3.3.1.1. Metabolism and Excretion of [^{14}C]SC-65872 After a Single Oral Dose to Mice; Date: 15-May-2000, Document No. M3098347. (Vol. 1.20)

Report №: M3098347

Study Aim: To determine the total radioactivity recovery in mice following a single oral administration of [^{14}C]SC-65872 at 5 mg/kg, to obtain metabolic profiles in selected plasma, RBC, urine and fecal samples, to identify the major metabolites of SC-65872, and to estimate plasma and RBC pharmacokinetic parameters for total radioactivity, SC-65872, and M1.

Compound: [redacted]

Vehicle:

Dose & Route: 5 mg/kg po and 25 mg/kg of [^{14}C]SC-65872 + [^{13}C]SC-65872 for metabolite identification study

Dosing Frequency: single dose

Animals: ♂ + ♀ CD-1 mice ([redacted] 8-13 weeks of age, weighing 20-40 g

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

GLP/QAU Compliance: N/A

Study Date (In-Life): 1/31/2000 to 2/1/2000.

Sample Collection: Blood - 0.5, 1, 2, 4, 6, 24, 48, 72, 96, 120 and 168 hr
Urine - Pre-R and at 24 hr intervals for 7 days
Feces - Pre-R and at 24 hr intervals for 7 days

Analysis Methods: [redacted]

Results:

- Radioactivity and PK Parameters of SC-65872 and M1 (SC-66905) in Plasma and Blood - Mean PK parameters of SC-65872 and M1 in plasma and RBC are presented in the following table. SC-65872 and M1 might be preferentially partinioned into RBC as much higher C_{max} and AUC values were noted in the RBC. Plasma metabolic profiling showed that SC-65872 and M1, a hydroxylated metabolite, were the major radioactive components circulating in plasma and RBC.

PK Parameter in Blood and Plasma		T_{max} (hr)		C_{max} (μg eq/ml)		$AUC_{0-\infty}$ (μg•hr/ml)		AUC_{0-t} (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀
Plasma[a]	Total Radioactivity	0.5	0.5	2.69	1.70	22.2	24.6	19.8	21.1
	SC-65872	0.5	0.5	2.07	1.20	3.58	2.08	3.52	2.05
	SC-66905	0.5	1	0.334	0.418	0.850	1.63	0.707	1.35
Blood[b]	Total Radioactivity	1	6	10.4	8.93	398	287	383	275
	SC-65872	0.5	0.5	5.55	3.75	12.1	6.42	12.8	6.38
	SC-66905	1	1	5.03	5.90	22.6	35.2	30.4	44.4

[a] AUC_{0-t} where t = last time point, for total radioactivity it was 168 hr, for SC-65872 and M1 it was 6 hr.
[b] AUC_{0-t} where t = last time point, for total radioactivity it was 168 hr, for SC-65872 and M1 it was 24 hr.

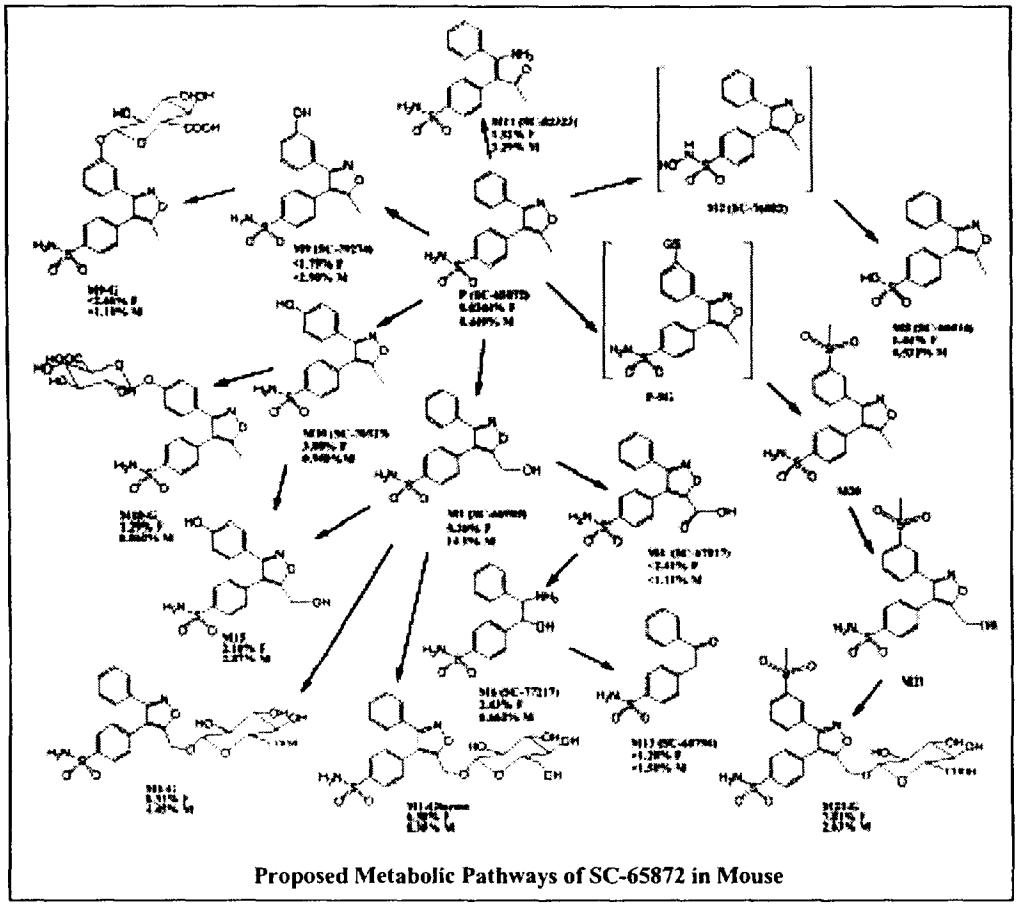
- Radioactivity in Urine and Feces - Aproximately 95-100% of dosed radioactivy was elimeinated in 0-178 hr urine and feces. The percentages of radioactive dose excreted in urine and feces are shown in the following table.

Sampling Time (hr)	Urine		Feces		Urine + Feces	
	♂	♀	♂	♀	♂	♀
0-24	33.3	43.6	52.3	42.3	85.6	86.0
0-48	35.4	46.0	57.6	44.6	93.0	90.6
0-72	36.5	46.6	59.3	46.4	95.8	93.1
0-96	37.0	46.9	60.0	46.8	97.0	93.7
0-120	37.2	47.1	60.8	46.9	98.1	94.0
0-144	37.8	47.3	61.5	47.1	99.3	94.5
0-168	38.0	47.5	61.8	47.2	99.8	94.7

- Metabolic Profiles In Urine and Feces - The major urinary metabolites were M1-G, M1-glucose and M21-G. SC-65872, M1, M4, M6, M8, M9, M9-G, M10, M10-G, M11, M13, and M15 were also observed in mouse urine. M1 was the major metabolite detected in the 24-hr fecal sample. Mean % of total radioactive dose exreted in urine and feces as SC-68572 and it metabolites are listed in the following table.

Parent Drug & Metabolite	Mean % Radioactive Excreted as SC-65872 and Metabolites in Urine and Feces					
	♂			♀		
	0-24 hr Urine	0-24 hr Feces	Total	0-24 hr Urine	0-24 hr Feces	Total
SC-65872	a	0.449	0.449	a	0.0244	0.0244
M1	2.68	11.4	14	1.26	4.00	5.26
M1-Glucose	7.07	1.28	8.35	5.95	0.430	6.38
M1-G	1.97	2.48	4.45	6.15	2.16	8.31
M4 + M9-G	1.11	a	1.11	2.41	a	2.41
M6	0.662	a	0.662	2.43	a	2.43
M8	0.207	0.325	0.532	1.00	0.439	1.44
M9	1.65[b]	1.25	2.90	1.43[b]	0.357	1.79
M10	a	0.948	0.948	a	3.08	3.08
M10-G	0.562	a	0.562	1.29	a	1.29
M11	1.42	1.87	3.29	0.573	0.751	1.32
M13	b	1.51	1.51	b	1.20	1.20
M15	0.895	1.97	2.87	1.60	0.502	2.10
M21-G	2.63	a	2.63	7.81	a	7.81
Total =			44.4			44.8

- Metabolic Pathway - The metabolic pathways for SC-65872 in mice are illustrated in the following fogure. The metabolites identified during Phase I metabolism were M1, M4, M8, M10, M11, M13, and M15. Inaddition several Phase II metabolites were also identified. There were M1-G, M1-glucose, M9-G, M10-G, M20, M21 and M21-G.



Proposed Metabolic Pathways of SC-65872 in Mouse

3.3.1.2. Isolation and Identification of Metabolites of SC-65872 in Rats; Date: 11-Apr-1996, Document No. M3096047. (Vol. 1.20)

Report Nº: M3096047

Study Aim: To isolate and identify the major plasma and urinary metabolites of SC-65872 in rats following a single oral dose of 200 mg/kg [phenyl-^{14}C6(U)]SC-65872.

Compound: [redacted]

Dose & Route: 200 mg/10 ml/kg po single dose

Animals: 4 ♂ and 4 ♀ rats (Sprague Dawley), weighing 175-275 g.

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

Analysis Method: [redacted]

Compliance with GLP/QAU: N/A

Study Date: Not Indicated

Study Design: Groups of rats were orally dosed with 200 mg/kg of [5-^{14}C]SC-65872 in PEG 400:H_2O (2:1, v/v) solution or [phenyl-^{14}C6(U)]SC-65872 in distilled H_2O by gavage. Blood was collected at 1.5 hours postdose from two rats. Urine and fecal samples were collected from the remaining rats for 24 hours after dose administration. Radioactivity in urine and feces was determined by scintillation counting. Plasma extract, fecal extract and urine were analyzed by HPLRC for metabolic profile

Results: Incubation of urine and fecal extract prepared from samples collected in rats orally treated with 2 mg/kg of [5-^{14}C]SC-65872 study with β-glucuronidase did not reveal any significant changes in the HPLRC profiles. The hydroxylated metabolite (SC-66905) was the main urinary metabolite in the rat as determined by [redacted] MS analysis. A minute amount of unchanged parent SC-65872 was detected in urine, indicating that SC-65872 was extensively metabolized.

3.3.1.3. Formation of [^{14}C]CO_2 After Oral Administration of [5-^{14}C]SC-65872 to Male and Female Sprague-Dawley Rats; Date: 30-Jul-1996, Document No. M2096231. (Vol. 1.20)

Report Nº: M2096231
Study Aim: To determine whether [^{14}C]CO_2 was formed following oral administration of [5-^{14}C]SC-65872 to ♂ and ♀ Sprague-Dawley rats.
Compound: [redacted]
Vehicle:
Dose & Route: 2 mg/5 ml/kg po
Dosing Frequency: single dose
Animals: ♂+♀ CD Sprague-Dawley [redacted] 49 days of age, weighing 294-303 g for ♂ and 187-198 g for ♀; 3/sex/group
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: No.
Study Date: Not Stated.
Study Design: Groups of 3/sex SD rats were given a single oral dose of 2 mg/kg of [5-^{14}C]SC-65872. Expired gases, urine, feces and cage washes were collected for a period of 4 days. Animal carcasses were also analyzed for radioactivity.

Results: The mean total radioactive recovery was 91% for ♂ and 93.3% for ♀, respectively. The major elimination of radioactivity for ♂ was through fecal excretion with value of 50.4%. However, in ♀ rats, approximately equal amount of radioactivity was excreted in urine and feces. The cumulative mean percent of recovered dose at 96 hr following oral administration of 2 mg/kg of [5-^{14}C]SC-65872 are summarized in the following table.

Sex	% Dose Recovered					
	Expired Air	Urine	Feces	Cage Washes	Carcasses	Total
♂	3.0	32.7	50.4	3.4	1.5	91
♀	3.7	44.3	40.6	3.2	1.6	93

3.3.1.4. The Excretion of Total Radioactivity in Male and Female Rats Following Oral Administration of 2 mg/kg of [5-^{14}C]SC-65872; Date: 27-Nov-1996, Document No. M3096048. (Vol. 1.20)

Report Nº: M3096408
Study Aim: To determine recovery of [^{14}C] in urine and feces following oral administration of 2 mg/kg [5-^{14}C]SC-65872 to ♂ and ♀ Sprague-Dawley rats.
Compound: [redacted]
Vehicle:
Dose & Route: 2 mg/2 ml/kg po
Dosing Frequency: single dose
Animals: ♂+♀ CD Sprague-Dawley rats, weighing 175-275 g; 4/sex/group
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: No.
Study Date: Not Stated.

Study Design: Groups of 4/sex SD rats were given a single oral dose of 2 mg/kg of [5-^{14}C]SC-65872. Urine and feces were collected at 24-hr intervals for 7 days. Radioactivity in urine and fecal samples was determined by liquid scintillation counting (LSC).

Results: The mean cumulative percentages of radioactivity excreted in the urine and feces after oral administration of [5-^{14}C]SC-65872 are presented in the following table.

Sampling Time (hr)	Urine		Feces		Urine + Feces	
	♂	♀	♂	♀	♂	♀
0- 24	20.1	26.9	47.4	34.2	67.5	61.1
0- 48	21.0	29.3	56.0	40.9	77.0	70.2
0- 72	21.3	29.7	56.6	41.5	77.9	71.2
0- 96	21.4	29.9	56.8	41.6	78.2	71.5
0-120	21.5	30.0	56.9	41.8	78.5	72.3
0-144	21.6	30.1	57.0	41.8	78.6	72.4
0-168	21.6	30.1	57.1	41.9	78.7	72.5

3.3.1.5. Metabolism and Excretion of [phenyl-^{14}C(U)]SC-65872 Following Intravenous or Oral Administration to Rats; Date: 19-Jul-1996, Document No. M2096020. (Vol. 1.20)

Report Nº: M32096020

Study Aim: To determine to determine the plasma concentration profile and to obtain information on the metabolism of [phenyl-^{14}C(U)]SC-65872 following a single oral or iv administration.

Compound: [redacted]

Vehicle:

Dose & Route: 0.33 mg/kg iv or po single dose

Dosing volume: iv - 1 ml/kg; po - 5 ml/kg

Animals: Sprague-Dawley [redacted] 7-9 weeks of age, weighing 175-275 g; 3/sex/group

Study Location: [redacted]

GLP/QAU Compliance: No.

Study Date: 2/28/1996 - 3/19/1996

Study Design: Six groups of 3/sex SD rats were given a single oral or iv dose of 0.33 mg/kg of [phenyl-^{14}C(U)]SC-65872. Urine and fecal samples were collected at 24-hr intervals for 168 hr. Blood samples were collected at 5 min and 2, 5, 12, 24, 48, 72, 96, and 144 hr post iv dose or at 2, 5, 12, 24, 48, 72, 96, and 144 hr post oral dose. Radioactivity in blood, urine and fecal samples was determined by liquid scintillation counting (LSC).

Results:

- Radioactivity in Blood, Plasma, and RBC - Mean PK parameters for SC-65872 in blood , plasma, and RBC following a single iv or oral dose of [phenyl-^{14}C(U)]SC-65872 to rats are presented in the following table. Higher C_{max} and AUC values were noted in ♀, an indication of gender differece in pharmacokinetics of SC-65872. In addition, raadioactivity concentrations in blood and erythrocytes were higher than those in plasma indicating that a high partitioning of total radioactivity into erythrocytes might have occurred. The bioavailability of total radioactive dose was 94% and 82% in ♂ and ♀, respectively.

