Day of Dosing	Dose mg/kg	Clearance Rate	N	T_{max} (hr)	C_{max} (μg/ml)	AUC (μg•hr/ml)
1	5	F	6	1.50 ± 0.22	0.229 ± 0.046	0.950 ± 0.333
1		S	6	3.33 ± 1.74	0.583 ± 0.146	4.44 ± 0.80
14		F	6	1.50 ± 0.13	0.250 ± 0.055	0.818 ± 0.221
14		S	6	1.58 ± 0.15	0.389 ± 0.044	2.95 ± 0.18
1	15	F	3	2.17 ± 0.67	0.870 ± 0.077	3.80 ± 0.75
1		S	9	2.83 ± 0.45	1.56 ± 0.36	11.5 ± 2.6
14		F	3.	1.67 ± 0.33	0.384 ± 0.117	1.38 ± 0.46
14		S	9	3.89 ± 1.54	0.965 ± 0.192	8.25 ± 1.76

Phase II:

- Mean (±SEM) (Analyzed by sex) Pharmacokinetic Parameters of SC-58635 for Phase II of the Study

Day	Dose mg/kg/day	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
		♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)
1	5	1.33 ± 0.11	1.25 ± 0.11	0.306 ± 0.042	0.297 ± 0.018	2.56 ± 0.57	1.44 ± 0.30
	15	3.25 ± 1.76	3.00 ± 1.06	0.615 ± 0.107	1.03 ± 0.26	4.24 ± 0.88	7.64 ± 2.71
14	5	1.17 ± 0.11	1.67 ± 0.38	0.347 ± 0.057	0.547 ± 0.085	2.73 ± 0.74	2.47 ± 0.65
	15	1.25 ± 0.17	1.83 ± 0.36	0.681 ± 0.134	0.998 ± 0.250	4.22 ± 1.14	8.55 ± 2.92

- Mean (± SEM) Pharmacokinetic Parameters of SC-58635 for Phase II of the Study : Compound Administered as Neat Chemical in Gelatin Capsule

Day of Dosing	Dose mg/kg	Clearance Rate	N	T_{max} (hr)	C_{max} (μg/ml)	AUC (μg•hr/ml)
1	5	F	6	1.33 ± 0.11	0.279 ± 0.016	0.972 ± 0.132
1		S	6	1.25 ± 0.11	0.324 ± 0.040	3.03 ± 0.32
14		F	6	1.17 ± 0.11	0.453 ± 0.110	1.17 ± 0.31
14		S	6	1.67 ± 0.38	0.441 ± 0.048	4.02 ± 0.27
1	15	F	3	1.67 ± 0.44	0.841 ± 0.210	3.43 ± 1.33
1		S	9	3.61 ± 1.28	0.815 ± 0.188	6.77 ± 1.83
14		F	3.	1.33 ± 0.17	0.451 ± 0.127	1.52 ± 0.06
14		S	9	1.61 ± 0.27	0.968 ± 0.166	8.01 ± 1.89

Phase III: No data were presented.

Phase IV:

- Mean (±SEM) (Analyzed by sex) Pharmacokinetic Parameters of SC-58635 for Phase IV of the Study

Day of Dosing	Dose mg/kg	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
		♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)	♂ (n=6)	♀ (n=6)
COMPOUND ADMINISTERED WITH FOOD							
1	25	9.67 ± 1.09	8.92 ± 1.96	2.41 ± 0.40	1.52 ± 0.41	25.9 ± 6.4	11.7 ± 3.1
14	25	7.83 ± 2.33	8.67 ± 2.11	2.34 ± 0.70	1.29 ± 0.28	27.8 ± 10.8	9.62 ± 2.28
COMPOUND ADMINISTERED WITHOUT FOOD							
1	25	3.67 ± 1.68	6.58 ± 1.93	1.18 ± 0.35	3.16 ± 0.79	7.57 ± 2.74	38.1 ± 11.5
14	25	4.00 ± 1.62	3.67 ± 0.53	1.69 ± 0.74	4.56 ± 1.00	12.3 ± 6.25	52.5 ± 17.5

- Mean (± SEM) (by Clearance) Pharmacokinetic Parameters of SC-58635, 25 mg/kg iv, for the Phase IV Study

Day of Dosing	Clearance Rate	N	T_{max} (hr)	C_{max} (μg/ml)	AUC (μg•hr/ml)
COMPOUND ADMINISTERED WITH FOOD					
1	F	6	9.00 ± 1.61	1.38 ± 0.33	8.42 ± 1.82
1	S	6	9.58 ± 1.56	2.55 ± 0.41	29.10 ± 5.0
14	F	6	8.25 ± 1.86	1.35 ± 0.28	7.78 ± 2.31
14	S	6	8.25 ± 2.54	2.29 ± 0.72	29.60 ± 10.1
COMPOUND ADMINISTERED WITHOUT FOOD					
1	F	3	5.67 ± 3.17	1.18 ± 0.25	7.51 ± 3.97
1	S	9	4.94 ± 1.49	2.50 ± 0.65	28.00 ± 9.1
14	F	3	3.17 ± 0.33	1.84 ± 0.53	11.90 ± 6.4
14	S	9	4.06 ± 1.09	3.55 ± 0.94	39.30 ± 13.6

3.1.3.14. The Pharmacokinetics Of SC-58635 Following Multiple Dose (Q.D. And B.I.D.) Administration To Dogs, Document No.: MRC-95S-0050; Date: 02-Feb-1996 (Vol. 1.69, p. 410-457)

Report Nº MRC95S-005 (HWI 6127-237)
Study Aims: To determine the plasma levels of SC-58635 following oral administration of the drug in a gelatin capsule for 7 days.
Compound: SC-58635 (Lot Nº 94K014-A2B)
Dose and Route: 7.5 and 12.5 mg/kg/day (bid, po) and 20 mg/kg/day (qd, po) for 7 days
Animals: 6♂ & 6♀ beagle dogs, ~9-10 months of age, weighing 7-12 kg.
Study Location:
Compliance with GLP: N/A
Study Design

Group	Dose (mg/kg)	Dosing Frequency	Nº of Animals
1	7.5	bid	2/sex
2	12.5	bid	2/sex
3	20	qd	2/sex

Blood Collection:

- Group 1 & 2 - 0.5, 1, 2, 3, 4, 8, 12, 12.5, 13, 14, 15, 16, 20 and 24 hr post 1st daily dose on Day1 and 0.5, 1, 2, 3, 4, 8, 12, 12.5, 13, 14, 15, 16, 20, 24, 36, 48 hr post 1st daily dose on Day 7.
- Group 3 - 0.5, 1, 2, 2.5, 3.4, 6, 8, 12, 20 and 24 hr post dose on Day 1.

