Freq./ Duration	Nº ♂/ Group
1	Control	0	0	bid	6
2	SC-65872	7	14	42-day	6

The following observations were monitored:

- Clinical Signs and Mortality - 1x/day.
- Body Weights, Food Consumption and H_2O Intake- Pre-℟ and 1x/week.
- Instrumented Renal Blood Flow and Selected Hemodynamic Determinations - Pre-℟ and 2x/week (3 hr post dose). A radiotelemetry device was implanted in the right inguinal area to measure systemic arterial pressure and an ultrasonic renal flow probe was placed around the left renal artery to measure renal arterial blood flow. The following parameters were analyzed: systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, heart rate, and arterial pulse pressure
- Clinical Pathology -
  Inulin and PAH (p-aminohippuric Acid) Clearance Determinations: 2x/pre-℟ and 1x/week. Blood samples were collected at 0.5, 1.5, 2.5, 3.5 and 4.5 hr and urine was collected at urine, via an indwelling bladder catheter, at 1.5, 2.5, 3.5 and 4.5 hours after the beginning of infusion (0.5 hour samples discarded without analysis). The following parameters (steady-state, 4.5 hr values only) were reported: inulin clearance, renal plasma flow, renal blood flow, filtration fraction, and plasma osmolality.
  Clinical Chemistry, Hematology, Urinalysis and Urine Chemistry: Day 1 and 1x/week. The following parameters were determined. Plasma Renin Activity (PRA) was assessed on days that inulin/PAH infusions were performed.

SERUM/PLASMA CHEMISTRY			
Sodium	Alkaline Phosphatase (AP)	Calcium	Total Protein
Potassium	Aspartate Aminotransferase (AST)	Inorganic Phosphorus	Albumin
Chloride	Alanine Aminotransferase (ALT)	Glucose	Globulin
Total Bilirubin	Urea Nitrogen (BUN)	Creatinine	Albumin/Globulin Ratio
Total Bile Acid	Triglycerides	Cholesterol	Renin
HEMATOLOGY/COAGULATION			
RBC	WBCs/Differential	MCV	MCH / MCHC
Hematocrit (Ht)	Hemoglobin (Hb)	Mean Platelet Volume	Platelet Counts
URINE CHEMISTRY/URINALYSIS			
Color/Character	Urobilinogen	Glucose	Sodium / Chloride
pH/Specific Gravity	Creatinine	Ketones	Occult Blood
Urine Flow Rate	Potassium	Bilirubin	Quantitative Protein
Urine Vol.	Phosphorus	Protein	Microscopics*
PGE_2	6-Keto PGF1α	Ca	11-Dehydro-TXB_2
Osmolality	N-Acetyl-β-D-Glucosaminidase (NAG)	β2-Microglobulin	Creatinine Clearance

- TK/PK - Days 1, 12, and 40. Blood was collected from all dogs at 2 and 12 hr (prior to the 2nd daily dose). Plasma SC-65872 and SC-66905 levels were determined by an
- Necropsy - Days 43 and 49. Kidneys were weighed prior to fixation. Kidneys and all lesions were preserved in 10% buffered formalin and processed for microscopic examination.

- Special Stains - Immunohistochemical evaluations of COX-1 and COX-2 were performed on the kidneys from all dogs.

Results:

- Clinical Signs and Mortality - There were no remarkable clinical signs noted. One dog that had a large swelling (10x7 cm) on the left rib cage and a skin abrasion (6-10 cm diameter) in the neck region was sacrificed on Day 12 for humane reasons. Exudate from the swelling was cultured and found to contain *Staphylococcus intermedius.*
- Body Weights, Food Consumption and H_2O Intake- No treatment related body weight changes were recorded. A significant decrease in food consumption was noted in dogs @ 14 mg/kg/day SC-65872 by ~20% during Weeks 4-6. In addition, SC-65872 treated dogs had significant less (↓21%) water intake during Week 4.
- Rectal Temperature and Fecal Occult Blood - No treatment-related changes were noted.
- Cardiovascular Functions - No significant changes in systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, heart rate, and arterial pulse pressure were recorded.
- Renal Function -

  Renal Blood Flow (RBF): A mild to moderate decrease (↓26-45%) in mean RBF with a mild increase in renal vascular resistance was observed in dogs treated with SC-65872 following the intake of salt-depleted diet and results are presented in the below table.

SC-65872 (mg/kg/day)	Mean (±SD) Renal Blood Flow (ml/min/kg)						
	Week -1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
0.0	27.95 ± 11.19	20.50 ± 4.88	22.49 ± 9.83	27.33 ± 3.33	32.59 ± 9.33	27.84 ± 14.64	25.54 ± 8.81
14.0	23.32 ± 3.09	16.93 ± 5.63	24.53 ± 10.48	19.74 ± 5.07*	17.81 ± 5.43*	14.74 ± 5.72	13.84 ± 8.44*

Glomerular Filtration Rate (GFR): GFR was evaluated by inulin and creatinine clearances. No treatment-related changes in GFR during the 1st two weeks of study. A moderate decrease (↓61-77%) in mean RBF with a mild increase in renal vascular resistance was observed in dogs treated with SC-65872 following the intake of salt-depleted diet (Weeks 3→6).

Filtration Fraction: Filtration fraction (FF) was calculated from renal plasma flow and GFR. There were no changes in the FF.

Serum Urea Nitrogen and Creatinine: A mild increase in BUN (up to 1.5x of the control) was noted in SC-65872 treated dogs during Weeks 1 and 2. However, significant increases (up to 7x of the control) in BUN and creatinine levels were observed in SC-65872 treated dogs during Weeks 3→6 (one week after salt-depleted diet). Results from serum urea nitrogen and creatinine determinations are listed in the below table.

Group	Parameters (mg/dl)	Week of Study[a]							
		-2	-1	1	2	3	4	5	6
Control	BUN	14.1	12.8	14.1	16.4	18.6	19.9	19.1	20.8
SC-65872		13.6	12.4	18.8**	25.4**	109.0**	129.6**	132.8**	126.4**
Control	Creatinine	0.68	0.70	0.67	0.68	0.67	0.68	0.68	0.65
SC-65872		0.73	0.75	0.72	0.76*	1.2*	1.2*	1.3*	1.3*

[a] Weeks -2→2 : normal diet; Weeks 3→6: sodium depleted diet.

* $p \leq 0.05$, ** $p \leq 0.01$.

Urine Chemistry: Administration of SC-65872 to dogs caused mild to moderate decreases in urine volume and urine flow rates (~30 to 50%) and urinary excretion of sodium, chloride, and calcium (~50 to 70%) that resulted in an increase in urine osmolality (~70%) during first two weeks of the study. Salt depleted diet did not cause additive effects on urine calcium levels, urine output and osmolality; however, it caused a further decrease in the urine sodium and chloride excretion (↓ >90%). Salt-depleted diets caused moderate decreases in urine volume and urine flow rates (~30 - 60%) and marked decreases (up to >90% reduction) in urinary excretion of

sodium and chloride in the control dogs as compared to the pre-treatment or pre-low salt diet values. Higher urinary excretion of inorganic phosphorus (up to 2.4x) was noted in SC-65872 treated dogs during Weeks 3→6. A moderate increase (1.8-2.7x) in urine NAG (N-acetyl-β-D-glucosaminidase) levels was observed during weeks 3 to 6.

Urinalyses: No significant differences between control and SC-65872 treated dogs were observed.

Urinary Prostaglandins: Treatment with SC-65872 caused a significant decrease in urinary PGE2 (3.5-10x), 6-keto-PGF1α (9.1- 22x), and 11-dehydro-TXB_2 (2.7-3.7x).

Plasma Renin Activity (PRA): Treatment of SC-65872 caused a decrease in PRA up to 71% during the 1st two weeks as shown in the following table. PRA values increased significantly in both control and SC-65872 treated dogs one week following the intake of salt-depleted diet.

SC-65872 (mg/kg/day)	Mean (±SD) Plasma Renin Activity (ng/ml)						
	Week -1	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
0.0	3.00 ± 1.151	2.50 ± 0.837	3.20 ± 1.709	11.80 ± 5.212	6.13 ± 3.920	2.15 ± 2.359	2.07 ± 1.603
14.0	2.17 ± 1.727	1.63 ± 1.013	0.94 ± 0.555	14.18 ±3.930	5.26 ± 2.285	3.48 ± 1.827	3.10 ± 1.435

Plasma Osmolarity: Salt depletion did not affect plasma osmolality in the control dogs; however, increased plasma osmolarity (1.1x of the control) was noted in dogs treated with SC-65872.

- Clinical Pathology - Slight decreases (↓12-13%) in erythroid parameters (RBC, Ht, and Hb) during Weeks 4→6 was noted in SC-65872 treated dogs. These findings were secondary to blood loss in the GI tract as evidenced by necropsy findings of GI ulcers/erosions..
- TK/PK - SC-65872 was absorbed and systemically available. Mean plasma SC-65872 and SC-66905 levels at 2 and 12 hr post dose on Days 1, 12, and 40 are listed in the following table.

Study Day	Time (hr)	N[a]	SC-65872 (μg/ml)	SC-66905 (μg/ml)
1	2	6	1.45 ± 0.369	0.655 ± 0.149
	12		0.0760 ± 0.0210	0.336 ± 0.0608
12	2	5	3.34 ± 0.859	3.43 ± 0.835
	12		0.452 ± 0.106	1.12 ± 0.164
40	2	5	4.03 ± 0.431	3.90 ± 0.328
	12		0.900 ± 0.122	2.10 ± 0.326

[a] One dog was sacrificed on Day 12.

- Necropsy -

  Unscheduled Sacrifice: Cellulitis in the path of renal flow probe cables and suppurative renal capsulitis adjacent to the flow probe were observed in one Group 2 dog that was necropsied on Day 12

  Terminal Sacrifices: Treatment-related GI lesions of jejunal/ileal ulceration/erosion were observed in 4 SC-65872-treated dogs. Microscopic lesions of multifocal, mild→marked tubular epithelial atrophy and fibrosis were observed in the outer cortex of all SC-65872-treated dogs. Moderate multifocal infarcts were observed in the right renal cortex of one control dog and were considered incidental findings.
- Special Stains - Results from the immunohistochemical studies for renal localization of COX-1 and COX-2 showed mild COX-1 immunoreactivity in the papillary and cortical collecting ducts, papillary interstitial cells and blood vessels in both control and SC-65872-treated dogs. Mild COX-2 immunoreactivity was observed in the macula densa, thick ascending limb of loop of Henle (TAL), and papillary interstitial cells in the control group. The intensity of COX-2 staining in SC-65872-treated dogs was markedly higher in all terminal sacrificed than that in the controls. Similar intensity of COX-2 staining was observed in the unscheduled sacrificed Group 2 dog and the control dogs.

Therefore, treatment of 14 mg/kg/day SC-65872 to dogs fed a salt-depleted diet for 6 weeks caused GI (jejunal/ileal ulceration/erosion) and renal toxicity (↑BUN, tubular epithelial atrophy and fibrosis in the outer renal cortex, and alterations in renal hemodynamics).