Sample Matrix	PK Parameters following IV Administration						PK Parameters following Oral Administration					
	$T_{½}$ (hr)		C_{max} (μg eq/ml)		$AUC_{0-\infty}$ (μg eq•hr/ml)		$T_{½}$ (hr)		C_{max} (μg eq/ml)		$AUC_{0-\infty}$ (μg eq•hr/ml)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Whole Blood	35.3	35.5	2.33	2.79	21.2	34.4	41.9	36.2	1.80	2.26	23.7	36.5
Plasma	49.6	57.0	0.170	0.216	1.18	2.05	45.0	36.7	0.124	0.166	1.11	1.67
RBC	35.8	36.4	3.69	4.52	35.0	60.6	37.3	35.6	2.58	3.34	40.4	61.1

- Radioactivity in Urine and Feces - The mean cumulative percentages of radioactivity excreted in the urine and feces after oral administration of [phenyl-^{14}C(U)]SC-65872 are presented in the following table. It appeared that ♂ rats excreted higher percentage of radioactive dose through feces.

Sampling Time (hr)	Urine				Feces				Cage Wash + Cage Wipe			
	iv		po		iv		po		iv		po	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0- 24	28.1	31.2	24.9	29.4	48.4	36.0	61.2	38.5				
0- 48	30.9	40.3	27.0	36.5	64.7	52.2	68.3	54.8				
0- 72	31.8	42.4	27.8	38.1	66.1	54.4	69.5	57.4				
0- 96	32.3	43.3	28.3	39.0	66.6	55.0	70.0	57.9				
0-120	32.6	43.8	28.7	39.6	66.9	55.3	70.3	58.2				
0-144	32.8	44.2	28.8	40.0	67.0	55.5	70.5	58.4				
0-168	33.0	44.4	29.0	40.3	67.2	55.6	70.6	58.5	0.55	0.95	0.62	1.25

3.3.1.6. Metabolism Profiling of [phenyl-^{14}C(U)]SC-65872 Following Intravenous or Oral Administration to Rats; Date: 23-Sep-1998, Document No. M3096151. (Vol. 1.20)

This study report was not reviewed. Similar information could be obtained from the following study, Report Nº M3098145

3.3.1.7. Metabolism of [^{14}C]SC-65872 After Oral Administration to Male and Female Rats; Date: 12-Nov-1999, Document No. M3098145. (Vol. 1.20)

Report Nº: M3098145
Study Aim: To identify metabolites of [^{14}C]SC-65872 after a single oral administration of 2.5 mg/kg [^{14}C]SC-65872 to rats.
Compound: [redacted]
Dose & Route: 2.5 mg/5 ml/kg, po single dose
Animals: ♂ + ♀ Sprague-Dawley rats [redacted] weighing 234-359 g; 5/sex for blood, urine and feces collection and 3/sex for bile collection.
Sample Collection: Blood (2/sex) - 1 and 5 hr postdose
Urine and Feces (3/sex) - Days -1 and 2
Bile (3/sex) - 6 hr postdose
Analysis Method: [redacted]
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
Compliance with GLP/QAU: N/A
Study Date: Not Stated.

Results:

- Radioactivity in Plasma and RBC - SC-65872 and metabolite M1, SC-66905, the hydroxymethyl metabolite of SC-65872 were the major radioactive components circulating in blood at 1 and 5 hours post dose. The calculated SC-65872 and M1 levels in plasma and RBC, and percentages of SC-65872, M1 radioactivity in HPLRC profiles are shown in the following table. No apparent sex-associated difference in the concentrations of SC-65872 and M1 was detected in RBC samples. Higher levels of SC-65872 in RBC than those in plasma were noted.

Sampling Time (hr)	% Radioactivity in HPLRC Profiles of Pooled Rat RBC or Plasma							
	RBC				Plasma			
	M1		SC-65872		M1		SC-65872	
	♂	♀	♂	♀	♂	♀	♂	♀
1	20.9	12.0	79.0	88.0	8.05	5.21	92.0	93.8
5	45.8	29.1	53.9	69.5	19.7	11.2	79.5	84.1
Sampling Time (hr)	Calculated Concentrations in Pooled Rat RBC or Plasma (μg/g)							
	RBC				Plasma			
	M1		SC-65872		M1		SC-65872	
	♂	♀	♂	♀	♂	♀	♂	♀
1	0.906	0.785	3.26	5.49	0.0398	0.0327	0.432	0.560
5	5.23	4.45	5.86	10.1	0.0811	0.0784	0.311	0.559

- Radioactivity and Metabolic Profile in Urine and Feces - Cumulative (0-48 hr) recovery of administered radioactive dose in both urine and feces was 93.7% for ♂ and 87.7% for ♀. The percentages of radioactive dose excreted in urine and feces are listed in the following table.

Time (hr)	Mean (±SE) % of Dose Excreted								
	Urine			Feces			Total		
	♂	♀	♂ + ♀	♂	♀	♂ + ♀	♂	♀	♂ + ♀
0-24	22.0±1.7	33.9±3.4		52.8±4.0	37.6±4.5		74.8±5.6	71.5±8.0	
24-48	4.33±0.34	5.36±0.45		14.6±3.0	10.9±3.5		18.9±2.8	16.2±3.3	
0-48	26.4±1.9	39.2±3.4	32.8±3.4	67.3±2.5	48.4±2.7	57.9±4.5	93.7±3.2	87.7±5.4	90.7±3.1

M1 was the major metabolite excreted in the urine. In the 48 hr urine and fecal samples, 7.71% and 11.2% of the radioactive dose were excreted as SC-65872 and M1, respectively. Mean percentages of total radioactive dose excreted in urine and feces as SC-65872 and its major metabolites are presented in the following table. Metabolites, M1-G, M1-glucose, M9-G, and M10-G were converted to M1, M9 and M10, respectively after incubation of urine sample with β-glucuronidase, indicating that M1-G, M9-G, and M10-G may be ether-linked glucuronide conjugates and M1-glucose is also an ether-linked glucoside conjugate.

Time (hr)	Sex	Mean Percentages of Dosed Radioactivity Excreted in Urine as the Metabolite[a]												
		M6	M3-G1	M12	M14	M1-G	M3	M15	M7	M8	M11	M1	M13	SC-65872
0-24	♂	0	0.737	3.93	1.35	0.715	0.260	1.01	0.425	1.18	0.500	6.71	0.570	0
0-24	♀	1.11	0.220	6.31	2.17	0.674	0.0481	0.837	1.49	4.14	1.66	12.8	0.442	0.101
0-48	♂	0	1.20	4.24	1.46	0.765	0.260	1.10	0.443	1.23	0.522	7.38	0.838	0
0-48	♀	1.58	0.272	6.85	2.36	0.704	0.0481	0.885	1.57	4.36	2.28	14.4	0.631	0.101
0-48	♂+♀	0.792	0.737	5.54	1.91	0.735	0.154	0.992	1.00	2.80	1.40	10.9	0.735	0.0504
		Percentage of Dosed Radioactivity Excreted in Feces as Identified Metabolite[a]												
0-24	♂	1.14	2.10	0	0	0.429	0.101	0.555	0.625	0.301	0.689	0	3.24	7.61
0-24	♀	0.668	2.18	0	0	0.170	0	0.374	0.302	0.146	0.170	0.184	1.24	7.73
0-48	♂	1.76	2.16	0.0738	0.0372	0.948	0.303	1.56	0.876	0.422	1.03	0.354	3.46	7.61
0-48	♀	1.28	2.80	0.0166	0.0084	0.457	0.0681	1.19	0.413	0.199	0.170	0.209	1.32	7.73
0-48	♂+♀	1.52	2.48	0.0452	0.0228	0.702	0.185	1.37	0.645	0.310	0.602	0.281	2.39	7.67
Total (0-48)	♂+♀	2.31	3.21	5.59	1.93	1.44	0.339	2.37	1.65	3.11	2.00	11.2	3.13	7.71

[a] 84.6% (♂: 73.7%; ♀: 91.9%) and 31.7% (♂: 30.6%; ♀: 32.7%) total excreted radioactivity was identified in urine and feces, respectively; the metabolites were listed in the order of their HPLRC retention times.

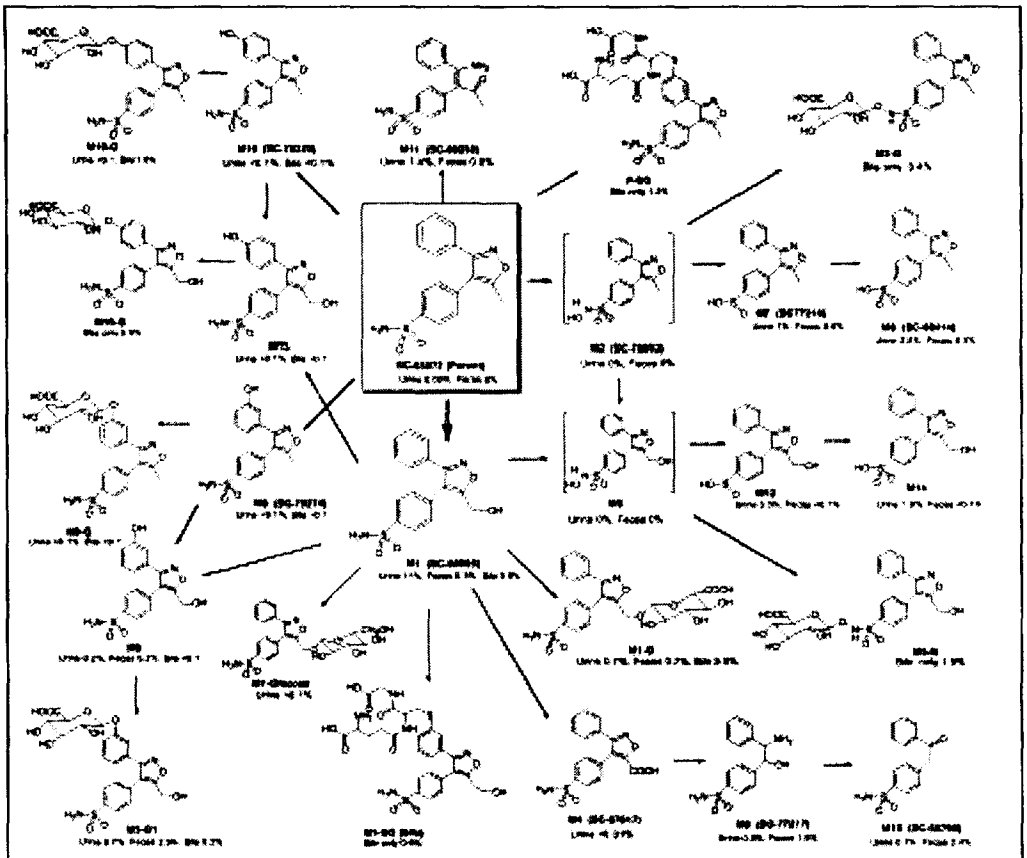
- Radioactivity and Metabolic Profile in Bile - Approximately 13.4% (♂: 10.0%; ♀: 16.9%) of the dosed radioactivity was excreted in the 6 hr post-dose bile samples. Percentages of radioactive dose as SC-65872 and its identified metabolites in HPLRC profiles of bile samples are listed in the following table.

Sex	% Dose Excreted	Percentages of Dosed Radioactivity as Metabolites in 0-6 hr Post Dose Bile Samples[a]										
		M15-G	M3-G1	M1-SG	P-SG	M10-G	M1-G[b]	M15	M5-G	M1	M2-G	SC-65872
♂	10.0	0	0.201	1.03	0	0.688	5.11	0.118	1.39	0.611	0.378	0.172
♀	16.9	1.23	0.316	0.163	2.39	2.27	6.03	0	2.32	0.412	0.463	0.169
♂+♀	13.4	0.615	0.259	0.596	1.20	1.48	5.57	0.0592	1.86	0.512	0.421	0.171

[a] 95.4% (97.3% in males and 93.6% in females) total excreted radioactivity was identified in bile; the metabolites were listed in the order of their HPLRC retention times.

[b] M1-G was not separated completely from M9-G. Percentage for M1-G included small amount of M9-G.

The metabolic pathways of SC-65872 in the rat are elucidated in the following figure.



Metabolic Pathways of SC-65872 in Rat

3.3.1.8. The Excretion of Total Radioactivity in Bile Duct-Cannulated Rats Following a Single Oral Administration of [^{14}C]SC-65872; Date: 18-Aug-2000, Document No. M2000231; Metabolism of [^{14}C]SC-65872 in Bile Duct Cannulated Rats Following a Single Oral Administration of [^{14}C]SC-65872; Date: 4-Oct-2000, Document No. M3000247. (Vol. 1.21)

Report Nº: [redacted]

Study Aim: To determine the excretion of radioactivity and metabolic profiles following a single oral administration of [^{14}C]SC-65872 to bile duct-cannulated rats.

Compound: [redacted]

Vehicle:

Dose & Route: 5 mg/5 ml/kg po single dose

Animals: Bile duct-cannulated ♂ & ♀ Rat/Hla:(SD)CVF [redacted] 7-8 weeks of age, weighing 279-308 g; 5/sex/group

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

GLP/QAU Compliance: N/A

Study Date (In-Life): 7/11-14/2000

Sample Collection: Bile - Predose, 0-2, 2-4, 4-8, 8-12, -12-24, 24-48, and 48-72
Urine - Predose, 0-12, 12-24, 24-48, and 48-72
Feces: Predose, and 24-hr intervals for 72 hr
Carcass/Cage Wash /Cage Wipe/Bile Cannula/Jacket Rinse - 72 hr (terminal sacrifice)

Analysis Methods: [redacted]

Results:

- Radioactivity in Urine, Feces and Bile - The total recovery of administered radioactivity in ♂ and ♀ rats, was 98.0% and 101%, respectively. Mean cumulative recovery of radioactive dose in urine feces and bile at different collection time points are shown in the following table. More than 93% of the total radioactivity was recovered by 48 hr postdose. No apparent gender-related differences in elimination of radioactivity.

Samples	Collection Time (hr)	Mean (±SE) Cumulative % Radioactive Dose Recovered	
		♂	♀
Urine	0-12	14.6 ± 1.8	12.6 ± 1.1
	0-24	23.6 ± 1.6	23.8 ± 2.1
	0-48	25.8 ± 1.9	30.4 ± 2.6
	0-72	26.1 ± 1.9	31.8 ± 2.7
Feces	0-24	9.54 ± 1.91	8.56 ± 1.52
	0-48	10.0 ± 1.9	10.8 ± 1.7
	0-72	10.2 ± 1.9	11.2 ± 1.7
Bile	0-2	0.26 ± 0.13	0.46 ± 0.22
	0-4	6.04 ± 0.58	4.54 ± 0.97
	0-8	27.9 ± 1.7	17.6 ± 2.8
	0-12	43.7 ± 1.7	28.5 ± 3.8
	0-24	57.0 ± 1.9	44.9 ± 4.9
	0-48	59.8 ± 2.2	52.4 ± 5.3
	0-72	60.1 ± 2.2	53.5 ± 5.4
Carcass	72 - Carcass	0.70 ± 0.10	1.03 ± 0.12
Cage Wash /Cage Wipe/ Bile Cannula/Jacket Rinse	72 - Cage Wash	0.72 ± 0.17	1.32 ± 0.57
	72 - Cage Wipe	0.13 ± 0.02	2.21 ± 1.19
	72 - Bile Cannula	0.00 ± 0.00	0.01 ± 0.00
	72 - Jacket Rinse	0.00 ± 0.00	0.01 ± 0.00
Total		98.0 ± 3.7	101 ± 9

- Metabolic Profiles in Bile, Urine and Feces - SC-65872 was extensively metabolized. Aproximately 78% of recovered radioactivity in the 48 hr bile, urine and fecal samples was identified. Total percentage of radioactive dose recovered as parent compound was 6.27% in ♂

and 8.21% in ♀. Mean percentages of radioactive dose as SC-65872 and its metabolites in HPLRC profiles of bile, urine, and fecal samples are presented in the following table.