Results: Individual and mean PK parameters are presented in the following table.

Dose	Time	AUC_{0-12} (μg•hr/ml)			C_{max} (μg/ml)			T_{max} (hr)		
(mg/kg)	(Day)	♂	♀	Mean	♂	♀	Mean	♂	♀	Mean
7.5	7	5.23/5.71	7.06/5.43	5.86	0.773/1.03	0.872/0.732	0.852	2.0/2.0	2.0/2.0	3.5
12.5	7	7.58/9.87	24.5/8.03	12.5	1.13/1.75	2.80/1.32	1.75	1.0/0.5	3.0/2.0	1.63
20[a]	1	8.93/4.68	21.9/5.3	10.2	0.763/0.304	1.69/1.03	0.947	24.0/12.0	12.0/1.5	12.4

[a] AUC was calculated from 0-12 hr.

3.1.4. CYNOMOLGUS MONKEY

3.1.4.1. The Pharmacokinetics And Metabolism Of SC-58635 After Intravenous Administration To The Female Cynomolgus Monkey (An Exploratory Study), Document No.: MRC-94S-0210; Date: 17-May-1995 (Vol. 1.70, p. 1-68)

Report Nº MRC-94S-0210

Study Aim: To evaluate pharmacokinetics and metabolism of [^{14}C]SC-58635 following intravenous bolus (1 & 15 mg/kg) ♀ cynomolgus monkey in a non-randomized crossover design

Compound: [^{14}C]SC-58635 dissolved in PEG-400:H_2O, 2:1, v/v

Dosage & Route: 15 & 1 mg/kg, 1 ml/kg iv; each dose level was given once to each animal

Animals: 3♀ Cynomolgus monkey, weighed 3.4 - 3.8 kg

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

Compliance with GLP/QAU: N/A

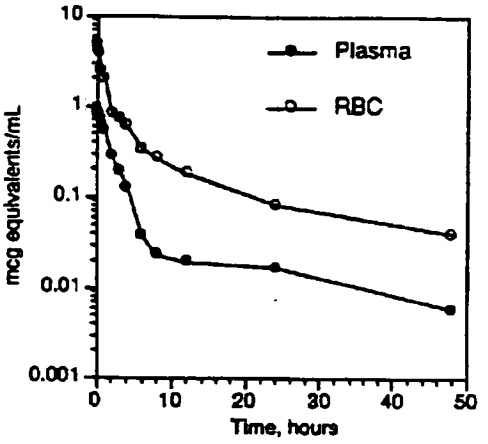
Study Design: Each animal was given once with each dose level through the left jugular vein and the 15 mg/kg dose was given prior to 1 mg/kg dose. There was a washout period of ≥1 wk. Blood samples were collected at 0, 2, 5, 15, 30, and 45 min, and 1, 2, 3, 4, 6, 8, 12, 24, and 48 hr post dose administration. Urine and fecal samples were collected by free-catch in containers surrounded by dry ice at -18-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-160 hr. Plasma concentrations of SC-58635 were determined by the analysis.

Results: The plasmas concentrations of SC-58635 and PK parameter after iv administration at dose of 1 and 15 mg/kg to ♀ cynomolgus monkey are listed as follows:

Time (min)	Plasma Concentration (ng/ml)		Time (hr)	Plasma Concentration (ng/ml)		PK PARAMETERS (1 mg/kg)	
	1 mg/kg	15 mg/kg		1 mg/kg	15 mg/kg		
2	0.636 ± 0.156	10.6 ± 3.26	2	0.106 ± 0.006	2.77 ± 0.627	Clp (ml/min•kg)	22.7 ± 1.0
5	0.489 ± 0.122	8.75 ± 2.98	3	0.07 ± 0.10	1.49 ± 0.353	$T_{½}$ (hr)	1.66 ± 0.50
15	0.312 ± 0.035	6.68 ± 2.49	4	-*	0.785 ± 0.205	Vd (l/kg)	3.58 ± 1.02
30	0.278 ± 0.019	5.77 ± 1.39	6	-	0.233 ± 0.041	Vdss (l/ml)	3.22 ± 0.88
45	0.210 ± 0.029	4.76 ± 1.77	8	-	0.244 ± 0.086	* Value below sensitivity limit of the	
60	0.176 ± 0.029	4.17 ± 1.25	12	-	0.93 ± 0.042	assay.	

The volume of distribution was greater than total body water (≈0.7 l/kg), suggesting that SC-58635 was distributed into intracellular space and/or was bond to specific tissue sites. The major metabolite (SC-62807) of SC-58635 was eliminated through feces and urine and no parent drug was present in the excretions.

The concentrations of total ^{14}C in plasma and red blood cells of a female monkey following iv administration of 1 mg/kg of [^{14}C]SC-58635 are shown in the right figure. Radioactivity partitioned into red blood cells with RBC/plasma ratio ranging



Metabolic Profile -

Plasma: The mean percentages of total radioactivity present as [^{14}C]SC-58635, [^{14}C]SC-60613 and [^{14}C]SC-62807 in are shown in following table. [^{14}C]SC-62807 was the major circulating component in the plasma following the iv administration of a 1 mg/kg dose of [^{14}C]SC-58635.