2.6.3.2. Seven-Week Oral Capsule Exploratory Study to Determine the Potential Effects of SC-65872 on Renal Function in the Male Dog, EX4793; Date: 28-Aug-2000, Document No. P30E4793. (Vol. 1.119)

Study Nº: EX4793
Report Nº: No. P30E4793 & M3098088
Study Aim: To characterize the time-course of changes in renal parameters following valdecoxib or naproxen sodium treatment of dogs.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: SC-65872 - 14 and 28 mg/kg/day po
Naproxen Sodium - 5.0 and 30 mg/kg/day
Dosing Frequency: bid (10-14 hr apart) for 26-48 days
Animals: ♂ beagle dogs [redacted] ~5-7 months of age, weighing 8.1-9.2 kg for Groups 1 and 2 and 7.8-9.5 kg for Group 3.
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: No.
Study Date: 3/6/1998 - 4/23/1998
Study Design: Dogs (♂) were randomly assigned to 3 dose groups as shown in the following table and orally dosed with vehicle, SC-65872 or naproxen 2x/day for various length of periods.

Group	Nº ♂ /Group	Compound	Dose (mg/kg/day)				Duration (Day)	Nº of Dog Sacrificed	
			Day 1-8	Day 9-42	Day 23-36	Day 36-48		Day 43	Day 49
1	4	Control	0	0	0	0	42[a]/48	2	2
2	4	SC-65872	14	28	na	na	42	4	
3	4	Naproxen	na	na	5.0	30	26		3

[a] Group split so that 2 animals could be euthanized on the same day as the Group 2 and 3 animals.

The following observations were monitored:

- Clinical Signs and Mortality - 1x/day.
- Body Weights - Pre-R and 1x/week.
- Food Consumption - not stated.
- Clinical Pathology -
  Inulin and PAH Clearance Determinations: Days 5, 8, 11, 14, 20, 27/5, 28/6, 34/12, 35/13, 41/19, 42/20 and 48/26. Blood samples were collected at 0.5, 1.5, 2.5, 3.5 and 4.5 hr and urine was collected at 4.5 hr after the beginning of infusions on Days 5, 8, 11, 14, 20, 27, 28, 34, 35, 41, 420 and 48.
  Clinical Chemistry, Hematology, and Urine Chemistry: Day 46.
- TK/PK - Blood was collected from all dogs at 2 and 12 hr (prior to the 2nd daily dose) on Days 1 and 14 (Groups 1 and 2 only), and at 2 and 12 hr after the morning dose on the day prior to the animal's scheduled sacrifice (all animals).
- Special Procedure: Fluorescent Microsphere Extraction to Determine Regional Renal Blood Flow - At scheduled sacrifice, fluorescent microsphere suspension was injected into the left atrium. An arterial reference blood sample was collected from the abdominal aorta (caudal to the kidneys) starting approximately 5-10 seconds before injection of the fluorescent microspheres. Blood was withdrawn by a Harvard withdrawal pump at a constant rate of 10 ml/min for a period of

approximately 60 seconds. Sections of the kidneys and the arterial reference blood samples were collected and reserved for analysis of regional renal blood flow.

- Necropsy - Days 43 and 49. Kidneys and all lesions were preserved in 10% buffered formalin and processed for microscopic examination.

Results:

- Clinical Signs and Mortality - One Group 3 was found dead on Day 23 with gross findings of multiple adhesions of the serosal surfaces, ~150 ml of sero-sanguinous exudate in the abdominal cavity, and a 1-2 cm diameter perforation in the pyloric region of the stomach..
- Body Weights - No treatment-related changes were recorded
- Food Consumption -
- Clinical Pathology - A slight ↓ in RBC (11-23% relative to control) with ↓Ht (15-18%) and ↓Hb (13-20%) and a slight to mild ↑ in serum urea (1.6-2x) were noted in dogs treated with SC-65872. However, a moderate to marked ↓ in RBC numbers (16-57%) with ↓Ht (15-55%) and ↓Ht (16-58%) (relative to pre-treatment values) was observed in naproxen sodium-treated dogs that correlated with clinical findings of changes in stool color/melena and gross/histologic findings of ulcers in the stomach and small intestine. Slight decreases in serum chemistry parameters including ↓total protein (9-23%), ↓albumin (14-33%), and ↓calcium (3-9%) were also observed in one naproxen sodium-treated dog. Decreases in urine output (42 to 72%) and urinary excretion of sodium, chloride, and calcium (45 to 86%) were noted in dogs treated with SC-65872. Similarly, decreases in urine output (57%) and urinary excretion of sodium and chloride (87-89%) were observed in naproxen sodium-treated dogs.
- Renal Function -
  Glomerular Filtration Rate (GFR) (Inulin Clearance):
  - SC-65872 treated dogs: ↓18-42% from Days 27-42.
  - naproxen sodium-treated dogs: ↓37-43% from Days 19-26.

  Renal Plasma Flow (RPF) (PAH Clearance):
  - SC-65872 treated dogs: ↔.
  - naproxen sodium-treated dogs: ↓47% from Day 26.
- TK/PK - The test articles, SC-65872 and naproxen sodium, were absorbed and systemically available. Mean (±SE) plasma SC-65872, SC-66905, and naproxen level at 2 and 12 hr post dose on Days 1, 14, 42, and 48 are shown in the following table.

Study Day	Time (hr)	N	Dose (mg/kg/day)	SC-65872 (µg/ml)	SC-66905 (µg/ml)	Naproxen (µg/ml)
1	2	4	14[a]	4.37 ± 0.905	1.59 ± 0.393	
	12	4		1.26 ± 0.267	2.94 ± 0.450	
14	2	4	28[a]	10.4 ± 1.16	6.96 ± 0.768	
	12	4		6.68 ± 0.534	7.24 ± 1.01	
42	2	4	28[a]	8.54 ± 0.331	5.66 ± 0.517	
	12	4		3.20 ± 1.36	3.71 ±0.712	
48	2	3	5.0/30[b]			24.4 ± 4.30
	12	3				19.1 ± 5.10

[a] Escalated SC-65872 doses: 7 mg/kg/dose bid during Days 1-8 and 14 mg/kg/dose bid dose of 28 mg/kg/day during Days 9-42.

[b] Naproxen doses: 2.5 mg/kg/dose bid during Days 23-36 and dose was escalated to15 mg/kg/dose bid during Days 36-48. The dosing regimen was twice a day for a total of approximately 4-weeks.

- Necropsy and Histopathology - Treatment-related GI toxicity characterized as slight to marked mucosal ulceration of the small intestine was noted in both SC-65872- and naproxen sodium-treated dogs. In addition, naproxen sodium-treated dogs had lesions of pyloric ulceration,

peritonitis, hydroperitoneum, hydropericardium, renal papillary degeneration/necrosis and multifocal tubular epithelial degeneration and atrophy in the outer cortex.

Therefore, SC-65872 (14 mg/kg/day→28 mg/kg/day) and naproxen sodium (5.0 mg/kg/day→30 mg/kg/day) treatment-related toxicity was limited to GI and kidney.

2.6.3.3. Six-Week Toxicity Study of SC-65872 and Naproxen Sodium Administered Orally to Cynomolgus Monkeys Fed a Low Sodium Diet, EX4847; Date: 17-Oct-2000, Document No. P20E4847. (Vol. 1.120)

Study Nº: EX4847[redacted]0693-26
Report Nº: P20E4847 & M3099252
Study Aim: to determine the potential effects of SC-65872 and naproxen sodium on renal function following oral administration 2x/day for 42 days to cynomolgus monkeys that were fed a low sodium diet during Days 15-42.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: SC-65872 - 12 mg/kg/day (6/mg/kg/dose) po
Naproxen Sodium - 150 mg/kg/day (75 mg/kg/dose) po
Dosing Frequency/Duration: bid (10-14 hr apart) for 42 days
Animals: Experimentally naive cynomolgus monkeys [redacted] 2 to 6 years of age, weighing 2.2-3.4 kg, 3/sex/group
Study Location: [redacted]
GLP/QAU Compliance: Yes/No
Study Date: 5/27-28/1999 - 7/8-9/1999
Study Design: Groups of 3/sex monkey were randomly assigned to one of three groups and orally dosed with vehicle, SC-65872 or naproxen 2x/day for 42 days as shown in the following table. These monkeys were placed under commercially prepared low sodium diet (0.057% Na vs 0.22-0.24% Na in certified regular diet) during Days 15→42.

Group	Nº/sex/group	Compound	Dose (mg/kg/dose)	Dose (mg/kg/day)	Dosing/Freq. /Duration	Dose Vol. (ml/kg/day)	Dose Solution Conc. (mg/ml)
1	3	Vehicle Control	0 (control)	0	bid 42-day	3	0
2	3	SC-65872	6	12		3	4
3	3	Naproxen Sodium	75	150**		3	50

The following observations were monitored:

- Clinical Signs and Mortality - 2x/day.
- Body Weights - Pre-R and 1x/week.
- Food Consumption - Visual assessment, 1x/day.
- Clinical Pathology - Weeks 2, 4, and 6. The following parameters were analyzed. Creatinine and urea clearance (absolute and normalized to body weight) were determined.

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
Blood Smear	Hemoglobin (Hb)	Blood Cell Morphology	Platelet Counts
PLASMA CHEMISTRY			
Renin	Thromboxane	Vasopressin (or Antidiuretic Hormone)	
URINALYSIS			
Color/Character	Urobilinogen	Glucose	Sodium Chloride
pH/Specific Gravity	Creatinine	Ketones	Occult Blood
Nitrite	Potassium	Bilirubin	Quantitative Protein
Leukocyte Esterase	Phosphorus	Protein	Microscopics*
PGE_2	6-Keto PGF1α	2,3-Dinor 6-Keto PGF1α	11-Dehydro-TXB_2

- PK/TK - Days 13 and 42. Blood was collected at 0 (prior to the morning dose) and 0.5, 1, 2, 3, 5, 8, and 12 hr following the morning dose (prior to the next dose).
- Necropsy - Day 43. Kidneys from each animal were weighed prior to fixation. Kidneys, animal number tattoo and gross lesions from each animal were collected and preserved in 10% formalin. The kidneys and treatment-related gross lesions were subjected to microscopic examination.

Results:

- Clinical Signs and Mortality - No deaths occurred. No remarkable clinical signs were noted.
- Body Weights and Food Consumption - A decrease in body weight (up to 12%) with a reduction in food consumption (as shown in the following table) was observed in animals @ 150 mg/kg/day naproxen sodium during the course of study. In addition, Groups 3 had statistically significant lower mean body weight by 21% at Week 6 relative to the controls.

Group	Compound	Dose (mg/kg/day)	Number of Occasions of Incomplete Food Consumption*		
			Prestudy	Weeks 1-2	Weeks 3-6**
1	Control	0	0/6 (0%)	5/63 (8%)	7/147 (5%)
2	SC-65872	12	0/6 (0%)	4/63 (6%)	3/147 (2%)
3	Na Naproxen	150	0/6 (0%)	27/63 (43%)	31/147 (21%)

* Sum (for each group) of the number of occasions each animal had incomplete food consumption during the indicated period / total number of observations.

