Parameters		Dose Group (mg/kg/day)			
		Control	2	6	10
Nº of Inseminated ♀		24	24	24	24
Nº of pregnant ♀		24	23	24	24
Nº of ♀ with Viable Fetuses		24	23	24	23
Nº of ♀ with Non-viable Fetuses		0	0	0	1
Mean Nº of Implantation Sites		14.9 ± 1.8	14.5 ± 1.7	15.5 ± 2.2	14.2 ± 3.0
Pre-implantation Loss		9.3 ± 9.3	7.2 ± 6.0	8.5 ± 7.4	12.3 ± 13.2
Mean Nº of Early Resorptions		0.6 ± 1.0	0.6 ± 1.0	0.8 ± 1.0	1.2 ± 1.9
Total Nº of Early Resorptions		15	14	18	28
Post-implantation Loss		4.2 ± 5.7	4.3 ± 6.1	5.2 ± 7.5	10.0 ± 21.1
Total Live Fetuses (♂+♀)		342	319	353	312
Mean Fetal Body Weight (g)		3.60 ± 0.28	3.65 ± 0.22	3.61 ± 0.23	3.48 ± 0.29
External Malformations					
Acaudate	Fetal Incidence	1 (0.3%)	0	0	0
	Litter Incidence	1 (4.2%)	0	0	0
Soft Tissue Variations					
Dilatation of Lateral Ventricles	Fetal Incidence	3 (1.8%)	1 (0.6%)	0	4 (2.6%)
	Litter Incidence	1 (4.2%)	1 (4.3%)	0	2 (8.7%)
Dilatation of 3rd Ventricle	Fetal Incidence	1 (0.6%)	0	0	0
	Litter Incidence	1 (4.2%)	0	0	0
Increased Renal Pelvic Cavitation	Fetal Incidence	2 (1.2%)	0	3 (1.7%)	3 (1.9%)
	Litter Incidence	2 (8.3%)	0	3 (13%)	3 (13%)
Total Soft Tissue Variation	Fetal Incidence	5 (2.9%)	2 (1.2%)	3 (1.7%)	7 (4.5%)
	Litter Incidence	3 (13%)	2 (8.7%)	3 (13%)	5 (22%)
Soft Tissue Malformations					
Heart and/or Great Vessel Malformation	Fetal Incidence	0	0	1 (0.6%)	0
	Litter Incidence	0	0	1 (4.2%)	0

- PK/TK - Following oral administration of SC-65872 to rats, SC-65872 and SC-66905 were readily detectable in the blood. Mean C_{max} and $AUC_{0\text{-}12hr}$ values for SC-65872 and SC-66905 increased with dose. Increased C_{max} and $AUC_{0\text{-}12hr}$ values for SC-65872 and SC-66905 at doses ≥6 mg/kg/day were noted on Gestation Day 17, an indicative of accumulation following repeated dosing. Plasma concentrations of SC-66905 were much lower than plasma concentrations of SC-65872 on both Gestation Days 6 and 17. The following table shows mean PK parameters for SC-65872 and an active metabolite, SC-66905.

Gestation Day	Dose (mg/kg/day)	SC-65872			SC-66905		
		T_{max} (hr)	C_{max} (µg/ml)	$AUC_{0\text{-}12}$ (µg•hr/ml)	T_{max} (hr)	C_{max} (µg/ml)	$AUC_{0\text{-}12}$ (µg•hr/ml)
6	2	2.0	0.666	4.32	7.0	0.0514	0.487
	6	2.0	1.77	12.2	7.0	0.162	1.46
	10	1.0	2.51	17.2	4.0	0.206	1.90
17	2	4.0	0.596	4.46	4.0	0.0690	0.682
	6	2.0	2.12	17.7	7.0	0.189	1.88
	10	1.0	3.67	28.6	4.0	0.251	2.66

It appeared that the doses used in the current study did not reach MTD. Therefore, the NOAEL was 10 mg/kg/day under current testing conditions.

2.3.2.3. A Study of the Effects of Parecoxib Administered Intravenously on Embryo/Fetal Development in Rats, SA4963; Date: 26-Apr-2000, Document No. P20S4963. (Vol. 1.76-77)

Study Nº: SA4963/WIL-111114
Report Nº: P20S4693 and M3099335 (PK)

Study Aims: To evaluate the maternal and embryo/fetal toxicity and teratogenic potential of SC-69124A when administered iv to pregnant rats.

Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 3.0, 6.25, 12.5, and 25 mg/2 ml/kg iv bid
Dosing Duration: 12 days, Gestation Days (GD) 6→17
Animals: [redacted] Crl:CD®(SD)IGS Br rats, ~13 weeks of age, weighing 238-300 g (on GD 0), 25/group for Toxicology study and 9/group for PK study.
Study Location: [redacted]
In-Life: 8/26-9/19/1999
GLP/QAU Compliance: Yes
Study Design: Groups of 25 mated ♀ rats were randomly assigned to 5 dose groups as shown in the following table.

Group	Dose (mg/kg/day)[a]	Dose (mg/kg/dose)	Dose Vol. ml/kg/dose	Route/ Frequency	Dosing Duration	N° of Animals	
						Toxicology	PK
1	0	0	2	iv/bid	GD 6→17	25	-
2	3	1.5					9
3	6.25	3.125					
4	12.5	6.25					
5	25	12.5					

[a] The dose level and dose concentration represent units of the free acid form of SC-69124A.

The following parameters were monitored:

- Mortality and Clinical Signs - 2x/day.
- Body Weights and Food Consumption - GD 0, 6-18, and 20.
- PK/TK - Blood was collected (3/dose/time point) approximately 5, and 30 min and 1, 3, 7, and 12 hr post-dose on Gestation Days 6 and 17. Control group blood samples were taken from both females at 1 and 4 hr postdose on Days 6 and 17. Plasma samples were shipped to the [redacted] for analysis of SC-69124A and SC-66905 levels by a validated [redacted] procedure.
- Necropsy and Uterine Examination - Gestation Day 20. The uterus from each gravid ♀ was excised, weighed, and examined for the number and placement of implantation sites, live and dead fetuses, early and late resorptions, and any abnormalities of the placenta or amniotic sac. The ovaries of gravid females were examined for the number of corpora lutea. The uterus of apparently non-pregnant rats was stained with ammonium sulfide for verification.
- Fetal Examinations - Each fetus was sexed, weighed, examined for external abnormalities. Heads from approximately ½ of all the fetuses from each litter were randomly selected and processed for visceral examination by the Wilson Technique for assessing soft tissue development. Heads from the remaining fetuses were examined by a mid-coronal slice. All carcasses were eviscerated were fixed in 100% ethyl alcohol and processed for skeletal examination using the [redacted] staining method.

Results:

- Clinical Signs and Mortality - Two dams @ 25 mg/kg were found dead on GD 14 and 17, respectively with macroscopic findings of intestinal adhesions and/or abdominal cavity red fluid filled and clinical observations of soft stool and moderate dried brown matting in the anogenital area at the daily examination, and dried red material on the forelimbs and around the eyes and nose prior to death. Signs of including decreased defecation, red material or matting around the nose, eyes, and forelimbs, yellow matting in the urogenital area, ventral abdominal area, or at the base of the tail and dried brown matting in the anogenital area, were generally observed for animals in the 25 mg/kg/day group.

- Body Weight and Food Consumption - A significant decrease in mean maternal body weight gain (↓22.6%) and food consumption (↓17.4%) was observed at 25 mg/kg/day on GD 18-20. Reduced food consumption (↓9.1%) was noted in the high-dose group on GD 12-18. These reductions were mainly observed in animals that had gastrointestinal injury. Mean maternal body weight, net body weight and gravid uterine weights were unaffected. Sporadic decreases in food consumption were also observed in animals @ 12.5 mg/kg/day.
- Necropsy - Treatment-related GI toxicity was noted in 1 dam @ 12.5 mg/kg and 6 dams @ 25 mg/kg. Two of these high-dose dams were found dead on GD 14 and 17, respectively.
- Female Reproductive Parameters - Comparable results were noted for all examined parameters (corpora lutea, implantations, resorptions, live or dead fetuses, and pre- and post-implantation losses) in both SC-69124A treated and control groups.
- Fetal Parameters - No treatment-related increased incidences in fetal external, skeletal or soft tissue malformations/variations were noted. Reduced fetal body weights by 6% were noted for ♂ fetuses (3.4 vs. 3.6 g in control, significant at $P \leq 0.05$) and female fetuses (3.2 vs. 3.4 g in control) at 25 mg/kg/day.
- PK/TK - Following iv administration of SC-69124 to rats, SC-69124 converted to SC-65872 rapidly. Mean C_{max} and $AUC_{0\text{-}12hr}$ values for SC-65872 and SC-66905 increased with dose. Increased C_{max} and $AUC_{0\text{-}12hr}$ values for SC-65872 were noted on Gestation Day 17, an indicative of accumulation following repeated dosing. Plasma concentrations of SC-66905 were much lower than plasma concentrations of SC-65872 on both Gestation Days 6 and 17. The following table shows mean PK parameters for SC-69124, SC-65872, and an active metabolite, SC-66905.

Gestation Day	Dose (mg/kg/day)	SC-69124		SC-65872			SC-66905		
		$C_{5\ min}$ (μg/ml)	$AUC_{0\text{-}12}$ (μg•hr/ml)	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0\text{-}12}$ (μg•hr/ml)	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0\text{-}12}$ (μg•hr/ml)
6	3	2.51	0.784	0.5	0.344	1.78	1	0.0919	0.453
	6.25	4.43	2.69	1	0.937	4.79	0.5	0.260	1.26
	12.5	10.8	4.22	0.5	2.05	9.81	0.5	0.621	2.17
	25	19.0	7.44	0.5	4.12	24.1	0.5	1.13	5.36
17	3	3.78	1.29	1	0.622	4.08	1	0.0951	0.665
	6.25	5.79	2.44	0.5	1.32	9.14	1	0.208	1.35
	12.5	15.0	5.37	0.5	3.13	25.5	0.5	0.485	3.42
	25	33.7	12.1	1	7.95	59.6	1	0.910	5.73

Therefore, the NOAEL for maternal and development toxicity were 6.25 mg/kg/day and 12.5 mg/kg, respectively by the evidence that GI toxicity was identified in dams @ ≥12.5 mg/kg and reduced mean fetal body weights were noted in fetuses @ 25 mg/kg/day.

2.3.2.4. An Oral Range-Finding Study of Embryo-Fetal Development in the Rabbit with SC-65872, EX4527; Date: 30-Oct-1997, Document No. P30E4527. (Vol. 1.78)

Study Nº: EX4527/CTBR 96158
Report Nº: P30E4527/M3096462
Study Aim: To provide information for the selection of dosages for a subsequent developmental toxicity study of SC-65872.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 1, 5, 25, and 50 mg/5ml/kg/dose po bid (12 ± 2 hr apart) for 13 days (GD 7→19).
Animals: ♀ New Zealand White rabbits [Hra:(NZW)SPF], ~ 5 months of age, 3.1-3.6 kg, 6/group.

Study Location: [redacted]

GLP/QAU Compliance: Not Stated.
Study Date (In-Life): 7/31/1996 – 8/23/1996
Study Design: Rabbits were assigned to 4 dose groups as shown in the following table and given oral administration of SC-65872 twice daily by gavage for 13 days (GD 7→19).

Group	Dose (mg/kg/Dose)	Dose Vol. (ml/kg/dose)	Dosage (mg/kg/day)	Dosing Freq/Duration	Nº of Mated ♀
1	(Vehicle Control)	5	0	po bid GD 7→19	6
2	1	5	2		6
3	5	5	10		6
4	25	5	50		6
5	50	5	100		6

The following parameters were evaluated during the study:

- Clinical Signs - 2x/day.
- Body Weight - Gestation Days 0, 7, 9, 12, 15, 18, 24, and 29.
- Food Consumption - 1x/day for entire gestation period.
- Gross Pathology - A complete necropsy was performed on animals sacrificed at moribund condition and terminal sacrifice on GD 20.
- Necropsy and Gross Pathology - GD 29. Any abnormal tissue was preserved in 10% formalin for possible future histopathological examination.
- Uterine Examination - GD 29. The gravid uterine was weighed and the number of corpora lutea, live fetuses, dead fetuses, sex ratios, and early, mid, and late resorption was recorded. The implantation sites were examined and recorded. The uterus of any non-pregnant animal was stained with 10% (aq) v/v ammonium sulfide solution and examined for implantation sites. The following formulations were used to calculate pre- and post-implantation loss.
  - Pre-implantation Loss (%) = [(Nº of corpora lutea - Nº of implants)/Nº of corpora lutea] x 100
  - Post-implantation Loss (%) = [(Nº of implants - Nº of live fetuses)/ Nº of implants] x 100
- Fetal Examination - Detailed external examination and weight measurement were performed on each fetus.
- PK Determination - Blood samples were collected for drug levels on GD 7→19 at 30 min and 1, 3, 7, and 12 hr post 1st daily dose.

Results:

- Clinical Signs and Mortality - No treatment-related deaths occurred. One Group 5 animal died on Gestation Day 11 as a result of dosing error (perforated esophagus).
- Body Weight and Food Consumption - Significant weight losses during GD 9-18 with reduced food consumption (↓12-51% between Gestation Days 8-22) were noted for the high-dose (100 mg/kg/day) group. The following table lists mean body weight gains for each group during gestation period.

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Mean Body Weight Gains (kg)					
Gestation Day	Dose (mg/kg/day)				
	0	2	10	50	100
0-7	0.15	0.08	0.06	0.07	0.12
7-9	-0.03	0.06	0.08	0.02	0.04
9-12	0.10	0.06	0.08	0.08	0.00
12-15	0.07	0.08	0.10	0.03	-0.05
15-18	0.07	0.02	0.04	0.05	-0.08
18-24	0.07	0.14	0.14	0.10	0.15
24-29	0.15	0.14	0.16	0.12	0.18

- Gross Pathology - No treatment-related macroscopic changes were observed.
- Reproductive Performance - There were significant ↑ in mean numbers of resorptions (early) and post implantation losses and significant ↓ in the numbers of live fetuses in the 50 and 100 mg/kg/day groups as shown in the following table. No live fetuses were observed in the 100 mg/kg/day group.

Parameters		Dose Group (mg/kg/day)				
		Control	2	10	50	100
Nº of Inseminated ♀		6	6	6	6	6
Nº of non-gravid ♀		6	5	5	6	5
Nº of Unscheduled Death		0	0	0	0	1
Nº of ♀ Aborting Prior to Scheduled Sacrifice		0	0	0	0	1
Nº of ♀ with Total Resorption		0	0	0	0	3
Pregnancy Rate (%)		100	83.3	83.3	100	83.3
Nº of ♀ with Non-viable Fetuses		0	0	0	0	0
Mean Live Fetuses/Litter		7.5 ± 2.6	5.8 ± 2.4	8.2 ± 1.6	2.8 ± 1.2	0.0 ± 0.0
Nº of Early Resorptions		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	2.5 ± 2.5	6.0 ± 4.3
Nº of Mid Resorptions		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.5	0.0 ± 0.0
Nº of Late Resorptions		0.3 ± 0.8	0.0 ± 0.0	0.0 ± 0.0	0.2 ± 0.4	0.0 ± 0.0
Total Resorption		0.3 ± 0.8	0.0 ± 0.0	0.0 ± 0.0	3.0 ± 2.6	6.0 ± 4.3
Empty Implantation Sites		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	1.8 ± 3.5
Pre-Implantation Loss		30.4 ± 24.0	34.6 ± 23.7	13.8 ± 19.6	42.8 ± 18.5	9.0 ± 11.9
Post-Implantation Loss		4.2 ± 10.2	0.0 ± 0.0	0.0 ± 0.0	42.8 ± 31.1	100.0 ± 0.0
Mean Fetal Weights (g)	♂	47.5 ± 4.5	53.2 ± 6.0	50.3 ± 2.5	50.7 ± 2.8	-
	♀	49.0 ± 3.4	50.0 ± 2.7	50.8 ± 2.0	46.1 ± 8.0	
	♂ + ♀	48.0 ± 4.0	52.3 ± 5.3	50.6 ± 1.8	50 ± 3.9	

- Fetal Parameters - A slight reduction in ♀ fetal body weights was observed in 50 mg/kg/day group as shown in the above table. No external anomalies were identified.
- PK - SC-65872 was absorbed and systemically available following oral administration to the rabbit during GD 7→19. Mean (±SEM) PK parameters for SC-65872 and SC-66905 on GD 7 and 19 are presented in the following table.