Parameters	♂						♀					
	Bile		Urine		Feces	Total	Bile		Urine		Feces	Total
Time (hr)	0-24	24-48	0-24	24-48	0-24	0-48	0-24	24-48	0-24	24-48	0-24	0-48
% Dose Recovered	57.0	2.81	23.6	2.17	9.54	95.1	44.9	7.43	23.8	6.62	8.56	91.4
% Dose Identified	45.3	1.43	21.6	1.07	5.20	74.6	35.3	5.25	21.3	4.55	5.05	71.4
M6	1.21	0.0134	2.32	0.131	0.0858	3.76	0	0.0136	0.118	0.0776	0.0825	0.292
M3-G1	3.62	0.120	1.18	0.2566	0.0082	5.19	0.885	0.283	0.157	0.0299	0	1.36
M1-SG	2.72	0.110	0.475	0.0069	0.0161	3.33	1.05	0.641	0.263	0	0	1.96
P-SG	0.905	0.106	0.341	0.0214	0.0159	1.39	0.743	0.00	0.736	0.0236	0.104	1.61
M12	1.20	0.0649	1.76	0	0	3.03	1.41	0.377	1.89	0.104	0	3.78
M14	0.413	0.0224	0.607	0	0	1.04	0.485	0.130	0.650	0.0359	0	1.30
M9-G	0.105	0.0206	2.17	0.171	0.0087	2.47	0.197	0	1.93	0	0.0135	2.14
M1-G	20.7	0.743	0.843	0.0119	0.0079	22.3	17.0	2.39	0.0486	0.504	0.0207	19.9
M15	2.47	0.0724	0.174	0	0	2.71	1.82	0.577	0.116	0.0667	0.0598	2.64
M5-G	1.59	0.0378	0	0.0113	0	1.64	1.45	0.170	0.0454	0	0.0032	1.66
M8	2.02	0	0.851	0.0293	0	2.90	2.61	0.0601	1.33	1.71	0	5.72
M11	0	0	1.10	0	0	1.10	0	0	3.30	0	0	3.30
SC-66905 (M1)	2.27	0.113	9.56	0.434	1.53	13.9	2.07	0.374	10.27	1.89	1.47	16.1
M10	3.37	0.00	0	0	0	3.37	1.13	0.00	0.0480	0	0	1.18
M9	0	0	0.0726	0	0	0.0726	0	0	0.0278	0	0	0.0278
M13	0	0	0.0550	0	0.0090	0.0640	0	0	0.156	0.0794	0	0.236
SC-65872	2.70	0.0098	0.0380	0	3.52	6.27	4.46	0.236	0.187	0.0291	3.29	8.21

3.3.1.9. Amendment M3198348: Metabolism and Excretion of [^{14}C]SC-65872 After a Single Oral Dose to the Female Rabbits; Date: 20-Sep-1999, Document No. M3098348. (Vol. 1.21)

Report Nº: M3098348
Study Aim: To determine the metabolism and excretion of [^{14}C]SC-65872 following a single oral dose of 5 mg/kg [^{14}C]SC-65872 to ♀ rabbits.
Compound: [redacted]
Vehicle: [redacted]
Dose & Route: 5 mg/kg po single dose
Animals: 3♀ non-pregnant New Zealand Rabbits [redacted] 5-6 months old, weighing 2.6-3.2 kg
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not stated.
Analysis Methods: [redacted]
Sample Collection: Blood - 0.5, 1 and 4 hr
Urine - Pre-R (-18-0 hr) and 24 hr intervals for 7 days
Feces - Pre-R (-18-0 hr) and 24 hr intervals for 7 days

Results:

- Radioactivity in Plasma and RBC - Mean radioactivity levels in plasma and RBC at 0.5, 1, and 4 hr post dosing are presented in the following table. Higher radioactivity concentrations were detected in RBC than those in plasma at each time point, an indication of preferential distribution of circulating radioactivity into RBC.

Collection Time (hr)	Mean (±SE) [^{14}C]SC-65872 (ng eq/g)	
	Plasma	RBC
0.5	238 ± 25	552 ± 60
1	419 ± 58	1012 ± 148
4	472 ± 15	2134 ± 77

- Metabolic Profiles in Plasma and RBC - There were 7 metabolites identified in the plasma and M1-G was the major matabolite present in plasma. On contrast, M1 iwas the major metabolite detected in RBC. Mean concentrations of SC-65872 and it metabolites identified in plasma and RBC at 0.5, 1, anfd 4 hr post dose are listed in the following table.

Metabolites	Mean (±SE) Plasma Conc. (ng eq/g) Sampling Time (hr)			Mean (±SE) RBC Conc. (ng eq/g) Sampling Time (hr)		
	0.5	1	4	0.5	1	4
SC-65872	48.8±11.2	67.2±11.0	59.4±6.9	92.3±21.4	84.7±16.3	135±18
M1	27.7±10.1	74.8±8.0	81.9±10.5	403±41	851±132	1779±143
M1-G	158±17	316±55	401±11	20.2±7.1	76.3±31.6	82.3±28
M4	10.7±4.7	6.75±3.96	6.92±3.57			
M9-G	6.48±1.44	4.11±2.07	1.81±1.81			
M10-G	20.3±2.9	49.9±14.6	26.2±4.6			
M16	2.93±1.39	6.75±1.62	14.9±6.7			
M17	15.5±7.2	18.4±2.2	22.4±4.7	0±0	0±0	117±43

- Excretion of Radioactivity in Urine and Feces - Mean cumulative percentages of radioactive dose excreted in urine and feces are shown in the following table. Majority of radioactivity was eliminated by 48 hr post dose with ~43% and 58% being excreted in urine and feces, respectively.

Collection Time (hr)	Cumulative Percent of Radioactive Dose Excreted		
	Urine	Feces	Urine & Feces
0-24	37.3	54.1	91.5
0-48	42.7	57.5	100
0-72	42.9	57.9	101
0-96	43.1	58.0	101
0-120	43.2	58.0	101
0-144	43.3	58.1	101
0-168	43.3	58.1	101

- Metabolic Profiles in Urine and Feces - Mean (±SE) percentages of total radioactivity excreted in urine (0-168 hr) and feces (0-48 hr) as [^{14}C]SC-65872 or its metabolites are presented in the following table. M1-G was the major metabolite detected in urine and accounted for ~32% of administed radioactive dose. Little or no (<0.01%) parent compound coulbe detected in urine. M1-G, M3-G1, M9-G and M10-G were converted to M1, M3, M9 and M10, respectively following the incubation of urine with β-glucuronidase. The majority of radioactivity excreted in feces over 0-48 hr after dosing was derived from SC-65872 and M1-G that accounted for 25% and 32% of administered radioactive dose, respectively.

Metabolites	Mean % Radioactive Dose Excreted		
	Sampling Intervals (hr)		Subtotal
	Urine (0-168)	Feces (0-48)	
SC-65872	<0.01	25.3	25.3
M1	1.98	4.95	6.93
M1-G	31.8	0	31.8
M3	<0.01	0	<0.01
M3-G1	0.749	0	0.749
M4	1.88	0	1.88
M6	0.249	0	0.249
M8	<0.01	0	<0.01
M9	<0.01	0.276	0.276
M9-G	0.524	0	0.524
M10	<0.01	2.48	2.48
M10-G	0.93	0	0.93
M13	<0.01	1.7	1.7
M16	2.22	0	2.22
M17	0.00775	0	0.00775
Total	40.4	34.8	75.2

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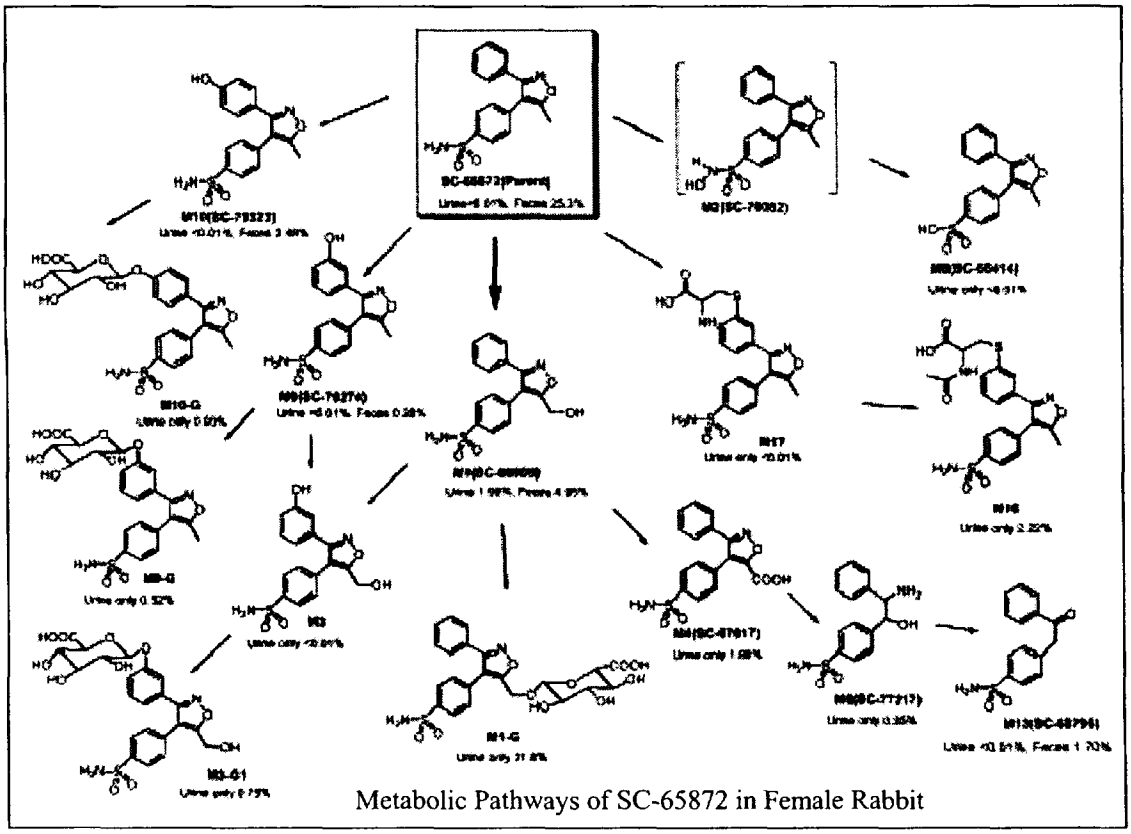
The proposed metabolic pathways of SC-65872 in the female rabbit are illustrated in the following figure.



Metabolic Pathways of SC-65872 in Female Rabbit

3.3.1.10. Pharmacokinetics, Metabolism, and Excretion of [phenyl-^{14}C(U)]SC-65872 Following Intravenous or Oral Administration to Dogs; Date: 30-Jul-1996, Document No. M2096040. (Vol. 1.22)

Report Nº: [redacted]
Study Aim: To determine the blood, plasma, and erythrocyte radioactivity concentration profiles and to obtain information on the excretion and metabolism of [phenyl-^{14}C(U)]SC-65872 given as a single oral or intravenous (iv) dose to dogs.
Compound: [redacted]
Vehicle: [redacted]
Dose & Route: 0.2 mg/kg iv and po
Dosing Frequency: single dose with a 20-day washout period between treatments
Animals: 3/sex beagle dogs [redacted] 8-10 months of age, weighing 9.7-13.7 kg
Study Location: [redacted]
GLP/QAU Compliance: N/A
Study Date (In-Life): 3/12/1996 - 4/15/1996
Study Design:

Phase	Nº of Dogs	Route	Dose (mg/kg)	Dose Vol. (ml/kg)
I	3/sex	iv	0.2	1
II	3/sex	po	0.2	1

Blood Collection: iv - 3, 15, and 30 min, and 1, 2, 3, 5, 7, 10, 16, 24, 48, 72, 96, 144, and 168 hr
po - 15 and 30 min, and 1, 2, 3, 5, 7, 10, 16, 24, 48, 72, 96, 144, and 168 hr
Urine and Feces Collection: at 24-hr intervals for 168 hr
Analysis Methods: [redacted]

Results:

- Radioactivity in Blood, Plasma, and RBC - Mean PK parameters for total radioactvity in blood, plasma, and RBC following a single iv and oral dose of 0.2 mg/kg [phenyl-^{14}C(U)]SC-65872 to dogs are summarized in the following table. No apparent sex-related differences in PK parameters ($T_{½}$,C_{max} ,$AUC_{0-\infty}$, and T_{max}) in blood , plasma and RBC were noted. Mean bioavailability calculated from plasma data was ~88%. Radioactivity concentrations in whole blood and erythrocytes were 2-4x higher than concentrations in plasma, an indication of of preferential distribution of circulating radioactivity into RBC.

PK Parameters	Blood			RBC			Plasma		
	♂	♀	♂ + ♀	♂	♀	♂ + ♀	♂	♀	♂ + ♀
iv									
C_{max} (μg eq/ml)	0.45	0.49	0.47	0.757	0.734	0.745	0.21	0.234	0.222
T_{max} (hr)	0.05	0.05	0.05	0.05	0.05	0.05	0.7	0.05	0.4
AUC_{0-t} (μg eq•hr/ml)	6.75	7.00	6.87	11.6	11.3	11.4	1.85	1.83	1.84
$AUC_{0-\infty}$ (μg eq•hr/ml)	8.15	8.24	8.19	13.9	13.2	13.5	2.48	2.24	2.36
$T_{½}$ (hr)	83.40	78.90	81.20	77.4	74.0	75.7	136	139	138
po									
C_{max} (μg eq/ml)	0.389	0.43	0.41	0.575	0.526	0.551	0.215	0.254	0.235
T_{max} (hr)	0.4	0.7	0.5	0.5	0.7	0.6	0.9	0.7	0.8
AUC_{0-t} (μg eq•hr/ml)	6.68	6.34	6.51	11.9	10.8	11.3	1.83	2.20	2.01
$AUC_{0-\infty}$ (μg eq•hr/ml)	8.23	8.04	8.13	14.7	12.8	13.8	2.26	2.74	2.50
$T_{½}$ (hr)	87.1	98.6	92.9	83.9	80.7	82.3	133	106	119
F (%)	94.9	93.2	94.1	NA	NA	NA	87.5	114	101

- Excretion of Radioactivity - The cumulative percentages recovered in urine and feces following a single iv and oral dose of 0.2 mg/kg [phenyl-^{14}C(U)]SC-65872 are presented in the below table. The primary route of excretion of radioactivity was via the feces. By 48 hours postdose, >80% of the dose had been excreted. No apparent sex-related differences in the rate or extent of excretion

of total radioactivity and the patterns of elimination of total radioactivity following iv or oral administration were observed.