** Low sodium diet was fed to the animals during this period.

- Clinical Pathology - Treatment-related changes were noted in animals @ 150 mg/kg/day naproxen sodium including
  - increases in BUN (2.4-3x of of prestudy levels), creatinine (~2x of prestudy levels), calcium (↑8-24% of prestudy levels), bilirubin (1.0-1.2 vs 0.7 of pretreatment levels), globulin (↑19-24%) and triglycerides (~2x of prestudy levels) during Weeks 3-6;
  - slight decreases in albumin (↓10-15% of prestudy levels) and phosphorus (↓21-40% of prestudy levels);
  - changes in hemato- and leuko-grams: ↓RBC by 21% with ↓Hb (25%) and Ht (23%), ↑platelet (37%), and ↑WBC by 17% with ↑PMN (1.5x) at Week 6;
  - posible decreases in the urine prostaglandins (2,3-dinor 6-keto PGF1α, 6-keto-PGF1α, PGE_2, and 11-dehydro-TXB_2) as the result of pharmacological action of naproxen;

Analyte	Group	Pre-R	Week 2	Week 3	Week 4	Week 6
2,3-dinor 6-keto PGF1α (pg/ml)	Control	1663	410	250	420	390
	SC-65872 - 12 mg/kg/day	1110	196	128	135	163
	Naproxen Sodium - 150 mg/kg/day	1559	187	73	57	46
6-keto-PGF1α (pg/ml)	Control	728	169	51	167	137
	SC-65872 - 12 mg/kg/day	620	107	60	41	90
	Naproxen Sodium - 150 mg/kg/day	1026	58	41	29	18
PGE_2 (pg/ml)	Control	1158	561	432	453	421
	SC-65872 - 12 mg/kg/day	1291	746	697	507	916
	Naproxen Sodium - 150 mg/kg/day	1516	465	302	169	77
11-dehydro-TXB_2 (pg/ml)	Control	2877	1067	737	883	1101
	SC-65872 - 12 mg/kg/day	2845	1115	790	692	971
	Naproxen Sodium - 150 mg/kg/day	4771	294	243	302	243

- ↓ renal clearance for creatine and urea in Weeks 3, 4, and 6 a shown in the following table.

Renal Clearance	Group	Pre-R	Week 2	Week 3	Week 4	Week 6
Urine Creatinine (mg/dl)	Control	99.8	54.2	37.3	46.5	40.4
	SC-65872 - 12 mg/kg/day	99.1	77.3	59.0	46.2	57.4
	Naproxen Sodium - 150 mg/kg/day	127.3	47.8	26.7	28.0	22.7
Urine Urea Nitrogen (mg/dl)	Control	603	451	348	332	394
	SC-65872 - 12 mg/kg/day	821	560	419	362	358
	Naproxen Sodium - 150 mg/kg/day	982.7	339.2	229	368	292

- PK/TK - Both SC-65872 and naproxen were absorbed and systemically available. The mean PK parameters for SC-65872, SC-66905, and naproxen are presented in the following table.

Study Day	Sex	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)	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12} (μg•hr/ml)
		SC-65872 (12 mg/kg/day)			SC-66905			Naproxen (150 mg/kg/day)		
13	♂	1.17	2.52	11.0	1.17	0.0783	0.388	1.33	289	1957
	♀	1.67	3.20	11.8	1.50	0.180	0.568	1.17	419	2247
	♂+♀	1.42	2.86	11.4	1.33	0.129	0.478	1.25	354	2102
42	♂	1.17	2.50	10.3	1.33	0.172	0.613	0.500	526	2500
	♀	2.00	2.85	12.3	2.67	0.142	0.491	1.00	224	1335
	♂+♀	1.58	2.68	11.3	2.00	0.157	0.552	0.750	375	2034

- Necropsy -

  Organ Weights: Groups 3 had ↑ absolute kidney weight and kidney/body weight ratio by 44% and 83%, respectively relative to the controls.

  Gross and Histopathology: No treatment-related gross and histopathological alterations were observed in Groups 1 and 2. However, drug-related renal and GI toxicity was identified in Group 3. The renal gross changes seen in 3/3 Group 3 monkeys included white or pale wedge-shaped or linear streaks of the cortex and/or medulla, minimal to mild enlargement, and yellow speckling of the papilla with microscopic characteristics of increased in amounts of basophilic-staining in the interstitium of the medulla and medullary rays extending into the cortex, minimal to mild fibrosis of the interstitium, and minimal to moderate tubular dilatation in the cortex and medulla. GI cross lesions seen in 4/6 Group 3 monkeys included depressions and black foci of the mucosa of the stomach, a red focus of the mucosa of the duodenum, and pink foci of the mucosa of the jejunum with microscopic observations of minimal to mild ulceration of mucosal of the stomach and duodenum .

Therefore, oral administration of 12 mg/kg/day SC-65872 to monkeys that were fed low-salt diet did not cause any morphologic alterations in the outer renal cortex or changes in renal functions and GI lesions. On contrast, GI lesions and morphologic alterations in the kidney with changes in renal functions secondary to obstructive nephropathy were noted in naproxen sodium-treated monkeys.

2.6.4. IN VITRO COMPATIBILITY WITH HUMAN BLOOD

2.6.4.1. In Vitro Assessment of the Hemolytic Potential of SC-65872 in Human Blood; Date: 28-Jun-2000, Document No. P30E4968 (Vol. 1.120)

Study Nº: EX4968
Report Nº: P30E4968
Study Aim: To evaluate the hemolytic potential of a parenteral formulation of SC-65872 in human blood.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 50 and 250 µl at 0.2 mg/ml, *in vitro*
Blood Samples: Heparinized human blood from four donors
Study Location: Clinical Pathology Laboratory of G.D. Searle and Co., Skokie, IL
GLP/QAU Compliance: N/A
Study Date: 8/5/99
Study Design: The hemolytic potential of SC-65872 was assessed using a modified method of adopted from Salauze and Decouvelaere[8]. Hemolysis was assessed by measuring the free hemoglobin concentration via spectophotometry and the amount of hemolysis was calculated with reference to a fully hemolyzed blood sample.

Results: Neither SC-65872 nor vehicle did cause hemolysis of human RBC.

3. ADME

3.1. ABSORPTION AND PHARMACOKINETICS

3.1.1. SINGLE DOSE

3.1.1.1. Pharmacokinetics of SC-65872 in the Mouse; Date: 21-Jan-2000, Document No. M3098267. (Vol. 1.17)

Report Nº: M3098267
Study Aim: To investigate pharmacokinetics of SC-65872 and its active metabolite, SC-66905, in mice following a single intravenous and oral dosing of SC-65872.
Compound: [redacted]
Vehicle: [redacted]
Dose & Route:

[8] Salauze, D. and Decouvelaere, D. In vitro assessment of the haemolytic potential of candidate drugs. Comp of Haematology Int 4 (1994):34-36

Study Date	Sex	Route	Dose Vol. (ml/kg)	Dose (mg/kg)	Lot Nº	Vehicle
09/17/1998	♂	po	5	5.10	96K016-C26	0.5% methylcellulose (w/v) 0.1% Polysorbate 80 (v/v) in water
09/15/1998	♀	po	5	5.26	96K016-C26	0.5% methylcellulose (w/v) 0.1% Polysorbate 80 (v/v) in water
03/30/1999	♂	po	5	5.05	E90098	PEG 400/Water, 1/2, v/v
03/30/1999	♀	po	5	5.15	E90098	PEG 400/Water, 1/2, v/v
09/28/1999	♂	iv	1	5.49	96K016-C26	PEG 400/Saline, 2/1, v/v
09/29/1999	♀	iv	1	6.61	96K016-C26	PEG 400/Saline, 2/1, v/v
09/10/1998*	♂	iv	5	5.19	96K016-C26	PEG 400/Saline, 2/1, v/v
09/14/1998*	♀	iv	5	5.27	96K016-C26	PEG 400/Saline, 2/1, v/v
04/06/1999*	♂	iv	5	5.05	E90098	PEG400/Saline, 1/2, v/v
04/08/1999*	♀	iv	5	5.15	E90098	PEG 400/Saline, 1/2, v/v

* PK data were calculated for the study but not used in this report

Dosing Frequency: single dose
Animals: ♂ + ♀ CD-1 mice [redacted] weighing 21-48 g
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: 9/15/1998 - 9/29/1999
Blood Collection: iv - Pre-R, 0.05, 0.167, 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 12 hr; 3/sex/time point.
po - Pre-R, 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 12 hr post-dose; 3/sex/time point.
Analysis Methods: [redacted]

Results: Mean PK parameters for SC-65872 and its active metabolite, SC-66905, in mice following a single dose of administration are presented in the following tables.

SC-65872 Plasma Pharmacokinetic Parameters										
Route	Dose[a] (mg/kg)	Sex	T_{max} (hr)	C_{max} (μg/ml)	$T_{½}$ (hr)	Cl (ml/min/kg)	$AUC_{0\text{-last}}$ (μg•hr/ml)	$AUC_{0\text{-}\infty}$ (μg•hr/ml)	Vd (l/kg)	BA (%)
iv	5.49[b]	♂	-	-	0.76	23.6	3.80	3.87	1.56	-
iv	6.61[b]	♀	-	-	0.33	43.2	2.52	2.55	1.23	-
po	5.10[c]	♂	0.50	1.99	-	-	2.51	2.55	-	70.9
po	5.05[d]	♂	0.25	2.25	-	-	3.19	3.20	-	89.8
po	5.26[c]	♀	0.25	1.66	-	-	2.08	2.15	-	106
po	5.15[d]	♀	0.25	2.35	-	-	1.99	1.99	-	100

[a] Dose volume: 1 ml/kg for iv studies and 5 ml/kg for po studies
[b] SC-65872 solution in PEG 400/saline, 2/1, v/v.
[c] SC-65872 suspension in 0.5%Methylcellulose, 0.1% Polysorbate 80.
[d] SC-65872 solution in PEG 400/water, 1/2, v/v.
BA = $[AUC_{0\text{-}\infty\ (po)}/Dose_{(po)}]/[AUC_{0\text{-}\infty\ (iv)}/Dose_{(iv)}] \times 100$

SC-66905 Plasma Pharmacokinetic Parameters						
Route	Dose[a] (mg/kg)	Sex	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0\text{-last}}$ (μg•hr/ml)	$AUC_{0\text{-}\infty}$ (μg•hr/ml)
iv	5.49[b]	♂	0.25	0.913	1.60	1.62
iv	6.61[b]	♀	0.50	1.62	2.43	2.50
po	5.10[c]	♂	0.50	0.348	0.629	0.645
po	5.05[d]	♂	0.50	0.709	1.16	1.21
po	5.26[c]	♀	1.00	0.551	1.28	1.36
po	5.15[d]	♀	0.50	0.693	1.44	1.51

[a] Dose volume: 1 ml/kg for iv studies and 5 ml/kg for po studies
[b] Solution in PEG 400/saline, 2/1, v/v.
[c] Suspension in 0.5%Methylcellulose, 0.1% Polysorbate 80.

[d] Solution in PEG 400/water, 1/2, v/v.

3.1.1.2. Pharmacokinetics of SC-65872 in Blood and Plasma in Male Rats Following Oral Administration; Date: 26-Aug-1999, Document No. M3097310. (Vol. 1.17)

Report Nº: M3097310
Compound: [redacted]
Dose/Route: 3 mg/5 ml/kg po single dose
Animals: 18 adult ♂ rats (Charles River [redacted] weighing 250-350 g
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: The pharmacokinetics and metabolism of SC-65872 were determined in rats following a single oral dose of 3 mg/kg SC-65872. Blood samples (N=3/time point) were collected at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hr post-dose. The concentrations of SC-65872 and SC-66905 in plasma were determined in the whole blood and plasma samples using an [redacted] procedure. The limit of detection of the assay for SC-65872 and SC-66905 was 0.01 μg in plasma and 0.05 μg/ml in blood, respectively.

Results: The PK parameters for SC-65872 and SC-66905 in plasma and blood are shown in the following table. Higher concentrations of SC-65872 and SC-66905 were detected in blood than those in plasma.