Gestation Day	Dose[a] mg/kg	N	SC-65872			SC-66905		
			T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0\text{-}12hr}$ (μg•hr/ml)	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0\text{-}12hr}$ (μg•hr/ml)
7	1	6	0.5	0.133 ± 0.036	0.368	1	0.103 ± 0.015	0.642
	5	6	0.5	0.757 ± 0.184	2.07	1	0.685 ± 0.081	2.99
	25	6	1.0	9.38 ± 3.19	71.1	1	3.05 ± 0.766	18.1
	50	6	3.0	36.5 ± 11.4	382	3	8.88 ± 1.46	76.7
19	1	3	0.5	0.268 ± 0.073	0.356	1	0.856 ± 0.783	1.38
	5	6	0.5	0.864 ± 0.544	2.17	0.5	0.474 ± 0.190	2.01
	25	6	1.0	11.3 ± 3.39	54.7	1	3.23 ± 0.895	16.5
	50	5	1.0	13.2 ± 8.77	95.7	1	6.31 ±1.01	32.6

[a] bid dosing regimen: 1, 5, 25, and 50 mg SC-65872/kg/day.

Findings from the current dose-range finding study revealed that reproductive performance parameters were altered in the pregnant rabbits receiving SC-65872 ≥50 mg/kg/day from GD 7→19. These changes included significant ↑ in mean numbers of early resorptions and post implantation loses, significant ↓ in the numbers of live fetuses. Moreover, the high-dose group (100 mg/kg/day) females had total resorption (100% of post-implantation loss). The NOAEL of SC-65872 for the rabbit was 10 mg/kg/day.

2.3.2.5. Amendment: P21S4528: An Oral Study of Embryo-Fetal Development in the Rabbit with SC-65872, SA4528; Date: 09-Mar-1998, Document No. P20S4528. (Vol. 1.79)

Study Nº: SA4528/CTBR 96084
Report Nº: P20S4528/M3096455 (PK)
Study Aims: To evaluate the developmental toxicity of SC-65872 when administered daily to New Zealand White rabbits by oral gavage.
Compound: [redacted]
Vehicle Control: [redacted]
Dose and Route: 0, 1.5, 5, and 20 mg/5ml/kg po bid (12 ± 2 hr apart) for 13 days (Gestation Days 7→19).
Animal: ♀ New Zealand White rabbits [Hra:(NZW)SPF], ~6 months of age, 2.7-3.8 kg, 22/group for teratology study and 2-6/group for PK study.
Study Site: [redacted]
In-Life: 9/26/1996 - 10/25/1996
Study Date: 9/18/1996 - 3/5/1998
GLP/QAC Compliance: Yes
Study Design: Rabbits were assigned to 4 dose groups as shown in the following table and given oral administration of SC-65872 twice daily by gavage for 13 days (Gestation Days 7→19).

Group	Dose (mg/kg/Dose)	Dose Vol. (ml/kg/dose)	Dosage (mg/kg/day)	Route/ Frequency	Dosing Duration	Nº of Mated ♀	
						Tox	PK
1	(Vehicle Control)	5	0	po bid	13-day (GD 7→19)	22	2
2	1.5	5	3			22	6
3	5.0	5	10			22	6
4	20.0	5	40			22	6

The following parameters were evaluated during the study:

- Clinical Signs - 2x/day for entire gestation period.
- Body Weight - Recorded on Gestation Days 0, 7, 9, 12, 15, 18, 24, and 29.
- Food Consumption - 1x/day for entire gestation period.
- Gross Pathology - A complete necropsy was performed on animals sacrificed at moribund condition and terminal sacrifice on Gestation Day 20.
- Terminal Examination - Gestation Day 29.
- Uterine Examination - Gestation Day 29. The gravid uterine was weighed and the number of live fetuses, dead fetuses, and early, mid, and late resorption was recorded. The implantation sites were examined and recorded. The uterus of any non-pregnant animal was stained with 10% (aq) v/v ammonium sulfide solution and examined for implantation sites. The following formulations were used to calculate pre- and post-implantation loss.
  - Pre-implantation Loss (%) = [(Nº of corpora lutea - Nº of implants)/Nº of corpora lutea] x 100
  - Post-implantation Loss (%) = [(Nº of implants - Nº of live fetuses)/Nº of implants] x 100
- Fetal Examination - Detailed external and internal examinations and weight measurement were performed on each fetus. Skeletal and visceral examinations were also performed.

- PK Determination - Blood samples were collected for drug levels on Gestation Days 7 and 19 at 30 min and 1, 3, 7, and 12 hr post 1st daily dose.

Results:

- Clinical Signs and Mortality - No treatment-related deaths occurred. A total of 15 deaths (3 @ 0, 1 @ 3, 3, @ 10 and 8 @ 40 mg/kg/day) due to dosing errors. Abortion was observed for 1 in Group 1, 2 in Group 2 and 3 in Group 3. Some of these abortions was attributable to trauma caused by the dosing error.
- Body Weight and Food Consumption - Treatment with SC-65872 did not cause significant changes in body weights, weight gains and food consumption.
- Reproductive Performance - There were significant ↑ in mean numbers of resorptions (early and late) and post implantation losses and significant ↓ in the numbers of live fetuses in the ♀ @ 40 mg/kg/day as shown in the following table.

Parameters		Dose Group (mg/kg/day)			
		Control	3	10	40
Nº of Inseminated ♀		24	28	28	29
Nº of non-gravid ♀		4	7	2	0
Nº of Unscheduled Death		3	1	3	8
Nº of ♀ Aborting Prior to Scheduled Sacrifice		0	1	2	3
Nº of ♀ with Total Resorption		1	0	1	3
Pregnancy Rate (%)		83.3	75.0	92.9	100.0
Nº of ♀ with Non-viable Fetuses		0	0	0	0
Nº of Early Resorptions	Including ♀ with Total Resorption	0.4 ± 1.22	0.1 ± 0.33	0.1 ± 0.34	2.4 ± 2.65
	Excluding ♀ with Total Resorption	0.1 ± 0.25			2.1 ± 2.64
Nº of Late Resorptions	Including ♀ with Total Resorption	0.0 ± 0.00	0.2 ± 0.39	0.3 ± 0.45	0.9 ± 1.56
	Excluding ♀ with Total Resorption	0.0 ± 0.00			1.0 ± 1.65
Total Resorption	Including ♀ with Total Resorption	0.4 ± 1.23	0.3 ± 0.59	0.4 ± 0.50	3.3 ± 2.70
	Excluding ♀ with Total Resorption	0.1 ± 0.34			3.2 ± 2.79
Mean Live Fetuses/Litter	Including ♀ with Total Resorption	6.6 ± 2.81	7.6 ± 2.55	7.1 ± 1.57	4.6 ± 2.77
	Excluding ♀ with Total Resorption	7.0 ± 2.31			5.3 ± 2.15
Pre-Implantation Loss	Including ♀ with Total Resorption	25.6 ± 22.62	24.0 ± 21.25	16.2 ± 16.77	21.5 ± 20.6
	Excluding ♀ with Total Resorption	24.8 ± 23.15			17.5 ± 17.25
Post-Implantation Loss	Including ♀ with Total Resorption	7.7 ± 24.33	3.6 ± 7.31	4.7 ± 6.42	43.1 ± 35.57
	Excluding ♀ with Total Resorption	1.9 ± 5.31			33.7 ± 28.44
Nº of Empty Implantation Sites	Including ♀ with Total Resorption	0.0 ± 0.00	0.2 ± 0.71	0.5 ± 1.54	1.2 ± 2.65
	Excluding ♀ with Total Resorption	0.0 ± 0.00			1.3 ± 2.79

- Fetal Parameters - Slight but not statistical significant reduction in fetal body weights was observed in 40 mg/kg/day group. Increased incidence of fetuses with major malformations was noted. The major malformations observed were as followings.
  - 3 mg/kg/day: Microcaudia was noted in one fetus (Nº 296/1).
  - 10 mg/kg/day: Interventricular septal defect in the heart with stenosis of the pulmonary truncus and dilatation of the aorta were identified in one fetus (Nº 367/4).
  - 40 mg/kg/day: The 1st fetus (Nº 456/10) had micrognathia of the upperjaw, reduced nares and hydrocephaly. Acephaly, gastroschisis, aphalangia of the forepaws, microdactyly of the forepaws and hindpaws, clinodactyly of the forepaws and hindpaws and microcaudia were observed in the 2nd fetus (Nº 460/4). The 3rd fetus (Nº470/6) had micrognathia of the upper and lower jaws, hydrocephaly, nares absent, cleft palate, and microcaudia. The 4th fetus (Nº 465/7) had opacity of the lenses.

  In addition, increased minor skeletal anomalies was noted in the 40 mg/kg/day group as the results of ↑ in the incidence of fetuses with semi-bipartite thoracic vertebra centra and fused sternebrae. Significant findings in the fetal parameters (Mean ± SD) are shown in the following table.

Parameters	Dose Group (mg/kg/day)			
	Control	3	10	40
Fetal Body Weight (g)	47.57 ± 5.77	47.07 ± 5.57	46.64 ± 5.2	45.84 ± 4.5
External, Visceral and Skeletal Examination (Nº Litter Examine/Nº Fetuses Examine)	16/112	17/130	16/113	12/64
Total Major Malformations (Nº Litter /Nº Fetuses)	0/0	1/1	1/1	4/4
Nº Fetuses with Minor Skeletal Anomalies	5/7	5/9	5/5	10/16
Thoracic Vertebral Centrum Semi-Bipartite	3/4	4/5	2/2	7/9
Sternebrae Fused	1/1	1/1	2/2	4/6

- PK - Significant accumulation of SC-65872 had occurred following repeated oral bid administration to the pregnant rabbits by the evidence of much higher C_{max} and AUC values obtained on Gestation Day 19 as compared with those values obtained on Gestation Day 7. This observation was more prominent in the mid- and high-dose groups as shown in the following table.

Gestation Day	Dose[a] mg/kg	N	SC-65872			SC-66905		
			T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0\text{-}12hr}$ (μg•hr/ml)	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0\text{-}12hr}$ (μg•hr/ml)
7	1.5	6	0.5	0.067 ± 0.033	0.168	1	0.033 ± 0.015	0.160
	5	6	1	0.384 ± 0.069	1.42	1	0.365 ± 0.047	1.61
	20	6	0.5	3.66 ± 1.14	10.6	1	2.52 ± 0.142	8.57
19	1.5	6	1	2.90 ± 2.66	4.96	1	0.420 ± 0.248	0.977
	5	6	1	1.75 ± 0.535	11.6	1	0.602 ± 0.116	2.79
	20	5	1	16.8 ± 1.45	116	3	1.79 ± 0.0769	13.8

[a] bid dosing regimen: 3, 10, and 40 mg SC-65872/kg/day.

Data showed that placental transfer of SC-65872 and SC-66905 did occur and the concentrations SC-65872 and SC-66905 measured on GD 20 were lower than those in the maternal plasma measured on GD 19. The following table presents pooled (by litter) fetal plasma concentrations of SC-65872 and SC-66905.

Gestation Day	Time (hr)	Animal ID Nº	Dose* mg/kg/dose	Fetal Plasma Concentration (μg/ml)		Maternal Concentration (μg/ml)	
				SC-65872	SC-66905	SC-65872	SC-66905
20	3	251	1.5	<0.200	<0.200	0.112	0.148
20	3	351	5	0.0554	0.0913	0.208	0.391
20	3	352	5	0.153	<0.0857	1.08	0.347
20	3	452	20	3.70	0.430	17.4	1.51
20	3	455	20	3.17	0.501	12.7	1.89
20	3	373	5	<0.0857	<0.0857	0.697	0.338
20	3	376	5	<0.050	0.0502	0.438	0.402
20	3	476	20	1.12	0.327	8.96	1.96
20	3	277	1.5	<0.0273	< 0.0273	0.0537	0.103
20	3	477	20	2.10	0.628	12.4	1.78

* bid dosing regimen: 3, 10, and 40 mg SC-65872/kg/day.
< Indicates that the diluted sample concentration values were below assay quantitation.

In conclusion, the NOAEL of SC-65872 for the rabbit was 10 mg/kg/day in the current study and it caused a significant ↑ in mean numbers of resorptions (early and late) and post implantation losses and a significant ↓ in the numbers of live fetuses in the ♀ @ 40 mg/kg/day.

2.3.2.6. A Study of the Effects of Valdecoxib Administered Orally on Embryo/Fetal Development in Rabbits, SA4992; Date: 07-Jul-2000, Document No. P20S4992. (Vol. 1.80-81)

Study Nº: SA4992/WIL-111122

Report Nº: P20S4992/M3099428 (TK)
Study Aim: To evaluate potential maternal and developmental toxicity of SC-65872 following oral administration to rabbits.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 3, 10 and 40 mg/kg/day po at 2 ml/kg/dose
Dosing Frequency: bid (12±2 hr apart)
Dosing Duration: 12 Days (Gestation Days 7→18)
Animals: New Zealand White rabbits [Hra(NZW)SPF] [redacted] ~6 months of age, weighing 2938-4049 g for Toxicology study group and 3028-4408 g for PK/TK study groups; 25 (Groups 2-4)-50 (Control)/group for Toxicology study and 6/group for PK/TK study.
Study Location: [redacted]
GLP/QAU Compliance: Yes
Study Date: 12/15/1999 (Dosing Initiation) - 1/6/2000
Study Design: Groups of 25-50 rabbits were randomly assigned to 4 dose groups and orally received SC-65872 at dose levels as shown in the following table.

Group	Compound	Dose (mg/kg/day)	Dosage (mg/kg/dose)	Dose Conc. (mg/ml)	Route/ Frequency	Dose Vol. (ml/kg)	Dosing Duration	Nº of Rabbits	
								Tox	PK
1	Vehicle Control	0	0	0	po bid	2	GD 7→18	50	-
2 (low)	SC-65872	3	1.5	0.75				25	6
3 (mid)		10	5	2.5				25	6
4 (high)		40	20	10				25	6

The following parameters were monitored:

- Mortality and Clinical Signs - 2x/day.
- Body Weights - GD 0, 7→19 (daily), 24 and 29.
- Food Consumption - GD 0→29, 1x/day.
- PK/TK - Blood samples were obtained from 3/group rabbits at 5 and 20 min, and 1, 4, 8, and 12 hr post the 1st daily dosing on GD 7 and 18. Plasma samples were shipped to [redacted] for drug level analysis. The limit of quantitation for both SC-65872 and SC-66905 in undiluted plasma samples was 0.02 μg/ml.
- Necropsy - GD 19 (PK animals) and GD 29. The ovaries and uterus were removed, the uterus was weighed, and the numbers of corpora lutea were recorded for each ovary. The uterus was examined and implantation sites were determined. Uterine implants, Nº of live/dead fetuses and resorption were determined. Uteri with no grossly recognizable implantations were placed in 10% ammonium sulfide solution for detection of early implantation loss as described by Salewski[2].
- Fetal Examination - The following parameters were determined.
  - Fetal Weight;
  - Fetal Sex;
  - External Morphology;
  - Viseral and Skeletal Examination.

Results:

[2] Salewski, E., 1964. Färbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. Naunyn - Schm. Archiv. für Exper. Pathologie und Pharm. 247:367.

- Mortality and Clinical Signs - Two dams in the control group had aborted on GD 23 and 27, respectively and one dam @ 40 mg/kg aborted on GD 25. No treatment-related clinical signs were noted.
- Body Weights and Food Consumption - Comparable mean body weights were recorded for each group. However, significantly lower mean body weight gains were observed in Groups 3 (↓43%, P≤0.05) and 4 (↓70%, P≤0.01) during GD 13-19. Additionally, Groups 3 and 4 had lower mean body weight gains during the treatment period (GD 7→19) by 30% and 49% (≤0.01), respectively as compared with the control group.
- Gross Pathology - There were no treatment-associated gross changes noted.
- Female Reproductive Parameters - There were significant ↑ in post implantation losses with ↑ in the numbers of early resorptions and lower post-implantation survival index as a result of significant ↓ in the numbers of live fetuses in the ♀ @ 40 mg/kg/day as shown in the following table.