Time (hr)	% SC-58635	% SC-60613	% SC-62807
0.083	72.6	0	27.4
0.25	34.4	1.57	64.0
0.5	28.6	1.31	70.1
2	34.2	0.624	64.8
3	20.5	0	79.5
4	24.7	0	75.3
6	9.92	0	90.1

Urine and Feces: The percentage of the dose excreted in the urine as [^{14}C]SC-58635, [^{14}C]SC-60613 and [^{14}C]SC-62807 were 0, 0, and 18.7%, respectively. No parent drug was excreted in the feces. The following table shows cumulative % of the dose excreted as total carbon in urine and feces, and % of dose in feces profiles present as [^{14}C]SC-58635, [^{14}C]SC-60613 and [^{14}C]SC-62807 from one female cynomolgus monkey following iv administration of 1 mg/kg [^{14}C]SC-58635.

	% Dose Excreted as Total Carbon				% Dose in Feces		
Time (hr)	Urine	Feces	Urine + Feces	Time (hr)	SC-58635	SC-60613	SC-62807
0-24	18.9	0.0215	18.9	0-24	0	0	0.0214
0-48	27.0	6.38	33.4	24-48	0	0	6.27
0-72	27.0	40.6	67.6	48-72	0	0	33.8
0-96	27.6	53.6	81.2	72-96	0	0	12.6
0-120	27.7	61.5	89.1	0-96	0	0	52.7
0-144	27.8	63.3	91.1				
0-168	27.9	63.5	91.4				

Therefore, SC-58635 was extensively metabolized and no parent drug was excreted in urine or feces. The major metabolite of SC-58635 excreted in urine and feces was SC-62807. The major circulating metabolite of SC-58635 was SC-62807. SC-58635 was eliminated by metabolism followed by excretion of the metabolites in feces and urine.

3.1.4.2. The Pharmacokinetics And Metabolism Of SC-58635 After Intravenous Administration To The Female Rhesus Monkey (An Exploratory Study), Document No.: MRC95S-30-950167; Date: 14-Sep-1995 (Vol. 1.70, p. 69-139)

Report Nº MRC95S-30-950167
Study Aims: To determine the PK and metabolism of SC-58635 after iv administration of 1 and 15 mg/kg of SC-58635 to the female rhesus monkey in a non-randomized crossover design.
Compound: [^{14}C]SC-58635 (143 μCi/mg) and SC-58635, 1 mg/ml
Vehicle: polyethylene glycol 400 (PEG): H_2O (2:1, v/v)
Dosage and Route: [^{14}C]SC-58635 - 1 mg/kg iv; SC-58635 - 1 or 15 mg/kg iv
Animals: 3 ♀ Rhesus monkey, weighing 6.45-6.75 kg
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077
Compliance with GLP: N/A
Study Design

Monkey ID	Compound	Dose (mg/kg)	Route	Sample Collected
581	SC-58635	15	iv	Plasma
587	SC-58635	15	iv	Plasma
588	SC-58635	15	iv	Plasma
581	[^{14}C]SC-58635	1	iv	Plasma, Urine, RBC, Feces
587	SC-58635	1	iv	Plasma
588	SC-58635	1	iv	Plasma

Sample Collection:

- Blood - 0, 2, 5, 15, 30 and 45 min, 1, 2, 3, 4, 6, 8, 12, 24, and 24 hr post dosing.
- Urine and Feces - Urine and fecal samples were collected for consecutive 24 hr periods: -18-0, 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hr.

Results:

- Concentrations of total radioactivity in plasma and RBC following iv injection of 1 mg/kg of [^{14}C]SC-58635 -

Time (min)	Concentration (μg eq/ml)			Time (hr)	Concentration (μg eq/ml)		
	Plasma	RBC	RBC/Plasma Ratio		Plasma	RBC	RBC/Plasma Ratio
2	0.743	3.73	5.02	1	0.601	2.34	3.89
5	0.735	3.51	4.78	2	0.334	1.10	3.29
15	0.792	2.85	3.60	3	0.191	0.778	4.07
30	0.740	2.90	3.92	4	0.118	0.463	3.92
45	0.662	2.67	4.03	6	0.0396	0.196	4.95
				8	0.0229	0.0948	4.14
				12	0.0021	0.0299	14.3
				24	-	0.0234	-
				48	-	0.0013	-

- Concentration of SC-58635 in the plasma and PK parameters following iv injection of 1 and 15 mg/kg of SC-58635 -

Time (min)	Plasma Concentration (μg/ml)		Time (hr)	Plasma Concentration (μg/ml)	
	1 mg/kg	15 mg/kg		1 mg/kg	15 mg/kg
2	0.702	14.4	1	0.245	5.54
5	0.507	9.9	2	0.154	3.98
15	0.446	8.49	3	0.097	2.92
30	0.375	7.29	4	0.067	1.63
45	0.287	7.09	6	-[a]	0.515
PK Parameters			8	-	0.294
Clp (ml/min•kg)	17.8		12	-	0.093
$T_{½}$ (hr)	1.5		24	-	-
Vd (l/kg)	2.73		48	-	-
Vd_{ss} (l/kg)	2.34				

[a] value < 0.025 μg/ml (limit of detection)

- Metabolic profiles of SC-58635 following iv injection of 1 mg/kg of SC-58635

Sample	Time (hr)	% SC-58635	% SC-60613	% SC-62807
Plasma	3	36.7	0	59.1
	4	30.2	0	69.8
Urine	0-24	0	0	21.1
Feces	0-24	0	0	18.4
	24-48	0	0	56.7

3.2. PROTEIN BINDING

3.2.1. RAT, MOUSE, DOG AND HUMAN

3.2.1.1. Rat And Human Plasma Protein Binding Of [^{14}C]SC-58635 (A Pilot Study), Document No.: MRC-94S-0136; Date: 17-May-1995 (Vol. 1.70, p. 140-157)

Report Nº: MRC-94S-0136
Study Aim: To determine the extent of SC-58635 binding to protein in rat and human plasma.
Compound: [^{14}C]SC-58635 (Lot Nº GDS-4095-25, 146 μCi/mg)
Blood Samples: Rat and Human
Study Location: G.D. Searle & Co., 800 N. Lindbergh Blvd., St. Louis, MO 63167
Compliance with QAU: N/A
Study Design: Plasma protein binding of [^{14}C]SC-58635 was performed *in vitro* at concentrations ranging from 0.3 to 3.0 μg/ml, using rat and human plasma by using a dextran-coated charcoal method.