	SC-65872				SC-66905			
	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12} (μg•hr/ml)	$AUC_{0-\infty}$ (μg•hr/ml)	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12} (μg•hr/ml)	$AUC_{0-\infty}$ (μg•hr/ml)
Blood	1	6.65	35.5	38.2	4	4.30	33.4	40.2
Plasma	1	1.06	4.44	4.57	4	0.140	0.933	0.990
Blood/Plasma Ratio	1.00	6.26	8.00	8.37	1.00	30.7	35.8	40.6

3.1.1.3. Amendment: M3196106: Bioavailability of Micronized SC-65872 in Male and Female Sprague-Dawley Rats; Date: 13-Jun-1996, Document No. M3096106. (Vol. 1.17)

Report Nº: M3096106
Compound: [redacted]
Dose/Route: 0.11, 0.33, or 1.1 mg/5 ml/kg po single dose
1.1 mg/2 ml/kg iv single dose
Animals: adult Sprague-Dawley rats [redacted] weighing 200-250 g
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: Groups of 6 (3♂ & 3♀) rats were orally given SC-65872 suspension in 0.5% methylcellulose (w/v) and 0.1% polysorbate 80 (v/v) at doses of 0.11, 0.33, or 1.1 mg/kg via gavage. Another group of 6 rats received 1.1 mg SC-65872 in PEG 400:saline (2:1, v/v) by iv injection. Blood samples were collected at 3, 10, and 30 min and 1, 3, 5, and 8 hr after iv dose and at 15 and 30 min and 1, 2, 3, 5, and 8 hr after oral dose. Plasma levels of SC-65872 and its metabolite, SC-66905, were determined by an [redacted] The limit of detection of the assay for SC-65872 and SC-66905 was 0.01 μg and 0.02 μg/ml, respectively.

Results: A summary of PK parameters for SC-65872 following po and iv administration is shown in the following table.

Parameters	Dose (po, mg/kg)						Dose (iv, mg/kg)	
	0.11		0.33		1.1		1.1	
	♂	♀	♂	♀	♂	♀	♂	♀
C_{max} (μg/ml)	0.05	0.04	0.08	0.13	0.31	0.32	-	-
$T_{½}$ (hr)	-	-	-	-	-	-	2.76	4.17
T_{max} (hr)	0.83	1.75	1.67	0.83	2.67	2.67	-	-
$AUC_{0\text{-}8\ hr}$ (hr•μg/ml)	0.146	0.209	0.478	0.629	1.58	1.90	-	-
$AUC_{0\text{-}\infty}$ (μg•hr/ml)	0.154	0.300	0.541	0.856	1.89	2.94	1.78	2.92
Vd (l/kg)	-	-	-	-	-	-	2.56	2.30
CL (ml/kg/min)	-	-	-	-	-	-	10.8	6.65
$BA_{0\text{-}8\ hr}$ (%)	81.7	71.8	89.3	71.8	88.7	65.0	-	-
$BA_{0\text{-}\infty}$ (%)	86.2	103	101	97.7	106	101	-	-

Similar volume distribution values were found in both ♂ and ♀ rats. C_{max} and AUC values increased with dose. It appeared that female rats had longer elimination $T_{½}$, lower plasma clearance values and lower bioavailability of SC-65872 than male rats. Therefore, a gender difference in drug metabolism for SC-65872 did exhibit in rats. The plasma concentrations for active metabolite, SC-66905 were low and below the detection limits (<0.02 μg/ml).

3.1.1.4. Amendment: M3395286; M3295286; M3195286: The Pharmacokinetics and Metabolism of SC-65872 in the Male Rat; Date: 05-Sep-1996, Document No. M3095286 (Vol. 1.17)

Report №: M3095286
Compound: [redacted]
Dose/Route: SC-65872 - 10 mg/kg po or iv
[5-^{14}C]SC-65872 - 2 mg/kg po
Animals: adult ♂ Sprague-Dawley rats [redacted],
weighing ~ 300 g
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: Rats were dosed with 10 mg/kg of SC-65872 (oral suspension or solution or iv bolus) or 2 mg/kg of [5-^{14}C]SC-65872 (oral solution). Multiple blood samples were collected for PK analysis. In the radio-labeled study, tissues, urine and fecal samples were also collected for PK analysis.

Results: Plasma SC-65872 and SC-66905 concentrations and PK parameters following oral or iv administration of 10 mg/kg of SC-65872 are presented in the following table.

Parameters	Dose (mg/kg po) (N=4)				Dose (iv, mg/kg) (N=4)	
	10 mg/kg Solution[a]		10 mg/kg Suspension[b]		10 mg/kg	
	SC-65872	SC-66905	SC-65872	SC-66905	SC-65872	SC-66905
C_{max} (μg/ml)	3.15	1.63	1.67	0.70	5.56	1.78
$T_{½}$ (hr)	-	-	-	-	2.13	8.60
T_{max} (hr)	1.50	3.00	2.50	5.50	0.08	2.25
$AUC_{0\text{-}\infty}$ (hr•μg/ml)	16.2	-	7.97	-	16.7	23.0
Vd (l/kg)	-	-	-	-	1.90	-
CL (ml/kg/min)	-	-	-	-	9.98	-
BA (%)	96.5	-	55.2	-	-	-

[a] Vehicle = PEG:H_2O, 2:1 (v/v); [b] Vehicle = 0.5% methylcellulose + 0.1% Tween 80, aqueous.

At 2 hr post [5-^{14}C]SC-65872 dose, most radioactivity was present in muscle (19.3%), fat (11.5%), liver (8.3%), and skin (7.0%). Seven days post dosing, <0.7% of radioactive dose could be detected in the tissues. On contrast, 65.2% and 17.8% of radioactivity (as % of dose) were recovered in the feces and urine, respectively from 0-168 hr.

3.1.1.5. The Pharmacokinetics and Metabolism of SC-66905 in the Male Rat; Date: 13-Nov-1996, Document No. M3096062. (Vol. 1.17)

Report Nº: M3096062
Compound: [redacted]
Dose/Route: IV & Oral Solution - SC-66905 in PEG 400:saline (2:1, v/v), 2 or 10 mg/kg
Oral Suspension - SC-66905 in 0.025% Tween 80 (v/v) + 0.5% methylcellulose (w/v), 10 mg/kg
Animals: ♂ Sprague Dawley rats [redacted] weighing ~0.3 kg; 3/group.
Study Site: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Design: Male Sprague Dawley rats (3/group), were dosed with 10 mg/kg of SC-66905 (oral suspension or solution or iv bolus) or 2 mg/kg of [5-^{14}C]SC-66905 (oral solution). Multiple blood samples were collected for PK analysis. In the radiolabeled study, tissues, urine and fecal samples were also collected for PK analysis.

Results: Plasma SC-66905 concentrations and PK parameters following oral or iv administration of 10 mg/kg of SC-66905 are presented in the following table.

Parameters	10 mg/kg iv	10 mg/kg po Solution	10 mg/kg po Suspension
$T_{½}$ (hr)	2.65	-	-
T_{max} (hr)	0.083	1.50	2.25
C_{max} (μg/ml)	7.67	3.70	0.763
$AUC_{0-\infty}$ (hr•μg/ml)	21.2	19.9	5.08
CL (ml/kg/min)	7.86	-	-
Vd (l/kg)	1.78	-	-
BA (%)	-	93.9	24.0

Most radioactivity in the tissues was present in liver (3.86%), kidney (1.53%), skin (2.68%), muscle (8.24%), and fat (1.13%) at 2 hr post dosing. Little or no radioactivity (≤0.7%) remained in tissues at 7 days after dosing. SC-66905 was also excreted into urine (~24% of dose) and feces (~11% of dose). Data from the β-glucuronidase treatment of urine samples showed that glucuronide metabolites were present in the 0-24 and 24-48 hr urine. The fecal excretion analysis suggested that the majority of administered SC-66905 was metabolized.

3.1.1.6. The Pharmacokinetics of SC-65872 After Intravenous Administration to the Male Guinea Pig at 2 mg/kg (An Exploratory Study); Date: 05-Mar-1996, Document No. M3096068. (Vol. 1.17)

Report Nº: M3096068
Compound: [redacted]
Dose/Route: 2 mg/2 ml/kg iv single dose
Animals: 3 adult ♂ guinea pigs [redacted] weighing 420-450 g
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A

Study Design: Guinea pigs were dosed with 2 mg/kg of SC-65872 by iv injection. Blood samples were collected at 3, 10, and 30 min and 1, 2, 3, 5, 7, and 24 hr after dosing for PK analysis by an [redacted] The assay sensitivity for both SC-65872 and SC-66905 was 0.010 μg/ml.

Results: Data analysis showed that the elimination of SC-65872 in plasma followed an open one-compartment model first order kinetics. Plasma concentrations of active metabolite, SC-66905, were below the limit of detection. Mean (±SE) plasma levels of SC-65872 at different time points and PK parameters after iv dosing are shown in the following table.

Time (hr)	Plasma SC-65872 Levels (μg/ml)
0.05	0.932 ± 0.079
0.167	0.706 ± 0.145
0.5	0.263 ± 0.097
1	0.0764 ± 0.0358
2	-[a]
3	-[a]
5	-[a]
7	-[a]
24	-[a]
PK Parameters of SC-65872	
$T_{½}$ (hr)	0.280 ± 0.057
Vd (l/kg)	1.88 ± 0.41
CL (ml/min•kg)	78.4 ± 11.0
$AUC_{0-\infty}$ (μg•hr/ml)	0.444 ± 0.064

[a] Value below sensitivity limit of assay (0.010 μg/ml).

3.1.1.7. The Pharmacokinetics and Metabolism of SC-65872 After Intravenous Administration of [5-^{14}C]SC-65872 to the Male Guinea Pig at 10 mg/kg; Date: 24-Apr-1996, Document No. M3096045. (Vol. 1.21)

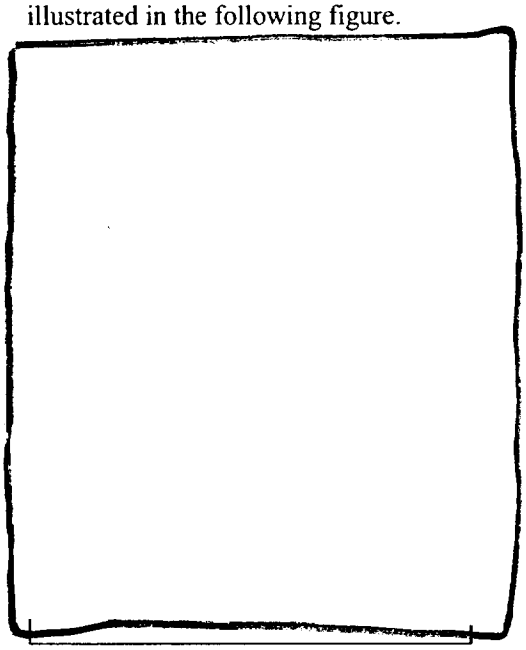
Report Nº: M3096045
Compound: [redacted]
Dose/Route: 10 mg/2 ml/kg iv single dose
Animals: 8 adult ♂ guinea pigs [redacted] weighing 430-470 g
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: Guinea pigs were dosed with 10 mg/kg of SC-65872 by iv injection. Blood samples were collected at 3, 10, and 30 min and 1, 2, 3, 5, 7, and 24 hr after dosing for PK analysis by an [redacted] Urine and fecal samples were collected from 4 animals at 0-24 hr post dose. The representative distribution of radioactivity in plasma, RBC, and urine was determined by an [redacted] method. Radioactivity was measured with liquid scintillation spectrometers (LSC). The assay sensitivity for SC-65872 and SC-66905 was 0.010 μg/ml.