Samples	Collection Time (hr)	Mean (±SE) Cumulative % Radioactive Dose Recovered			
		iv		*po*	
		♂	♀	♂	♀
Urine	0-24	12.9	15.3	13.1	17.9
	0-48	17.6	20.1	15.7	21.0
	0-72	19.1	22.2	16.8	22.6
	0-96	19.7	22.8	17.2	23.1
	0-120	20.1	23.2	17.5	23.3
	0-144	20.3	23.5	17.7	23.5
	0-168	20.4	23.6	17.8	23.6
Feces	0-24	45.2	40.7	47.8	43.1
	0-48	65.4	61.1	67.9	62.3
	0-72	71.1	66.0	71.5	65.7
	0-96	72.3	68.2	72.4	66.7
	0-120	72.7	68.9	12.7	67.0
	0-144	72.9	69.2	72.9	67.3
	0-168	73.2	69.5	73.1	67.4
Cage Wash	168 - Cage Wash	0.78	0.74	0.40	0.82
/Cage Wipe	168 - Cage Wipe	0.18	0.62	0.37	0.70
Total		94.6	94.5	91.7	92.5

3.3.1.11. Isolation and Identification of Metabolites of [^{14}C]SC-65872 in the Beagle Dog; Date: 27-Jul-1999, Document No. M3098306. (Vol. 1.22)

Report Nº: M3098306

Study Aim: to obtain the metabolic profiles in plasma, red blood cells, urine and fecal samples and to identify the metabolites following a single 5 mg/kg oral administration of [^{14}C]SC-65872 to male dogs.

Compound: [redacted]

Dose & Route: 5 mg/2 ml/kg po single dose

Animals: 3 ♂ beagle dogs, weighing 9.6-10.3 kg

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

GLP/QAU Compliance N/A:

Study Date: Not Stated.

Study Design: Dog (3♂) are given a single oral dose of 5 mg/kg [^{14}C]SC-65872. Urine, feces and blood samples were collected for determination of radioactivity. Metabolic profiles of [^{14}C]SC-65872 were determined for plasma, red blood cells, urine and feces by an HPRLC. The chemical structures of metabolites were elucidated by LC-MS/MS and comparison with authentic synthesized standards.

Results:

- Excretion of Radioactivity - The majority of radioactivity was excreted over 0-48 hr after dosing. Approximately 77% of radioactivity was recovered from the urine and feces during 0-72 hr. The cumulative percent of radioactive dose excreted in urine and feces at various collection time periods are presented in the following table.

Collection Interval (hr)	Cumulative % (Mean±SE) Radioactive Dose Excreted		
	Urine	Feces	Urine + Feces
0-24	4.39 ± 0.41	51.0 ± 16.2	55.4 ± 16.6
24-48	6.02 ± 0.26	67.6 ± 5.4	73.6 ± 5.6
48-72	6.62 ± 0.13	70.0 ± 5.1	76.6 ± 5.1

- Metabolic Profiles in Plasma and RBC - HPLRC profiling of plasma samples revealed that majority of the radioactivity in plasma was associated with the parent compound and M1. On contrast, the radioactivity in red blood cells was associated with SC-65872, M1 and M11 as revealed by the HPLRC analysis. The following table showed percentages of total radioactivity and concentrations of [^{14}C]SC-65872 and its metabolites in RBC and plasma HPLRC chromatograms.

Time (hr)	Sample	Mean (±SE) % Total Radioactivity			Concentrations (Mean±SE) (μg/g)		
		SC-65872	M1[a]	M11	SC-65872	M1[a]	M11
1	RBC	73.3 ± 1.0	26.7 ± 1.0	ND	66.4 ± 11.0	25.0 ± 3.2	ND
5		21.0 ± 4.6	76.1 ± 6.0	6.85[b]	32.9 ±12.8	107 ±24	13.4[b]
12		2.33[b]	40.4 ±15.1	52.3 ± 14.1	3.48[b]	61.2 ± 26.4	66.1 ± 14.7
1	Plasma	20.2±1.0	79.5±1.2	ND	0.114±0.061	0.421±0.212	ND
5		75.8±7.8	32.0±1.1	ND	0.394±0.140	0.232[b]	ND
12		95.2[b]	ND	ND	0.207[b]	ND	ND

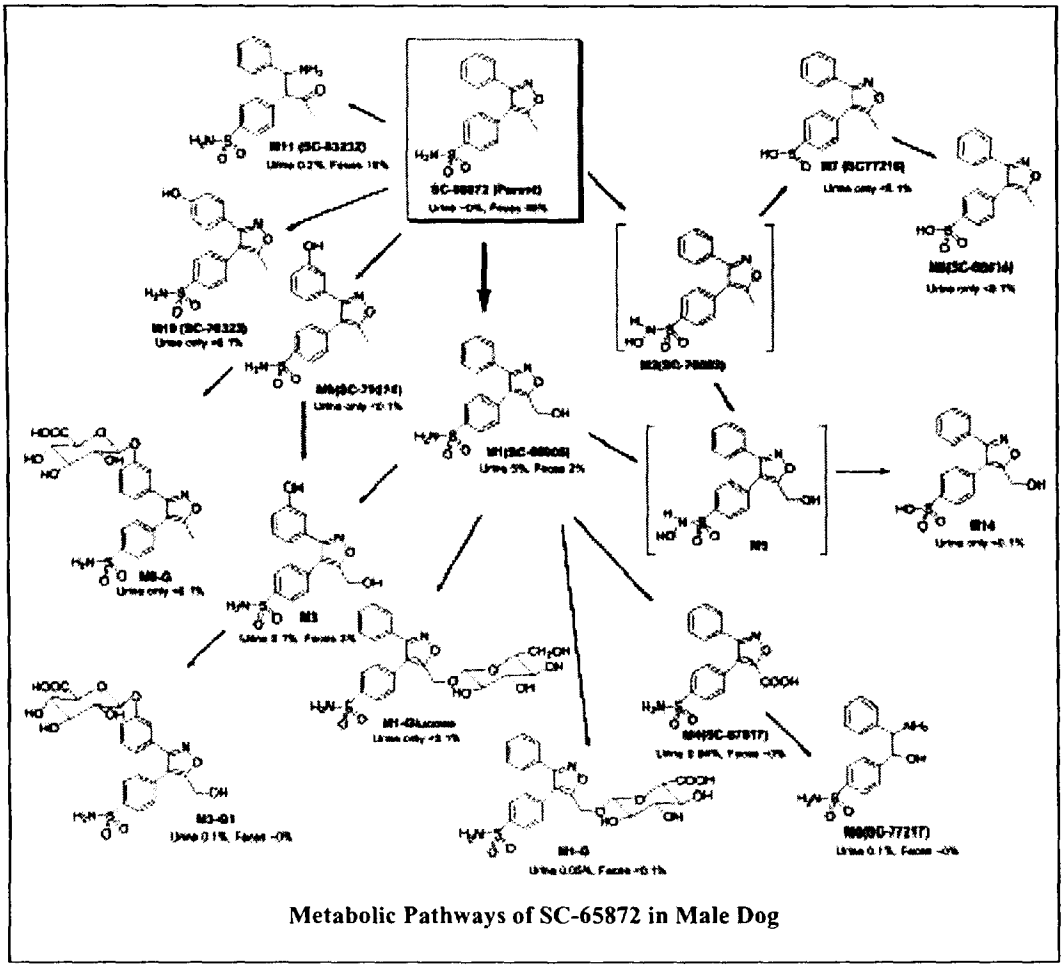
[a] SC-66905; ND = Not Detected; [b] Denotes that there were insufficient samples for SE (n=1)

- Metabolic Profiles in Urine and Feces - M1 was the most abundant metabolite excreted in urine. However, the majority of radioactivity excreted in feces was derived from SC-65872 and M11 as shown in the below table. Mean percent of HPLRC peak and radioactive dose of SC-65872 and its metabolites excreted in urine and feces are summarized in the following table.

Collection Interval (hr)	Sample	Mean % HPLRC Peak							
		M6	M3-G1	M4	M1-G	M11	M1	SC-65872	Total
0-24	Urine	0.410	1.32	a	1.12	1.00	94.3	a	98.2
24-48		4.04	2.84	a	a	8.06	79.5	a	94.5
0-24	Feces	a	a	0.070	4.60	26.3	1.86	64.2	97.0
24-48		a	a	a	6.12	14.9	3.51	75.0	99.6
		Mean % Radioactive Dose Excreted							
0-24	Urine	0.018	0.058	a	0.049	0.044	4.14	a	4.31
24-48		0.066	0.047	a	a	0.132	1.30	a	1.55
0-24	Feces	a	a	0.036	2.34	13.4	0.948	32.7	49.4
24-48		a	a	a	1.02	2.48	0.584	12.5	16.6

a: Not detected; other minor metabolites (M1-Glucose, M5, M7, M8, M9, M9-G, M10 and M14) were less than 0.1% of the dose excreted in the urine and feces.

The proposed metabolic pathways of SC-65872 in the male dog are illustrated in the following figure.



Metabolic Pathways of SC-65872 in Male Dog

3.3.1.12. Uptake of Radioactivity By Kidney, Skin And Brain Tissues in Female Dogs After Oral Administration of [^{14}C]SC-65872; Date: 05-Jun-2000, Document No. M3096319. (Vol. 1.22)

Report Nº: M3096319/EHL 97128

Study Aim: to determine the concentrations of both SC-65872 and SC-6905, and profile the radioactivity of plasma and kidney tissues and to determine localization of drug-related radioactivity in these tissues following repeated oral administration of SC-65872 for 3 days.

Compound: [redacted]

Dose & Route: 5 mg/kg/day po bid with an approximately12 hr dosing interval

Dosing Frequency: 2x/day for 3 days

Animals: 6 ♀ beagle dogs, weighing approximately 7-10 kg

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

GLP/QAU Compliance: N/A

Study Date: Not stated.

Sample Collection: Blood - 2 and 12 hr (post 1st daily dose) and 12 hr post the last dose
Tissues for Autoradiography - kidney, brain and skin

Results:

- Radioactivity in Blood and Plasma - Mean total radioactivity in blood and plasma and plasma SC-65872 and SC-66905 levels following oral administration of 5 mg/kg/day of [^{14}C]SC-65872 are listed in the below table

Study Day	Sampling Time (hr)	Post-Dose Time (hr)	SC-65872 Conc. (μg eq/ml)		Plasma Conc. (μg/ml)	
			Blood	Plasma	SC-65872	SC-66905
1	2	2	1.02	0.598	0.336	0.192
1	12	12	1.36	0.204	0.0236	0.102
2	26	2	2.30	0.515	0.232	0.160
2	36	12	2.24	0.396	0.0385	0.215
3	50	2	2.61	0.606	0.199	0.208
3	60	12	2.97	0.613	0.0843	0.289
4	72	12	3.20	0.517	0.0744	0.217

- Radioactivity in Kidney - Total radioactivity concentrations of cortex, medulla and papilla tissues were 5.21, 1.34 and 1.56 μg eq/g of tissue as determined by [redacted]. The majority of the radioactivity was in the cortex of kidney. SC-65872 concentrations in renal cortex, medulla and papilla were lower than SC-66905 as shown in the following table. In addition, tissue concentrations of SC-65872 and SC-66905 in cortex were higher than the concentrations in either medulla or papilla. This concentration difference in these kidney tissues was in agreement with the findings of kidney autoradiography.

Tissue	Mean (±SE)Conc. In Tissue (μg/g or ml)		Mean (±SE) Tissue/Plasma Ratio	
	SC-65872	SC-66905	SC-65872	SC-66905
Cortex	0.145 ± 0.016	2.93 ± 0.29	1.99 ± 0.08	13.6 ± 0.9
Medulla	0.0585 ± 0.0040	0.592 ± 0.085	0.824 ± 0.058	2.71 ± 0.21
Papilla	0.0849 ± 0.0140	0.218 ± 0.026	1.13 ± 0.12	1.00 ± 0.06
Plasma	0.0744 ± 0.0157	0.217 ± 0.033	-	-

- Distribution of Radioactivity in Brain, Kidney and Skin -
  - Brain: Autoradiograms of head revealed that an extensive of radioactivity was located in blood vessels. High levels of radioactivity were identified in meninges, choroid plexus, oropharyngeal duct and portions of the nasal cavity. Radioactivity was also detected in nasal turbinate (in the surface epithelium) as well as in the pituitary gland. No obvious presence of radioactivity was seen in brain parenchyma.
  - Kidney: Cortex>medulla>papilla
  - Skin: Localization of radioactivity was observed in the various sections of skin (epidermis, superficial dermis, and probably in hair follicles).

3.3.1.13. Pharmacokinetics and Excretion of Total Radioactivity Following a Single Oral Administration of [^{14}C]SC-65872 to Male Monkeys; Date: 11-May-1999, Document No. M2098367. (Vol. 1.22)

Study Nº: [redacted]
Report Nº: M2098367
Study Aim: To determine the pharmacokinetics, metabolism, and excretion of [^{14}C]SC-65872 and metabolites in ♂ cynomolgus monkeys after a single oral dose of 5 mg/kg [^{14}C]SC-65872.
Compound: [redacted]
Dose & Route: 5 mg/2.0 ml/kg po single dose
Animals: 3 ♂ cynomolgus monkeys, approximately 2 to 5 years old, weighing 3.4-4.1 kg.
Study Location: [redacted]

GLP/QAU Compliance: N/A
Study Date (In-Life): 12/21-28/1998
Study Design: Cynomolgus monkeys (3♂) were given a single dose 5 mg/kg of [^{14}C]SC-65872 by gavage. blood was collected at 0, 0.5, 1, 2, 4, 8, 12, 16, 24, 48, 72, 96, 120, 144, and 168 hr post dosing. Urine and feces were collected prior to dosing (-24 to 0 hours) and at 24-hour intervals through 168 hours postdose. Radioactivity in blood, urine and feces were determined.

Results: Mean PK parameters of total radioactivity in plasma and cellular fraction following a single oral administration of 5 mg/kg [^{14}C]SC-65872 are listed in the following table. Long terminal elimination half-life values of total radioactivity were noted in plasma (218 hr) and cellular fraction (101 hr).

Sample	C_{max} (μg eq/g)	T_{max} (hr)	$T_{½}$ (hr)	AUC_{0-168} (μg eq•hr/ml)	$AUC_{0-\infty}$ (μg eq•hr/ml)
Plasma	4.64 ± 0.365	1.83 ± 1.09	218 ± 32.3	181 ± 8.81	439 ± 43.5
Cellular Fraction	11.8 ± 0.841	0.667 ± 0.167	101 ± 2.05	209 ± 41.9	267 ± 46.7

Following a single oral dose of [^{14}C]SC-65872, the total mean radioactive recovery was 103%, with 42.5% of the total radioactivity in urine and 42.2% in feces as shown in the below table.

Collection Intervals (hr)	Cumulative Mean (±SE) % Radioactive Dose				
	Urine	Feces	Cage Wash	Cage Wipe	Total
0-24	26.2 ± 1.92	17.6 ± 0.46			
0-48	33.1 ± 0.72	35.2 ± 2.22			
0-72	37.9 ± 1.77	40.3 ± 3.17			
0-96	40.3 ± 1.99	41.2 ± 3.34			
0-120	41.3 ± 2.22	41.8 ± 3.49			
0-144	41.8 ± 2.24	42.0 ± 3.46			
0-168	42.5 ± 2.42	42.2 ± 3.49	11.7 ± 2.76	6.36 ± 2.16	103 ± 3.29

3.3.1.14. Isolation and Identification of Metabolites of [^{14}C]SC-65872 in Male Monkeys; Date: 15-Jul-1999, Document No. M3099133. (Vol. 1.23)

Report Nº: M3099133
Compound: [redacted]
Dose & Route: 5 mg/2.0 ml/kg po single dose
Animals: 3 ♂ cynomolgus monkeys, approximately 2 to 5 years old, weighing 3.4-4.1 kg.
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date (In-Life): 12/21-28/1998
Study Design: Three male cynomolgus monkeys were given a single oral dose of 5 mg/kg [^{14}C]SC-65872. Urine, feces and blood samples were collected. Metabolites of [^{14}C]SC-65872 were separated [redacted] and their chemical structures were identified by LC-MS/MS.