Results: The percentages of [^{14}C]SC-58635 bound to plasma *in vitro* are listed as follows. The binding of [^{14}C]SC-58635 to plasma protein appeared to be concentration-dependent.

[^{14}C]SC-58635 (μg/ml)	% [^{14}C]SC-58635 bound to plasma	
	Rat	Human
0.3	95.6	97.3
1.0	85.3	-
3.0	88.3	90.6

3.2.1.2. The Binding Of SC-58635 To Mouse, Rat, Dog And Human Plasma Proteins, Document No.: M3097065; Date: 16-Feb-1998 (Vol. 1.70, p. 158-216)

Report Nº: M3097065

Study Aim: To determine the extent of SC-58635 binding to plasma protein in vitro for mouse, rat, dog and human, as well as for human serum albumin and human α_1 acid glycoprotein and to evaluate the plasma concentrations of free and total SC-58635 in mouse, rat and dog after oral administration of SC-58635.

Compound: SC-58635 (Lot Nº 94K031-A2A); [^{14}C]SC-58635 (Lot Nº GDS-4671-84, 141 μCi/mg) in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) suspension or in capsule.

Animals: ♂ CD-1 mice, 20-40 g; ♂ & ♀ rats, 250-350 g; ♀ Beagle dogs, 8-12 kg.

Dose: Mouse, 10 or 300 mg/kg po; Rat, 1 or 400 mg/kg po; Dog, 1 or 100 mg/kg po.

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

Compliance with QAU: N/A

Study Design: The binding of [^{14}C]SC-58635 to plasma protein was evaluated *in vivo* for mouse, rat and dog. Male Charles River CD-1 mice (n=36/dose) were administered a single dose of 10 and 300 mg SC-58635/kg in of 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) suspension. Female SD rats (n=24/dose) were administered a single oral dose of 1 or 400 mg/kg SC-58635 in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) suspension. Female beagle dogs (n=3) were administered single doses of SC-58635 at 1 mg/kg of suspension in 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) and 100 mg/kg capsule. Blood samples were collected from all animals after dose administration and plasma was prepared by of blood. Plasma concentrations of total SC-58635 were determined by the method. Plasma concentrations of free SC-58635 were determined

The binding of [^{14}C]SC-58635 to plasma protein was evaluated *in vitro* using plasma prepared from mouse, rat, dog, and human blood and also in solutions of human serum albumin and α_1 acid glycoprotein. Blood was obtained from ♂ CD-1 mice, ♂ rats, a ♂ beagle dog, and a healthy ♂ human subject. Plasma samples for each species and the 0.067M KH_2PO_4-Na_2HPO_4 buffered (pH 7.4) solutions of human serum albumin (40 mg/ml) and human α_1 acid glycoprotein (1.80 mg/ml) were split into five equivalent aliquots that were fortified with concentrations of 0.1, 0.3, 1.0, 3.0, and 10 μg/ml. The protein binding of [^{14}C]SC-58635 to plasma proteins was evaluated for each concentration using an method.

Results: SC-58635 was highly bound to plasma protein in the mouse, rat, dog and human. Data from *in vitro* plasma protein binding experiment are listed in the below table.

Species	*In Vitro* % Plasma Protein Binding				
	[^{14}C]SC-58635 Concentrations (μg/ml)				
	0.1	0.3	1.0	3.0	10
Mouse	94.4	-	-	-	93.5
Rat	98.4	94.3	91.4	95.9	84.2
Dog	98.2	96.7	97.0	97.0	97.1
Human	98.2	97.9	96.5	96.7	96.3
human α_1 acid glycoprotein	92.4	91.6	91.0	88.4	78.6
human albumin	100	100	99.8	99.9	99.8

Plasma C_{max} values for SC-58635 and % SC-58635 bound to protein at C_{max} following single oral administration of SC-58635 to the mouse, rat, and dog are presented in the following table.

SC-58635	Mouse		Rat		Dog	
Dose (mg/kg)	10	300	1	400	1	100
C_{max} (μg/ml)	2.57	12.7	0.198	6.74	0.275	3.62
% Plasma Protein Binding	98.1	99.2	98.8	99.1	98.9	99.5

3.3. TISSUE DISTRIBUTION AND ACCUMULATION

3.3.1. RAT

3.3.1.1. Tissue Distribution And Excretion Of Radioactivity Following A Single Oral Dose Of [^{14}C] SC-58635 In Male Rats, Document No.: MRC-94S-0182; Date: 21-Jul-1995 (Vol. 1.70, p. 217-363)

Report Nº: MRC94S-0182
Study Nº HWI-6127-226
Study Aim: To assess the tissue distribution and excretion of [^{14}C]SC-58635 in Male Rats following a single oral dose
Compound: [^{14}C]SC-58635 in PEG 400/H_2O
Dosage: 2 mg/kg po
Animals: 31 ♂ Long-Evans rats, weighting 196-230 g, ~51 days old.
Study Location:
Compliance with QAU: Yes
Study Design: One animal served as control and was sacrificed for the blood and tissue collection. Total 30 animals were dosed with 2 mg/kg [^{14}C]SC-58635. The mean radioactive dose administered to each rat was 18.4 ± 0.81 μCi. Animals were sacrificed (3/time point) at 0.5, 1, 3, 8, 24, 72, 96, 144, and 168 hr postdose. Tissues and blood were collected following each sacrifice. Urine, feces and expired air were collected at selected intervals from the rats sacrificed for tissue collection at 168 hr postdose. The radioactivity in the blood, urine and feces samples and tissues distribution of radioactivity were determined.