Results: Data analysis showed that the elimination of SC-65872 in plasma after a single iv dose followed an open one-compartment model first order kinetics with a $T_{½}$ value of 0.279 hr. Mean (±SE, n=4) plasma concentrations of SC-65872 and an active metabolite, SC-66905, at different time points following a single iv dose are listed in the following table.

Time (hr)	SC-65872 Levels (μg/ml)	SC-66905 Levels (μg/ml)
0.05	6.23 ± 0.68	0.145 ± 0.06
0.167	4.95 ± 0.65	0.198 ± 0.087
0.5	2.07 ± 0.50	0.151 ± 0.094
1	0.615 ± 0.296	0.107 ± 0.093
2	0.0797 ± 0.0452	0.0405 ± 0.0354
3	0.0188 ± 0.0117	0.0134 ± 0.0134
5	0.00900 ± 0.00455	0.00357 ± 0.00357
7	0.00370 ± 0.00370	-[a]
24	-[a]	-[a]
PK Parameters	SC-65872	SC-66905
$T_{½}$ (hr)	0.279 ± 0.042	NC
V_d (l/kg)	1.35 ± 0.06	NC
CL (ml/min•kg)	59.0 ± 10.2	NC
$AUC_{0-\infty}$ (μg•hr/ml)	2.95 ± 0.65	NC
CL (ml/min•kg)	59.0 ± 10.2	NC
$AUC_{0-\infty}$ (μg•hr/ml)	2.95 ± 0.65	NC

[a] Values below sensitivity limit of assay (0.010 μg/ml).
NC = Not Calculated.

HPLRC profile analysis showed the majority of the radioactivity in 0-24 hr urine was present as polar metabolites and only a minute amount of SC-65872, and the active metabolite, SC-66905, was detected in the urine. On contrast, the majority of the radioactivity in plasma was present as the parent compound, SC-65872 (51%), while the majority of the radioactivity in RBC fraction was derived from SC-65872 (51%) and SC-66905 (41%). Representative HPLRC profiles of urine, plasma and RBC following iv administration of 10 mg/kg [^{14}C]SC-65872 to male guinea pigs are illustrated in the following figure.



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3.1.1.8. Pharmacokinetics of SC-65872 After a Single Oral or Intravenous Dose to Pregnant Rabbit; Date: 13-Mar-2000, Document No. M3099301. (Vol. 1.17)

Report Nº: M3099301
Compound:

Dosage Form: iv - [redacted] 1.01 mg/ml
oral solution - [redacted] 4.78 mg/ml
oral suspension - [redacted]
[redacted] 1.0 mg/ml
Dose/Route: 5 mg/kg po or iv
Animals: 9 pregnant ♀ New Zealand white Hra:SPF rabbits [redacted]
[redacted] weighing ~3 kg; 3/group
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: Pregnant New Zealand rabbits were dosed with 5 mg/kg of SC-65872 by iv or oral administration. Blood samples were collected at 3, 10, 15, and 30 min and 1, 2, 3, 4, 8, 12, and 24 hr after iv dosing and at 15 and 30 min, and 1, 2, 3, 4, 8, 12 and 24 hr after oral dosing. The samples were shipped to [redacted] for PK analysis by a validated [redacted] method. The assay sensitivity for SC-65872 and SC-66905 was 0.020 μg/ml.

Results: The elimination of SC-65872 from plasma was rapid following iv administration of 5 mg/kg SC-65872. Mean PK parameters for SC-65872 and SC-66905 following iv or oral administration are summarized in the following table.

Dose Route		$C_{min\ or\ max}$ (μg/ml)	$T_{½}$ (hr)	T_{max} (hr)	V_d (l/kg)	V_{ss} (l/kg)	CL (ml/min/kg)	AUC_{0-12} (μg•hr/ml)	$AUC_{0-\infty}$ (μg•hr/ml)	BA (%)
IV Solution	SC-65872	15.4	1.07	-	0.521	0.322	0.522	14.1	14.2	-
	SC-66905	4.38	1.18	0.583	-	-	-	8.08	8.01	-
PO Solution[a]	SC-65872	0.530	5.09	0.500	-	-	-	1.62	1.98	14.0
	SC-66905	0.626	10.2	1.00	-	-	-	2.93	4.58	-
PO Suspension	SC-65872	0.544	3.32	0.500	-	-	-	1.61	1.73	12.9
	SC-66905	0.404	2.32	2.00	-	-	-	1.94	2.01	-

[a] 2/3 animals not pregnant at the end of the study.

3.1.1.9. Amendment: M3195287: The Pharmacokinetics and Metabolism of SC-65872 in Female Dog Following Single Dose Administration; Date: 28-Aug-1996, Document No. M3095287. (Vol. 1.17)

Report Nº: M3095287
Compound: [redacted]
Dose/Route: 10 mg/kg iv (2 ml/kg) or po (5 ml)
Animals: 3 ♀ beagle dogs, weighing 9-13 kg
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: This was a non-randomized crossover study with a total 3♀ beagle dogs. The dosing sequence was as followings: iv with 10 mg/kg solution→oral with 10 mg/kg s0lution→oral with 10 mg/kg capsule (neat chemical). Blood samples were taken at various time points. Plasma concentrations of SC-65872 and SC-66905 were determined with an [redacted]

Results: The following table shows plasma SC-65872 and SC-66905 concentrations and PK parameters for SC-65872 following oral or iv administration.

Sampling Time (hr)	Plasma Concentration (μg/ml)					
	10 mg/kg Oral Solution		10 mg/kg Oral Capsule		10mg/kg iv	
	SC-65872	SC-66905	SC-65872	SC-66905	SC-65872	SC-66905
0.0833	-	-	-	-	9.300	0.463
0.167	-	-	-	-	8.430	0.693
0.25	6.02	0.861	0.116	0.011	-	-
0.333	-	-	-	-	9.770	1.59
0.5	6.48	1.40	0.340	0.065	-	-
0.583	-	-	-	-	10.40	2.97
1	5.82	2.34	0.636	0.203	8.68	3.68
2	5.41	3.72	1.270	0.630	5.62	4.56
3	4.02	4.26	1.270	0.961	4.65	6.14
4	2.30	4.43	0.644	1.13	-	-
5	-	-	-	-	2.55	5.40
7	0.57	2.16	0.155	0.453	0.698	2.63
24	0.014	0.415	0.658	0.894	0.031	0.719
48	BLQ	0.086	BLQ	0.152	BLQ	0.112
PK Parameters for SC-65872						
C_{max} (μg/ml)	7.33		1.52		10.80	
$T_{½}$ (hr)	-		-		2.76	
T_{max} (hr)	0.50		9.67		-	
AUC_{0-24} (hr•μg/ml)	29.9		12.2		38.5	
$AUC_{0-\infty}$ (μg•hr/ml)	31.6		20.7		38.7	
Vd (l/kg)	-		-		1.01	
CL (ml/kg/min)	-		-		4.33	
BA (%)	81.0		48.0		-	

BLQ = Value below sensitivity limit of assay (0.01 μg/ml).

3.1.1.10. The Pharmacokinetics and Metabolism of SC-66905 in Female Dog Following Single Dose Administration; Date: 06-Nov-1996, Document No. M3096064. (Vol. 1.18)

Report Nº: M3096064
Compound: [redacted]
Dose/Route: 10 mg/2 ml/kg in PEG 400:H_2O, 2:1 (v/v) po or iv or 10 mg/kg (neat chemical) in capsule
Animals: ♀ beagle dogs, weighing 9-13 kg; 3/group
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: Dogs (n=3) were dosed with 10 mg/kg of SC-66905 by iv or oral administration. Blood samples were taken at various time points after dosing for PK analysis by an [redacted]
The assay sensitivity was 0.010 μg/ml.

Results: Mean plasma levels and PK parameters for SC-66905 following iv or oral administration are presented in the following table. Low systemic absorption of SC-66905 was noted when dogs were given neat chemical in gelatin capsule with a bioavailability of 9.05%.

Time (hr)	IV	PO-Sol.	PO-Cap.
0.0833	18.9		
0.167	17.9		
0.25		5.17	BLD
0.333	15.1		
0.5		9.94	0.229
0.583	13.2		
1	15.6	11.7	0.700
2	15.9	13.9	1.85
3	13.9	13.1	1.62
5	12.6	8.89	1.07
7	11.3	3.37	0.457
24	0.760	0.335	0.352
48	0.0567	0.0310	0.0160
PK Parameters			
C_{max} (μg/ml)	19.5	14.0	1.85
T_{max} (hr)	0.111	2.33	2.00
$T_{½}$ (hr)	5.11	NC	NC
AUC_{0-24} (μg•hr/ml)	210	104	19.0
CL (ml/min•kg)	0.794	NC	NC
V_d (l/kg)	0.346	NC	NC
BA (%)	NC	49.5	9.05

BLQ = Below Limit of Detection (0.01 μg/ml)
NC= Not Calculated

3.1.1.11. The Pharmacokinetics of SC-65872 After Intravenous Administration of SC-65872 to the Male Beagle Dog at 2 mg/kg (an exploratory study); Date: 23-Feb-1996, Document No. MS306046. (Vol. 1.18)

Study Nº: MRC96S-30-96046
Report Nº: MS306046
Compound: [redacted]
Dose/Route: 2 mg/1 ml/kg
Animals: 3 ♂ beagle dogs, weighing 9-11 kg; 3/group
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: Dogs (n=3) were given a single dose of 2 mg/kg SC-65872 by iv administration. Blood samples were taken at 2, 7, 15, 25, and 40 min and 1, 1.5, 3, 5, 8, 12, and 24 hr post dosing. The concentrations of SC-68572 and SC-66905 in plasma were determined using a non-validated [redacted]

Results: The disappearance of SC-65872 from plasma following iv administration of 2 mg/kg SC-65872 followed first order kinetics. PK parameters for SC-65872 and SC-66905 are presented in the following table.

	$T_{½}$ (hr)	T_{max} (hr)	C_{max} (μg/ml)	V_d (l/kg)	CL (ml/min/kg)	$AUC_{0-\infty}$ (μg•hr/ml)
SC-65872	1.48			1.38	12.3	3.21
SC-66905		3.17	0.44			4.79

3.1.1.12. Amendment: M3196096: Bioavailability of Micronized SC-65872 in Male and Female Beagle Dogs at 5 mg/kg; Date: 21-Oct -1996, Document No. M3096096. (Vol. 1.18)

Report Nº: M3096096
Compound: [redacted]

Dosage Forms: IV Solution - SC-65872 in PEG 400:saline (2:1, v/v) (0.5 ml/kg)
Oral Solution - SC-65872 in PEG 400:H_2O (2:1, v/v) (2.5 ml/kg)
Oral Capsule - SC-65872 (neat compound) in gelatin capsule
Dose/Route: 5 mg/kg iv or po
Animals: 3/sex beagle dogs, weighing 8-14 kg
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Blood Collection: IV - 0, 0.05, 0.167, 0.5, 1, 2, 3, 5, 8, 12, 16 and 24 hr
PO Capsule - 0, 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 14, 16, 18, 20, 22 and 24 hr
PO Solution - 0, 0.25, 0.5, 1, 1.5, 2, 3, 5, 8, 12, 16, 24 hr
Study Design: Beagle dogs (3♂ & 3♀), 8-14 kg, were given SC-65872, 5 mg/kg, in a cross-over design. The dosing sequence was as followings: iv with Lot Nº GDS6050-031→po with Lot Nº GDS6111-163→po capsule with Lot Nº GDS6050-031→po capsule with Lot Nº GDS6111-137→po solution with Lot Nº GDS6111-163→iv with Lot Nº GDS6111-163→iv with Lot Nº GDS6111-163. Plasma concentrations of SC-65872 and SC-66905 were determined with a validated [redacted]. Assay sensitivities were 0.010 μg/ml for SC-65872 and 0.020 μg/ml for SC-66905.