Results:

- Metabolic Profile in Plasma and Blood - Most of the radioactivity present in monkey plasma was derived from SC-65872, M1, M1-G, M2-G and M3-G. The metabolites, M9, M10 and M9-G, were also detected in the plasma. HPLRC profiling revealed that SC-65872, M1, M1-G and M3-G were accounted for the majority of the radioactivity present in the RBC. The metabolites, M3, M9, M10, M2-G and M9-G were also identified in the RBC.

- Metabolic Profiles in Urine and Feces - About 32.1% of the administered dose was identified as either unchanged parent compound or its metabolites in urine. The mean percentages of radioactive dose excreted as metabolites in urine samples and cage wash/wipe over 168 hr post-dose are shown in the following table. HPLRC chromatograms showed that M1-G and M3-G, the glucuronide conjugates of M1 and M3, were the major urinary metabolites. The majority of the radioactivity in cage wash/wipe samples was from SC-65872, M1, M3, M1-G, M4, M3-G and M3-G1. The metabolites idetified cage wash/wipe samples were similar to the urine profiles.

Collection	Mean % Radioactive Dose Excreted in Urine											
Interval (hr)	M3-G1	M3-G	M9-G	M3	M1-G + M4[a]	M5-G	M8	M1	M10	M9	SC-65872	Total
0-168	1.31	13.6	0.222	2.08	13.2	0	0.0879	0.909	0.409	0.0166	0.211	32.1
CW/CP	0.443	8.01	0	0.426	6.93	0	0	0.216	0	0	0.356	16.4
Subtotal	1.76	21.6	0.222	2.51	20.1	0	0.0879	1.12	0.409	0.0166	0.567	48.5

[a] The ratio of M1-G to M4 was estimated to be 6:1 based on the profiling of urine samples treated with β-glucuronidase; CW/CP = Cage wash and cage wipe.

Data presented in the previous study report (Report Nº M2098367) showed that approximately 42% total radioactivity was excreted in feces with <3% of the administered radioactive dose recovered as SC-65872. The metabolites, M1, M3, M4, M9, M13 and M1-S were identified in fecal samples by LC-MS/MS. The mean percentages of dose excreted as each metabolite are listed in following table.

Collection	Mean Percent of Radioactive Dose Excreted in Feces							
Interval (hr)	M3	M4	M1	M9	M13	M1-S	SC-65872	Total
0-24	0.983	0.746	0.959	0.327	0.112	0.617	2.01	5.75
24-48	0.983	0.559	0.332	0.251	0.121	0.142	0.543	2.93
Subtotal	1.97	1.31	1.29	0.578	0.233	0.759	2.55	8.68

The proposed metabolic pathways of SC-65872 in the male cynomolgus monkeys are illustrated in the following figure.

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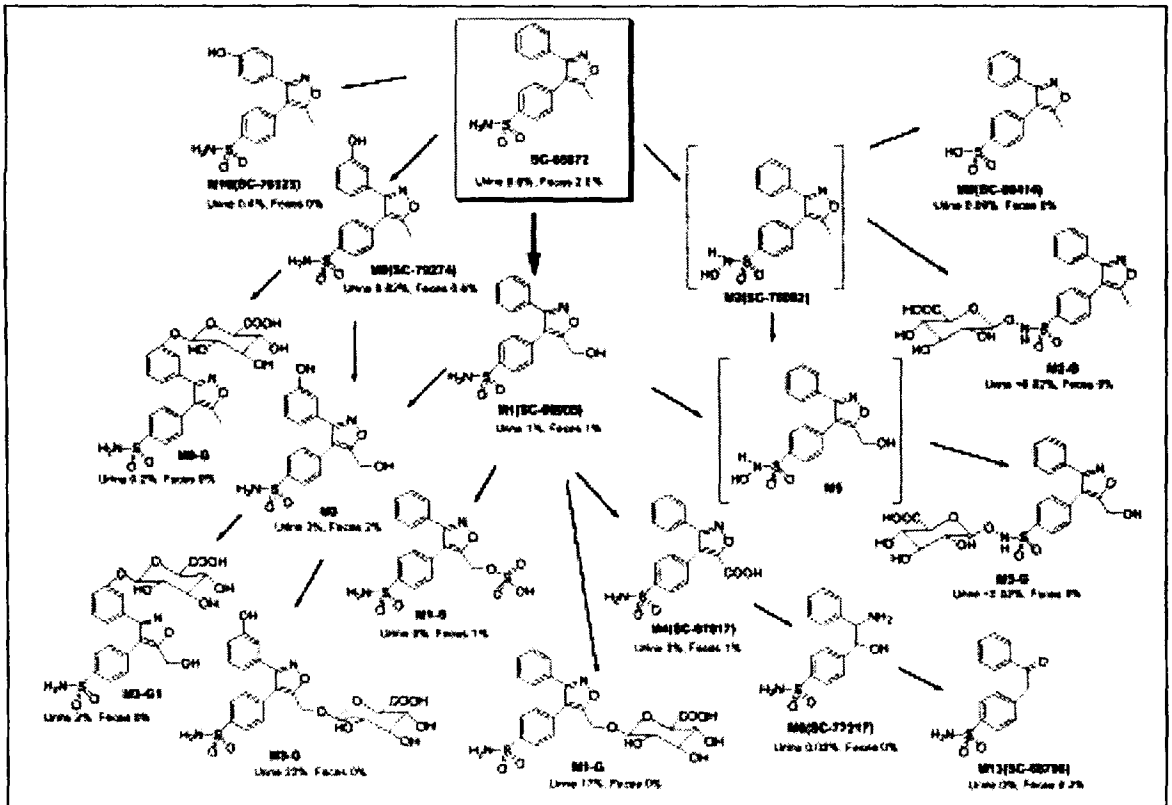

Metabolic Pathways of SC-65872 in Male Monkey

3.3.1.15. Investigation of The Possible Occurrence of Valdecoxib N-Glucuronide Metabolite in Male Cynomolgus Monkeys; Date: 03-Nov-2000, Document No. M3000351. (Vol. 1.23)

Report Nº: M3000351
Study Aim: to determine the possible occurrence of the N-glucuronide conjugate metabolite of SC-65872 in male monkeys after administration of 60 mg/kg of SC-65872.
Compound: [redacted] +
Vehicle: [redacted]
Dose & Route: 60 mg/5 ml/kg po via nasogastric gavage
Dosing Frequency: single dose
Animals: 3♂ cynomolgus monkeys [redacted] weighing 6-9 kg.
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: 10/4/2000
Study Date: Not Stated
Urine Collection: 0-6, 6-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hr
Analysis Method: [redacted]

Results: The mean total recovery of administered radioactive dose in the urine was ~42% during a 168 hr period as shown in the following table. Less than 0.12% of administered dose excreted in urine as N-glucuronide conjugate of SC-65872.

Time (hr)	Cumulative Percent of Dose Excreted in Urine (%)			
	M67-24	M27-73	M27-147	Mean ± SE
0-6	1.10	1.88	2.06	1.68 ± 0.30
0-24	5.88	10.2	14.9	10.3 ± 2.6
0-48	12.6	21.1	26.1	19.9 ± 3.9
0-72	15.2	39.8	42.3	32.5 ± 8.6
0-96	17.2	46.5	50.6	38.1 ± 10.5
0-120	18.3	48.9	53.2	40.1 ± 11.0
0-144	18.9	50.4	54.3	41.2 ± 11.2
0-168	19.1	50.8	54.8	41.6 ± 11.3

3.4. IN VITRO METABOLISM

3.4.1.1. Effect of SC-65872 Oral Administration to Cynomolgus Monkeys During a Two-Week Toxicity Study, SA4901, on *In Vitro* Liver Microsomal Metabolism of [^{14}C]SC-65872; Date: 04-Jan-2000, Document No. M3099366. (Vol. 1.23)

Study Nº: SA4901
Report Nº: M3099366
Study Aim: to determine the rate of metabolism of SC-65872 in vitro by liver microsomes from cynomolgus monkeys which had received oral gavage doses of SC-65872 for 2 weeks.
Compound: [redacted]
Vehicle Control:
Dose & Route: 0, 30, 60, and 120 mg/24 ml/kg bid po
Dosing Frequency: bid (1-14 hr apart) for 14-day
Animals: 10♂ + 10♀ naive cynomolgus monkeys, 2-6 years of age, weighing 2.2-4.1 kg for ♂ and 1.7-2.4 kg for ♀.
Study Location (In-Life): [redacted]
GLP/QAU Compliance: Yes.
Study Date (In-Life): 3/8-9/1999 - 3/23/1999
Study Design: Animals were assigned to treatment groups as shown in the table below and given either vehicle control or SC-65872 by oral gavage 2x/day for 14 days. Liver samples were collected and microsomes were prepared. Microsomal samples were incubated with [^{14}C]SC-65872 and an NADPH generating system and metabolism of the [^{14}C]SC-65872 was determined by a high performance liquid radiochromatography (HPLRC) procedure.

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

Results: A dose-dependent decrease in the rate of [^{14}C]SC-65872 metabolism *in vitro* by liver microsomes obtained from monkeys that were orally dose with SC-65872 for 2-week as shown in the following table.

Dose (mg/kg/Day)	[^{14}C]SC-65872 Metabolism[a]	
	μg/min/mg Protein	μg/min/nmole P450
0	0.243	0.407
60	0.196	0.333
120	0.103	0.231
240	0.0795	0.202

3.4.1.2. Interaction Of Valdecoxib Transport Through Caco-2 Cell Monolayer with P-Glycoprotein; Date: 10-Aug-2000, Document No. M3000019. (Vol. 1.23)

Report Nº: M3000019
Study Aim: To determine whether valdecoxib was a potential substrate for P-Glycoprotein (Pgp).
Compound: [redacted]
Dose: [^{14}C]valdecoxib - 0.05, 0.10, 0.5, 1.0, 5.0, 10 and 50 μM
[^{3}H]vinblastine - 0.05, 0.10, 0.5, 1.0, 5.0, 10 and 50 μM
[^{3}H]Mannitol - 0.1 μM
Indicator Cells: Caco-2 cells (derived from human colon adenocarcinoma)
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not Stated.
Study Design: Apical-to-basal (A-to-B) and basal-to-apical (B-to-A) transport of [^{14}C]valdecoxib through a Caco-2 cell monolayer system was evaluated. The net secretion (ratio of B-to-A transport to A-to-B transport) of [^{14}C]valdecoxib was determined.

Results: Net secretion values for valdecoxib at various concentrations were close to 1.0 as shown in the following table. Therefore, valdecoxib did not appear to be a substrate for Pgp.

Time (min)	Compound	Mean % Transport		Net Secretion
		B to A	A to B	
60	Valdecoxib	0.387	0.340	1.16
	Vinblastine[a]	0.686	0.0785	8.94
	Mannitol[b]	0.244	0.313	0.779
120	Valdecoxib	0.945	0.854	1.13
	Vinblastine	1.46	0.246	6.03
	Mannitol	0.631	0.803	0.784

[a] Positive Control; [b] Negative Control

3.4.1.3. The In Vitro Metabolism of [5-^{14}C]SC-65875 by Rat, Dog and Human Liver Microsomes and Human Hepatocytes; Date: 31-Oct-1996, Document No. M3096061. (Vol. 1.23)

Report Nº: M3096061
Study Aim: To evaluate metabolism of SC-65872 by liver microsomes, hepatocytes, and recombinant human cytochrome P450 enzymes.
Compound: [redacted]
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not stated.

Results: Liver microsomes from rat, dog, and human were able to metabolize SC-65872 to SC-66905 after 15 minutes and data are shown in the following table. Rat hepatic microsomes metabolized [5-^{14}C]SC-65872 in vitro more rapidly than human or dog hepatic microsomes. SC-66905 was the major metabolite.

Species	Sex	Treatment	N	Incubation Time
Rat	♂	Saline	1	15 min
Rat	♂	Corn Oil	1	15 min
Rat[a]	♂	Nphflv[a]	1	15 min
Rat[a]	♂	Phenob	1	15 min
Rat[a]	♂	Isonzd	1	15 min
Rat[a]	♂	DEX	1	15 min
Rat[a]	♂	Pregnln	1	15 min
Rat[a]	♂	Clfibt	1	15 min
Dog	♂	None	8	15 min
Dog	♀	None	8	15 min
Human	♂+♀	None	4	15 min
Human	♂+♀	None	10	1 hr
Human	♂+♀	None	-[b]	2 hr

[redacted]

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[a] Rats treated with P450 inducers as indicated; [b] Pooled microsomes; mean of two separate incubations.
Nphflv = β-Naphthoflavone; Phenob = Phenobarbital; Isonzd = Isoniazid; DEX = Dexamethasone; Pregnln = Pregnenalone; Clfibt = Clofibrate.

Metabolism of SC-65872 by recombinant human cytochrome P450 isozymes was also determined. Results as presented in the below table indicated that the greatest metabolism of SC-65872 to SC-66905 occurred with CYP3A4 and CYP2C19.

Enzyme	Incubation Time (hr)
Wild Typeb	2
CYP-1A2	2
CYP-2A6	2
CYP-2B6	2
CYP-2E1	2
CYP-2C9	2
CYP-2C19	2
CYP-2D6	2
CYP-3A4	2
CYP-3A5	2
CYP-1A2[a]	2
CYP-2C9[a]	2
CYP-2C19[a]	2
CYP-2D6[a]	2
CYP-3A5[a]	2

[redacted]

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[a] Microsomes prepared from different batches of cells.
[b] SF9 microsomes (no recombinant enzyme expressed).

3.4.1.4. In Vitro Metabolism of [^{14}C]Valdecoxib and [^{14}C]SC-66905 by Dog and Human Kidney; Date: 20-Apr-1999, Document No. M3097001. (Vol. 1.23)

Report Nº: M3097001

Study Aim: To determine the rate of metabolism and metabolic profile of valdecoxib and SC-66905 in vitro by dog and human kidney S9.

Compound: [redacted]

[redacted]

Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not stated.

Results: Data presented in the following table showed that dog kidney S9 was not able to metabolize [^{14}C]Valdecoxib and [^{14}C]SC-66905 *in vitro*. Contrarily, human kidney S9 was able to metabolize 10.7% of [^{14}C]Valdecoxib in 30 min of incubation. Dog kidney S9 was able to metabolize (±)-Bufuralol and 7-Ethoxycoumarin but not [^{14}C]Testosterone.