Results: The absorption of [^{14}C]SC-58635 was rapid with C_{max} values of 4.18 and 0.966 μg equivalents/g for blood and plasma, respectively. The T_{max} for the blood and plasma was 1 hr postdose. The highest mean C_{max} values in various tissues were liver, RBCs, blood, adrenal glands, lacrimal glands, and bone marrow, with levels of 6.28, 5.70, 4.18, 3.31, 3.24 and 2.99 μg equivalents/g, respectively. By 72 hr postdose, concentrations in the most tissues were below the limit of detection. The mean & cumulative (n=3) percent of radioactive dose in urine, and feces was presented in the following table. At 168 hr post administration, 0.71%, 14.9%, and 6.71% of

radioactivity was recovered in the feces, urine and cage wash, respectively indicating that the major route of excretion was through the faces.

Collection Time	Mean % of Radioactive Dose		Collection Time	Cumulative % of Radioactive Dose	
(hr)	Urine	Feces	(hr)	Urine	Feces
0-6	5.08	12.1	0-6	5.08	12.1
6-24	5.71		0-24	10.8	
24-48	1.99	50.8	0-48	12.8	46.0
48-72	0.94	13.7	0-76	13.7	59.7
72-96	0.38	9.84	0-96	14.1	69.6
96-120	0.24	0.72	0-120	14.3	70.3
120-144	0.24	0.40	0-144	14.6	70.7
144-168	0.30	0.17	0-168	14.9	70.9

3.3.1.2. The Pharmacokinetics And Metabolism Of [^{14}C] SC-58635 After Oral Administration To the Pregnant Rat, Document No.: M3097235; Date: 22-Sep-1997 (Vol. 1.71, p. 1-81)

Study Nº: Covance 6127-328
Study Report Nº: M3097235
Study Aims: To obtain information on the PK and metabolism of [^{14}C]SC-58635 after a single oral administration to pregnant rats and to determine whether drug-associated radioactivity reached the fetuses or the amniotic fluid.
Compound: [^{14}C]SC-58635 (Lot Nº: GDS 4671-84, 97.5% purity with 141 μCi/mg of specific activity) in PEG400/H_2O (2:1), 0.5 mg/ml and 30 μCi/mg
Vehicle: PEG400/H_2O (2:1)
Dose and Route: 5 mg/10 ml/kg
Animals: 19 timed-pregnant ♀ rats, Crl:CD®(SD)BR, weighing 303-346 g
Study Site:
Study Date: 11/20-11-21/96
GLP/AUC: N/A
Study Design: Pregnant rats were given a single oral dose of [^{14}C]SC-58635, 5mg/kg, by gavage on Day 18 of gestation. Maternal blood, amniotic fluid and all fetuses from each animal were collected at different time as shown in the following table.

Group	Nº of Pregnant ♀	Compound	Dose (mg/ml/kg)	Sampling Time (hr)
1	1	-	-	Pre-dose
2	3	[^{14}C]SC-58635	5/10	0.5
3	3	[^{14}C]SC-58635	5/10	1
4	3	[^{14}C]SC-58635	5/10	2
5	3	[^{14}C]SC-58635	5/10	4
6	3	[^{14}C]SC-58635	5/10	8
7	3	[^{14}C]SC-58635	5/10	24

Results:

- TISSUE DISTRIBUTION OF RADIOACTIVITY - Mean (±SE) % radioactive dose and PK parameters in plasma, amniotic fluid and fetuses following a single oral dose of [^{14}C]SC-58635 (5 mg/kg) are shown in the below table.

Sampling Time (hr)	μg Equivalent [^{14}C]SC-58635/g		
	Plasma	Amniotic Fluid	Fetuses
0.5	0.728 ± 0.074	0.057 ± 0.018	0.444 ± 0.055
1	0.837 ± 0.143	0.052 ± 0.008	0.666 ± 0.046
2	0.814 ± 0.034	0.089 ± 0.010	0.772 ± 0.055
4	1.07 ± 0.103	0.130 ± 0.022	0.984 ± 0.104
8	2.28 ± 0.225	0.192 ± 0.012	1.51 ± 0.061
24	0.557 ± 0.04	0.066 ± 0.009	0.594 ± 0.043
PK PARAMETERS			
T_{max} (hr)	8	8	8
C_{max} (μg eq/ml)	2.28	0.192	1.51
$AUC_{0-\infty}$ (μg eq•hr/g)	37.8	3.7	30.6

- DISTRIBUTION OF RADIOACTIVITY IN EXTRACTS - The following table illustrates the distribution of radioactivity in extracts of samples of plasma, amniotic fluid, and fetus collected at specified times postdose for pregnant female rats following a single oral dose of [^{14}C]SC-58635 (5 mg/kg) and analysis of extracts.

Hours Postdose	Composite Conc.[b]	% TR[c]	Extract Conc.	HPLC Analysis of Aqueous Extracts					
				SC-62807		SC-60613		SC-58635	
				% TR	Conc.	% TR	Conc.	% TR	Conc.
PLASMA									
Control[a]	NA	98.1	NA	ND	NA	0.3	NA	92	NA
1	0.8335	92.8	0.774	0.9	0.007	3.8	0.032	84.9	0.708
8	2.281	92.7	2.115	0.6	0.013	4.7	0.106	87.2	1.988
24	0.5566	93.8	0.522	1 0.8	0.004	4.5	0.025	8 6.6	0.483
AMNIOTIC FLUID									
Control[a]	NA	97.2	NA	ND	NA	0.3	NA	94.9	NA
1	0.0523	130.6	0.068	12.3	0.006	17.6	0.009	94.4	0.049
8	0.1921	93.6	0.18	6.7	0.013	12.1	0.023	70	0.134
24	0.0661	76.8	0.051	ND	ND	8.2	0.005	63.4	0.042
FETUS									
Control[a]	NA	93.8	NA	ND	NA	0.2	NA	89.7	NA
1	0.2635	97.2	0.256	ND	ND	1.8	0.005	92.5	0.243
8	0.5733	96.9	0.556	ND	ND	3.2	0.018	92.8	0.532
24	0.2176	98.2	0.214	ND	ND	4.7	0.01	88	0.192

[a]Fortified control; [b]Concentration: μg eq/g; [c]TR = Total radioactivity

3.3.1.3. Milk Secretion Of [^{14}C] SC-58635 In The Rat, Document No.: M3097236; Date: 02-Sep-1997 (Vol. 1.71, p. 82-163)