Results: PK parameters of SC-65872 and SC-66905 after oral administration of 5 mg/kg SC-65872 to male and female dogs are shown in the following table. Sex-differences in AUC and bioavailability values were noted.

Parameters	GDS6050-031 Capsule				GDS6111-137 Capsule				GDS6111-163 Capsule				GDS6111-163 Solution			
	SC-65872		SC-66905		SC-65872		SC-66905		SC-65872		SC-66905		SC-65872		SC-66905	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
C_{max} (μg/ml)	2.21	1.71	0.96	0.92	3.58	2.81	2.09	1.69	2.23	2.94	1.95	1.94	4.14	4.20	2.67	2.46
T_{max} (hr)	2.17	2.50	3.00	4.00	2.00	1.75	4.33	4.00	2.17	2.50	5.00	4.00	1.58	1.75	4.33	3.00
$AUC_{0\text{-}24hr}$ (hr•μg/ml)	10.0	7.68	8.72	6.73	15.8	12.0	15.5	10.6	12.0	12.4	13.7	13.1	19.9	15.3	19.3	14.0
$AUC_{0\text{-}\infty}$ (μg•hr/ml)	10.1	7.71			15.9	12.1			12.1	12.4			20.1	15.3		
BA (%)	42.5	34.8	-	-	68.3	54.0	-	-	55.1	56.4	-	-	85.4	69.2	-	-

The following table shows PK parameters of SC-65872 after iv administration (5 mg/kg).

Sex	$T_{½}$ (hr)	Vd (l/kg)	CL (ml/kg/min)	$AUC_{0\text{-}\infty}$ (hr•μg/ml)
♂	2.15	0.867	5.15	22.5
♀	1.82	0.610	3.83	22.0

3.1.1.13. Pharmacokinetics of SC-65872 and SC-66905 in Plasma and Blood After Oral Capsule Administration of SC-65872 to Female Dogs; Date: 21-Sep-1999, Document No. M3097298. (Vol. 1.18)

Report Nº: M3097298
Compound: [redacted]
Dose/Route: 3 mg/kg in capsule (neat chemical) po
Animals: 3 ♀ beagle dogs, weighing 9-13 kg
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: Three ♀ beagle dogs were orally given 3 mg/kg of micronized SC-65872 in a gelatin capsule. Blood samples were taken from each dog at 0, 0.25, 0.5, 1, 2, 3, 5, 7, 9, 12, 24, 48 and 72 hr post-dose. Plasma and blood concentrations of SC-65872 and SC-66905 were determined at [redacted] with ar[redacted]. The assay sensitivities were 0.01 μg/ml for plasma and 0.05 μg/ml for blood.

Results: The following table shows PK parameters for SC-65872 and SC-66905 following oral administration of 3 mg/kg SC-65872 to ♀ dogs.

Sample Matrix	SC-65872			SC-66905		
	C_{max} (μg/ml)	T_{max} (hr)	$AUC_{0-\infty}$ (μg•hr/ml)	C_{max} (μg/ml)	T_{max} (hr)	$AUC_{0-\infty}$ (μg•hr/ml)
Blood	1.64	1.8	9.65	1.37	6.3	23.4
Plasma	1.12	2.0	5.25	0.787	4.3	8.20
Blood/Plasma Ratio	1.60	ND	1.84	1.78	ND	2.75

ND: Not Determined.

3.1.1.14. Bioavailability of Formulated Immediate Release Formulations of SC-65872 In Female Beagle Dogs; Date: 03-Mar-1999, Document No. M3096443. (Vol. 1.18)

Report Nº: M3096443
Study Aim: To determine the systemic bioavailability of SC-65872 following administration of several immediate release formulations (capsules or tablets) to dogs.
Compound: [redacted]
Vehicle Control:
Dose & Route: iv - 5 mg/kg; po - 5 or 50 mg/kg.
Each treatment was administered after an overnight fast (except for iv dosing) with a ≥7-day washout period between each study session.

Animal Nº	IV 1	PO 1	PO 2	PO 3	PO 4	PO 5	IV 2
2682788	Soln	Cap	Tab 1	Tab 2	Cap1	Cap 2	Soln
2686368	Soln	Cap	Tab 1	Tab 2	Cap 1	Cap 2	Soln
2688522	Soln	Cap	Tab 1	Tab 2	Cap 1	Cap 2	Soln

Soln = IV solution; Cap = capsule formulation, Lot Nº RCT10311; Cap 1 = capsule formulation, Lot Nº. 9605601;
Cap 2 = capsule formulation, Lot Nº RCT10337; Tab 1 = tablet formulation B-50, Lot Nº F-030-003;
Tab 2 = tablet formulation A-50, Lot Nº F-030-001.

Dosing Frequency: single dose with a ≥7-day washout period
Animals: 3♀ Beagle dogs, weighing ~10 kg
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: 1/9/1997 - 2/20/1997
Blood Collection: po - 0 (Pre-Ⓡ), 15 and 30 min, and 1, 2, 3, 5, 8, and 12 hr;
iv - 0 (Pre-Ⓡ), 3, 10 and 30 min, and 1, 2, 3, 5, 8, and 12 hr (IV 2 only).
Method of Analysis: HPLC; limit of quantitation for both SC-65872 and SC-66905 was 0.01 μg/ml.

Results: Mean PK parameters for SC-65872 and SC-66905 are summarized in the following table. Apparently, Cap 2 formulation provided the best bioavailability.

Dose (mg/kg)	Route	Mean PK Parameters of SC-65872						
		C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg•hr/ml)	$T_{½}$ (hr)	MRT (hr)	CL (ml/min•kg)	Vss (l/kg)	BA[a] (%)
5	iv	4.64	14.5	1.97	2.96	7.03	1.25	-
50	Cap	1.16	5.85	1.33	2.61	4.77	-	43.2
5	Cap 1	0.394	1.32	1.33	1.41	2.70	-	96.2
5	Cap2	0.436	1.56	1.33	1.44	2.94	-	115
50	Tab 1	1.56	7.11	1.83	2.16	4.19	-	48.6
50	Tab 2	0.693	3.69	1.67	4.76	7.43	-	26.6
Mean PK Parameters of SC-66905								
5	iv	1.74	21.7	9.05	14.2	-	-	-
50	Cap	0.829	7.71	5.63	10.5	-	-	-
5	Cap 1	0.182	1.58	5.48	9.00	-	-	-
5	Cap2	0.236	1.68	3.57	6.61	-	-	-
50	Tab 1	1.05	9.79	5.19	9.76	-	-	-
50	Tab 2	0.397	5.52	11.3	18.3	-	-	-

3.1.1.15. Effects of Food on the Plasma Concentrations of SC-65872 Following Oral Administration to Dogs; Date: 14-Apr-1997, Document No. M2096057. (Vol. 1.18)

Study Nº: CHW 6127-291
Report Nº: M2096057
Study Aim: To study the effect of feeding diets with various fat contents on the PK of SC-65872 and SC-66905 in dogs following an oral administration of 2 mg/kg of SC-65872.
Compound: [redacted]
Dose & Route: 2 mg/kg po
Dosing Frequency: single dose with a 7-day washout period
Animals: 3/sex Beagle dogs [redacted] ~7-8 months old, weighing 9.5-14.1 kg.
Study Location (In-Life): [redacted]
GLP/QAU Compliance: N/A
Study Date: 7/18/1996 - 8/9/1996
Study Design: Dogs (3/sex) were fasted overnight prior to dose administration until ~4 hr postdose during Phase 1 study. For Phase 2-4, dogs were given an oral dose of SC-65872, 2 mg/kg, in a gelatin capsule. There was a 7-day washout period between phases.

Phase	Diet	Dose	Nº of Dogs
1	Fasted	2 mg/kg	3/sex
2	Low Fat[a]		
3	Medium Fat[a]		
4	High Fat[a]		

[a] low-fat diet - homogenized of 1 slice of toasted white bread spread with jelly + 8 oz skim milk + 6 oz of orange juice;
[b] medium-fat diet - homogenized of 1 slice of toasted white bread spread with jelly and peanut butter + 1oz corn flake + 8 oz skim milk + 6 oz of orange juice;
[c] high-fat diet - 2 slices of toasted white bread spread with butter + two eggs fried in butter + 2 slices of cooked bacon + 2 oz hash brown potatoes fried in butter + 8 oz whole milk.

Blood Collection: 0, 0.5, 1, 2, 3, 5, 8, 12, and 18 hr.

Results: Mean PK parameters for SC-65872 and SC-66905 in dogs that were given various diets are presented in the following table. It appeared that fat contents in the diets affect T_{max} value of SC-65872 and SC-66905 and AUC value of SC-66905.

Diet Condition	Sex	PK Parameters of SC-65872					PK Parameters of SC-66905				
		$T_{½}$ (hr)	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-t} (μg•hr/ml)	$AUC_{0-\infty}$ (μg•hr/ml)	$T_{½}$ (hr)	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-t} (μg•hr/ml)	$AUC_{0-\infty}$ (μg•hr/ml)
Fasted	♂	1.95	1.67	0.963	4.01	4.12	6.65	3	0.915	5.20	6.04
	♀	4.39	1.33	0.659	1.88	1.98	12.1	3	0.657	3.77	4.87
Low Fat	♂	2.46	3	0.951	4.64	4.78	4.73	5	0.726	6.95	7.93
	♀	1.60	3.67	0.445	1.79	1.89	5.28	7	0.686	6.66	8.26
Medium Fat	♂	2.41	4.33	0.666	3.94	4.08	7.81	7	0.651	6.33	8.90
	♀	2.57	4.33	0.268	1.23	1.43	6.43	9.67	0.484	4.49	5.69
High Fat	♂	2.50	4.33	0.920	4.95	5.07	8.52	6	0.698	7.41	11.2
	♀	2.46	5	0.304	1.60	1.83	5.29	10.7	0.598	6.29	7.74

3.1.1.16. Dose Proportionality of SC-65872 in the Male and Female Cynomolgus Monkey; Date: 06-Jul-1999, Document No. M3097028. (Vol. 1.18)

Report Nº: M3097028
Study Aim: To determine dose proportionality of SC-65872 pharmacokinetics after administration of single oral doses of micronized SC-65872 to ♂ and ♀ cynomolgus monkeys.
Compound: [redacted]
Vehicle:
Dose & Route: 3, 7.5 and 15 mg/2 ml/kg po via nasogastric tube
Dosing Frequency: single dose
Animals: ♂ + ♀ cynomolgus monkeys, weighing 3.8-5.9 kg
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: 2/18/1997 - 3/13/1997
Blood Collection: 0, 0.25, 0.5, 1, 3, 5, 8, 12 and 24 hr
Analysis Method: [redacted] limit of quantitation for both SC-65872 and SC-66905 was 0.01 μg/ml.
Study Design: This was a cross-over study. Cynomolgus monkeys (n=3sex) were orally dosed with 3, 7.5 or 15 mg/kg of SC-65872 with a one-week wash-out period between each dose.