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Parameters		Group 1 Control	Group 2 3 mg/kg/day	Group 3 10 mg/kg/day	Group 4 40 mg/kg/day
Nº of Gravid ♀ at Scheduled Sacrifice		40 (83.3%)	19 (76%)	20 (80%)	22 (91.7%)
Nº of Gravid ♀ with Viable Fetuses		40 (100%)	19 (100%)	19 (95%)	13 (59.1%)
Nº of Gravid ♀ with Resorptions Only		0	0	1 (5%)	9 (40.9%)
Nº of Non-Gravid ♀		8 (16.7%)	6 (24%)	5 (20%)	2 (8.3%)
Corpora Lutea	Mean±SD	10.5±2.81	10.1±3.21	11.5±3.79	10±2.44
	Total	421	191	230	219
Implantation Sites	Mean±SD	7.3±2.61	6.5±3.13	6.7±3.13	6.8±2.15
	Total	291	123	133	150
Mean (±SD) Preimplantation Loss (%/Litter)		29.7±21.99	36.2±20.58	37.8±29.28	29.7±20.62
Nº (Mean ±SD) of Resorptions	Early	21 (0.5±0.22)	3 (0.2±0.37)	7 (0.4±0.81)	96 (4.4±3.09)
	Late	2 (0.1±0.22)	0	3 (0.2±0.37)	4 (0.2±0.66)
Postimplantation Loss (%/Litter)		7.1±11.26	3.7±9.22	12.9±27.8	66.4±35.02
Total Nº Dead Fetuses		0	0	1	0
Live Fetuses	Mean±SD	6.7±2.44	6.3±3.25	6.1±3.45	2.3±2.49**
	Total (♂/♀)	268 (132/136)	120 (57/63)	122 (57/65)	50 (24/26)
Postimplantation Survival Index		92.1	97.6	91.7	33.3
Mean (±SD) Fetal Weight (g)	♂	48.5±6.40	49.0±6.36	46.8±4.55	47.8±5.2
	♀	47.3±5.25	48.9±6.84	47.5±6.95	48.2±6.31
FETAL EXAMINATIONS					
Nº of Fetuses/Litter Examined		268/40	120/19	122/19	50/13
Nº Fetuses/Litter w/ Malformation (%/litter)		4/2 (1.9%)	1/1 (0.5%)	3/3 (1.7%)	4/4 (10.9%)*
Total Nº Fetuses/Litter w/ Eternal Malformation (%/litter)		1/1 (0.4%)	0	0	0
Nº Fetuses/Litter w/ Soft Tissue Malformations (%/litter)		0	0	0	1/1 (3.8%)
Nº Fetuses/Litter w/ Skeletal Malformations (%/litter)		3/2 (1.5%)	1/1 (0.5%)	3/3 (1.7%)	3/3 (7.1%)
EXTERNAL MALFORMATION - Nº of Fetuses/Nº of Litter (%/litter)					
Exencephaly w/ or w/o Open Eyelid		1/1 (0.4%)	0	0	0
Microphthalmia and/or Anophthalmia		1/1 (0.4%)	0	0	0
VISCERAL MALFORMATION - Nº of Fetuses/Nº of Litter (%/litter)					
Mal-positioned Kidney(s)		0	0	0	1/1 (3.8%)[a]
Hydrocephaly		0	0	0	1/1 (3.8%)[a]
SKELETAL MALFORMATION - Nº of Fetuses/Nº of Litter (%/litter)					
Vertebral Anomaly w/ or w/o Rib Anomaly		2/2 (1.2%)	1/1 (0.5%)	1/1	1/1 (2.6%)
Rib Anomaly		1/1 (0.4%)	0	1/1 (0.5%)	1/1 (2.6%)
Sternebrae Mal-aligned (Severe)		1/1 (0.4%)	0	0	0
Sternebrae Fused		0	0	1/1 (0.7%)	1/1 (1.9%)
Total %/Litter with Variations		76.9	74.5	81.5	95.9**
%/Litter with External Variations		0	0	0	0
%/Litter with Soft Tissue Variations		25.9	21.7	26.1	32.0
%/Litter with Skeletal Variations		71.3	71.2	73.9	92.0**

[a] fetus with multiple malformations

- Fetal Examination - Data presented in the above table showed that higher incidence of fetuses with skeletal malformations and variations was recorded for the high-dose (40 mg/kg/day) group.
- PK/TK - SC-65872 was systemically available after oral administration and rapidly metabolized to SC-66905 as similar T_{max} values for SC-65872 and SC-66905 were noted. Increased SC-65872 plasma levels were observed on GD 18 at doses ≥10 mg/kg/day, an indicative of accumulation. Plasma concentrations of SC-66905, the active metabolite, proportionally increased with the dose. However, no accumulation of SC-66905 occurred after repeated dosing.

Day	Dosage (mg/kg)		S C-65872			S C-66905		
	Dose (bid)	Daily (Total)	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12hr} (μg•hr/ml)	T_{max} (hr)	C_{max} (μg/ml)	AUC_{0-12hr} (μg•hr/ml)
7	1.5	3	1.00	0.238	0.526	1.00	0.167	0.572
	5	10	0.33	0.423	1.26	1.00	0.697	2.52
	20	40	1.00	2.55	14.5	1.00	2.51	12.5
18	1.5	3	1.00	0.281	0.875	1.00	0.140	0.611
	5	10	0.33	1.02	2.97	1.00	0.677	2.82
	20	40	4.00	13.4	107	4.00	1.63	12.7

Only one pooled fetal plasma sample from a litter at 10 mg/kg/day group had detectable levels of SC-65872 (2.43 μg/ml) and SC-66905 (0.347 μg/ml) on GD 19, indicating that placental transfer of SC-65872 and it's metabolite, SC-66905, might have occurred. Data from a previous Seg II study (Study Nº SA4528) in the rabbits showed that low levels of SC-65872 and SC-66905 were detected in the fetal plasma at 3 hr post-dose.

Therefore, SC-65872 at a dose level of 40 mg/kg/day caused reduced body weight gains, fetal lethality by the evidence of ↑ post-implantation losses with ↓ number of live fetuses, and increased incidence of fetuses with skeletal malformations following oral administration to pregnant rabbits throughout the organogenesis.

2.3.2.7. Study of Effects on Pre- and Post-Natal Development in CD Rat by Oral Gavage Administration of SC-65872, SA4776; Date: 26-Apr-2000, Document No. P20S4776. (Vol. 1.82)

Study Nº: SA-4476/MON104/984706
Report Nº: P20S4476
Study Aims: To assess potential toxicity of SC-65872 on pre- and post-natal development and reproductive performance of the F_1 offspring following oral administration to rats.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 2, 6, and 10 mg/kg/day po (gavage) at 5 ml/kg/dose
Dose frequency: bid (12±2 hr apart)
Dosing Duration: Gestation Days (GD) 6→Lactation Day (LD) 20 for 2 and 6 mg/kg/day groups and GD 6→CD 6-15 for 10 mg/kg/day group
Animals: Crl:CD®BR [redacted] rats [redacted] 10-11 weeks of age, weighing 211-273 g; 25/group.
Study Location: [redacted]
Study Date: 04/27/1998 (Dosing Initiation) - 8/30/1998
GLP/QAU Compliance: Yes
Study Design: Groups of 25 rats were randomly assigned to 4 dose groups and orally received SC-65872 at dose levels as shown in the following table. Animals in the PK/TK groups received an additional dose on GD 19. Due to the excessive toxicity (GI perforations), Group 4 (10 mg/kg/day) animals were terminated early. Litters of dams @ 10 mg/kg/day were terminated before weaning.

Group	Compound	Dose (mg/kg/day)	Dosage (mg/kg/dose)	Route/ Frequency	Dose Vol. (ml/kg/dose)	Dosing Duration	Nº of Rabbits
1	Vehicle	0	0	po bid	5	GD 6→LD 20	25
2 (low)	SC-65872	2	1				25
3 (mid)		6	3				25
4 (high)		10	5			GD 6→LD 6-15	25

The following parameters were monitored.

Observations of F_0:

- Mortality and Clinical Signs - 2x/day and 6x/day from GD 20.
- Body Weights - GD 0, 3, 6, 10, 14, 17, and 20 to parturition (daily); LD 1, 4, 7, 11, 14, 18, and 21.
- Food Consumption - GD 0-2, 3-5, 6-9, 10-13, 14-16, and 17-20; LD 1-3, 4-6, 7-10, 11-13, 14-17, and 18-20.
- Necropsy - LD 21 or on the day of litter loss. The uterus was examined and implantation sites were determined. Specimens of any abnormal tissues were retained in appropriate fixative. When a litter died before weaning, the mammary tissue of the female was examined and a specimen retained. Kidneys were retained in appropriate fixative for animals that were sacrificed after May 28, 1998.

Observations of F_1

- External Examination - PND 1.
- Clinical Signs and Mortality - 1x/day.
- Litter Size - PND 1→21 (1x/day) and 28.
- Sex Ratio - PND 1, 4, and 21.
- Culling - Day 4, 4/sex/litter.
- Body Weights - Postnatal Days (PND) 1, 4 (prior to culling), 7, 11, 14, 18, 21, and 28.
  - F_1 unselected offspring and selected ♂ - 1x/week until termination;
  - F_1 selected ♀ offspring - 1x/week until mating detected; GD 0, 7, 14, and 21 and LD 1, 4, and 7.
- Sensory, Behavioral and Neuromuscular Function Examinations - Groups 1-3 only.
  - Auditory Function - Day 25.
  - Visual Function - Day 25.
  - Nocturnal Activity - Day 26/27.
  - Learning Ability (Water-Filled Y-Maze) - Day 27.
  - Neuromuscular Function (Traveling Rods, Rotarod Treadmill, Mid-air Righting Reflex, Wire- and Grid Gripping Ability) - Days 28-30.
- Selection of F_1 - Week 5, 20/sex/group (1/sex/litter if possible)
- Sexual Maturation - ♂: 1x/day from Day 38 until balano-preputial separation occurs; ♀: 1x/day from Day 28 until vaginal opening occurs.
- Mating Performance - 1:1 pairing at ~9-10 weeks of age for up to 3 weeks.
- Necropsy - No macroscopic examinations were performed on fetuses from dams found dead or sacrificed during gestation.
  - F_1 unselected offspring - after completion of selections (Week 5).
  - F_1 ♀ successfully mated - LD 7. The number of implantation sites were recorded. The kidneys and any abnormal tissues were retained in appropriate fixative.
  - F_1 ♀ failing to mate - after group fertility established.
  - F_1 ♂ - after necropsy of F_1 ♀. Kidneys from each F_1 ♂ were retained.

Observations of F_2

- Litter Size - PND 1→7.
- Sex Ratio - PND 1 and 7.
- Necropsy - PND 7. Kidneys from 1/sex/litter and any abnormal tissues were retained.

Results:

Observations of F_0:

- Clinical Signs and Mortality - Signs of pile-erection, hunched posture, pallor, reduced activity and changes in respiratory pattern were noted in some mid- (6 mg/kg/day) and high-dose (10 mg/kg/day) groups. There were a total of 24 unscheduled deaths, 12 each @ mid- and high-dose groups. Data as presented in the following table showed that most of these unscheduled deaths were attributable to treatment-related GI damage as the evidence of intestinal perforations, adhesion of ileum and abdominal viscera, or fluid in the abdomen identified at necropsy. Due to the excessive toxicity observed in the in high-dose group, the animals were terminated early (LD 7→16). The maximal incidence of treatment-related gastrointestinal injury occurred between 1-2 weeks post 10 mg/kg/day dosing and between 4-5 weeks post 6 mg/kg/day treatment.

Group	Animal Number	Day of Death	Type of Death	Doses Received	Major findings related to ileum		
					Adhesions	Perforation	Fluid in Abdomen
4	1090	15 pc	HK	19	+	+	
	1088	16 pc	HK	21	+	+	
	1093	16 pc	HK	21	+	+	
	1084	17 pc	HK	22	+		
	1079	18 pc	FD	24	+		+
	1095	19 pc	HK	27	+	+	
	1077	19 pc	KIE	28			
	1082	21 pc	HK	30	+		
	1091	6 pp	HK	45	+		
	1092	9 pp	KIE	51	+		+
	1086	*11 pp*	TLL	*52*	+		
	1078	15 pp	KIE	62	+		+
Totals	12				11	4	3
3	1051	19 pc	KIE	26	+	+	
	1054	20 pc	HK	29	+	+	
	1062	22 pc	HK	32			
	1075	1 pp	KIE	35	+		
	1067	*2 pp*	TLL	37			
	1060	12 pp	KIE	57	+		+
	1058	13 pp	KIE	59	+	+	+
	1071	14 pp	HK	61	+		
	1073	16 pp	KIE	65	+	+	
	1074	18 pp	HK	69	+		+
	1065#	19 pp	FD	70			
	1068#	19 pp	HK	71	+		+
Totals	12				9	4	4

pc = postcoitum; pp = postpartum; HK = humane kill; KIE = killed in extremis; FD = found dead; TLL = total litter loss; # = litter survived and used to provide animals for the F_1 generation

- Body Weights and Food Consumption - Mean body weight and body weight gains were not affected. However, poor bodyweight gains or body weight losses were noted in some animals that died or were terminated in extremis. No significant effects on food consumption were observed during gestation. On contrast, reduced food intake was noted in animals @ 6 or 10 mg/kg/day during LD 4-17. The following table shows group mean (±SD) food consumption (g/rat/day) during lactation period.

Group	Mean (±SD) Food Consumption (g/rat/day)					
	LD 1-3	LD 4-6	LD 7-10	LD 11-13	LD 14-17[a]	LD18-20[a]
1	38 ± 6	49 ± 4	62 ± 6	71 ± 8	77 ± 8	82 ± 15
2	37 ± 7	47 ± 6	59 ± 8 (↓5%)	70 ± 9 *	74 ± 9	84 ± 12
3	38 ± 5	46 ± 7 (↓6%)	56 ± 9* (↓10%)	67 ± 9 (↓6%)	66 ± 17 (↓14%)	78 ± 14 (↓5%)
4[b]	37 ± 5	44 ± 6 (↓10%)	51 ± 11** (↓18%)	60 ± 11 (↓15%)	37 ± 11 (↓52%)	-

[a] Included diet consumed by offspring; [b] Terminated during lactation period.
* p≤0.05; **p≤0.01.

- Gestation Length, Parturition and Gestation Index - Longer gestation period (540-hr vs 520-hr in the control) was seen in the SC-65872 treated groups. However, all gestation lengths fell within the expected biological range of values for Crl:CD®BR (IGS) rats of this age. No significant effects on the duration of parturition and gestation index were noted.
- Necropsy - No treatment-related gross changes in the low-dose group (2 mg/kg/day). Seven of 14 surviving high-dose females that were terminated between LD 7-16 had treatment-caused GI injuries by the evidence of ileal adhesions and/or perforations. One of 13 females @ 6 mg/kg/day that survived to scheduled sacrifice at weaning had ileal perforations.

Observations of F_1

- Litter Size and Survival - There were no differences in the number of implantation sites and litter size at birth between control and SC-65872 treated groups. However, due to increased neonatal deaths observed in the mid- and high-dose groups, significantly reduced litter sizes relative to the control were noted in these two groups on LD 4. Similarly, neonatal survival (expressed as group mean) was significantly lower than that of control noted in the mid- and high-dose groups after the culling on LD 4 as shown in the following table.

Group		Post-implantation survival index	Live birth index	Viability index	Lactation index on Day of age				
					7	11	14	18	21
1	Mean	93	100	99	99	97	96	96	96
	SD	7	0	2	5	1.	13	13	13
	n	25	25	25	25	25	25	25	25
2	Mean	90	99	93	95	95	95	94	94
	SD	7	2	15	8	8	8	11	11
	n	25	25	25	25	25	25	25	25
3	Mean	89	95	92	93	90	89	87	86
	SD	15	21	13	1.	15	13	14	14
	n	23	22	20	20	20	18	16	15
4*	Mean	93	96	90	90	75	60		
	SD	9	7	17	15	37	45		
	n	16	17	17	13	9	5		

SD Standard deviation
n Number of litters with live offspring at the start of the period; litters killed because of maternal death excluded from time of death
* Group 4 terminated on 28 May 1998.
Statistical analysis not performed because of incidence of maternal death

- Sex Ratio - There were no effects on sex ratio.

- Body Weights - Both ♂ and ♀ F_1 of SC-65872 treated groups had slightly higher mean body weight than F_1 of the control group by 6-8% at birth. No effects on post-natal body weight and weight gains were recorded.
- Visual Function - Comparable results were seen in all groups for the visual placing and pupillary closure.
- Sexual Maturation - There were no treatment-related effects on the mean days of preputial separation. The mean day of development of tooth eruption and the values for righting reflex, negative geotaxis and auricular startle were similar between groups.
- Sensory, Learning Behavior, and Neuromuscular Function - No significant effects on any of parameters examined with an exception that a slight higher numbers of F_1 ♂ @ 6 mg/kg/day failed on the rotarod treadmill.
- Reproductive Performance - There were no significant differences in the parental and maternal performance parameters (mating and fertility index, conception rate, gestation index, length of gestation, implantation sites and live birth index).
- Necropsy - No significant gross pathological changes were attributable to the treatment.