Included as an appendix To This Report were:
Milk Secretion Of [^{14}C] SC- 58635 In The Rat, Document No.: M2096302; Date: 29-Aug-1997 (Vol. 1.71, p. 103- 159)
Final Report Amendment No. 1: Milk Secretion Of [^{14}C]SC-58635 In The Rat, Document No.: M3197236; Date: 24- Sep- 1997 (Vol. 1.71, p. 160- 163)

Study Nº: Covance 6127-329
Report Nº: M3097236/M2096302
Study Aims: (1) To determine the extent of transfer of [^{14}C]SC-58635 from maternal blood to milk in the rat and to assess the nature of the radioactive residues in plasma and milk.
(2) To determine tissue distribution of [^{14}C]SC-58635 in rats using whole body autoradiography (WBA) and microautoradiography (MAR).
Compound: [^{14}C]SC-58635 (Lot Nº: GDS 4671-84, 97.5% purity with 141 μCi/mg of specific activity) in PEG400/H_2O (2:1)

Dose and Route: 5 mg/kg po by gavage
Animals: 24 adult Sprague-Dawley lactating rats, Crl:CD®(SD)BR, weighing 262-358 g.
Study Site: Corning Hazleton Inc., 3301 Kinsman Boulevard, Madison, WI 53704.
GLP Compliance: N/A
Study Date (In-Life): 11/13-15/1996,
Study Design: Lactating rats (4-20 days postpartum) were treated with [^{14}C]SC-58635, 5 mg/kg, by oral gavage. Blood and milk were collected at 0.5, 1, 2, 3, 5, 8, 24 and 48 hours postdose (3/time point). Plasma and milk were assayed for total radioactivity by liquid scintillation counting (LSC). Plasma samples were also analyzed for SC-58635 using a validated . Samples were analyzed at

Results: The concentrations of SC-58635 in plasma and milk following a single oral administration of [^{14}C]SC-58635 were similar. The distribution of radioactivity in extracts of plasma and milk samples collected at specified times postdose following a single oral dose of [14C]SC-58635 (5 mg/kg) to female lactating rats and analysis of extracts are presented in the following two tables.

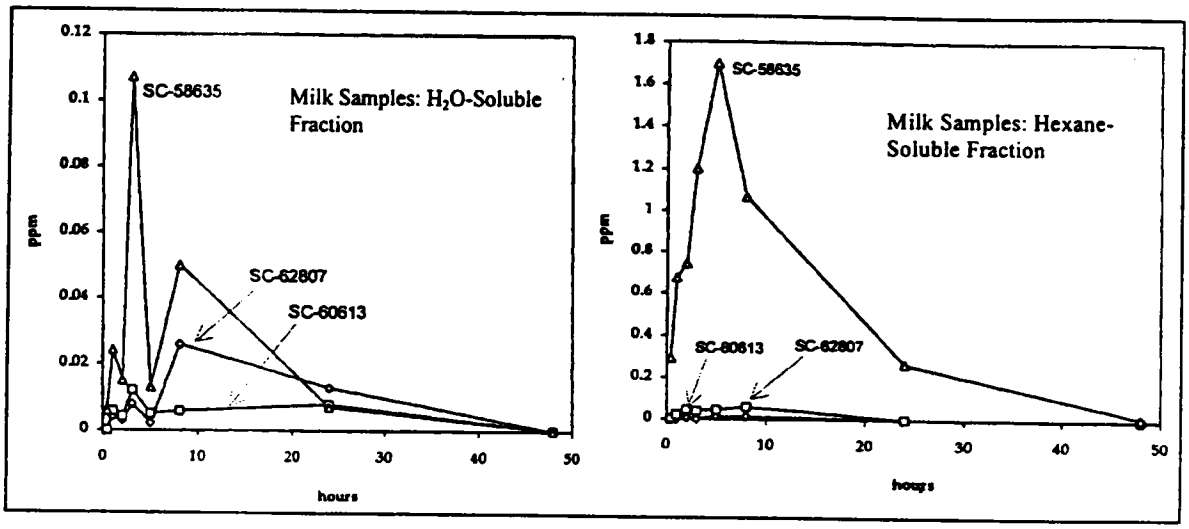
PLASMA SAMPLES		Collection Time (hr)		
		Control	5	24
Pooled Sample Conc.		NA	1.266	0.279
ACN/ACN: H_2O Extract %TR		98.1	94.3	95.7
Extracted Conc.		NA	1.193	0.267
HPLC Analysis of Aqueous Extracts				
SC-62807	%TR	ND	1.2	1.7
	Conc.	ND	0.015	0.005
SC-606 13	%TR	0.3	3.7	4.8
	Conc.	NA	0.047	0.013
SC-58635	%TR	92.0	86.6	85.2
	Conc.	NA	1.096	0.238

MILK SAMPLES		Collection Time (hr)								
		Control	0.5	1	2	3	5	8	24	48
Pooled Sample Conc.		NA	0.398	1.114	1.391	1.520	1.891	1.694	0.303	0.024
Acetone: H_2O Extract		86.8	79.6	72.0	66.2	97.8	106.4	79.3	99.9	92.3
Extracted Conc.		NA	0.317	0.802	0.874	1.487	2.012	1.342	0.303	0.022
%TR Aqueous 1		1.2	1.6	2.8	1.4	8.4	1.7	5.3	11,9	7.7
%TR Aqueous 2		NA	0.6	0.5	0.6	0.6	NA	0.3	NA	0.2
HPLC Analysis of Aqueous Extract of Pooled Samples										
SC-62807	%TR	0.1	ND	0.4	0.2	0.5	0.1	1.5	4.4	2.8
	Conc.	NA	ND	0.004	0.003	0.008	0.002	0.026	0.013	<0.001
SC-606 13	%TR	0.1	0.2	0.5	0.3	0.8	0.2	0.3	2.5	ND
	Conc.	NA	<0.001	0.006	0.004	0.012	0.005	0.006	0.008	ND
SC-58635	%TR	0.6	1.4	2.1	1.1	7.0	0,7	3.0	2.3	ND
	Conc.	NA	0.006	0.024	0.015	0.107	0.013	0.050	0.007	ND

Percentages are reported to one decimal place; concentration values are reported to three decimal places.
Conc. = Concentration, μg equivalents/g; TR = Total radioactivity; NA = Not applicable; ND = Not detected.