Results: SC-65872 was absorbed and systemically available. The C_{max} and AUC values of SC-65872 and SC-66905 increased proportionally with dose. Mean PK parameters for SC-65872 and SC-66905 in monkeys following a single oral dose are shown in the following table.

Dose (mg/kg)	Sex	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)
3	♂	1.42	1.31	4.32	2.33	0.112	0.380
	♀	0.833	1.30	4.24	0.500	0.115	0.363
	♂+♀	1.13	1.31	4.28	1.42	0.113	0.372
7.5	♂	1.67	2.07	8.04	1.67	0.160	0.530
	♀	1.42	3.11	8.61	1.50	0.138	0.437
	♂+♀	1.54	2.59	8.32	1.58	0.149	0.483
15	♂	1.50	6.63	23.8	3.00	0.314	1.33
	♀	1.00	4.35	16.9	0.833	0.374	1.43
	♂+♀	1.25	5.49	20.4	1.92	0.344	1.38

3.1.1.17. Effect of Drug Particle Size on Relative Bioavailability of Five 20 mg SC-65872 Tablet Formulation After Oral Administration to Male Cynomolgus Monkeys; Date: 30-Sep-1999, Document No. M3098345. (Vol. 1.18)

Report Nº: M3098345

Study Aim: To evaluate the relative oral bioavailability of five SC-65872 (Valdecoxib) 20 mg tablet dosage forms manufactured by using different SC-65872 particle sizes and/or dosage form processing conditions in a 5-way cross-over study.

Compound: SC-65872

Tablet ID	SC-65872 API Lot No.	Size Distribution Sympatec (μm)	Formulated Tablet Lot Nº	Particle Size Reduction
A	97K023-C5B Nº R00174	d_{10}: 0.5 d_{50}: 2.6 d_{90}: 6.5	GDS8712-154-A	Micronized Fluid Energy Mill, Aljet 8
B	97K006-C2B Nº R04365	d_{10}: 1.0 d_{50}: 4.2 d_{90}: 15.8	GDS8712-154-B	Micronized Fluid Energy Mill, Aljet 8
C	97K006-C2B Nº R04365	d_{10}: 1.0 d_{50}: 4.2 d_{90}: 15.8	GDS8712-154-B2	Micronized Fluid Energy Mill, Aljet 8
D	97K023-C5D Nº R 02511	d_{10}: 3.5 d_{50}: 27.4 d_{90}: 106	GDS8712-154-C	Pre-Milled fitzmill, 80 mesh
E	97K023-C5C Nº R04365	d_{10}: 32.4 d_{50}: 222 d_{90}: 348	GDS8712-154-E	Unmilled Recrystallized

Dose & Route: 20 mg po

Dosing Frequency: single doe with a ≥6-day washout period

Animals: 5♂ cynomolgus monkeys, weighing between 6.55 to 8.50 kg

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

GLP/QAU Compliance: N/A

Study Date: 11/10/1998 - 12/08/1998

Blood Collection: Pre-B, 0.25, 0.5, 1, 3, 5, 8, and 12 hr.

Analysis Method: [redacted] the assay lower limits of quantitation were 0.010 and 0.020 μg/ml for SC-65872 and SC-66905, respectively.

Study Design: Each animal received a 20 mg SC-65872 of different formulation on various dates as shown in the following table.

Study Date	SC-65872 20 mg Tablets Used for Each Cynomolgus Monkey				
	M-27-026	M-27-147	M-27-166	M-27-191	M-27-204
11/10/1998	A	B	C	D	E
11/17/1998	E	A	B	C	D
11/24/1998	D	E	A	B	C
12/01/1998	C	D	E	A	B
12/08/1998	B	C	D	E	A

Results: SC-65872 was absorbed and systemically available following administration of each tablet dosage form. Mean PK parameters of SC-65872 are summarized in the following table. Tablet A, B, C, and D with SC-65872 particle sizes ranging 2.6-27.4 μm gave better oral bioavailability than Tablet E that was formulated with an average SC-65872 particle size of 222 μm.

Tablet ID*	SC-65872 PK Parameters			
	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12} (μg•hr/ml)	AUC_{0-12}/Dose
A	8.4	0.511	2.31	0.867
B	7.6	0.979	3.89	1.48
C	8.4	0.587	3.29	1.22
D	6.0	0.385	2.17	0.830
E	6.4	0.144	0.977	0.371

* 20 mg/kg/animal with an average dose of 2.64±0.13 mg/kg.

3.1.1.18. Amendment: M3196341: Bioavailability of Micronized SC-65872 in Female Cynomolgus Monkeys at 5 mg/kg; Date: 04-Aug-1998, Document No. M3096341. (Vol. 1.18)

Report Nº: M3096341
Compound: [redacted]
Dose/Route: 5 mg/kg po or iv single dose
Vehicle: [redacted]
Animals: 3 ♀ cynomolgus monkeys, weighing 4-6 kg
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: This was a cross-over study. Cynomolgus monkeys (n=3) were dosed with 5 mg/kg of SC-65872 by iv injection then by oral gavage with a ≥7-day washout period. Blood samples were taken at 3, 10, and 30 min, and 1, 2, 3, 5, 8, and 12 hr after iv dosing and 15 and 30 min and 1, 2, 3, 5, 8, 12, and 24 hr post oral dosing for PK analysis by an [redacted] The assay sensitivity for SC-65872 and SC-66905 was 0.010 μg/ml.

Results: The mean PK parameters for SC-65872 and SC-66905 are presented in the following table. Elimination of SC-65872 in plasma after a single iv dose of 5 mg/kg SC-65872 to female monkeys followed an open one-compartment model with first order kinetics.

PK Parameters	iv	oral	
	SC-65872	SC-65872	SC-66905
C_{max} (μg/ml)		1.39	0.162
$T_{½}$ (hr)	1.83		
T_{max} (hr)		1.83	1.83
$AUC_{0-\infty}$ (μg•hr/ml)	15.7	8.23	0.655
Vd (l/kg)	0.913		
CL (ml/kg/min)	5.97		
BA (%)		56.8	

3.1.2. MULTI-DOSE PHARMACOKINETICS

3.1.2.1. The Pharmacokinetics of SC-65872 in the Male Lewis Rat After Repeated Oral Administration of [^{14}C]SC-65872; Date: 08-Dec-1995, Document No. MRC95S-30-950212. (Vol. 1.18)

Report Nº: MRC95S-30-950212
Compound: [redacted]
Vehicle: [redacted]
Dose/Route: SC-6587 at 0.11 mg/kg/day bid (6 hr apart) po for 9 days (Days 1→9); [^{14}C]SC-65872 at 0.11 mg/kg/day bid po for 1 day (Day 10)
Animals: 9 ♂ Lewis rats [redacted] weighing 181-212 g
Study Site: G.D. Searle & Co., Skokie, IL.
GLP/QAU Compliance: N/A
Study Design: Rats were dosed orally with 0.11 mg/kg/day of SC-65872 on Days 1→9 and 0.11 mg/kg/day of [^{14}C]SC-65872 on Day 10. Blood samples (3/time point) were collected at 0.25, 0.5, 1, 2, 4, 6, 6.5, 7, 9, 12, 15, and 24 hr on Day 10 for PK analysis.

Results: Mean plasma SC-65872 concentrations on Day 10 after bid oral administration of 0.11 mg/kg/day of SC-65872 for 10 days are shown in the following table. The AUC_{0-24} on Day 10 was 0.422 μg•hr/ml and the C_{max} was 0.0324 μg/ml with a $T_{½}$ value of 2.18 hr.

Time (hr)	SC-65872 Concentration (μg/ml)
0.25	0.0129
0.5	0.0126
1	0.0232
2	0.0214
4	0.0155
6	0.0192
6.5	0.0281
7	0.0324
9	0.0292
12	0.0203
24	0.0112

3.2. DISTRIBUTION

3.2.1.1. Tissue Distribution and Excretion of Radioactivity Following Oral Administration of [Phenyl-^{14}C(U)]SC-65872 to Male Pigmented Rats; Date: 01-Oct-1996, Document No. M2096039. (Vol. 1.19)

Study Nº: CHW 6127-288
Report Nº: M2096039
Study Aims: To obtain information on the tissue distribution and excretion of radioactivity following a single oral administration of [phenyl-^{14}C(U)]SC-65872 to male pigmented rats.
Compound: [redacted]
Dose & Route: 0.468 mg/5 ml/kg po single dose
Animals: 33♂ [redacted][Crl:(LE)BR] rats, 6-7 weeks of age, weighing 171-192 g
Study Location: [redacted]
In-Life: 3/22-29/1996
GLP/QAU Compliance: Yes
Study Design: A total of 33 ♂ [redacted] rats were given a single oral dose of 0.468 mg/kg [pheyl-^{14}C(U)]SC-65872 via gavage. Three animals per time point were sacrificed at 0.5, 1, 2, 4, 8, 14, 48, 72, 96, 144, and 168 hr post-dose. Blood and tissues were collected. Expired air and volatile organic compound were collected from treated animals scheduled to be sacrificed at 168 hr post-dose. In addition, urine and feces were collected from these animals 16 hr pre-dose, and at intervals of 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hr post-dose. Cage washes (50:50 solution of methanol:1% trisodium phosphate) and cage wipes were also harvested for radioactivity analysis. Tissues and blood from one additional animal without receiving test article were included for validation purpose.

Results: No deaths occurred. No drug-related overt clinical signs were observed. The PK parameters for SC-65872 in blood, RBC and plasma following oral administration are given in the following table.

Sample	C_{max} (μg eq/g)	T_{max} (hr)	$AUC_{0-\infty}$ (μg eq•hr/g)	$T_{½}$ (hr)
Whole Blood	1.90	2	30.0	55.5
RBC	3.14	2	48.8	45.6
Plasma	0.194	1	1.78	50.4

The mean total recovery of the radioactive dose (0-168 hr) in excreta and tissues is shown in the following table.

Matrix	Mean % Radioactive Dose Recovered
Urine	36.1
Feces	57.6
Cage Wash	0.69
Cage Wipe	0.65
CO_2 Trap Including backup CO_2 trap	ND
Organic Volatiles	<0.005
Tissues	0.74
Mean Total	96.0

The maximum mean tissue radioactivity was noted at approximately 1-2 hr post-dose. The T_{max} for subcutaneous fat, heart, stomach and vena cava was 0.5 hr and for eye lenses and GI was 4 and 8 hr, respectively. Tissues with highest mean C_{max} values were RBC (3.14 μg eq./g), blood (1.90 μg eq./g), liver (1.14 μg eq./g), bone marrow(1.13 μg eq./g), and kidney (0.772 μg eq./g). The C_{max} of the brain was 0.154 μg eq./g. By 48 hr post dosing, <0.05 μg eq./g of the radioactivity, equivalent to 0.01% of radioactive dose were found in most tissues except kidney (0.063 μg eq./g = 0.12% of radioactive dose). The $T_{½}$ values in most tissues were ranged between 11.1-60.7 hr. Adrenals, aorta, urinary bladder, eye and subcutaneous fat had long terminal elimination halve life with values of 80-360 hr. The following table summarized PK parameters for the elimination of radioactivity from blood, plasma, and representative tissues.