Observations of F_2

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

Therefore, the NOAEL for the maternal toxicity was 2 mg/kg/day and pre- and post-natal toxicity was 2 mg/kg/day.

2.4. GENETIC TOXICOLOGY

2.4.1. IN VITRO STUDIES

2.4.1.1. Evaluation of the Mutagenic Potential of SC-65872 in the Ames Salmonella/Microsome Assay (SA 4486); Date: 09-Apr-1996, Document No. P30S4486. (Vol. 83)

Study Nº: SA4486
Report Nº: P30S4486
Study Aim: To determine the mutagenic potential of SC-65732 in the Salmonella/microsome (Ames) assay.
Compound: [redacted]
Vehicle Control: [redacted]
Dose: 10, 50, 100, 500, 1000, and 5000 μg/plate
Positive Control:

S9	Compounds	Dose (μg/plate)	Indicator Cell Strain
-	Sodium Azide (NaN_3)	1.0	TA1535 & TA100
	2-Nitrofluorene	2.5	TA98
	ICR-191 Acridine	0.5	TA97a
	Cumen Hydroperoxide	100.0	T102
+	2-Aminoanthracene	1	TA97a, TA98, TA100, and TA1535
	Danthron	50	TA102

Indicator: Histidine auxotrophs *Salmonella typhimurium* strains TA1535, TA100, TA102, TA98, and TA97a
Duration of Exposure: 37°C, 2 days
Study Location: G.D. Searle, 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: Yes

Study Date: 2/27-29/96

Results: The data indicated that SC-65872 at concentrations up to 5000 μg/plate with or without S9 metabolic activation was not mutagenic under the present testing condition.

2.4.1.2. Summary Report: Mutagenic Potential of SC-66905 in the Ames/Salmonella Microsome Assay; Date: 05-Apr-2000, Document No. P3000106. (Vol. 1.83)

Report Nº: P3000106
Study Aim: To determine the mutagenic potential of SC-66905 in the Salmonella/microsome (Ames) assay in an exploratory study.
Compound: [redacted]
Vehicle Control: [redacted]
Dose: 10, 50, 100, 500, 1000, and 5000 μg/plate
Positive Control:

S9	Compounds	Dose (μg/plate)	Indicator Cell Strain
-	Sodium Azide (NaN_3)	1.0	TA1535 & TA100
	2-Nitrofluorene	2.5	TA98
	ICR-191 Acridine	0.5	TA97a
+	2-Aminoanthracene	1	TA97a, TA98, TA100, and TA1535

Indicator: Histidine auxotrophs *Salmonella typhimurium* strains TA1535, TA100, TA98, and TA97a
Duration of Exposure: 2 days
Study Location: G.D. Searle, 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: No
Study Date: 5/9-11/1995

Results: The data indicated that SC-66905 at concentrations up to 5000 μg/plate with or without S9 metabolic activation was not mutagenic under the present testing condition.

2.4.1.3. Evaluation of the Mutagenic Potential of SC-65872 in the CHO/HGPRT Mutation Assay (SA 4481); Date: 29-Jul-1996, Document No. P30S4481. (Vol. 1.83)

Study Nº: SA4481
Report Nº: P30S4481
Study Aim: To determine the mutagenic potential of SC-65732 in the Chinese hamster ovary cell hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) mutation assay.
Compound: [redacted]
Vehicle Control: [redacted]
Dose: 0.32-3200 μg/ml for dose range-finding; 12.5-200 μg/ml for mutation test
-S9: 12.5, 25, 50, and 100 μg/ml
+S9: 50, 100, and 200 μg/ml
Positive Control:
-S9: ICR-191 Acridine (ICR), 1.0 μg/ml.
+S9: 3-methylcholanthrene (MCA), 5.0 μg/ml.
Indicator: CHO cells (sub-line K_1-BH_4)
Duration of Exposure: 4-hr
Incubation Time: 37°C for 1 day and 7 days
Study Location: G.D. Searle, 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: Yes
Study Date: 3/6/96 - 4/4-96

Results: The data from a dose range-finding study showed that SC-65872 was toxic to indicator CHO cells at levels of 106.67 μg/ml with relative cell survival of 15% and ≥320 μg/ml with relative cell survival of ≤10% in the absence (24-hr exposure) and presence (4-hr exposure) of S9 metabolic activation, respectively. The results from the mutation experiment are presented in the following table.

Treatment	Dose (μg/ ml)		% Relative Cell Survival		Mutant Colonies/Dose		Mutant Colonies/10^6 Cells	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
DMSO	1% (v/v)	1% (v/v)	100	100	5	1	2.9	0.6
ICR	1.0		25		184		312.5	
MCA		5.0		75		109		89.5
SC-65872	12.5		61		4		2.6	
	25		50		6		3.8	
	50	50	39	65	3	2	1.8	1.2
	100	100	4	56	0	7	0	4.0
		200		10		1		0.9

Therefore, SC-65872 was not mutagenic under the current testing condition.

2.4.1.4. An Evaluation of the Potential of SC-65872 to Induce Chromosome Aberrations *In Vitro* in Chinese Hamster Ovary (CHO) Cells (SA 4476); Date: 19-Apr-1996, Document No. P30S4476. (Vol. 1.83)

Study Nº: SA4476
Report Nº: P30S4476
Study Aim: To determine the ability of SC-65732 to induce chromosomal aberrations *in vitro* in Chinese hamster ovary cells.
Compound: [redacted]
Dose: 0.32-3200 μg/ml for dose range-finding; 12.5-200 μg/ml for mutation test
-S9: 39, 58, and 117 μg/ml, 4-hr exposure; 25, 50, and 75 μg/ml, 24-hr exposure
+S9: 39, 58, and 117 μg/ml
Positive Control:
-S9: Mitomycin C (MMC) (0.1 μg/ml, 24-hr exposure & 0.5 μg/ml, 4-hr exposure)
+S9: Cyclophosphamide (CP) (5.0 μg/ml, 4-hr exposure)
Indicator: CHO cells (subclone WBL)
Duration of Exposure: 4 hr & 24 hr
Study Location: G.D. Searle, 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: Yes
Study Date: 2/27/96 - 3/21/96

Results: The precipitate and toxicity of SC-65872 were observed at concentrations ≥320 μg/ml in a dose range-finding experiment. In the aberration assay, cell viability was ~73% and 83% without or with metabolic activation, respectively when cells were exposed to SC-65872 at ≤58 μg/ml for 4-hr. However, only ~34 - 39% of cells were viable when exposed to SC-65872 at concentrations of 117 or 75 μg/ml for 4- or 24-hr. The data from metaphase analysis showed that SC-65872 was not clastogenic under the condition of the present assay.

2.4.1.5. Summary Report: The Potential of SC-66905 to Induce Chromosome Aberrations *In Vitro* in Chinese Hamster Ovary (CHO) Cells; Date: 05-Apr-2000, Document No. P3000107. (Vol. 1.83)

Report Nº: P3000107

Study Aim: To determine the ability of SC-66905 to induce chromosomal aberrations *in vitro* in Chinese hamster ovary cells in an exploratory study.

Compound: [redacted]

Dose: 0.35, 1.17, 3.5, 11.7, 35.0, 116.7, 350.0, 1166.7, and 3500 μg/ml for cytotoxicity test

-S9: 11.7, 35, 116.7, and 350 μg/ml, 4-hr exposure; 11.7, 35, and 116.7 μg/ml, 24-hr exposure

+S9: 35, 116.67, and 350 μg/ml

Positive Control:

-S9: Mitomycin C (MMC) (The concentrations used were no stated.)

+S9: Cyclophosphamide (CP) (The concentrations used were no stated.)

Indicator: CHO cells

Duration of Exposure: 4-hr (+/-S9) & 24-hr (-S9)

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

GLP/QAU Compliance: No

Study Date: 5/9/1995 - 6/6/1995

Results: SC-66905, at concentration ≥1166.7 μg/ml, was extremely toxic with relative cell viability of ≤4% without activation and ≤2% with activation, respectively. A summary of results from experiments with CHO cells that were exposed to SC-66905 for 4- or 24-hr without activation or 4-hr with activation is presented in the following table.

Dose (μg/ml)		# Cells Scored	Abs/Cells	% Cells w/ Abs	% Cells w/ >1 Abs	% Cytotoxicity
4 HR EXPOSURE WITHOUT ACTIVATION						
DMSO		100	0.000	0.0%	0.0%	0.0%
MMC		40	0.950	37.5%	22.5%	69.0%
SC-66905	35	100	0.000	0.0%	0.0%	0.0%
	116.7	100	0.000	0.0%	0.0%	0.0%
	350	100	0.000	0.0%	0.0%	33.0%
4 HR EXPOSURE WITH ACTIVATION						
DMSO		100	0.000	0.0%	0.0%	0.0%
CP		29	1.310	51.7%	37.9%	74.0%
SC-66905	35	100	0.000	0.0%	0.0%	0.0%
	116.7	100	0.010	1.0%	0.0%	0.0%
	350	100	0.000	0.0%	0.0%	33.0%
24 HR EXPOSURE WITHOUT ACTIVATION						
DMSO		100	0.000	0.0%	0.0%	0.0%
MMC		30	1.133	50.0%	26.7%	49.0%
SC-66905	11.7	100	0.010	1.0%	0.0%	0.0%
	35	100	0.000	0.0%	0.0%	0.0%
	116.7	100	0.000	0.0%	0.0%	20.0%

Therefore, SC-66905 did not cause chromosomal aberrations in CHO cell under the conditions as stated in this report.

2.4.2. IN VIVO STUDIES

2.4.2.1. An Evaluation of the Potential of SC-65872 to Induce Micronucleated Polychromatic Erythrocytes in the Bone Marrow of Rats (Micronucleus Test), SA4489; Date: 09-Dec-1996, Document No. P30S4489. (Vol. 1.83)

Study Nº: SA4489

Report Nº: P30S4489

Study Aim: To determine the potential of SC-65732 to induce micronuclei *in vivo* in the polychromatic erythrocytes (PCE) of rat bone marrow.

Compound: [redacted]

Vehicle Control: [redacted]

Positive Control: Cyclophosphamide (CP), 6 mg/ml in H_2O, 60 mg/kg po single dose.

Dose & Route: 0, 6.25, 12.5, and 25.0 mg/kg/dose bid po by gavage for 3 days, a total of 6 doses

Animals: Sprague Dawley CD(SD)BR rats, 10 weeks of age, weighing 308.1-338.0 g for the ♂ and 220.6-239.4 g for the ♀, 5/sex/group.

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

GLP/QAU Compliance: Yes

Study Date: 9/10/96 - 10/22/96

Study Design: Groups of rats were dosed with either with vehicle, positive control, CP, or different dosages of SC-65872 as shown in the following table.

Treatment Group	Dose (mg/kg)	Dosage (ml or mg/kg/day)	Dosing Duration	Nº Rats/Sex/Group
1. Vehicle Control	0[b]	10	bid for 3-Day	5/5
2. Positive Control (CP)	60[a]	60[a]	Single Dose	5/5
3. SC-65872	6.25[b]	12.5	bid for 3-Day	5/5
4. SC-65872	12.5[b]	25.0	bid for 3-Day	5/5
5. SC-65872	25.0[b]	50.0	bid for 3-Day	5/5

[a] Dissolved in water and dosed once on the day before sacrifice.

[b] The animals were dosed twice per 24 hour period. Doses were spaced approximately 12 hr apart.

Results: The data showed that treatment of SC-65872 did not increase the numbers of polychromatic erythrocytes with micronuclei. Therefore, SC-65872 was not a clastogen under the conditions of this test.

2.5. CARCINOGENICITY

2.5.1.1. Amendment: REP97091/SA4627 A-1: Dietary Admix Carcinogenicity Study of SC-65872 in the Mouse (SA4627/MSE-N 97091); Date 24-Oct-2000, Document No. REP97091/SA4627. (Vol. 1.84-97)

Study Nº: SA4627/MSE-N 97091

Report Nº: REP97091; M3098160 (PK/TK)

Study Aim: To evaluate the carcinogenic potential of SC-65872 when administered in feed to CD-1 mice for 102 (♀) to 104 (♂) weeks .

Compound: [redacted]

Dose & Route: ♂ - 0, 6.25, 12.5, and 25 mg/kg/day po via dietary admix
♀ - 0, 12.5, 25, and 50 mg/kg/day po via dietary admix

Dosing Duration: 102 (♀) to 104 (♂) weeks

Animals: ♂ + ♀ CD-1 mice [redacted] ~ 6-week of age, weighing 27.9-33.7 g for ♂ and 22.0-26.6 g for ♀.

Study Location: G.D. Searle & Co., Metabolism and Safety Evaluation [redacted]

GLP/QAU Compliance: Yes.

Study Date: ♂ - 4/2/1997 to 4/2/1999.
♀ - 4/3/1997 to 3/17/1999

Study Design: Animals were assigned to various treatment groups as shown in the following table. Due to excessive toxicity occurred during the first 27 weeks of the study, intended doses were reduced by 50% at beginning of Week 28.

Groups	Dose (mg/kg/day				N°/sex/group
	Weeks 1-27		Weeks 28-102/104		
	♂	♀	♂	♀	
Toxicology Study Groups					
N	0	0	0	0	100
1	12.5	25	6.25	12.5	100
2	25	50	12.5	25	100
3	50	100	25	50	100
PK/TK Study Groups					
4	0	0	0	0	15
5	12.5	25	6.25	12.5	66
6	25	50	12.5	25	66
7	50	100	25	50	66

The following observations were conducted:

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - Pre-R and 1x/week thereafter.
- Body Weights, and Food Consumption - 2x during pre-R, 1x/week during Weeks 1-26, 1x/2-week during the 2nd 6 months, and 1x/month thereafter.
- Clinical Pathology - Weeks 102/103 (♀) or 105 (♀). Blood samples were collected from toxicology study groups (Groups N-3). When possible, blood was collected from animals undergoing a moribund sacrifice. The following blood chemistry parameters were determined. If sufficient samples were collected, parameters from Priority 1 List were analyzed followed by the Priority 2 List.
  - Priority 1 - alanine aminotransferase, albumin, alkaline phosphatase, blood urea nitrogen, calcium chloride, creatinine globulin (calculated), inorganic phosphorous, potassium, sodium, and total protein.
  - Priority 2 - aspartate aminotransferase, cholesterol, glucose, sorbitol dehydrogenase, total bile acids, total bilirubin, triglycerides.
- PK/TK - Days 5, 202 and 363, (Weeks 1, 29, and 52, respectively). Blood was collected from 3 animals/group (survival permitting) from Groups 5, 6 and 7 at 5, 11, 15, 20 and 24 hr after lights-on (0630) for plasma levels of SC-65872 and SC-66905 determination. Blood from Group 4 (3/sex, control diet only) were also collected at the 5 hr timepoint. Plasma samples were stored upright in a freezer set to maintain -20°C (± 10°C) until and shipped to [redacted]
- Necropsy and Histopathology - All Toxicology animals found dead or sacrificed moribund were necropsied and all surviving animals were sacrificed during Weeks 102 and 103 (♀) and Week 105 (♂). The following tissues were collected from each Toxicology animal and preserved in 10% formalin and processed for microscopic examination. The microscopic examination was performed at Metabolism and Safety Evaluation, G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077. Bone marrow smears were prepared but not examined.

Aorta	Heart	Pancreas	Stomach
Adrenal Glands	Intestine, Small (Duodenum, Ileum, Jejunum)	Pituitary Gland	Testes
Bone, Femur (Including Articular Surface)	Kidneys	Prostate	Thymus
Bone, Sternum (Including Marrow)	Liver w/ Gall Bladder Drained	Rectum	Thyroid Glands (w/ Parathyroid)
Bone Marrow Smear (Except Animals Found Dead)	Lungs	Salivary Gland, Submaxillary	Tongue
Brain	Lymph Node, Mesenteric	Sciatic Nerve	Trachea
Cecum	Lymph Node, Submaxillary	Skeletal Muscle	Urinary Bladder
Colon	Mammary Gland (♀ Only, Attached to Skin)	Seminal Vesicle	Uterus
Epididymides		Skin (Caudal, Abdominal Region)	Vagina (w/ Cervix)
Esophagus	Nasal Turbinates	Spinal Cord (Lumbar)	Lesions
Eyes w/ Harderian Gland	Ovaries	Spleen	All Masses

Results:

- Intended Dosages and Dose Analysis - The intended doses for the low-, mid-, and high-dose groups study were 12.5, 25, and 50 mg/kg/day for ♂ and 25, 50, and 100 mg/kg/day for ♀, respectively. Due to excessive toxicity occurred during the first 27 weeks of the study, the intended doses were reduced by 50% at beginning of Week 28. The dosages were calculated using body weight, food consumption, and dose formulation data. The mean calculated doses during the study are listed in the following table.