Substrate/ Concentration	Metabolite Assayed	Time (min)	Dog Kidney S9		Human Liver S9	
			Metabolite Formation		Metabolite Formation	
			pmol/mg/incubation	(pmol/mg/min	pmol/mg/incubation	pmol/mg/min
[^{14}C]Valdecoxib 10 μg/ml	[^{14}C]SC-66905	0	BLD	BLD	BLD	BLD
		30	BLD	BLD	1700	56.7
		60	BLD	BLD	ND	ND
[^{14}C]SC-66905 10 μg/ml	[^{14}C]SC-67817	0	BLD	BLD	BLD	BLD
		30	BLD	BLD	BLD	BLD
		60	BLD	BLD	ND	ND
(±)-Bufuralol 100 μM	1'-Hydroxy-bufuralol	0	BLD	BLD	BLD	BLD
		30	8.78	0.293	937	31.2
		60	12.9	0.215	ND	ND
7-Ethoxycoumarin 100 μM	7-Hydroxy-coumarin	0	BLD	BLD	BLD	BLD
		30	5.18	0.173	2390	79.8
		60	7.83	0.131	ND	ND
[^{14}C]Testosterone 100 μM	6β-Hydroxy-testosterone	0	BLD	BLD	BLD	BLD
		30	BLD	BLD	17900	597
		60	BLD	BLD	ND	ND

BLD = Below Limit of Detection for A Given Assay
ND = Not Determined

3.4.1.5. Comparison of the *In Vitro* Rate of Metabolism of SC-65872 by Liver Microsomes from Male and Female Mice; Date: 21-Sep-2000, Document No. M2000179. (Vol. 1.23)

Report Nº: M2000179
Study Aim: To compare the rates of SC-65872 clearance in microsomes from male and female mice.
Compound: [redacted]
CD-1 mice Liver Microsomes: [redacted]
Study Location: [redacted]
GLP/QAU Compliance: N/A
Study Date: Not stated.

Results: The kinetic parameters K_m and V_{max} were estimated for both sexes by incubation of liver microsomes with various concentrations (10, 25, 50, 100, 150, and 200 μM) of SC-65872 and the formation of SC-66905 was measured. The estimated K_m and V_{max} for microsomes from ♂ mice were 190 μM and 1.85 nmol/min/mg, respectively with reveal in vitro intrinsic clearances of 9.74 μl/mg/min. The estimated K_m and V_{max} for microsomes from ♀ mice were 357 μM and 3.15 nmol/min/mg, respectively with reveal in vitro intrinsic clearances of 8.82 μl/mg/min.

3.4.1.6. Formation of $^{14}CO_2$ During Incubation of [5-^{14}C]SC-65872 with Cultured Rat and Human Hepatocytes; Date: 21-Nov-1996, Document No. M3096065. (Vol. 1.23)

Report Nº: M3096065
Study Aim: To determine if the radiolabeled carbon [5-^{14}C]SC-65872 and [^{14}C]SC-66905 can be metabolized to $^{14}CO_2$ by rat and human hepatocytes.
Compound: [redacted]
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not stated.

Results: A small amount of $^{14}CO_2$ was generated by hepatocytes when incubated [5-^{14}C]SC-65872 and [^{14}C]SC-66905. Dexamethasone induction of rat and human hepatocytes did not affect the amount of $^{14}CO_2$ was generated from the metabolism of [5-^{14}C]SC-65872 and [^{14}C]SC-66905 by hepatocytes.

3.4.1.7. The *In Vitro* Metabolism of [^{14}C]SC-65872 by Rat Intestinal Microsomes; Date: 23-Dec-1999, Document No. M3096323. (Vol. 1.23)

Report Nº: M3096323
Study Aim: To determine the rate of metabolism and metabolic profile of [^{14}C]SC-65872 and [^{14}C]SC-66905 in vitro by rat intestinal microsomes.
Compound: [redacted]
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not Stated
Study Design: Rat intestinal and liver microsomes were incubated with [^{14}C]SC-65872 at 37°C in reaction mixtures fortified with an NADPH-generating system. Reactions were terminated with methanol or strong precipitating acid after incubation for 30 minutes (liver) or 60 minutes (intestine). [^{14}C]SC-65872 samples were analyzed immediately by high performance liquid radiochromatography (HPLRC), 7-ethoxycoumarin samples were analyzed immediately by [redacted] fluorescence, and [^{14}C]testosterone samples were frozen at -20°C until analysis by HPLRC.

Results: Rat intestinal microsomes metabolized [^{14}C]SC-65872, [^{14}C]testosterone, or 7-ethoxycoumarin to 7-hydroxycoumarin (100 mM) at a much slower rate than rat liver microsomes. The rates of [^{14}C]SC-65872, [^{14}C]testosterone, or 7-ethoxycoumarin to 7-hydroxycoumarin metabolism by intestinal and liver microsomes are shown in the following table. No known hydroxytestosterone metabolites were measured after incubation of rat intestinal microsomes with [^{14}C]testosterone incubations for 60 min. Male rat liver microsomes metabolized 73.7% of 100 mM [14C]testosterone after 30 minutes, with 6β-, 16α- and 2α-hydroxytestosterone were the major metabolites detected following a 30 min incubation of 100 mM [^{14}C]testosterone with ♂ rat live microsomes. On contrast, 7α-hydroxytestosterone was the major metabolite generated followed by incubation of ♀ rat liver microsomes with [^{14}C]testosterone. In addition, the metabolism of [^{14}C]SC-65872 by male rat liver microsomes was 10x greater than for female rat liver microsomes.

Microsome Source	Microsome Conc. (mg/ml)	Incub. Time (min)	[^{14}C]SC-65872 Metabolized (%)	[^{14}C]SC-65872 Velocity (pmol/mg/min)	[^{14}C]Testo. Metabolized (%)	[^{14}C]Testo. Velocity (pmol/mg/min)	ECOD[a] Velocity (pmol/mg/min)
Rat Intestine	2.0	60	0.65	1.7	2.35	19.6	9.64
♂ Rat Liver	1.0	30	12.3	130	73.7	2460	434
♀ Rat Liver	1.0	30	1.25	13.3	52.8	1760	330

Testo. = Testosterone; ECOD = 7-Ethoxycoumarin O-Deethylase Activity

3.4.1.8. Correlation of Cytochrome P450 Isoform-Specific Marker Substrate Activity with Valdecoxib Metabolism in a Set of Phenotyped Human Liver Microsomes; Date: 12-Aug-1999, Document No. M3099135. (Vol. 1.24)

Report Nº: M3099135

Study Aim: To determine the importance of the indicated P450 enzymes to valdecoxib metabolism by correlation analysis of its rate of metabolism with the rate of marker substrate metabolism by a set of characterized human liver microsomes.

Compound: [redacted]

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

GLP/QAU Compliance: N/A

Study Date: Not stated

Study Design: The rate of metabolism of [^{14}C]Valdecoxib to SC-66905 was determined by HPLRC following *in vitro* incubation with human liver microsomes [redacted]

The relative contributions of specific cytochrome P450 isoforms to valdecoxib metabolism were evaluated by correlation of the rates of SC-66905 formation with the known specific activities for P450-specific marker.

Results: Regression analysis indicated a strong relationship between valdecoxib metabolism and CYP3A4 activity, as measured by either testosterone 6β-hydroxylase, or dextromethorphan N-demethylase. The correlation of Valdecoxib metabolism and isoform specific substrate metabolism by phenotyped human liver microsomes (N=15) is shown in the following table.

P450 Isoform (Substrate)	Regression (r^2)	Correlation (r)
CYP1A2 (Ethoxyresorufin)	0.076	0.276
CYP2A6 (Ethoxycoumarin)	0.100	0.317
CYP2C9 (Tolbutamide)	0.095	0.308
CYP2C19 (Mephenytoin)	0.046	0.214
CYP2D6 (Bufuralol)	0.128	0.358
CYP2E1 (Chlorzoxazone)	0.077	0.278
CYP3A4/5 (Testosterone)	0.862*	0.928
CYP3A4 (Dextromethorphan)	0.720*	0.848
CYP4A9/11 (Lauric Acid)	0.005	-0.073

* P≤0.001 for regression

3.4.1.9. Amendment: M2199314: Estimation of the Enzyme Parameters K_m and V_{max} for Biotransformation of SC-65872 in Human Liver Microsomes and in Expressed Enzymes; Date: 29-Mar-2000, Document No. M2099314. (Vol. 1.24)

Report Nº: M2099314

Study Aim: To identify the specific isoform(s) involved in the formation of SC-66905 and to estimate the enzyme parameters K_m and V_{max} in human liver microsomes and in the appropriate expressed P450 enzyme(s).

Compound: [redacted]

Study Location:
GLP/QAU Compliance: N/A
Study Date: Not stated
Analysis Methods: [redacted]

Results: The K_m and V_{max} estimated for conversion of SC-65872 to SC-66905 in human liver microsomes were 65.4 ± 3.58 μM and 1.92 ± 0.150 nmol/min/mg, respectively. CYPs 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4 but not CYPs 2A6, 2C8, and 2E1 mediated the formation of SC-66905. The K_m, V_{max} and CL_{int} for CYPs 1A2, 2C9, 2C19, 2D6 and 3A4 are summarized in the following table.

Enzyme	K_m (μM)	V_{max} (nmol/min/nmol)	CL_{int}* (ml/min/nmol)
CYP1A2	16.0	0.762	0.0476
CYP2D6	17.8	6.53	0.366
CYP3A4	53.3	2.35	0.0441
CYP2C9	123	0.412	0.00335
CYP2C19	59.7	0.985	0.0165

* These values were calculated using data generated in expressed enzyme systems. The extent of their contribution to SC-66905 formation in normal liver will result from a combination of CL_{int} and their respective levels of expression.

3.4.1.10. Identification of Isoforms that Mediate SC-65872 Biotransformation in Human Liver Microsomes: Use of Chemical Inhibitors; Date: 29-Mar-2000, Document No. M2099389. (Vol. 1.24)

Report Nº: M2099389
Study Aim: To identify the P450 isozymes involved in SC-65872 metabolism.
Compound:
Study Location: [redacted]
Source of Microsomes: Human Liver
GLP/QAU Compliance: 12/6-22/1999
Study Date: Not stated

Results: SC-65872 (2.0 or 10.0 μM) plus human liver microsomes was incubated in the presence of various competitive inhibitors, sulfaphenazole, quinidine, tranylcypromine, ketoconazole, and furafylline and SC-66905 formation velocity was measured. Inhibition (mean %) of SC-66905 formation by P450 inhibitors is summarized in the following table.

Competitive Inhibitor	P450 Marker	SC-65872	
		10.0 μM	2.0 μM
Control	-	0	0
Sulphaphenazole (2.0 μM)	CYP2C9	25.2	35.2
Tranylcypromine (50.0 μM)	CYP2D6	55.2	59.0
Quinidine (5.0 μM)	CYP2C19	42.4	51.6
Ketoconazole (0.3 μM)	CYP3A4	80.9	64.8
Furafylline (100 mg/ml)	CYP1A2	18.6	34.3

3.4.1.11. Inhibition of Cytochrome P4502E1 Catalytic Activity by SC-66905; Date: 06-Dec-1999, Document No. M2099295. (Vol. 1.25)

Report Nº: M2099295
Study Aim: To determine whether SC-66905, an active metabolite of SC-65872, inhibited human cytochrome P4502E1 catalytic activity.
Compound: [redacted]

Source of Microsomes: baculovirus-transfected insect cell expressed CYP2E1
Study Location: [redacted]
GLP/QAU Compliance: N/A
Study Date: 9/21-11/23/1999

Results: SC-66905 was not shown to inhibit CYP2E1. On contrast, 4-methylpyrazole, the positive control inhibitor, inhibited CYP2E1 activity by approximately 89% at 50 μM.

3.4.1.12. Inhibition of Cytochrome P4501A2, Cytochrome P4502C9, Cytochrome P450D6, Cytochrome P4502C19 and Cytochrome P4503A4 Catalytic Activities by SC-65872; Date: 28-Apr-1999, Document No. M2098119. (Vol. 1.24)

Report Nº: M2098119
Study Aim: To determine whether SC-65872 inhibited selected human cytochrome P450 catalytic activities.
Compound: [redacted]
Source of Microsomes: Human B-lymphoblastoid cell line expressed P450 1A2, 3A4, 2C9, and 2D6 or baculovirus-transfected insect cell expressed CYP2C19
Study Location: [redacted]
GLP/QAU Compliance: N/A
Study Date: 5/5/1998-4/23/1999
Method of Analysis: [redacted]
Results: SC-69124A inhibited CYP2C9 and CYP2C19 but not CYP1A2 catalytic activities with an IC_{50} of 19 and 41 μM, respectively. Slight inhibitions on CYP2D6, and CYP3A4 activities were noted with IC_{50} values of 100 and 141 μM, respectively.

3.4.1.13. Inhibition of Cytochrome P4502C9 and P4502C19 Catalytic Activities by the Test Substance SC-65872: Determination of Ki Values; Date: 20-Dec-1999, Document No. M2099265. (Vol. 1.24)

Report Nº: M2099265
Study Aim: To determine the K_i values for SC-65872 with cDNA-derived CYP2C9 and CYP2C19 in microsomes using substrates diclofenac and (s)-mephenytoin, respectively.
Compound: [redacted]
Source of Microsomes: Human B-lymphoblastoid cell line expressed CYP2C9 and baculovirus-transfected insect cell expressed CYP2C19
Study Location: [redacted]
GLP/QAU Compliance: N/A
Study Date: 9/2-11/30/1999

Results: Results showed that Ki values for SC-65872 were 15 μM and 3.1 μM for CYP2C9 and CYP2C19, respectively.

3.4.1.14. Inhibition of Cytochrome P4502C19 Catalytic Activity by the Test Substance SC-66905: Determination of Ki Value; Date: 20-Dec-1999, Document No. M2099266. (Vol. 1.24)

Report Nº: M2099266
Study Aim: To determine the K_i values for SC-66905 with cDNA-derived CYP2C19 in microsomes using substrate (s)-mephenytoin, respectively.
Compound: [redacted]
Source of Microsomes: baculovirus-transfected insect cell expressed CYP2C19

3.4.3. IN VITRO PROTEIN BINDING

3.4.3.1. Amendment #2: M3299224; Amendment #1: M3199224: Protein Binding of SC-66905 to Mouse, Rat, Rabbit, Cynomolgus Monkey, Dog and Human Plasma and to Human Serum Albumin and Alpha-1 Acid Glycoprotein; Date: 22-Oct-1999, Document No. M3099224. (Vol. 1.19)

Report Nº: M3099224
Study Aim: To determine *in vitro* plasma protein binding of SC-66905 to mouse, rat, rabbit, cynomolgus monkey, dog and human plasma and to human serum albumin and α1-acid glycoprotein.
Compound: [redacted]
Dose: 0.03, 0.3, 3.0 and 30.0 μg/ml
Blood Samples: mouse, rat, rabbit, dog, cynomolgus monkey and human blood
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not Stated.
Study Design: [^{14}C]SC-66905 was incubated with rat, dog and human plasma at concentrations of 0.03, 0.3, 3.0 and 30.0 μg/ml and binding to plasma proteins was determined using an ultrafiltration or an ultracentrifugation method.

Results: The percentages of [^{14}C]SC-66905 bound to various species plasma proteins and to purified human serum albumin and α1-acid glycoprotein are presented in the following table.