Matrix	C_{max} (μg eq./ml)	T_{max} (hr)	AUC_{0-t} (μg eq•hr/ml)	$AUC_{0-\infty}$ (μg eq•hr/ml)	$T_{½}$ (hr)
Adrenals	0.536	1	5.60	6.71	109
Aorta	0.373	1	8.77	20.0	216
Bladder (Urinary)	0.204	2	2.05	2.16	80.0
Blood	1.90	2	28.7	30.0	55.5
Bone (Both Femurs)	0.217	2	3.15	3.23	45.9
Bone Marrow (Both Femurs)	1.13	2	15.8	16.0	40.5
Brain	0.154	1	1.40	1.43	24.0
Cecum	3.63	8	68.7	69.3	31.9
Eye Lens	0.030	4	0.880	0.938	42.0
Eye (Remainder)	0.310	2	4.91	7.11	157
Fat (Brown)	0.162	2	1.22	1.24	18.6
Fat (Subcutaneous)	0.271	0.5	1.97	3.36	360
Heart	0.471	0.5	4.37	4.52	60.0
Kidneys	0.772	2	13.7	14.3	49.2
Lacrimal Glands	0.572	1	4.36	4.41	39.7
Large Intestine	1.68	8	31.0	31.1	27.0
Liver	1.14	2	11.6	12.0	52.6
Lungs	0.558	2	7.76	8.29	61.3
Lymph Nodes (Mesenteric)	0.207	1	1.66	1.70	30.3
Muscle (Thigh)	0.108	1	0.934	0.957	20.7
Pancreas	0.395	1	3.26	3.32	50.4
Plasma	0.194	1	1.72	1.78	50.4
Prostate	0.319	2	2.76	2.84	49.6
Red Blood Cells	3.14	2	47.3	48.8	45.6
Skin (Dorsal, Shaved)	0.148	1	2.23	2.42	60.7
Small Intestine	1.29	4	7.80	7.85	33.4
Spinal Cord	0.168	1	1.26	1.28	17.1
Spleen	0.720	2	8.45	8.71	50.8
Stomach	5.53	0.5	10.2	10.6	55.3
Testes	0.145	2	1.27	1.31	26.7
Thymus	0.168	1	1.31	1.34	18.6
Thyroid	0.321	1	2.90	3.01	11.1
Vena Cava	0.271	0.5	3.23	4.26	41.1

3.2.1.2. Milk Secretion of [^{14}C]SC-65872 Following a Single Oral Dose to Lactating Rats and Report Amendment No. 1; Date: 26-Oct-1998. Document No. M2097319. (Vol. 1.17)

Study Nº: [redacted]
Report Nº: M2097319
Study Aims: To obtain information on the extent of the drug transfer of [^{14}C]SC-65872 from maternal blood to milk in the rat.
Compound: [redacted]
Dose & Route: 1.01 mg/5 ml/kg po single dose
Animals: 28 timed-pregnant ♀ [Crl:CD(SD)BR] rats [redacted] 6-7 weeks of age, weighing 276-380 g.
Study Location: [redacted]
In-Life: 12/10-12/1997
GLP/QAU Compliance: N/A
Study Design: Lactating ♀ (LD 11-14) rats were given a single oral dose of [^{14}C]SC-65872 at 1.0 mg/kg or vehicle via gavage. Blood and milk samples were collected at selected time points as shown in the following table. Samples were analyzed by the [redacted]

Group	Nº of ♀	Compound	Dose (mg/kg)	Dose Vol. (mg/kg)	Blood and Tissue Collection
1	4	Vehicle	Control	5	48 hr
2	24	[^{14}C]SC-65872	1	5	0.5, 1, 2, 3, 5, 8, 24, and 48 hr (3/time point)

Results: Following a single oral dose of [^{14}C]SC-65872, radioactivity was rapidly transferred from maternal blood to milk. Several metabolites were identified in plasma and milk by [redacted]. The parent drug, SC-65872, accounted for 96.0% (0.171 μg eq [^{14}C]SC-65872/ml) of plasma radioactivity and 100% (0.123 μg eq [^{14}C]SC-65872/ml) of milk radioactivity at 0.5 hours postdose. The amount of SC-65872 in plasma and milk declined to <0.01% of total radioactivity at 48 hours postdose. [^{14}C]SC-66905 was the major metabolite that accounted for 12.9% and 17.5% of total radioactivity detected in 48 hr milk and plasma samples, respectively. PK parameters for total radioactivity, parent drug and SC-66905 are summarized in following table.

PK Parameters		$T_{½}$ (hr)	T_{max} (hr)	C_{max} (μg eq/ml)	AUC_{0-t} (μg eq•hr/ml)	$AUC_{0-\infty}$ (μg eq•hr/ml)
Total ^{14}C	Plasma	9.2	5.0	0.341	5.19	5.34
	Milk	8.1	3.0	0.317	5.42	5.51
		$T_{½}$ (hr)	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-t} (μg•hr/ml)	$AUC_{0-\infty}$ (μg•hr/ml)
[^{14}C]SC-65872	Plasma	4.2	5.0	0.259	3.14	3.14
	Milk	4.9	2.0	0.284	3.42	3.42
[^{14}C]SC-66905	Plasma	8.9	5.0	0.033	0.475	0.488
	Milk	7.5	5.0	0.051	0.960	0.971

3.2.1.3. Amendment: M2198100: Placental Transfer of [^{14}C]SC-65872 After Oral Administration to the Pregnant Rat; Date: 17-Aug-1999, Document No. M2098100. (Vol. 1.19)

Study Nº: [redacted]
Report Nº: M2098100
Study Aims: To determine the transfer of [^{14}C]SC-65872 from maternal blood to amniotic fluid and fetuses in the pregnant rat and the concentrations of SC-65872 and its active metabolite, SC-66905, in plasma, fetal tissues, and amniotic fluid.
Compound: [redacted]
Dose & Route: 0, 2.50 mg/kg/5 ml iv
Animals: Timed pregnant ♀ Crl:CD(SD)®BR rats, weighing 273-319 g
Study Location: [redacted]
Study Date (In-Life): 6/2-3/1998
GLP/QAU Compliance: N/A
Study Design: [^{14}C]SC-65872 (2.50 mg/kg) or vehicle control was given to pregnant ♀ rats on GD 17 by oral gavage. The Group 1 control animal was sacrificed at 24 hr postdose. Group 2 (3 rats/time point) were sacrificed at 1, 3, 5, 8 and 24 hr postdose as shown in the following table.

Group	Nº of ♀	Compound	Dose (mg/kg)	Dose Vol. (mg/kg)	Blood and Tissue Collection
1	1	Vehicle	Control	5	24 hr
2	15	[^{14}C]SC-65872	2.5	5	1, 3, 5, 8, and 24 hr (3/time point)

The following tissues plus blood samples were collected for radioactivity and drug level analysis. Tissues collected were excised, rinsed with saline, blotted dry, weighed, and placed on wet ice. Remaining Group 1 fetal carcasses were used for storage stability samples. The remaining Group 2 fetuses that were not collected for analysis were discarded. All maternal carcasses were discarded.

Maternal Tissues			Fetal Tissues (2 fetuses/dam)	
Adrenal glands	Kidneys	Placenta	Blood	Liver
Amniotic fluid	Liver	Uterus	Brain	Lungs
Brain	Lungs	Two Whole Fetal Carcasses	Heart	
Heart	Ovaries		Kidneys	

Results:

- Tissue Distribution of Radioactivity - The concentration of radioactivity and % radioactive dose in various maternal and fetal tissues at various time points following a single oral administration of [^{14}C]SC-65872 are presented in the following table. The highest radioactivity was detected in the liver. Radioactivity was rapidly distributed to the fetus after oral administration of [^{14}C]SC-65872 to pregnant rats on GD 17 with T_{max} of 3 hr and the highest concentration of radioactivity was detected in the fetal blood sample.

Matrix	Concentrations of Radioactivity and % Radioactive Dose									
	1 hr		3 hr		5 hr		8 hr		24 hr	
	μg eq/g	% Dose	μg eq/g	% Dose	μg eq/g	% Dose	μg eq/g	% Dose	μg eq/g	% Dose
Adrenal glands	2.46	0.02	4.01	0.04	3.39	0.03	3.20	0.03	0.776	0.01
Amniotic fluid	0.337	0.19	0.805	0.39	0.742	0.37	0.656	0.39	0.157	0.10
Blood[a]	4.29		5.75		6.41		6.52		3.04	
Brain	0.583	0.14	0.906	0.22	0.801	0.18	0.704	0.16	0.163	0.04
Heart	1.52	0.14	2.53	0.25	2.33	0.20	2.03	0.19	0.598	0.06
Kidneys	2.37	0.51	3.75	0.83	4.04	0.88	3.81	0.85	1.79	0.39
Liver	3.04	4.82	5.29	7.94	4.75	6.95	4.37	5.84	1.16	1.99
Lungs	1.78	0.22	2.80	0.35	2.61	0.34	2.54	0.35	1.03	0.13
Ovaries	1.58	0.03	2.63	0.05	2.29	0.04	2.04	0.03	0.417	0.01
Placenta	1.18	0.80	2.25	1.65	2.23	1.22	2.05	1.34	0.721	0.57
Plasma[a]	0.929		1.35		1.26		0.958		0.326	
Uterus	0.778	0.32	1.37	0.60	1.40	0.52	1.27	0.52	0.331	0.15
Fetus	1.17	0.11	2.21	0.24	2.01	0.18	1.73	0.21	0.411	0.07
Fetal Blood	1.40		2.71		2.36		2.14		0.741	
Fetal Brain	0.799		1.45		1.31		1.10		0.214	
Fetal Heart	0.983		1.78		1.63		1.19		0.308	
Fetal Kidneys	1.15		2.32		2.05		1.62		0.339	
Fetal Liver	1.41		2.61		2.48		2.16		0.691	
Fetal Lungs	0.941		1.91		1.58		1.36		0.358	

[a] Blood and plasma reported in μg eq/ml.

- Metabolites and PK analysis of Plasma, Amniotic Fluid and Fetuses - PK parameters for total ^{14}C radioactivity, [^{14}C]SC-65872, and [^{14}C]SC-66905 are listed in the following table.

	Sample	C_{max} (μg eq/ml or g)	T_{max} (hr)	AUC_{0-t} (μg eq•hr/ml)	$AUC_{0-\infty}$ (μg eq•hr/ml)	$T_{½}$ (hr)
Total ^{14}C	Plasma	1.35	3	19.0	23.7	10.1
	Amniotic Fluid	0.805	3	11.5	13.3	8.22
	Fetus	2.21	3	30.9	35.7	8.09
[^{14}C]SC-65872	Plasma	**1.09**	3	**13.5**	**14.5**	**6.18**
	Amniotic Fluid	**0.780**	3	**7.09**	**10.4**	**11.6**
	Fetus	**1.45**	3	**NC**	**NC**	**NC**
[^{14}C]SC-66905	Plasma	**0.079**	**8**	**NC**	**NC**	**NC**
	Amniotic Fluid	**0.028**	**8**	**NC**	**NC**	**NC**
	Fetus	**ND**	**ND**	**NC**	**NC**	**NC**

NC = Not calculated due to insufficient time points at the terminal elimination phase; ND = Not detectable.

3.3. METABOLISM AND EXCRETION