Group	Weeks 1-27				Weeks 28-103/105			
	Target Dose (mg/kg/day)		Calculated Mean Range (mg/kg/day)		Target Dose (mg/kg/day)		Calculated Mean Range (mg/kg/day)	
	♂	♀	♂	♀	♂	♀	♂	♀
Low	12.5	25	10.28 - 12.94	21.12 - 26.78	6.25	12.5	5.67 - 6.82	11.72 - 14.27
Mid	25	50	20.26 - 26.29	41.76 - 52.06	12.5	25	11.35 - 13.90	23.17 - 28.23
High	50	100	41.40 - 52.83	88.34 - 105.98	25	50	23.65 - 27.71	46.19 - 54.04

- Mortality and Clinical Signs - Treatment-caused deaths by the evidence of gross findings of GI perforation and adhesion at necropsy were observed in all SC-65872 groups. Due to high mortality caused by the treatment during the 1st 6-month of treatment the dosages were reduced by 50% on Day 190/191. The incidence of treatment-caused deaths due to GI injuries during various period of study is shown in the following table.

Week of Study	♂				♀			
	Control	Low	Mid	High	Control	Low	Mid	High
Weeks 1-27	0	0	4	13	0	2	2	18
Weeks 28-52	0	0	6	13	0	1	7	25
Weeks 53-65	0	0	5	14	0	3	5	5
Weeks 66-78	0	3	1	8	0	1	2	5
Weeks 79-92	0	2	2	3	0	3	8	2
Weeks 93-105	0	1	3	1	0	2	4	2
Terminal[a]	0	1	1	3	0	4	1	1
Total	0	7	22	55	0	16	29	58

[a] Animals that were sacrificed at study termination.

Note: This table excludes animals with spontaneous background lesions of slight to minimal severity or those associated with the spontaneous gastrointestinal neoplasia.

The following table summarizes the causes of deaths during the course of study.

Cause of Death	♂				♀			
	Control	Low	Mid	High	Control	Low	Mid	High
Gastrointestinal Injury[a]	0	4	16	51	0	9	25	56
Neoplasia	19	15	9	5	15	14	11	13
Amyloid Deposition	15	15	10	4	12	13	15	6
Heart Thrombosis	5	4	3	4	1	4	1	2
Undetermined	6	12	16	10	6	20	13	5
Multiple Causes[b]	11	12	7	4	10	5	9	1
Other[c]	14	9	17	6	10	7	3	5
Final Sacrifice	30	29	22	16	46	28	23	12

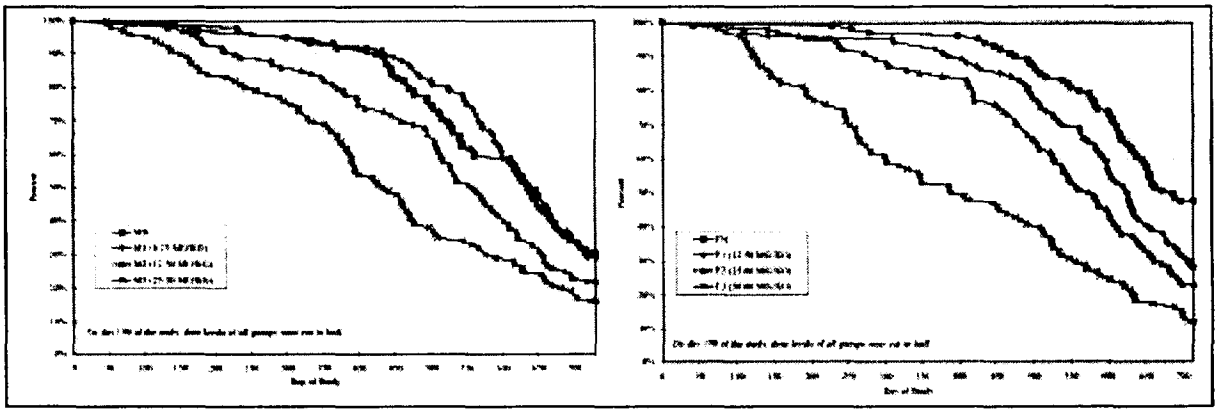
[a] Includes animals with erosion/ulceration of the glandular stomach or intestine and/or chronic active inflammation of the serosa surfaces (peritonitis) of various abdominal tissues.

[b] Multiple causes (include any combination of GI lesions, amyloid deposition, heart thrombosis, and neoplastic and non-neoplastic lesions).

[c] Includes other spontaneous age-related lesions and accidental deaths.

A dose-dependent and statistically significant increase in mortality was detected for the SC-65872 treated groups. The mortality incidences for both ♂ and ♀ mine during various period are presented in the following table and adjusted survival for each group is presented in the following figure (♂: left panel; ♀: right panel).

Week	Control		Low		Med		High	
	♂	♀	♂	♀	♂	♀	♂	♀
0-50	6	3	7	6	17	15	30	47
51-80	33	17	19	24	33	33	37	24
81-104	31	34	45	40	28	29	17	16
105-105	30	46	29	30	22	23	16	13
Total	100	100	100	100	100	100	100	100



- Body Weights, and Food Consumption - There were no treatment-related significant changes in body weights and food consumption. Minor changes (<5%), either ↑ or ↓, in these parameters were observed in both ♂ and ♀ in all groups occasionally during the study.
- Clinical Chemistry - No remarkable changes in blood chemistry evaluated parameters were attributable to the treatment.
- PK/TK - SC-65872, was absorbed and systemically available. Mean PK parameters of SC-65872 and its pharmacologically active metabolite, SC-66905, on Days 5, 202, and 363 are presented in the following table. The C_{max} and AUC_{0-24} values of SC-65872 and SC-66905 in ♂ and ♀ mice increased with increasing SC-65872 dietary dose. The mean C_{max} and AUC_{0-24} values of plasma SC-65872 and SC-66905 in ♂ were higher on Day 363 than Day 202 an indicative of accumulation.

Sampling	Dose		SC-65872						SC-66905					
			T_{max}[a] (hr)		C_{max} (μg/ml)		AUC_{0-24}[d] (μg•hr/ml)		T_{max}[a] (hr)		C_{max} (μg/ml)		AUC_{0-24}[d] (μg•hr/ml)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Week 1 (Day 5)	12.5	25	16	15	0.142	0.189	2.16	2.34	16	0	0.0730	0.247	0.672	3.54
	25	50	16	20	0.224	0.237	3.30	3.67	21	20	0.162	0.322	1.63	6.43
	50	100	1	0	0.306	0.440	5.14	5.60	16	0	0.360	0.519	4.52	9.31
Week 29 (Day 202)	6.25	12.5	15	15	0.107	0.119	1.42	1.79	15	15	0.0728	0.175	0.839	2.69
	12.5	25	20	20	0.150	0.173	2.67	2.41	15	20	0.110	0.220	1.62	3.92
	25	50	20	20	0.282	0.360	3.17	3.74	20	20	0.179	0.293	1.94	5.06
Week 52 (Day 363)	6.25	12.5	20	15	0.149	0.0343[b]	1.86	-[c]	20	0	0.0827	0.203	0.729	1.62
	12.5	25	20	15	0.321	0.105	3.80	1.47	15	0	0.126	0.165	1.79	2.32
	25	50	20	15	0.804	0.196	9.80	2.48	24	15	0.295	0.198	4.34	3.96

[a] Zero hr referred to the first time point (6:45 am) of the light cycle when samples were collected except for males on Day 5 for which the first sample was collected at approximately one hr post lights on.

[b] This C_{max} value was a mean of one valid concentration (0.103 μg/ml) and two 0.0 μg/ml values. The 0.0 μg/ml concentration values were the result from plasma sample analyses with raised sensitivities and they were set to 0 in the calculation.

[c] For this dose group, 4 out of 6 mean plasma concentrations used in AUC calculation were less than the [redacted] sensitivity limits (they were set to 0.0 μg/ml in calculations). The calculated AUC_{0-24} value of 0.305 μg•hr/ml was not used.

[d] The AUC_{0-24} values for males on Day 5 were calculated from concentrations between 1 to 25 hr which correspond to a 0-24 hr period.

The systemic exposures of SC-65872 and SC-66905 as measured by AUC_{0-24} in the rats at Week 52 were approximately 0.6x (♀) to 2x (♂) and 12x (♀) to 14x (♂), respectively with the respect to those at the maximum recommended human dose (MRHD), 20 mg/day.

- Necropsy -

Gross Pathology: Treatment-caused gross changes included GI perforation and/or abdominal visceral adhesions in all SC-65872-treated groups. These lesions were present most commonly in the small intestine (jejunum, ileum, and duodenum) followed by the glandular stomach and large intestine (colon and cecum) with enlarged spleen lymph nodes, and thymus were observed mainly in animals that died or were sacrificed in a moribund condition. These alterations of the GI tract were not common at the terminal necropsy. Adhesions involving the ileum in a low-dose male and adhesions involving the jejunum in a mid-dose male and a mid-dose female (with jejunal perforation) were among the few macroscopic alterations seen in the animals surviving to the end of the study. A mass/nodule was observed in the jejunum of a low-dose male and thickening of the duodenal or cecal mucosa was noted in a low-dose male and in 2 and 1 females, respectively, in the low- and high-dose groups. All other macroscopic findings in animals that died during the study or at terminal necropsy were commonly seen in CD-1 mice.

Neoplastic Findings: All primary tumors and relevant combinations of benign and malignant tumors were evaluated by the agency's statistician, Dr. Suktae Choi. With the exception of hepatocellular carcinoma (p=0.012) and squamous cell carcinoma of the skin (p=0.0294) in high dose ♂, the trend p-values of all spontaneous common neoplasms were >0.05. The incidence (%) of hepatocellular tumors in ♂ is presented in the following table. Hepatocellular carcinomas is a common tumor based on concurrent controls or historical data provided by the sponsor. Furthermore, the incidence of hepatocellular carcinomas was not dose-dependent. Therefore, the statistical value might not implicate any biological significance.

Parameters	Incidence of Hepatocellular Tumors in ♂ Mice[c]				
	Control	Low	Mid	High	Trend p-value
Adenoma	9	10	11	6	0.388
Carcinoma	6	11	4	11	0.016
Adenoma + Carcinoma	15	19[a]	15	16[b]	0.698

[a] Includes two animals with an adenoma and carcinoma.
[b] Includes one animal with an adenoma and carcinoma.
[c] Charles River Historical Control Data (Lang PL. Spontaneous neoplastic lesions in the Crl:CD-1 BR mouse. Charles River Laboratories, 1995.): adenoma (4.08-37.5%) and carcinoma (0 - 28%).

Squamous cell carcinoma of the skin (SCC) was seen in two high dose ♂ and none in the control or lower dose groups and gave a trend p-value of 0.0294 (FDA's analysis). Grossly, the subcutaneous mass was in the right abdominal area extending to the right hind limb in one animal and the other one was present in the left inguinal area. SCC involving the tongue was identified in one control group ♀. The sponsor considered that SCC in high dose ♂ was not treatment-related for the following reasons. The reviewer agreed with the conclusions drawn by the sponsor.

(1) It lacked evidence of a preneoplastic lesion, appeared in one sex only, and was within the historical control ranges (0 - 2%).
(2) The trend p-value of 0.034 (Sponsor's analysis) did not meet the statistical threshold ($p \leq 0.025$) for assigning a relationship of rare tumors to treatment in carcinogenicity studies[3,4]. Additionally, the multiplicity-adjusted p-value was >0.05.
(3) Chronic treatment with a related drug (celecoxib) has been shown to reduce the incidence of UV-induced skin tumors in mice (Pentland et al., 1999)[5].

The comparison of incidence of skin SCC in the current study with the historical control data in the CD-1 mice is presented in the following table.

Sex	Study Incidence (%)				Historical Control Incidence (%)
	Control	Low	Mid	High	
♂	0	0	0	2	0-2.00[a]
♀	0 (1)[b]	0	0	0	0-3.33[c]

[a] Charles River Lab Historical Control Data (1995) in 104 week studies: the incidence of SCC in ♂ in the 78-week studies was up to 1.25% .
[b] SCC of tongue observed in one control female.
[c] Charles River Lab Historical Control Data (2000) in 78 to 104 week studies.

Non-Neoplastic Microscopic Findings: Treatment-related microscopic changes were limited to GI (glandular stomach, duodenum, jejunum, ileum, cecum, and colon) with characteristics of mucosal necrosis with associated chronic active inflammation at one or more sites with predominantly in the glandular stomach, jejunum and ileum. A dose-dependent increase in lesion severity and distribution was noted. GI injury was of greater severity in animals that died or were sacrificed in a moribund condition than in those at scheduled sacrifice. Chronic active inflammation of the serosal surfaces (peritonitis) of several abdominal organs was also noted and was likely caused by the leakage of gastrointestinal contents into the abdominal cavity. The most common tissues with this serosal inflammation included: gastrointestinal tract, adrenal glands, pancreas, kidneys, gall bladder, ovaries, uterus, seminal vesicles, urinary bladder, mesenteric lymph nodes, and liver. These findings usually corresponded with the grossly observed abdominal adhesions, gastrointestinal perforation, and mass/nodule. In a few circumstances,

[3] Lin KK, Rahman MA. Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs. J Biopharm Stat. 8: 1-15, 1998.
[4] Fairweather WR, Bhattacharyya A, Ceuppens PP, Heimann G, Hothorn LA, Kodell RL, Lin KK, Mager H, Middleton BJ, Slob W, Soper KA, Stallard N, Ventre J, Wright J. Biostatistical methodology in carcinogenicity studies. Drug Info J. 32: 401-421, 1998.
[5] Pentland AP, Schoggins JW, Scott GA, Khan KNM, H Rujing. Reduction of UV-induced skin tumors in hairless mice by selective COX-2 inhibition. Carcinogenesis 20:1939-1944, 1999.

microscopic GI lesions were not present in the histologic sections evaluated for animals that had gross morphologic evidence of this injury. Furthermore, histologic GI lesions were observed in a few other animals with no gross morphologic alterations. The total incidence (gross and/or microscopic) of treatment attributable gastrointestinal lesions is summarized in the following table.

GI Lesions (Gross + Microscopic)	♂				♀			
	Control	Low	Mid	High	Control	Low	Mid	High
Total Treatment-Related	0	7	22	55	0	16	29	58
Unscheduled Sacrifice	0	6	21	52	0	12	28	57
Terminal Sacrifice	0	1	1	3	0	4	1	1
Unrelated to Test Article[a]	9	12	14	6	2	10	10	5

[a] Spontaneous background GI lesions of slight to minimal severity or those associated with spontaneous neoplasia were seen in numerous animals in all dose groups (including control); these were considered unrelated to test article and are included in this category.

Therefore, dietary administration of SC-65872 to mice for ≥104 weeks caused gastrointestinal toxicity and mortality in all dose groups and it is not carcinogenic as similar incidence of examined tumors was noted in all groups. The dosages used in this carcinogenicity assessment study exceeded a Maximum Tolerated Dose (MTD) in all treatment groups and the NOAEL for either ♂ or ♀ could not be determined.

2.5.1.2. Two Year Oral Gavage Combination Chronic Toxicity and Carcinogenicity Study of SC-65872 in the Rat (SA4630/MSE-N 97095); Date 3-Nov-2000, Document No. REP97095/SA4630. (Vol. 1.98-103)

Study Nº: SA4630/MSE-N 97095
Report Nº: REP97095; M3098103 (PK/TK)
Study Aim: To evaluate the carcinogenic potential of SC-65872 when administered to rats via oral gavage for 105 weeks
Compound:
Vehicle Control:
Dose & Route: ♂ - 0, 2.5, 5.0, and 12.5 mg/kg/10 ml/day po during Days 1-159 and 0, 2.5, 5.0, and 7.5 mg/kg/10 ml/day thereafter.
♀ - 0, 1.25, 2.5, and 5.0 mg/kg/10 ml/day po during Days 1-88, 0, 1.25, 2.5 and 3.75 mg/kg/day during Days 89-158, and 0, 0.5, 1.0 and 1.5 mg/kg/day thereafter.
Dosing Frequency: 1x/day
Dosing Duration: ♂ - 105 weeks
♀ - 98 weeks for Group 3 and 10 FV's (Control Females) and 105 weeks for remaining groups
Animals: Crl:CD®(SD)BR ~ 6-week of age, weighing 140.3 - 208.8 g for ♂ and 119.1 - 188.2 g for ♀
Study Location: G.D. Searle & Co., Metabolism and Safety Evaluation
GLP/QAU Compliance: Yes.
Study Date: ♂ - 4/15/1997 to 4/15/1999.
♀ - 4/16/1997 to 4/16/1999.
Study Design: Animals were assigned to various treatment groups as shown in the following table.