Species	Analysis Method	% Protein Bound [^{14}C]SC-65872			
		0.03	0.30	3.0	30.0
Mouse	Ultra-filtration	85.7	89.9	86.3	88.4
Rat	Ultra-filtration	87.5	90.4	83.7	90.5
Rabbit	Ultra-filtration	87.8	93.6	88.5	89.9
Dog	Ultra-filtration	91.1	95.2	90.9	94.3
Monkey	Ultra-filtration	81.9	82.7	77.8	80.8
Human	Ultra-filtration	88.4	90.7	87.2	88.9
HSA	Ultra-filtration	84.8	85.0	83.3	82.7
α1-AG	Ultra-filtration	56.5	55.6	44.7	22.3
α1-AG	Ultra-centrifugation	89.5	90.3	84.4	62.3

HSA = Human Serum Albumin; α1-AG = α1-acid glycoprotein

3.4.3.2. Amendment: M3195316: Plasma Protein Binding and Erythrocyte Partitioning of [^{14}C]SC-65872 in Human, Dog and Rat Blood; Date: 23-May-1996, Document No. M3095316. (Vol. 1.19)

Report Nº: M3095316
Study Aim: To determine *in vitro* plasma protein binding and RBC partitioning of SC-65872 in human dog, and rat blood.
Compound: [redacted]
Dose: 0.03, 0.1, and 0.3 μg/ml
Blood Samples: rat, dog and human blood
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not Stated.
Study Design: [^{14}C]SC-65872 was incubated with rat, dog and human plasma at concentrations of 0.03, 0.1, and 0.3 μg/ml and binding to plasma proteins was determined using

a dextran-coated charcoal method. Partitioning between erythrocytes and plasma was determined by centrifugation and measurement of [^{14}C]SC-65872 remaining in plasma.

Results: Protein bindings in the dog and human were concentration-dependent with higher binding at the lowest level (0.03 μg/ml). Based on data presented in the following table, at the concentration of the 0.03 μg/ml, binding sites were not saturated in dog and human blood as higher protein binding was observed.

Species	% [^{14}C]SC-65872 Bound to Proteins		
	[^{14}C]SC-65872 Conc. (μg/ml)		
	0.03	0.10	0.30
Rat	41.4%	42.2%	43.2%
Dog	73.7%	55.3%	54.5%
Human	76.7%	56.1%	54.1%

The percentages of [^{14}C]SC-65872 in red blood cells were higher than in the plasma. The distribution of [^{14}C]SC-65872 between plasma and RBC in rat, dog and human blood is shown in the following table.

Species	Matrix	[^{14}C]SC-65872 Conc. (μg/ml)					
		0.03		0.10		0.3	
		0-5 min	30 min	0-5 min	30 min	0-5 min	30 min
Rat	RBC	79%	80%	85%	80%	87%	87%
	Plasma	21%	20%	15%	20%	13%	13%
Dog	RBC	81%	82%	80%	80%	81%	86%
	Plasma	19%	18%	20%	20%	19%	14%
Human	RBC	86%	84%	84%	86%	83%	86%
	Plasma	14%	16%	16%	14%	17%	14%

3.4.3.3. Amendment: M3199048: Protein Binding of SC-65872 to Mouse, Rat, Rabbit, Cynomolgus Monkey, Dog and Human Plasma and to Human Serum Albumin and Alpha 1-Acid Glycoprotein; Date: 11-Feb-2000, Document No. M3099048. (Vol. 1.19)

Report Nº: M3099048
Study Aim: To determine *in vitro* plasma protein binding of SC-65872 to mouse, rat, rabbit, cynomolgus monkey, dog and human plasma and to human serum albumin and α1-acid glycoprotein.
Compound:
Dose: 0.03, 0.3, 3.0 and 30.0 μg/ml
Blood Samples: mouse, rat, rabbit, dog, cynomolgus monkey and human blood
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not Stated.
Study Design: [^{14}C]SC-65872 was incubated with rat, dog and human plasma at concentrations of 0.03, 0.3, 3.0 and 30.0 μg/ml and binding to plasma proteins was determined using the ultracentrifugation and ultrafiltration methods.

Results: The percentages of [^{14}C]SC-65872 bound to various species plasma proteins and to purified human serum albumin and α1-acid glycoprotein are presented in the following table.

Species	% Protein Bound [^{14}C]SC-65872							
	0.03		0.30		3.0		30.0	
	Method A	Method B	Method A	Method B	Method A	Method B	Method A	Method B
Mouse	93.9	95.9	95.9	96.8	96.1	96.5	95.6	95.3
Rat	95.9	97.8	96.3	98.8	95.8	99.9	96.9	98.7
Rabbit	92.6	97.9	97.8	98.9	98.3	98.9	97.8	98.8
Dog	88.0	93.8	96.9	94.9	97.2	95.2	93.5	94.5
Monkey	92.8	97.9	94.1	98.3	94.3	97.7	93.8	97.9
Human	98.3	97.2	98.3	99.4	98.6	97.5	98.4	98.9
HSA	91.0	93.3	94.0	95.4	94.6	96.2	93.6	84.9
α1-AG	-	85.7	-	90.0	-	87.0	-	67.2

Method A = Ultrafiltration; Method B = Ultracentrifugation; HSA = Human Serum Albumin; α1-AG = α1-acid glycoprotein

3.4.4. IN VITRO DRUG-DRUG INTERACTION

3.4.4.1. Evaluation of Interferences of Valdecoxib and Parecoxib with the Plasma Protein Binding of R- and S-Warfarin in Humans; Date: 11-Aug-2000, Document No. M3000126 (Vol. 1.19)

Report Nº: M3000126
Study Aim: to determine the effect of co-administration of valdecoxib on the plasma protein binding of R- and S-warfarin in humans.
Compound/Dose: [redacted]
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: N/A
Study Date: Not Stated
Study Design: The binding of [^{14}C]warfarin to human plasma in the presence of valdecoxib was determined using an ultrafiltration method.

Results: The plasma protein binding of [^{14}C]warfarin was ≥95% in the presence of valdecoxib. Warfarin enantiomer ratios remained relatively constant across all concentrations of valdecoxib tested.

3.4.4.2. *In Vitro* Drug-Drug Interaction Studies with SC-65872 and Selected Drugs in Human Liver Microsomes or in Human Plasma; Date: 08-Mar-2000, Document No. M2099307. (Vol. 1.24)

Study Nº: [redacted]
Report Nº: M2099307
Study Aim: To identify the *in vitro* effects of SC-65872 on the clearance of droperidol, metoclopramide, ondansetron and celecoxib and on the metabolism mediated by P450 isozymes CYP2D6 and CYP2C9 using dextromethorphan and tolbutamide, respectively and to identify the potential interactions between SC-65872 and mivacurium and cisatracurium in human plasma.
Compound: SC-65872 (Lot Nº RK4-31A and 97K006-02C)
Source of Microsomes: Pooled human liver microsomes [redacted]
Study Location: [redacted]
GLP/QAU Compliance: Yes
Study Date: 9/29/1999-2/25/2000
Analysis Method: [redacted]

Results: SC-65872 at concentrations up to 300 μM had no effects on the *in vitro* metabolism of droperidol or mivacurium or on the degradation of cisatracurium. A concentration-dependent inhibition of celecoxib and metoclopramide metabolism by SC-65872 was observed. In addition, SC-65872 suppressed CYP2D6-mediated O-demethylation of dextromethorphan and CYP2C9-mediated metabolism of tolbutamide with Ki values of 5.0 and 23 μM, respectively.

3.4.4.3. *In Vitro* Drug-Drug Interaction of SC-65872 and Warfarin in Human Liver Microsomes; Date: 20-Dec-1999, Document No. M2098363. (Vol. 1.24)

Study Nº: [redacted]
Report Nº: M2098363
Study Aim: To identify the *in vitro* effects of SC-65872 on the metabolism of warfarin.
Compound: [redacted]
Source of Microsomes: Pooled human liver microsomes [redacted]
Study Location: [redacted]
GLP/QAU Compliance: Yes
Study Date: Not Indicated
Analysis Method: [redacted]

Results: A concentration-dependent inhibition of disappearance of warfarin by SC-65872 was observed with a Ki of 28 μM for the inhibition of CYP2C9-mediated formation of 7-(S)-hydroxywarfarin .

3.5. BIOANALYTICAL METHOD VALIDATION

The following study reports related to analytical method development and validation submitted in this NDA were not reviewed.

[redacted]

1 page(s) of revised draft labeling has been redacted from this portion of the review.

5. SUMMARY AND EVALUATION:

5.1. PHARMACOLOGY/PHARMACODYNAMICS

5.1.1. ACTION-RELATED PHARMACOLOGY

Valdecoxib (SC-65872) was demonstrated to have following properties.

5.1.1.1. In Vitro -

Valdecoxib (SC-65872) and SC-66905, an active metabolite, preferentially inhibited human recombinant COX-2 mediated PGE_2 production with IC_{50} values of:

Compound	IC_{50} (μM)	
	hCOX-2	hCOX-1
Valdecoxib	0.005	140
SC-66905	0.18	1120

5.1.1.2. In Vivo -

- Anti-inflammatory Activity Valdecoxib (SC-65872) and SC-66905 were effective in the following animal models.
  (1) carrageenan-induced paw edema in rats with ED_{50} values of 5.9 and 1.06 mg/kg, respectively;
  (2) adjuvant induced arthritis in rats with an ED_{50} values of 0.036 and 1.68 mg/kg, respectively;
  (3) carrageenan-induced air pouch in rats by the inhibition of PGE_2 with ED_{50} values of 0.05 and 0.81 mg/kg, respectively..
- Analgesic Activity - Valdecoxib (SC-65872) were effective in the following animal models.
  (1) Hargreaves' hyperalgesia model in rats with ED_{50} values of 13.7 mg/kg;
  (2) post-surgical model in rats by the reduction of tactile allodynia and thermal hyperalgesia in a dose-dependent fashion.

- Anti-pyretic Activity - Valdecoxib (SC-65872) at a dose level of 5 mg/kg was shown to block LPS-induced fever but did not alter normal temperature in rats.

5.1.2. SAFETY PHARMACOLOGY

A summary of safety pharmacology study reports is presented in the following table.

Study Type	Species	Treatment/Route	Dose (mg/kg/day)	Findings
Effects on Neurobehavior	SD Rats 2-6/sex/group	Phase I - po single dose Phase II - po bid for 4-day	Phase I - 0, 0.165 Phase II - 0, 0.05. 0.11, 0.33	Slight ↑ in forelimb grip strength in ♀ @ 0.33 mg/kg/day.
Effect on Digestive system	Fasted ♂ SD Rats, 6/group	po single dose	0, 20, 200 mg/kg	GI injuries in 1/6 @ 20 mg/kg and 3/6 @ 200 mg/kg.
	Fed ♂ SD Rats, 6/group	po single dose	20, 200 mg/kg	↔
	Adjuvant-induced arthritic ♂ Lewis Rat, 6/group	bid po for 10-day	0, 10, 30, or 100 mg/kg/day	Deaths with GI injuries in 2/6 @ 100 mg/kg.
	♂ CD-1 mice, 10/group	po single dose	0, 20, 200 mg/kg	GI injuries in 1/10 @ 20 mg/kg and 1/10 @ 200 mg/kg
Effects on Cardio-pulmonary Functions	♂ Guinea Pigs 3/group	iv single dose	Loading Dose - 0.09-0.90 mg/kg/15 min Maintenance Dose - 0.0135-1.35 mg/kg/45 min	↔
Effects on Hemodynamic	6 ♂ Beagle Dogs (Anesthetized)	iv single dose	Loading Dose - 0.053-0.375 mg/kg/15 min Maintenance Dose - 0.008-0.053 mg/kg/15 min	↔
	♂ Beagle Dogs (Conscious)	po single dose	0, 4.7, 14, 47 mg/kg/day	↔
Effect on Renal Blood Flow and Renal Function	SD Rats 10/sex/group	po bid for 5-day	0, 0.11. 0.33. 1.1 mg/kg/day	No effects on urinalysis or urine chemistry parameters.
	Furosemide-Induced Na Deficient and Volume Depleted ♂ Munich Wistar Rats, 4-9/group	iv single dose	0.003-30 mg/kg/30 min	≥0.03 mg/kg: significantly ↓ mean arterial pressure ≥0.01 mg/kg: significantly ↓ urinary PGE_2 ≥0.10 mg/kg: significantly ↓ renal blood flow and urine flow
	Furosemide-Induced Na depleted ♀ Mongrel Dogs, 6-8/group	iv single dose	0.109, 0.398, and 0.99 mg/kg/2 hr	Dose-dependent ↓ in urine flow, GFR, urinary electrolytes and blood flow; dose-dependent ↑ in renal vascular resistance; no effect on COX-1 activity in whole blood.
	♀ Mongrel Dogs Na Replaced Control 8/group; Furosemide-Induced Na depleted ♀ 6/group	iv single dose	Loading Dose - 0.028-0.22 mg/kg Maintenance Dose - 0.0009 mg/kg/60 min → 0.00045 mg/kg/60 min 0.0032 mg/kg/60 min → 0.0018 mg/kg/60 min 0.014 mg/kg/20 min → 0.007 mg/kg/40 min → 0.0035 mg/kg/60 min	Dose-dependently ↓ renal blood flow and renal function in salt depleted; COX-1 activity in the blood: ↔.

5.2. TOXICOLOGY

5.2.1. ACUTE (SINGLE-DOSE)

Single-dose toxicity of valdecoxib was accessed in the rat and dog. Results are listed in the following table.

Species Nº of Animal/Group	Dose (mg/kg)/Route	Length of Observation	Observations	NOAEL (mg/kg)
CD IGS Rats 12/sex/group	♂ - 0, 400, 800, 1600 po ♀ - 0, 200, 400, 800 po	2-Week	♀ - deaths (2) @ 800 mg/kg; ↑ PMN and monocytes; GI ulceration/perforation @ ≥400 mg/kg	♂ - Undefined (>1600) ♀ - 200
CD IGS Rats 5/sex/group	0, 3.5 mg/kg iv infusion	2-Week	No effects MTD was not achieved.	Undefined (>3.5)
♂ Beagle Dogs 2/group	0, 60, 240, 480	2-Week	No effects MTD was not achieved.	Undefined (>480)

5.2.2. REPEATED-DOSE

The repeated-dose toxicity of valdecoxib was evaluated in mice, rats, dogs, and monkeys. Findings from each study are summarized as followings.