The PK parameters for SC-58635 in plasma and milk following a single oral administration of [^{14}C]SC-58635 are summarized as followings.

Sample	C_{max} (μg eq/g)	T_{max} (hr)	AUC_{0-24} (μg eq•hr/ml)	$AUC_{0-\infty}$ (μg eq•hr/ml)	$T_{½}$ (hr)
Plasma	1.22	5	22.2	23.5	5.38
Milk	1.90	5	30.7	30.9	5.93



3.3.1.4. Tissue Distribution Of [^{14}C] Celecoxib In Rats Using Whole-Body

Document No.: M2096278; Date: 24-Jun-1997 (Vol. 1.71, p. 164-210)

Study Report Nº: M2096278/EHL 96130 & M2196278

Study Aims: To determine tissue distribution of [^{14}C]SC-58635 in rats using whole body

Compound: [^{14}C]SC-58635 (Lot Nº: GDS 4671-84, 97.5% purity with 141 μCi/mg of specific activity) in PEG400/H_2O (2:1), 2 mg/ml for the bolus dose and 1 mg/ml for the infusion dose.

Vehicle: PEG400/H_2O (2:1)

Dose and Route: 2 mg/kg iv bolus or iv infusion at 0.4 mg/kg/hr for 5 hr

Animals: 9♂ rats, Crl:CD®(SD)BR, ~9 weeks of age, weighing 308 g, 3/group

Study Site:

Study Date: 8/27/96-**4/2/96(?) (How could the study be finished long before it was even started?)**

GLP/AUC: No

Study Design: Three groups of rats were given an iv bolus loading dose of [^{14}C]SC-58635, 2 mg/kg, followed by an iv infusion at 0.4 mg/kg/hr for 5 hr.

Group 1 - used for whole body

Group 2 - Tissues were processed

Group 3 - Brain was dissected, frozen and processed for metabolic profile determination. The following samples were collected for SC-58635 or radioactivity determinations.

- Blood Sampling - Blood was collected from the carotid artery (Groups 1 & 2 rats) at 1 and 4 hr after iv infusion initiated.
- Organ and Tissues - Aliquots of the liver, heart, blood, lung, brain, testes, muscle, and gut content were obtained after whole-body sectioning of frozen animals for the analysis of radioactivity.

Results: Levels of radioactivity in whole blood, plasma, and cellular fraction, and analysis of tissue radioactivity are shown in the following two tables.

Time Point	Whole Blood		Plasma		Cell Fraction		Ratios		
	Mean dpm/g	μg eq/g	Mean dpm/g	μg eq/g	Mean dpm/g	μg eq/g	Plasma/Cell Fraction	Plasma/Blood	Cell Fraction/Blood
1 hr	430518	4.88	59040	0.67	815867	9.24	0.08	0.13	2.06
4 hr	412013	4.67	68448	0.78	759310	8.60	0.09	0.18	1.90
5 hr	328975	3.72	79257	0.90	557489	6.31	0.14	0.24	1.69

Tissue	Mean dpm/g[a]	Average μg eq/g[a]	Tissue/Blood Ratio
Liver	666643	7.54	1.61
Blood	409361	4.63	1.00
Lung[b]	452950	5.13	1.15
Testes	122037	1.38	0.29
Brain	164708	1.86	0.40
Muscle	255940	2.90	0.59
Gut Content[c]	11136949	126.05	30.80
Salivary Gland	215715	2.44	0.52
Kidney[c]	279661	3.17	0.75

[a]Mean of 3 animals except where noted; [b] Value from one animal; [c]Mean of two animals.

The liver, heart, lungs, kidney, and intestinal contents had the highest radioactivity. The Microradiogaphy study showed that the epithelium of the cecum and hepatocyes had specific localization of [^{14}C]SC-58635. The [^{14}C] radioactivity recovered from the brain, by a methanol extraction method. was 97.1-98.7% and was determined to be 100% unchanged drug [^{14}C]SC-58635.

3.4. METABOLISM CHARACTERISTICS AND METABOLITES

3.4.1. RAT

3.4.1.1. The Isolation And Identification Of In Vivo Metabolites Of [^{14}C]SC-58635 In Rats, Document No.: M3094211; Date: 11-Apr-1996 (Vol. 1.71, p. 211-243)

Report Nº: M3094211

Study Aim: To determine PK and metabolism profiles and identify metabolites eliminated in bile from 3♂ rats dosed orally with 5 mg/kg of [^{14}C]SC-58635.

Compound: [^{14}C]SC-58635 in PEG 400 : H_2O (2:1, v/v)

Dose & Route: 5 mg/kg, 10 ml/kg intragastrically

Animals: 3♂ rats, weighing 297-328 g.

Study Location: G.D. Searle, Skokie, IL

Compliance with QAU: Not Indicated.

Results: Two major metabolites, SC63807 (carboxyl metabolite) and the glucuronide conjugate of SC-60613, were identified in bile.