Group	Dosage (mg/kg/day)					N°/Sex	Terminal Sacrifice	
	♂		♀					
	Days 1-158	Days 159-	Days 1-88	Days 89-158	Days 159-		Week 99	Week 105
Toxicology Study Animals								
V-T (Vehicle Control)	0	0	0	0	0	100	10 ♀	All Surviving ♂+♀
1	2.5	2.5	1.25	1.25	0.5	100	-	All Surviving ♂+♀
2	5.0	5.0	2.5	2.5	1.0	100	-	All Surviving ♂+♀
3	12.5	7.5	5.0	3.75	1.5	100	All Surviving ♀	All Surviving ♂
Pharmacokinetic Study Animals								
4 (V-P, Control)	0	0	0	0	0	10[a]		
5	2.5	2.5	1.25	1.25	0.5	25[a]		
6	5.0	5.0	2.5	2.5	1.0	25[a]		
7	12.5	7.5	5.0	3.75	1.5	25[a]		

[a] Due to high mortality in the test groups, all surviving animals in the Pharmacokinetic groups were reassigned to the Toxicology groups after the Week 52 pharmacokinetic bleeds. After reassignment, these animals were treated the same as the Toxicology animals.

The following observations were conducted:

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - Pre-R and 1x/week thereafter.
- Body Weights - 2x during pre-R, 1x/week during Weeks 1-26, 1x/2-week during the 2nd 6 months, and 1x/4-week thereafter.
- Food Consumption - 1x during pre-R, 1x/week during Weeks 1-26, 1x/2-week during the 2nd 6 months, and 1x/4-week thereafter.
- PK/TK - Days 1, 177 (Week 26) and 359 (Week 52). Blood samples were collected from animals (3/sex/group) in Groups 5-7 at approximately 0.5, 1, 2, 6, 12 and 24 hours after dose. Samples were also collected from the Group 4 animals (3/sex) on the same days at one hour after administration of the vehicle. Plasma samples were stored at -20°C (±10°C) until and shipped to [redacted]
- Necropsy and Histopathology - Necropsy was performed on all Toxicology Study animals found dead or sacrificed moribund were necropsied and all surviving animals. Due to excessive mortality in the high-dose group, all surviving animals in the pharmacokinetic groups were reassigned to the toxicity/carcinogenicity groups on Day 367. In addition, all 12 surviving Group 3 females were terminated early on Day 687. To provide concurrent controls for these Group 3 females, 10 FV females were also sacrificed on Day 687. All other surviving animals were sacrificed at Weeks 104/105. The following tissues were collected from each Toxicology Study animal and preserved in 10% formalin and processed for microscopic examination with exception of eyes with Harderian gland that were preserved in 5% neutral buffered formalin/0.5% glutaraldehyde. In addition, the testes of male rats that died or were sacrificed moribund prior to Week 54 were preserved in 10% formalin and post-fixed in Bouin's fixative. Bone marrow smears were stained with Wright's stain for moribund sacrifices and from animals at the scheduled necropsies. Histopathology including histology preparation, histopathology evaluation and preparation of tissues for archiving was performed [redacted]

Aorta	Intestine, Small (Duodenum, Ileum, Jejunum)	Pancreas	Stomach
Adrenal Glands (2)		Pituitary Gland	Testes (2)
Bone, Femur (Including Articular Surface)	Intestine, Large (Cecum, Colon)	Prostate	Thymus
Bone, Sternum (Including Marrow)	Kidneys (2)	Rectum	Thyroid Glands (2) w/ Parathyroid
Bone Marrow Smear (Except Animals Found Dead)	Liver	Salivary Gland, Submaxillary	Tongue
	Lungs (2)	Sciatic Nerve	Trachea
Brain	Lymph Node, Mesenteric	Skeletal Muscle	Urinary Bladder
Epididymides (2)	Lymph Node, Submaxillary	Seminal Vesicle	Uterus
Esophagus	Mammary Gland (♀ Only, Attached to Skin)	Skin (Caudal, Abdominal Region)	Vagina (w/ Cervix)
Eyes (2) w/ Harderian Gland	Nasal Turbinates	Spinal Cord (Lumbar)	Lesions
Heart	Ovaries (2)	Spleen	All Masses

Results:

- Mortality and Clinical Signs - Treatment-caused deaths by the evidence of gross findings of GI perforation and adhesion at necropsy were observed in all SC-65872 groups. Due to high mortality caused by the treatment, the dosages were adjusted for the high-dose group ♂ on Day 159 from 12.5→7.5 mg/kg, high-dose ♀ on Day 89 from 5.0→3.75 mg/kg and ♀ in all dose groups on Day 159 from 1.25, 2.5, and 3.75 mg/kg to 0.5, 1.0, and 1.5 mg/kg. The incidence for major causes of deaths including GI injuries is summarized in the below table.

Major Causes of Death	♂				♂			
	Control	Low	Mid	High	Control	Low	Mid	High
GI Toxicity - Total	0	28	40	54	0	5	47	78
Jejunum, Erosion/Ulceration	0	24	31	52	0	2	39	63
Jejunum Erosion/Ulceration + Nonjejunal Lesions	0	3	6	2	0	3	8	14
Nonjejunal Intestinal Erosion/Ulceration	0	1	3	0	0	0	0	1
Gavage Errors	5	10	12	6	1	3	0	2
Nephropathy	5	3	4	3	3	2	0	0
Pituitary Tumors (Pars Distalis)	3	0	2	1	19	16	17	7
Mammary Tumors & Inflammatory Lesions	0	0	0	0	12	16	7	2
Multiple Lesions[a]	32	17	19	10	24	37	14	5

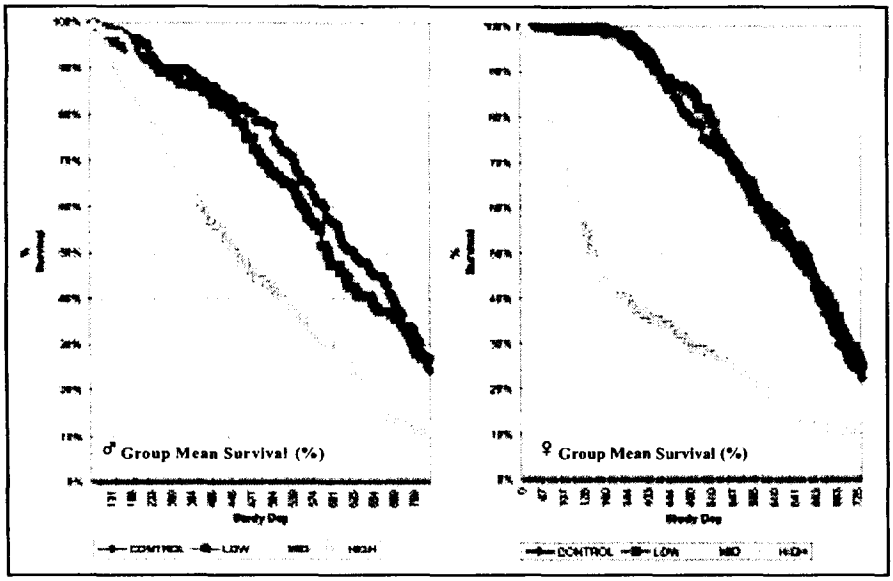
[a] Multiple causes include any combination of non-jejunal intestinal lesions, nephropathy, pituitary and mammary tumors, and inflammatory/degenerative and neoplastic lesions of various other tissues.

A dose-dependent reduction in survival was noted. The survival for each group during different periods of study are shown in the following table and adjusted survival for each group is depicted in the following figure (♂: left panel; ♀: right panel).

Week of Study	Survival at Different Stages of the Carcinogenicity Study							
	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
Week 27	97	93	96	82	100	98	72	39
Week 52	88	84	68	60	98	95	65	32
Week 65[a]	88	96	73	57	94	107	63	36
Week 78	74	77	54	42	77	86	49	27
Week 92	51	48	38	20	53	63	31	14
Terminal[b]	25	32	14	12	28	30	19	12

[a] 8, 20, 19, and 13 PK ♂ and 9, 23, 11, and 10 PK ♀ animals were assigned to the 0, 2.5, 5, and 7.5 mg/kg/day toxicology groups, respectively, following the Week 52 pharmacokinetic blood samplings.

[b] Includes animals sacrificed at Week 99.



- Body Weights and Food Consumption - There were no differences in ♂ mean body weights and weight gains (changes) among the dose groups. High-dose ♀ had lower mean body weights from Week 13 and thereafter by 6-16% with lower cumulative body weight changes by 5-22% from Week 4 and thereafter as compared to the control. A slight lower (5-12%) in cumulative weight gains was also noted in the mid-dose ♀. In general, the SC-65872 treated groups had lower cumulative weight gains compared to the control group. Periodically, minor changes (either ↑ or ↓) in food consumption were observed in both ♂ and ♀ for all groups throughout the study.
- PK/TK - The test article, SC-65872, was absorbed and systemically available. The mean PK parameters for SC-65872 and its active metabolite, SC-66905, on Days 1, 117, and 359 are presented in the following table.

	Dose (mg/kg/day)		SC-65872						SC-66905					
			T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)		T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Week 1	2.5	1.25	2	2	0.704	0.373	4.10	2.58	2	6	0.118	0.055	1.45	0.736
	5	2.5	1	2	1.62	0.889	7.98	5.58	6	6	0.255	0.095	2.61	1.04
	12.5	5	1	1	4.30	1.62	21.7	11.3	2	2	0.734	0.179	7.11	2.18
Week 26	2.5	0.5	0.5	0.5	0.744	0.210	5.12	1.40	6	0	0.116	0	1.31	0
	5	1	2	0.5	1.79	0.500	11.6	3.95	6	0.5	0.229	0.020	3.15	0.105
	7.5	1.5	1	2	2.93	1.51	41.4	8.36	6	2	0.356	0.091	5.20	0.656
Week 52	2.5	0.5	2	2	0.987	0.274	8.80	2.16	6	2	0.127	0.012	1.39	0.148
	5	1	1	1	2.01	0.524	16.9	5.07	6	6	0.256	0.032	3.29	0.445
	7.5	1.5	1	2	3.04	0.807	23.8	7.70	6	2	0.517	0.051	6.29	0.757

The systemic exposures of SC-65872 and SC-66905 as measured by AUC_{0-24} in the rats at Week 52 were approximately 2x (♀) to 6x (♂) and 2x (♀) to 20x (♂), respectively with the respect to those at the maximum recommended human dose (MRHD), 20 mg/day.

- Necropsy -

Gross Pathology: Treatment-related and dose-dependent increased incidences in GI lesions including intestinal erosion/ulceration, perforation and/or adhesions were identified in both SC-65872 treated ♂ and ♀. These changes were most commonly present in the jejunum and rarely in duodenum, ileum, colon and cecum, and were identified primarily in animals that died or were

sacrificed in a moribund condition during the study. The incidence of treatment-caused GI injuries during various period of study is shown in the following table.

Week of Study	Incidence of Intestinal Toxicity at Different Stages of the Study							
	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
Weeks 1-27	0	1	3	14	0	1	28	60
Weeks 28-52	0	5	17	16	0	0	5	7
Weeks 53-65	0	3	3	12	0	2	5	4
Weeks 66-78	0	8	10	11	0	2	6	3
Weeks 79-92	0	10	5	6	0	0	4	7
Weeks 93-105	0	7	10	3	0	4	5	0
Terminal[a]	0	4	4	3	0	5	7	2
Total	0	38	52	65	0	14	60	83

[a] Includes animals sacrificed at Week 99.

Neoplastic Findings: All primary tumors and relevant combinations of lesions were analyzed. There were no statistical differences in the incidence of neoplastic lesions between controls and animals treated with SC-65872. The incidence of pheochromocytomas in ♀ is presented in the following table. The trend p-value was 0.138 and 0.04 when the high dose group was excluded from the analysis.

Pheochromocytomas	Incidence (%) of in the ♀ Rat				Trend p-Value Analysis	
	Control	Low	Mid	High	FDA's	Sponsor's
Benign	3.7	10.6	8.1	0.9	0.138 (0.040)	0.21 (0.017)[a]
Malignant	2.8	0	0.9	0.9	0.599 (0.841)	0.67 (0.92)[a]
Combined	6.5	10.6	9.0	1.8	0.155 (?)	0.25 (0.061)[a]

[a] The p-value in parenthesis is with the high dose group excluded from analyses.

Astrocytomas (malignant) in the brain were observed in 1, 2, 4, and 2 males in control, low, mid, and high dose groups, respectively. The trend p-value was 0.056 as analyzed by the FDA's statistician. Both astrocytomas and pheochromocytomas are common tumors in Crl:CD®(SD)BR rats. The historical data showed that the incidence of astrocytomas was 2-4.3% and 1-5.7% for benign and malignant, respectively and the incidence of pheochromocytomas was 1-14.5% for benign and 1.4-4% for malignant, respectively.

Non-Neoplastic Microscopic Findings: Treatment-related microscopic changes were limited to GI. Intestinal lesions were observed in the duodenum, jejunum, ileum, cecum, and colon with characteristics of mucosal erosion/ulceration at one or more sites (mainly in the jejunum) with associated chronic active inflammation. The severity of GI lesions increased with dose and noted in animals that died or were sacrificed in a moribund condition. Chronic active inflammation of the serosal surfaces (peritonitis) of several abdominal organs was also identified. The most common tissues with this serosal inflammation included: gastrointestinal tract, adrenals, pancreas, spleen, kidney, mediastinum, stomach, vagina, ovary, uterus, epididymis, testis, seminal vesicles, prostate, coagulating gland, ductus deferens, ureter, urinary bladder, mesenteric and pancreatic lymph nodes, and liver. These findings usually correlated with the grossly observed abdominal adhesions and intestinal perforation, ulcer, and mass/nodule. The following table summarizes the incidence and histologic severity grades of microscopic GI lesions.

Parameters	Incidences (Mean Severity)[a] of Erosion/Ulceration in Selected Intestinal Segments							
	Control		Low		Mid		High	
	♂	♀	♂	♀	♂	♀	♂	♀
Nº Rats/Group	108	109[b]	120	123	119	111	113	110[b]
Jejunum	0 (0)[a]	0 (0)[a]	32 (4.7)	8 (3.9)	41 (4.8)	51 (4.7)	58 (4.9)	78 (4.9)
Ileum	2 (1.5)	0 (0)	5 (3.0)	1 (1.0)	5 (4.6)	2 (1.0)	10 (3.2)	5 (4.2)
Duodenum	0 (0)	0 (0)	0 (0)	1 (3.0)	2 (5.0)	1 (4.0)	0 (0)	3 (4.3)
Cecum	2 (3.0)	0 (0)	6 (2.5)	3 (2.3)	7 (1.9)	2 (2.5)	3 (3.0)	3 (1.7)
Colon	0 (0)	0 (0)	1 (1.0)	0 (0)	3 (3.7)	0 (0)	2 (4.5)	0 (0)

[a] Severe = Grade 5

[b] Included the animals transferred from PK study groups during interim sacrifice (Week 99).

Based on presented findings, administration of SC-65872 to rats for 104 weeks did not cause an increase in the incidence for all examined tumors. The dosages used in this carcinogenicity assessment study exceeded a Maximum Tolerated Dose (MTD) in all treatment groups as treatment-related GI toxicity (necrosis/perforation/inflammation with secondary peritonitis) and deaths were noted in all does levels for ♂ and ♀. The NOAEL could not be established under current study.