APPEARS THIS WAY
ON ORIGINAL

Species Nº of Animal	Dose (mg/kg/day)	Duration and Route	Findings	NOAEL (mg/kg/day)
MOUSE STUDIES				
CD-1 mice 10/sex/group	0, 30, 100, 300, 1000 in diet mix	po for 2-week	↓ weight gains (♂-31%, ♀-59%), ↑ALT (~2x) and GI necrosis/ulceration (2/10♂) @ 1000 mg/kg/day; centrilobular hepatocellular hypertrophy with increased mitoses (moderate→marked in ♂ and mild→moderate in ♀) @ ≥300 mg/kg/day	♂ - 100 ♀ - 300
CD-1 mice 20/sex/group	♂ - 0, 30, 100, 300, 600; ♀ - 0, 60, 200, 600, 1000 in diet mix	po for 13-week	Deaths due to GI toxicity (necrosis, erosion/ulceration), slight→mild, multifocal→diffuse hepatocellular hypertrophy (centrilobular) and ↑ PMN (1.6x) in ♂ @ ≥100 and ♀ @ ≥200; ↓ ovary absolute and relative weights with ↓ size and Nº of corpora lutea in ♀ @ ≥60.	♂ - 30 ♀ - Undefined (<60)
♀ CD-1 mice 40/group	0, 30, 60, 200 via diet mix	po 1-15 weeks with 4-week recovery	Deaths due to GI toxicity, transient ↑ adrenal absolute (22-38%) and relative (15-35%) weights, reversible ↓ ovary absolute and relative weights (16-21%) with ↓ size and Nº of corpora lutea @ 200	60
RAT STUDIES				
SD rats 5/sex	Phase I - 0, 100, 200, 400, 600 or 800 Phase II - 100	Phase I: po bid dose-escalation with 3-day intervals Phase II: po bid for 5-day	Death due to GI toxicity (perforation); ↑ cytochrome P450 contents (1.3-1.5x); ↑ WBC with ↑ lymphocyte and PMN counts	
CD rats 10/sex/group	0, 1, 10, 50	po bid for 2-week	GI ulceration/necrosis; slight to mild hypertrophy of centrilobular hepatocytes and cells of adrenal zona fasciculata in ♀ @ 50 mg/kg/day	♂ - Undefined (>50) ♀ - 10
CD rats 10/sex	0, 10, 30, 100, 300 in diet mix	po for 2-week	Death due to GI toxicity and ↓ body weight with ↓ food consumption @ ≥100; ↓ weight gains in ♀ @ ≥10.	♂ - 30 ♀ - Undefined (<10)
Crl:CD®BR rats 10/sex	0, 10, 50	po bid for 2-week	Death due to GI toxicity @ 50.	
♀ CD(IGS) & CD rats 5-10/group	0, 6, 25	po bid for 4-week	Death due to GI toxicity @ ≥6; mortality: CD(IGS) rats > CD rats.	
Crl:CD®BR rats 15-25/sex	♂ - 0, 5, 10, 25, 50 ♀ - 0, 2.5, 5.0, 12.5, 25	po bid for 4-week	Death (1♀) due to GI toxicity @ 25; ↑ relative and absolute kidney, liver and adrenal weights were seen in ♂ @ 50 and ♀ @ ≥12.5.	♂ - 25 ♀ - 5
Crl:CD®BR rats 15-25/sex	♂ - 0, 5, 10, 25, 50, 100 ♀ - 0, 2.5, 5.0, 12.5, 25	po bid for 13-week	Death due to GI toxicity and GI lesions in ♂ @ ≥10 and ♀ @ ≥5; slight → moderate diffuse vacuolization/hypertrophy in zona fasciculata of adrenal cortex in ♂ @ ≥50 and ♀ @ ≥12.5	♂ - 5 ♀ - 2.5
CD rats 15-25/sex	♂ - 0, 5, 12.5, 25 ♀ - 0, 2.5, 5.0, 10/7.5/5.0[a] [a] The dose was dropped to 7.5 on Day 88 and then to 5 on Day 107	po for 26-week	Death due to GI toxicity, GI lesions, and ↑ absolute and relative adrenal, kidney, and spleen weights in ♂ @ ≥12.5 and ♀ @ ≥5; hypertrophy of endocrine cells in the zona fasciculata of adrenal cortex in ♂ @ 25 and ♀ @ ≥2.5.	♂ - 5 ♀ - Undefined (<2.5)
CD rats 15-25/sex	♂ - 0, 0.06, 0.2, 0.6, 2 ♀ - 0, 0.03, 0.1, 0.3, 1	po for 26-week	Jejunal ulceration in 1♀ @ 1.0	♂ - 2.0 ♀ - 0.3

Species Nº of Animal	Dose (mg/kg/day)	Duration and Route	Findings	NOAEL (mg/kg/day)
DOG STUDIES				
Beagle dogs 2/sex	0, 5, 15, 30	po bid for 2-week	GI lesions (ulcers in duodenum, jejunum, and ileum) in 1♂ @ 30; degeneration/necrosis of the renal papilla in 2♀ @ 15	5
♂ Beagle dogs 4-8/group	0, 5	po bid for 2-week	No toxicity noted. MTD was not achieved.	Undefined (>5)
Beagle dogs 4/sex/group	0, 2.5, 5	po bid for 2-week	No toxicity noted. MTD was not achieved.	Undefined (>5)
Beagle dogs 4-6/sex/group	0, 1, 2.5, 5	po bid for 4-week	Microscopic lesions of degeneration of the interstitium in the renal papilla @ ≥2.5	1.0
Beagle dogs 4-7/sex/group	0, 1, 2, 4	po bid for 4-week	No toxicity noted. MTD was not achieved.	Undefined (>4)
Beagle dogs 8-14/sex/group	0, 3, 6, 14	po bid for 52-week	Skin sores, discolored feces, and renal tubular atrophy with fibrosis @ ≥6.	3
MONKEY STUDIES				
Cynomolgus monkeys 2-4/sex	0, 60, 120, 240	po bid for 2-week	Body weight loss with ↓ food consumption, ↑ BUN (1.5-4.8x) with ↑ creatinine (~1.5x) and GI lesions @ ≥120	60
Cynomolgus monkeys 2/sex	0, 6, 14, 28	po bid for 4-week	No toxicity noted. MTD was not achieved.	Undefined (>28)
Cynomolgus monkeys 6-10/sex	0, 5, 15, 45	po bid for 12-month	↑ incidence of skin lesions (laceration or sores on the tail/digits), reversible ↑ in BUN (1.8x) @ 45; and adrenal changes (diffuse hypertrophy/hyperplasia in the zona fasciculata, cellular degeneration, and depletion of cells in the zona reticularis) @ ≥15	5

5.2.3. CARCINOGENICITY

Rat Study - Groups of Crl:CD®(SD)BR rats were given SC-65872 in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 as a suspension once daily by oral gavage at a dose schedule as shown in the following table for 104 weeks.

Group	Dosage (mg/kg/day)					Nº/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 doses selected in this study were based on the results of a 13-week oral gavage study at doses of 0, 5, 10, 25, 50, and 100 mg/kg for ♂ and 0, 2.5, 5, 10, and 25 mg/kg for ♀ in which it was shown that NOAEL was 5 mg/kg for ♂ and 2.5 mg/kg for ♀.

Treatment-related deaths increased with dose and occurred in all SC-65872 treated groups. Due to excessive toxicity, the high dose ♀ were sacrificed at Week 99. The major non-neoplastic finding were dose-dependent increased incidence of GI necrosis/perforation/inflammation with secondary peritonitis. Based on GI (necrosis/perforation/inflammation with secondary peritonitis) toxicity findings as well as mortality observed in this study, MTD was reached for both ♂ and ♀. There was no treatment-induced increases in the tumor incidence rates. The exposure to SC-65872 in the high dose ♂ and ♀ rats, as measured by $AUC_{0\text{-}24}$ was ~2x and 6x of that observed in humans at the dose of 20 mg/day, respectively. The exposure to SC-66905, an active metabolite of SC-65872, in the high dose ♂ and ♀ rats, as measure by $AUC_{0\text{-}24}$ was ~2x and 20x of that observed in humans at 20 mg/day, respectively. The NOAEL for ♂ and ♀ was not perceptible for ♀.

Mouse Study - CD-1 mice were given valdecoxib at the doses shown in the following table via dietary admix. The doses selected in this study were based on toxicity findings of a 13-week dietary admix (♂: 0, 30, 100, 300, and 600 mg/kg; ♀: 0, 60, 200, 600, and 1000 mg/kg). Due to excessive toxicity that 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

Treatment-caused histopathological changes were limited to the GI tract (erosion/ulceration with associated chronic active inflammation in the glandular stomach, duodenum, jejunum, ileum, cecum, and colon at one or more sites). The GI injury was the most common cause of death in mid- and high-dose animals. Therefore, the MTD was reached. No treatment-induced increases in the tumor incidence rates were identified. The exposure to SC-65872 and SC-66905, as measured by $AUC_{0\text{-}24}$, in the high dose ♂ and ♀ mice was equivalent to ~0.6-2x and 12-14x of values seen in humans (20 mg/day), respectively. The NOAEL for either ♂ or ♀ could not be determined for this study as treatment-induced toxicity was observed in all SC-65872 treated groups.

5.2.4. REPRODUCTIVE TOXICOLOGY

Fertility, Early Embryonic Development→Implantation - Treatment-related GI toxicity was noted in both high-dose ♂ and ♀ rats. No effects on male or female fertility, or male reproductive function including sperm counts and sperm motility in the rat at the highest dose (♂: 9 mg/kg/day; ♀: 6.0 mg/kg/day) were noted. However, significant ↑ in pre- and post-implantation losses with significant ↓ in the numbers of implantation sites, a slight ↑ in the numbers of early resorption, and a significant ↓ in the live fetuses were noted at doses ≥2.0 mg/kg/day. These observations are attributable to pharmacological inhibition of PG synthesis by valdecoxib and SC-66905 as similar effects are seen with conventional NSAIDs. It appears that with a 2-week reversal phase prior to mating the SC-65872 treatment related effects on numbers of corpora lutea, numbers of live fetuses and the pre-implantation loss could be reduced.

Teratology (Embryo-Fetal Development) - Results from a study in the rat with SC-65872 at 0, 2, 6, 10 mg/kg/day po bid showed no signs of toxicity. However, results from a rat study with SC-69124A showed GI toxicity with reduced mean body weight gains with food consumption in dams at ≥12.5 mg/kg/day (6.25 mg/kg bid) and reduced fetal weights in dams at ≥25 mg/kg/day (12.5 mg/kg bid).

Increased incidence of post-implantation losses with decreases in live fetuses and a slight increase in the incidence of fetuses with skeletal malformations and fetuses with semi-bipartite thoracic vertebra centra and fused sternebrae in the rabbits at 40 mg/kg/day (20 mg/kg po bid) were observed. Vertebral malformation with or without associated rib anomaly is a common skeletal malformation in NZW rabbits. However, results from Segment II studies with parecoxib showed a slight increase in the incidence of fetuses with skeletal malformation and vertebral anomaly with or without associated rib anomaly (6.3%/litter vs 0.3%/litter in the control) in rabbits at 40 mg/kg/day (20 mg/kg iv bid). In addition, parecoxib rapidly converted into valdecoxib. **Therefore, the relationship between malformations due to treatment with valdecoxib and parecoxib could not be excluded.**

Pre- and Post-Natal Development - Results from a study in the rat treated with SC-65872 at 0, 2, 6, and 10 mg/kg/day po bid from GD 6→LD 20 showed deaths due to GI toxicity and GI lesions occurred in dams @ ≥6 mg/kg/day. Due to the excessive toxicity (GI perforations), high-dose (10 mg/kg/day) animals were terminated early (LD 6-15). Litters of dams @ 10 mg/kg/day were terminated before weaning. Reduced food intake by up to 52% was noted in dams @ 6 or 10 mg/kg/day during LD 4-17. Increased neonatal deaths and reduced pup survivals were observed in 6 and 10 mg/kg/day groups.

The following table summarizes the effects of SC-65872 on fertility, reproductive functions, embryo-fetal development, and peri-/post-natal development.

Animals Species	Dose (mg/kg/day)	Treatment Duration	Observations
FERTILITY, EARLY EMBRYONIC DEVELOPMENT→IMPLANTATION			
Crl:CD®(SD)BR Rats 25/sex/group	♂ - 0, 0.3, 3.0, 9.0 mg/kg/day bid po ♀ - 0, 0.2, 2.0, 6.0 mg/kg/day po bid	♂: 4-wk prior to mating → necropsy ♀: 2-wk prior to mating →GD 7	GI ulceration/perforation @ 9 mg/kg/day for ♂ and 6.0 mg/kg/day for ♀; no effects on sperm mobility and total sperm count; ↓ live fetuses, ↑early resorption and post implantation loss, ↓corpora lutea and ↓ implantation sites @ ≥3 mg/kg/day. NOAEL: general toxicity 3.0 mg/kg/day for ♂ and 2.0 mg/kg/day for ♀, respectively; embryo development toxicity, 0.2 mg/kg/day.
TERATOLOGY- EMBRYO-FETAL DEVELOPMENT			
CD (VAF) Rats 8♀/group (Range-Finding)	0, 0.2, 2, 6, 12.5, 25 mg/kg/day po bid	GD 6→17	Deaths with gross GI findings, ↑ in resorptions with ↑ post-implantation loss, and ↓ live fetuses @ ≥12.5 mg/kg/day. NOAEL: 6 mg/kg/day
Crl:CD®(SD)BR Rats 24♀/group	0, 2, 6, 10 mg/kg/day po bid	GD 6→17	↓body weight changes (7.7%) during GD 6→20 and slight ↑ in pre- and post-implantation loss and total soft tissue variations (dilatation of lateral ventricles and increased renal pelvic cavitation) @ 10 mg/kg/day; MTD was not achieved. NOAEL: maternal toxicity, 10 mg/kg/day; embryo-fetal development toxicity, 10 mg/kg/day.
Crl:CD®(SD)IGS BR Rats 25♀/group	SC-69124 (parecoxib) - 0, 3, 6.25, 12.5, 25 mg/kg/day iv bid	GD 6→17	Deaths with gross GI findings, ↓ weight gains by 23% with ↓ food consumption by 9-17% during GD 12-20 @ 25 mg/kg/day; GI lesions @ ≥12.5 mg/kg/day; ↓ fetal body weights by 6% @ 25 mg/kg/day. NOAEL: maternal toxicity 6.25 mg/kg/day; embryo-fetal development toxicity, 12.5 mg/kg/day.
Hra:(NZW)SPF Rabbits 6♀/group (Range-Finding)	0, 2, 10, 50, 100 mg/kg/day po bid	GD 7→19	Weight loss during GD 9-18 with ↓ food consumption up to 51% during GD 8-22 @ 100 mg/kg/day; ↑ resorptions (early) and post implantation losses and ↓ live fetuses @ ≥50 mg/kg/day; no live fetuses @ 100 mg/kg/day group. NOAEL: maternal toxicity, 50 mg/kg/day; embryo-fetal development toxicity, 10 mg/kg/day.
Hra: (NZW)SPF Rabbits 22♀/group	0, 3, 10, and 40 mg/kg/day po bid	GD 7→19	↑ post implantation loss and early resorptions with ↓ viable fetuses @ 40 mg/kg/day; ↑ incidence of fetuses with major malformations; ↑ minor skeletal anomaly with ↑ incidence of fetuses with semi-bipartite thoracic vertebra centra and fused sternebrae @ 40 mg/kg/day NOAEL: maternal toxicity, not established; embryo-fetal development toxicity, 10 mg/kg/day.
Hra: (NZW)SPF Rabbits 25-50♀/group	0, 3, 10, and 40 mg/kg/day po bid	GD 7→18	↓ weight gains by 30- 49% during GD 7-19 @ ≥10 mg/kg/day; ↑ post implantation losses with ↑ early resorptions and ↓ in the live fetuses, and ↑ incidence of fetuses with skeletal malformations @ 40 mg/kg/day. NOAEL: maternal toxicity, 3 mg/kg/day; development toxicity, 10 mg/kg/day.
PRE AND POST NATAL DEVELOPMENT (COMBINED SEG II/SEG III)			
Crl:CD®BR(IGS) 25♀/group	0, 2, 6, 10 mg/kg/day po bid	GD 6→LD 20 GD 6→LD 6-15 for10 mg/kg/day	Deaths & GI toxicity in F_0 @ 6 mg/kg/day; ↑ neonatal deaths and ↓ pup survival @ 6 mg/kg/day; no effects on F_2. NOAEL: maternal toxicity and pre- and post-natal toxicity, 2 mg/kg/day

A comparison of exposure for SC-65872 at NOAEL on the last day of dosing in rat and rabbit reproductive studies to human clinical exposure at maximal recommended human dose (MRHD), 20 mg/day is presented in the following table.