2.6. SPECIAL TOXICOLOGY STUDIES

2.6.1. LOCAL (DERMAL AND OCULAR) TOLERANCE/IMMUNOGENICITY

2.6.1.1. Dermal Sensitization Study of SC-65872 in Guinea Pigs - Maximization Test, EX4721; Date: 28-Oct-1998, Document No. P20E4721. (Vol. 1.111)

Study Nº: EX4721
Report Nº: P20E4721
Study Aim: To assess the dermal sensitization potential of SC-65872 in guinea pigs (Crl:(HA)BR strain) via intradermal injection and topical application.
Compound:
Vehicle Control:
Positive Control: Hexylcinnamaldehyde (a known skin sensitizer), **the positive control was not performed concurrently but within 6 months of the conduct of this study**
Dose & Route: 5% in FCA (Freund's Complete Adjuvant)/H_2O intradermal injection for sensitization; 25% in Petrolatum dermal topical for induction and challenge
Animals: Young adult ♂ albino guinea pigs, Crl:(HA)BR strain 6 to 9 weeks of age, weighing 421-546 g, 10-20/group
Study Location:
GLP/QAU Compliance: Yes (EPA, 40 CFR 792)
Study Date (In-Life): 10/16/1997 - 11/22/1997
Study Design: The below table describes the detailed treatment schedules for the control and test groups.

Day	Treatment Schedule	Skin Induction Site (4 cm x 6 cm area)		
		Anterior Site	Medial Site	Posterior Site
CONTROL GROUP (10 ANIMALS)				
1	Intradermal Inj.[a]	0.1 ml FCA:H_2O=1:1	0.1 ml mineral oil	0.1 ml FCA:H_2O=1:1
7	Topical Pre-treat.	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	Petrolatum secured by an overwrap with Elastoplast® tape for 48 hr.		
22	1st Challenge	25% w/w SC-35872 in Petrolatum (Right)/Petroleum (Left) for 24 hr.		
TEST GROUP (20 ANIMALS)				
1	Intradermal Inj.	0.1 ml FCA:H_2O=1:1	0.1 ml of 5% SC-65872 in mineral oil	0.1 ml of 5% SC-69124 in FCA/H_2O (1:1)
7	Topical Pre-treat.	10% w/w Sodium Lauryl Sulfate suspension in Petrolatum		
8	Topical Induction	25% w/w SC-65872 in Petrolatum secured by an overwrap with Elastoplast® tape for 48 hr.		
22	1st Challenge	25% w/w SC-65872 in Petrolatum (Right)/Petroleum (Left) for 24 hr.		

[a] 6 intradermal injection sites were made within the boundaries of a 2x4 cm^2, 3 injections on each side of the midline.
[b] 5 new (naive) controls were used.

The following observations were made during the study:

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

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

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

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

Results: None of the animals in the test or control groups exhibited a dermal reaction to the challenge application of the test or control materials. The sponsor stated that based on the results, SC-65872 is not considered to be a dermal sensitizer in guinea pigs. However, the review pharmacologist do not concur with the conclusion drawn by the sponsor as positive controls were not conducted simultaneously. Therefore, the study itself may not be valid and no conclusion can be drawn from the present study.

2.6.1.2. Parenteral Irritation Study of SC-65872 in the Male Rabbit, SA4956; Date: 08-Mar-2000, Document No. P30S4956. (Vol. 1.111)

Study Nº: SA4956
Report Nº: P30S4956
Study Aim: To evaluate the potential of the test article to induce venous and muscle irritation at a concentration of 0.2 mg/ml.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: im (into the M. vastus lateralis) - 1 ml/site
iv (into the auricular vein) - 0.71 ml/site over ~30 minute period
Dosing Frequency: 1x/day
Dosing Duration: 1 day

Animals: ♂ New Zealand white rabbits [redacted] 6-8 months of age, weighing 3.4 and 3.8 kg,
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: Yes
Study Date: 6/22-6/25/1999
Study Design: Groups of rabbits received a single dose of either SC-65872 or vehicle control by intramuscular or intravenous injection as shown in the following table.

Group	Treatment Site	Treatment	Time of Evaluation
1	M. Vastus Lateralis (Left)	SC-65872 (1 ml @ 0.2 mg/ml)	24 hr
	M. Vastus Lateralis (Right)	Placebo	
2	M. Vastus Lateralis (Left)	SC-65872 (1 ml @ 0.2 mg/ml)	48 hr
	M. Vastus Lateralis (Right)	Placebo	
3	M. Vastus Lateralis (Left)	SC-65872 (1 ml @ 0.2 mg/ml)	72 hr
	M. Vastus Lateralis (Right)	Placebo	
4[a]	Auricular Vein (Left)	SC-65872 (0.71 ml @ 0.2 mg/ml)	24,48 and 72
	Auricular Vein (Right)	Placebo	
Day 1	Injection of all Groups (12 Rabbits)		
Day 2	Evaluation of Group 4 (3 Rabbits), Sacrifice and evaluation of Group 1 (3 rabbits)		
Day 3	Evaluation of Group 4 (3 Rabbits), Sacrifice and evaluation of Group 2 (3 rabbits)		
Day 4	Evaluation of Group 4 (3 Rabbits), Sacrifice and evaluation of Group 3 (3 rabbits)		

[a] Group 4 animals were euthanized and discarded after the Day 4 evaluation.

Groups 1-3 animals were sacrificed at 24, 48 or 72 hr post-dose and the right and left M. vastus lateralis with overlying muscles were evaluated for irritation using the method described by Shintani, et al[6] as shown in the following table. Intravenous irritation was evaluated at 24, 48 and 72 hr post-dose. The injection site and surrounding tissue were evaluated grossly and were scored for irritation using the following numerical scale of 0-3 as listed in the following table.

Scoring of Intramuscular Irritation		Scoring of Intravenous Irritation	
Reaction Criteria	Score	Reaction Criteria	Score
No discernible gross reaction	0	No discernible gross reaction	0
Slight hyperemia and discoloration	1	Slight erythema at injection site	1
Moderate hyperemia and discoloration	2	Moderate erythema and swelling with some discoloration of the vein and surrounding tissue	2
with the color of the surrounding area	3		
Brown degeneration with small necrosis	4	Severe discoloration and swelling of the vein and surrounding tissue with partial or total occlusion of the vein	3
Widespread necrosis with an appearance of "cooked meat" and occasionally an abscess involving the major portions of the muscle	5		
Average Score	Grade	Average Score	
0.0 to 0.4	None	0.0 to 0.4	None
0.5 to 1.4	Slight	0.5 to 1.4	Slight
1.5 to 2.4	Mild	1.5 to 2.4	Moderate
2.5 to 3.4	Moderate	≥2.5	Severe
3.5 to 4.4	Marked		
≥4.5	Severe		

Results: Data presented in the following table showed that the formulation of SC-65872 (2 mg/ml) used in this study caused a no→mild muscular irritation to both M. vastus lateralis and the overlying muscle by im injection and a slight irritation to the auricular vein by iv injection. The vehicle alone was rated as non-irritating to a slight irritant. Comparable irritation scores were recorded for the vehicle controls.

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[6] Shintani, S., Yamazaki, M., Nakamura, M., and Nakayama, I, 1967. A new method to determine the irritation of drugs after intramuscular injection in rabbits. Toxicol Appl Pharmacol, 11:293-301.

Irritation Score/Grade	M. Vastus Lateralis					
	SC-65872 (left)			placebo (right)		
	24 h	48 h	72 h	24 h	48 h	72 h
Mean Group Score	2	2	0	1.67	1	1.33
Irritation Grade	Mild	Mild	None	Mild	Slight	Slight
Irritation Score/Grade	Overlying Muscle					
	SC-65872 (left)			placebo (right)		
	24 h	48 h	72 h	24 h	48 h	72 h
Mean Group Score	2	0	1.67	1.33	1	0.67
Irritation Grade	Mild	None	Mild	Slight	Slight	Slight
Irritation Score/Grade	Auricular Ear Vein					
	SC-65872			placebo		
	24 h	48 h	72 h	24 h	48 h	72 h
Mean Group Score	1.33	1.33	1	1.67	1.33	1.33
Irritation Grade	Slight	Slight	Slight	Moderate	Slight	Slight

2.6.1.3. Primary Dermal Irritation Study of SC-65872 in Rabbits, EX4719; Date: 22-Apr-1998, Document No. P20E4719. (Vol. 1.111)

Study Nº: [redacted]
Report Nº: P20E4719
Study Aims: To evaluate the primary dermal irritation potential of SC-65872 in rabbits.
Compound: [redacted]
Dose and Route: 0.5 g moistened with 1.0 ml H_2O, skin topical
Animal: New Zealand White rabbits [Hra:(NZW)SPF], 14-18 weeks old, weighing 2.36-2.595 kg, 3/sex.
Study Site: [redacted]
In-Life: 10/15/1997 – 10/19/1997
Study Date: 10/15/1997 – 4/17/1998
GLP/QAC Compliance: Yes (EPA GLP Standards, 40 CFR 792)
Study Design: The back and/or flanks of each animal were clipped to obtain an unblemished skin site on Day -1. SC-65872, 0.5 g in 1.0 ml H_2O, was applied to the intact skin site on each animal's back (~6.25 cm^2). Then, the area of application was covered with an gauze patch (8-ply 2.5-cm x 2.5-cm) secured with paper tape, loosely overwrapped with Saran Wrap®, and secured with Elastoplast® tape. The patches were removed after a 4-hour exposure period, and the test sites were rinsed with H_2O. The test skin sites were evaluated at 30 to 60 min and 24, 48, and 72 hr after removal of the test material (4 hours after application). The degree of erythema and edema at each test site was read according to the Draize technique. No necropsy was performed.

Results: No erythema or edema was observed; therefore, SC-65872 was a non-irritant to rabbit skin under the current testing condition.

2.6.1.4. Primary Eye Irritation Study of SC-65872 in Rabbits, EX4720; Date: 22-Apr-1998, Document No. P20E4720. (Vol. 1.111)

Study Nº: [redacted]
Report Nº: P20E4720
Study Aims: To evaluate the primary dermal irritation potential of SC-65872 when instilled to rabbit eyes.
Compound: [redacted]
Dose and Route: 22 mg (0.1 ml weight equivalent), eye topical

Animal: 6 (3/sex) New Zealand White rabbits [Hra:(NZW)SPF], 14-18 weeks old, weighing 2.264-2.681 kg, 3/group.
Study Site:
In-Life: 10/17/1997 – 10/20/1997
Study Date: 10/15/1997 – 4/17/1998
GLP/QAC Compliance: Yes (EPA GLP Standards, 40 CFR 792)
Study Design: SC-65872, 22 mg (0. 1-ml, weight equivalent), was placed into the everted lower lid of the right eye, with the left eye serving as the untreated control. SC-65872 treated eyes of Group 1 rabbits remained unflushed immediately after treatment while the treated eyes of the rabbits in Group 2 were flushed with water for 1 min at 30 sec post instillation. The treated eyes were observed for ocular irritation at 1, 24, 48, and 72 hours after treatment. Irritation was scored according to the Draize technique.

Results: Redness (Group 1: 3/3; Group 2: 2/3) and chemosis (Group 1: 1/3) were observed in the treated eyes 1 hr post instillation. All treated eyes returned to a normal appearance by 24 hr post-treatment. The level of irritation observed in the eyes receiving a washout after treatment was slightly less than that observed in the unwashed treated eyes. Average primary eye irritation scores are presented in the following table.

Observation Period (hr)	Average Score[a]	
	Group 1 (Unwashed)	Group 2 (Washed)
1	2.7	1.3
24	0.0	0.0
48	0.0	0.0
72	0.0	0.0

[a] The average primary eye irritation score is the total eye irritation score for all the animals divided by the number of animals for each group (3) at each observation period.

Therefore, SC-65872 was considered to be none→minimal ocular irritant under current testing condition.

2.6.2. EFFECTS ON SUSCEPTIBILITY TO BACTERIAL INFECTION AND WOUND HEALING

2.6.2.1. An Exploratory Study to Determine the Effects of SC-65872 on Selected Parameters of Immune System and Wound Healing in Beagle Dogs (EX 4689); Date: 30-Jul-1998, Document No. P30E4689. (Vol. 1.115)

Study Nº: EX4689
Report Nº: P30E4689/P3097048 (Lymphocyte Immunophenotyping, PMN Oxidative Burst, Serum C' and Ig Levels)/M3097361 (PK/TK)
Study Aims: To determine the effect of SC-65872 on selected parameters of wound healing, immune functions, and response to bacterial infection in Beagle dogs.
Compound:
Dose & Route: 0 and 7 mg/kg bid po (~11 hr apart) for 28 days (56 Doses)
Animals: ♀ beagle dogs, 6-7 months of age, weighing 5.6-7.4 kg, 4-6/group
Bacterial Stocks: *Streptococcus* Group G, 10^8-10^9 cells/ml; *Staphylococci intermidius*, 10^8-10^9 cells/ml.
Study Location: G.D. Searle & Co., Skokie, IL
Study Date: 07/29/1997 (Day 1) - 08/26/1997 (Terminal Sacrifice, Day 29)
GLP/QAU Compliance: No
Study Design: Neat SC-65872 was administered orally in a gelatin capsule at dosages of 0 and 7 mg/kg twice a day. On Day 15, three incisions (~1 cm in length and 2-4 cm apart) were made on

both sides of the neck in the lateral cervical region of all dogs in Groups 1 & 2 (total of 6 incisions/dog). Skin biopsies were obtained from the above incision sites using 6 mm and 4 mm biopsy punches on Days 15, 16, 18, 21, 24 of the study and at necropsy for the wound healing process evaluation. The wound healing process was monitored by clinical observations, morphological evaluations, and COX-2 expression. On Day 15, the Group 4 dogs were inoculated with *Streptococcus* Group G (10^6 cells/ ml normal saline) and *Staphylococcus intermedius* (10^6/ml normal saline) on the right and left side of the neck, respectively. Group 3 animals (control) were inoculated subcutaneously with 1.0 ml normal saline on both sides of the neck. On Day 18, Group 3 animals were inoculated subcutaneously with pure cultures of *Streptococcus* Group G on the right side of the neck and *Staphylococcus intermedius* on the left side of the neck. These sites were monitored for swelling and abscess formation. Specimens from either the site of abscess or injection site if abscess did not form were collected at necropsy for histopathological and immunohistochemical evaluations.

Group		Dose* (mg/kg/dose)	Dose (mg/kg/day)	Nº Animals	Procedure Day**
1	Wound Healing	0 (Empty Capsule)	0	4♀	15
2		7	14	4♀	15
3	Bacterial	0	0	6♀	15 & 18
4	Inoculation	7	14	6♀	15
5	Control	7	14	4♀	N/A

* Animals received test article bid to achieve the total daily dosage listed.
** Day of wound initiation or subcutaneous inoculation.

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 -7), Weeks 1, 2, 3, and 4 .
- Body Weights - Days 4, 11, 16, and 23.
- Food Consumption - Not Recorded.
- Clinical Pathology - Days -13, 14, 22, 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	Cortisol	ACTH

- Total Complement (C') and Immunoglobulin (Ig) (G, M, & A) Levels - Days -13, -4, 14, 22, and 29.
- Lymphocyte Subset Immunophenotyping and Leukocyte Functional (Phorbol Myristate Acetate (PMA)-Induced Oxidative Burst) Analysis - Days 1 (prior to 1st dose), 14 (prior to and 2 hr after 1st dose), 22 (prior to and 2 hr after 1st dose), and 29.
- COX-2 mRNA Expression in PMN - Days 14, 22, and 28.
- Blood and Skin Bacterial Cultures - Day 29.
- PK/TK - Blood samples were collected from all animals at 2 and 12 hr (prior to 2nd daily dose) after the 1st daily dose on Days 1, 4, and 28. The samples were stored at approximately -20°C then shipped on dry ice [redacted]
- Special Stains -
  Immunohistochemical evaluations of COX-1 and COX-2 were performed on incision sites 1-6 (biopsies A-F) and biopsy Y from Groups 1 and 2 animals; skin and gastric lesions of Animal Nº 46892401; streptococcus inoculation sites (skin lesions) of Animal Nº 46892402, 46892404,

46892405, and 46892406 and heart lesions of Animal Nº 46892403. Gram's staining was performed on skin and gastric lesions of Animal Nº 2401, streptococcus inoculation sites (skin lesions) of Animal Nº 46892402, 46892404, 46892405, and 46892406, and heart lesions of Animal No. 46892403.

- Necropsy - Day 29. There were two 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. Tissues with an asterisk were weighed and paired organs were weighed together. The retropharyngeal lymph node of 1 Group 1 (Animal Nº 46892104) and the adrenal gland (one) of 1 Group 5 (Animal Nº 46892503) were not collected at necropsy. Section from all collected tissues were examined microscopically.

Adrenal Glands* (Both)	Lymph Node, Mesenteric
Bone, Femur (Including Articular Surface)	Lymph Node, Retopharyngeal
Bone, Sternum (Including Marrow)	Skin (Including Wound And Bacterial Inoculation Sites)[a]
Bone Marrow Smear (Except for Animals Found Dead) (Not Examined)	Spleen*[b]
All Lesions	Thymus*

[a] Approximately half of the skin section (subdividing the wound site) was retained for possible EM analysis (except for the found dead animal 48692403).

[b] A section of spleen was collected, weighed and submitted to the flow cytometry lab for analysis of lymphocyte subsets (except for unscheduled sacrifices).

Results:

- Clinical Signs and Mortality - Two unscheduled deaths occurred in Group 4. One dog (46892401) had spontaneous subcutaneous swelling and open wounds with *streptococci* infection in the neck/shoulder area and was sacrificed for humane reasons on Day 17. The other dog (46892403) was found dead on Day 28 with septicemia due to severe subcutaneous lesions at the streptococcal inoculation site. Increased incidence of soft, watery, mucoid and black stool was observed in SC-65872 treated dogs.
- Clinical Observation of Bacterial Inoculation Sites and Wound Healing - Transient slight swellings (1.125-2 cm^3 in area) for 2-4 days at *Staph./Strep.* inoculation sites were noted in 2 Group 3 dogs. In contrast, severe swellings (50-243 cm^3 in area) persisted for **8-13** days at *Strep.* inoculation sites that subsequently developed into large open sores were observed in all Group 4, SC-65872-treated, dogs. A summary of injection site swellings and open sores/wounds in Groups 3 & 4 is presented in the following table.

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Injection Site Swelling										
Group	Treatment	Animal Nº	Inoculation Day	Onset Day	Days Affected (Nº of Occurrence)	Largest Occur. Day	Length (cm)	Width (cm)	Depth (cm)	Area (cm^3)
LEFT - *Staphylococcus intermedius* INJECTION SITE										
3	Control	46892302	18	20	Days 20-22 (6)	22	1.5	1.5	0.5	1.125
		46892304	18	19	Days 19-22 (7)	22	2	2	0.5	2
4	SC-65872	46892406	15	16	Days 16-17 (3)	17	5	3	1	15
RIGHT – *Streptococcus* Group G INJECTION SITE										
3	Control	46892305	18	19	Days 19-20 (4)	20	1.5	1.5	0.5	1.125
4	SC-65872	46892402	15	16	Days 16-28 (26)	24	9	9	3	243
		46892403	15	16	Days 16-24 (18)	21	7	5	2	70
		46892404	15	16	Days 16-23 (16)	19	5	4	2.5	50
		46892405	15	16	Days 16-24 (18)	18	6	6	2	72
		46892406	15	16	Days 16-25 (20)	18	8	6	2.5	120
OPEN SORE										
Group	Treatment	Animal Nº	Inoculation Day	Onset Day	Days Affected (Nº of Occurrence)	Largest Occur. Day	Length (cm)	Width (cm)	Area (cm^2)	
4	SC-65872	46892401	N/A	12	Days 12-17 (10)	17	9	4	36	
		46892402	15	25	Days 25-28 (8)	24	9	8	72	
		46892403	15	22	Days 22-27 (12)	27	3	2	6	
		46892404	15	20	Days 20-26 (14)	25	5	4	20	
		46892405	15	19	Days 19-28 (20)	25	5	3	15	
		46892406	15	21	Days 21-24 (8)	24	4	1	4	

Delayed wound healing by 2-3 days was noted in SC-65872-treated (Group 2) as compared to controls (Group1). Mean number of days of discharge observed at biopsy site "Y" was 0 and 2.5 days for Groups 1 and 2, respectively and biopsy site "Z" was 1 and 2 days for Groups 1 and 2, respectively. The following table showed summary data derived from wound healing observations.

WOUND HEALING						
Treatment	Animal Nº	Day of Onset	Day "Y" Scabbed Over	Day "Z" Scabbed Over	"Y" Discharge	"Z" Discharge
Group 1 Control	46892101	16	17 (20)(24)[a]	16		
	46892102	17	17	18		
	46892103	16	16	17		
	46892104	17	17	16		Day 18
Group 2 SC-65872	46892201	17	17 (21)	21	Days 18-19	Day 19
	46892202	21	21 (22)	21	Days 18-21	Days 18-20
	46892203	22	22	21	Days 18-19	Days 18-19
	46892204	20	20	21	Days 17-18	Days 18, 20

a Values in the ( ) – Study Day biopsy site scabbed over.

- Body Weights - There were no significant alterations in body weights and body weight changes attributable to the treatment.
- Clinical Pathology - Significantly ↑ WBC 14.1-16.2 $x10^6$ vs 11.8 $x10^6/\mu l$) and PMN (10.05-11.5$x10^6$ vs 8.17 $x10^6/\mu l$), slightly ↑ serum globulin (2.6 - 2.9 vs 2.2 g/dl), and slightly ↓ albumin (2.9 vs 3.3 g/dl) were identified in Group 4 dogs during Weeks 3 and 4.
- Blood and Skin Bacterial Cultures - No bacteremia was found for all blood samples. The bacterial swab bacterium identified were common skin and oral microflora. Results of these swab cultures are summarized in the table below:

Animal Nº	Location of Swab Sampling	Sampling Day	Bacterial Isolates
46892401	Right Shoulder Swelling Aspirate	18	*Strep. bovis*, Group G β *strep.*
	Right Shoulder Open Wound		*Strep. spp.*, *Staph. intermedius*, β hemolytic *strep.*
	Right Shoulder Abscess	20	*Pseudomonas chloraphis*, *Staph. intermedius*
	Neck Abscess		No growth.
46892403	Right Shoulder Abscess	24	*Strep. lactis/diacetylactis*
46892404	Right Neck Abscess	24	*Strep. lactis/diacetylactis*
46892405	Right Neck ABCs	24	*Strep. lactis/diacetylactis, Staph. intermedius*
46892406	Right Neck ABCs	24	*Strep. lactis/diacetylactis,*
46892101	Left Neck; Skin Biopsy Site	24	*Strep. lactis/diacetylactis, Staph. intermedius*
46892104	Left Neck Incision Site	24	*Strep. lactis/diacetylactis, Staph. intermedius*
46892201	Right Neck Incision Site	24	*Strep. lactis/diacetylactis, Staph. intermedius*
46892202	Right Neck Incision Site	24	*Strep. lactis/diacetylactis, Staph. intermedius*
46892203	Left Neck Incision Site	24	*Strep. lactis/diacetylactis, Staph. intermedius*
46892204	Left Neck Incision Site	24	*Strep. lactis/diacetylactis, Staph. intermedius*
46892402	Right Neck ABCs	26	*Strep. lactis/diacetylactis*
46892403	Thoracic Cavity Sero-Sanguinous Fluid (At Necropsy)	31	Group G β *strep.*

- Peripheral and Splenic Lymphocyte Immunophenotyping (CD45, CD3, CD4, CD8α, CD21, CD45RA, and CD14) - There were no significant changes in any of the lymphocyte subset parameters measured.
- Whole Blood and Isolated PMN Oxidative Burst - Oxidative burst potential of PMN induced by PMA was measured by flow cytometry (using the conversion of dihydrorhodamine to rhodamine 123 as the endpoint) and ferricytochrome C reduction methods. Unscheduled sacrificed dogs, 4689401 on Day 14 (pre- and post-R) and 4689403 on Day 22 (pre- and post-R), had marked lower percentages of PMN either in the whole blood or isolated PMN preparations that had oxidative burst, produced H_2O_2 or generated O_2^- in response to PMA stimulation. Due to highly variable data were presented, it would require a larger sample size in each group to draw conclusions.
- Serum Hemolytic C' and Ig Levels - Mean (± SD) serum hemolytic C' (CH_{50}) and Ig (mg/dl) levels for each group are presented in the following table. Group dogs had slightly elevated total C' and IgA.

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Group	SERUM FUNCTIONAL HEMOLYTIC C' LEVELS (CH_{50})				
	Day -13	Day -4	Day 14	Day 22	Day 28
1	73.0 ± 22.35	88.7 ± 28.31	134.3 ± 30.82	141.8 ± 49.40	197.2 ± 110.15
2	99.7 ± 31.74	78.7 ± 30.51	174 ± 49.8	122.4 ± 30.40	181 ± 44.1
3	56.7 ± 36.14	56.6 ± 31.63	97.2 ± 68.14	86.0 ± 54.38	133.2 ± 70.40
4	71.5 ± 47.17	113.9 ± 46.74	229.8 ± 60.05	202.7 ± 116.61	269.5 ± 77.05
5	90.9 ± 72.06	115.6 ± 54.89	140.6 ± 64.47	91.7 ± 54.55	123.1 ± 87.30

Group	SERUM IG LEVELS (mg/dl)					
	Baseline Average			Day14 Pre-R		
	IgG	IgM	IgA	IgG	IgM	IgA
1	970.08 ± 194.47	263.08 ± 19.94	31.56 ± 4.85	1013.37 ± 115.28	238.36 ± 49.65	29.25 ± 5.14
2	894.60 ± 230.60	233.28 ± 65.78	26.69 ± 4.08	714.10 ± 156.77	155.37 ± 59.72	29.50 ± 10.08
3	944.64 ± 123.26	288.64 ± 80.46	35.30 ± 2.04	911.18 ± 86.32	249.27 ± 48.12	32.10 ± 4.16
4	1012.51 ± 432.08	242.49 ± 80.66	31.94 ± 4.46	924.23 ± 386.75	229.93 ± 121.60	34.00 ± 6.0
5	903.91 ± 272.13	258.57 ± 62.14	35.44 ± 12.40	824.00 ± 250.88	228.76 ± 55.05	34.63 ± 11.71
Group	Day 22 Pre-R			Day 28 Pre-R		
	IgG	IgM	IgA	IgG	IgM	IgA
1	846.24 ± 176.89	243.72 ± 94.82	31.50 ± 5.57	898.87 ± 126.88	237.25 ± 87.95	30.13 ± 2.66
2	897.80 ± 110.82	199.83 ± 79.76	28.00 ± 5.76	932.73 ± 232.06	223.18 ± 98.73	31.75 ± 7.98
3	741.44 ± 79.16	249.52 ± 66.53	32.70 ± 3.40	776.00 ± 88.43	246.35 ± 44.14	31.30 ± 3.03
4	997.65 ± 405.40	238.35 ± 112.19	55.00 ± 49.13	929.82 ± 191.97	221.20 ± 94.11	37.75 ± 9.54
5	678.78 ± 187.24	221.22 ± 51.60	31.00 ± 10.86	724.80 ± 228.32	217.09 ± 42.18	30.38 ± 13.68

- COX-2 mRNA Expression in PMN - A summary of COX-2 mRNA expression in peripheral blood neutrophils from dogs treated with SC-65872 is presented in the following table.

Treatment Group	COX-2 mRNA COPIES/CYCLOPHILIN[a]				
	Day 14 Pre-Dose	Day 14 Post-Dose	Day 22 Pre-Dose	Day 22 Post-Dose	Day 28 Pre-Dose
Group 1 & 3 combined[b]	1.95 ± 1.47	2.59 ± 1.85	-	-	-
Group 2, 4 & 5 combined[c]	2.73 ± 2.30	2.85 ± 1.48	-	-	-
Group 1	-	-	1.90 ± 1.26	1.22 ± 0.79	0.62 ± 0.45
Group 2	-	-	2.37 ± 1.82	1.62 ± 0.65	1.05 ± 1.00
Group 3	-	-	1.29 ± 0.57	0.70 ± 0.41	0.49 ± 0.11
Group 4	-	-	2.26 ± 1.97	1.68 ± 0.54	1.31 ± 0.28
Group 5	-	-	1.51 ± 1.24	1.31 ± 0.70	0.78 ± 0.24

[a] Data are presented as the mean (± standard deviation) COX-2 mRNA copy number per cyclophilin copy number.
[b] Combined results for animals in Groups 1 and 3 (n=10) on Day 14, one day before wounding or inoculation procedures were performed.
[c] Combined results for animals in Groups 2, 4 and 5 (n=14) on Day 14, one day before wounding or inoculation procedures were performed.

- PK/TK - SC-65872 and SC-66905 were detectable in plasma following oral administration of SC-65872 at dosages of 7.0 mg/kg bid for 28 days. Mean plasma SC-65872 and its active metabolite, SC-66905, levels on Days 1, 4 and 28 are presented in the following table.

Day	Dose (mg/kg)	Time (hr)	Mean (±SE) Plasma Levels (μg/ml)	
			SC-65872	SC-66905
1 (N=14)	7	2	1.48 ± 0.174	1.05 ± 0.128
		12	0.203 ± 0.033	1.57 ± 0.132
4 (N=14)	7	2	2.46 ± 0.186	3.25 ± 0.165
		12	0.792 ± 0.114	3.11 ± 0.301
28 (N=12)	7	2	2.10 ± 0.161	2.55 ± 0.154
		12	0.707 ± 0.143	3.20 ± 0.306

- Gross and Histopathology - Comparable terminal body weights, organ weights and relative organ/body weights were seen between SC-65872 treated and untreated dogs.

Unscheduled Death/Sacrifice:
Two Group 4 animals (46892401 and 46892403) died or were sacrificed due to humane reasons during the study. At necropsy, animal 46892401 had three large wounds (~9x8, 4x3, and 2x1 cm) with gross alterations of loss of skin, ulceration with serosanguinous exudate, and exposure of underlying skeletal muscles. The microscopic changes of these lesions were characterized by severe cellulitis with skin ulceration and infiltration of neutrophils, histiocytes, lymphocytes, and plasma cells. Slight myeloid hyperplasia in the bone marrow and mild lymphoid hyperplasia in the mesenteric lymph nodes observed. In addition, two slight focal erosions/ulceration were noted at the gastro-duodenal junction. No significant bacteria were observed within the gastric lesion by Gram's staining.
Gross lesions noted in dog Nº 46892403 included skin wounds at the *Strep.* inoculation site, subcutaneous abscess in the forelimb, pyothorax, hydroperitoneum, pyelonephritis, focal discoloration in the myocardium, single consolidated area in the lungs, and enlarged lymph nodes. Microscopic examination of the wound at the *Strep.* inoculation site showed cellulitis, skin ulceration, and infiltration of neutrophils, lymphocytes, histiocytes, and plasma cells. Other microscopic changes in this animal were pyelonephritis, suppurative pericarditis, valvular endocarditis, and myocarditis, pulmonary microabscess, and edematous lymph nodes as results of septicemia. Myeloid hyperplasia in the bone marrow and extramedullary hematopoiesis in the liver were considered secondary to bacterial skin lesions and septicemia. Other changes such as lymphoid depletion in the thymus, spleen, and lymph nodes were likely associated with septicemia-related stress.
Terminal Sacrifice:
Wound Healing - No significant differences in gross, histologic and immunohistochemical parameters of wound healing were observed between control (Group 1) and SC-65872-treated (Group 2) animals.
Histomorphologic evaluations of punch biopsy sites "Y" and "Z" revealed changes with the characteristics of wound healing including epidermal crust (blood elements and sloughed keratinocytes) and hyperplasia, dermal granulation tissue (fibroplasia and neovascularization), and infiltration by neutrophils, histiocytes, lymphocytes, and plasma cells. The incidence and severity of neutrophil infiltrate was slightly greater in control versus SC-65872 treated animals.
Histological changes of biopsy specimens from Incision Sites 1 through 6 were characterized by the appearance of the crust (blood elements and sloughed keratinocytes) and infiltration of neutrophils within 4 hours of the infliction of wounds followed by slight hyperplasia of epidermal keratinocytes by 24 hr post-incision, and proliferation of granulation tissue (neovascularization and fibroplasia) by Day 3. From Day 3 onward, increased incidence and/or severity of epidermal hyperplasia and dermal granulation tissue were identified. On Days 9 and 14, epidermal crust markedly reduced and the appearance of healed wounds with presence of abundant epidermal hyperplasia and dermal granulation tissue were characterized. There were no significant differences in the incidence, severity, and time of occurrence of above parameters between control and SC-65872-treated animals with the exception of the local neutrophil response. SC-65872-treated dogs had lower incidence and severity of neutrophil infiltration (especially for first 3 days). The biological significance of this change is unclear.
Immunohistochemical analysis of biopsy specimens collected from incision sites 1 to 6 and biopsy "Y" showed presence of basal levels of both COX-1 and COX-2 in the canine skin. In the normal skin, COX-1 immunoreactivity was present in epidermal keratinocytes, hair follicles, sebaceous and tubular glands and dermal blood vessels and COX-2 immunoreactivity was present in hair follicles (especially anagen hair follicles), tubular glands and several dermal blood vessels. No significant