3.4.1.2. Enterohepatic Circulation of [^{14}C]SC-58635 Following Oral Administration To The Male Rat, Document No.: M3096267; Date: 01-Dec-1997 (Vol. 1.71, p. 244-290)

Report Nº:	M3096267
Study Aim:	To determine the potential for enterohepatic circulation of SC-58635 in the rat
Compound:	[^{14}C]SC-58635 (Lot Nº: GDS 4671-84, 97.5% purity with 141 μCi/mg of specific activity) in PEG 400 : H_2O (2:1, v/v), 2mg/ml, 5 μCi/mg; SC-58635 (Lot Nº: E90077 and 94K-031-A2A)
Dose & Route:	5 mg/kg, 10 ml/kg intragastrically
Animals:	6♂ rats, weighing 254 - 262 g for donor rats and 249 - 261 g for recipient rats, 3/group
Study Location:	G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
Compliance with QAU:	Not Indicated.
Study Design:	Six male rats were surgically altered to allow bile to flow from a donor rat (n=3) into the duodenum of a recipient rat (n=3). [^{14}C]SC-58635 was administered orally at a dose of approximately 20 mg/kg to three donor rats. Blood was collected from the recipient rats (n=3) at 1, 2, 4 and 6 hr after oral dose administration to the donor rats. The donor rats were sacrificed at 6.5 hr post dose and bile was collected from the donor rats for 30 minutes immediately prior to sacrifice. Plasma was frozen immediately on dry ice and selected samples shipped frozen to . Plasma samples were analyzed for concentrations of SC-58635 and total radioactivity. The bile was analyzed for total radioactivity and profiled The major metabolites in the bile extracts were identified

Results: Concentrations of SC-58635 in the plasma collected from the three donor rats at sacrifice were 1.56, 1.93 and 0.446 μg/ml indicating that SC-58635 was systemically absorbed. There were no measurable levels (assay sensitivity limit, of SC-58635 in plasma from the recipient rats, indicating that enterohepatic circulation of SC-58635 does not occur in rats administered 20 mg/kg SC-58635. Six metabolites of SC-58635 were identified in rat bile a

3.4.1.3. The Pharmacokinetics And Metabolism Of [^{14}C]SC-58635 Following Multiple Dose Administration To The Rat, Document No.: MRC-94S-0132; Date: 07-Dec-1994 (Vol. 1.72, p. 1-256)

Report Nº MRC-94S-0132
Study Aim: To evaluate pharmacokinetics and metabolism of [^{14}C]SC-58635 following oral administration for 4 weeks
Compound: SC-58635 (Lot Nº 94L013-A1A) & [^{14}C]SC-58635 (used on Days 1 & 26) suspension in 0.5% methylcellulose and 0.1% Tween 80
Dosage & Route: 20, 80, 400 & 600 mg/kg, 10 ml/kg, for 4 week by oral gavage
Control Vehicle: 0.5% methylcellulose and 0.1% Tween 80
Animals: 96♂ & 96♀ rats, strain Crl:CD®(SD)BR, weighing 100 - 220 g, 3, 6 or 15/sex/ group
Study Location:
Compliance with GLP/QAU: N/A
Study Design: Group designation & dose levels were listed as followings:

Group	Nº of Animals	Dose levels (mg/kg)	
1[a]	15♂ & 15♀	20	[a] Each animal received [^{14}C]SC-58635 on Days 1 & 26, and SC-58635 on Days 2 -
2[a]	15♂ & 15♀	80	25. Blood samples were taken on Days 1 & 26 at specific time (0.5, 1, 2, 3, 4, 6, 8,
3[a]	15♂ & 15♀	400	and 24 hr) post dosing from 12 animals of each group. Liver was collected from
4[a]	15♂ & 15♀	600	3/sex/group on Day 26.
5[b]	6♂ & 6♀	20	[b] Three/sex/group received a single dose of [^{14}C]SC-58635 on Day 1, and
6[b]	6♂ & 6♀	80	3/sex/group received SC-58635 on Days 1 - 25, and a dose of [^{14}C]SC-58635 on
7[b]	6♂ & 6♀	400	Day 26; urine and fecal samples were collected at specific time intervals (-24-0,
8[b]	6♂ & 6♀	600	0-24, 24-48, 48-72, 72-96, 96-120 hr) after dosing with [^{14}C]SC-58635. All
9[c]	3♂ & 3♀	20	animals were sacrificed following the last excreta collection.
10[c]	3♂ & 3♀	80	[c] Each rat received a dose of SC-58635 from Day 1 to 26 and liver was collected
11[c]	3♂ & 3♀	400	from each one following dosing on Day 26.
12[c]	3♂ & 3♀	600	

Animals were checked 2x daily for moribundity and mortality. Animals were weighed on Days 1, 8, 15, 22, and 26. PK analysis was performed on blood, urine and fecal samples. Liver samples from the SC-58635 treated animals were used to prepare post-mitochondrial supernatant for cytochrome P-450 analysis.

Results: The observations from the present study were summarized as following:

The PK parameters for concentrations of total ^{14}C in plasma following oral administration of SC-58635 on Days 1 & 26 are presented in the following table

Dose	C_{max} (µg eq/g)		T_{max} (hr)		$T_{½}$ (hr)		K (hr^{-1})		AUC_{0-t} (µg eq•hr/g)		$AUC_{0-\infty}$ (µg eq•hr/g)	
(mg/kg/day)	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Day 1												
20	4.44	4.98	2	2	3.25	7.07	0.1954	0.0981	42.8	59.6	43.1	66.2
80	14.1	19.7	3	2	3.60	6.18	0.1925	0.1121	153.7	260.8	155.2	279.5
400	55.4	61.8	3	2	8.69	10.3	0.0798	0.0674	694.3	1015	813.9	1261
600	69.6	102	2	6	4.32	8.02	0.1604	0.0864	782.1	1721	795	2138
Day 26												
20	4.25	4.66	1	2	3.88	7.48	0.1785	0.0927	33.6	54.8	34.0	61.5
80	13.1	15.2	2	2	3.90	7.41	0.1776	0.0936	93.7	188.6	94.9	209.4
400	39.0	58.7	2	4	4.16	7.05	0.1667	0.0983	307.3	680.9	313.0	745.7
600	63.1	93.8	2	4	4.34	13.6	0.1596	0.0509	475.4	1471	484.6	2068

The PK parameters for concentrations of total ^{14}C in RBC following oral administration of SC-58635 on Days 1 & 26 are shown in the following table.

Dose (mg/kg/day)	C_{max} (µg eq/g)		T_{max} (hr)		$T_{½}$ (hr)		K (hr^{-1})		AUC_{0-t} (µg eq•hr/g)		$AUC_{0-\infty}$ (µg eq•hr/g)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Day 1												
20	19.8	23.0	2	2	5.62	14.6	0.1233	0.0474	230.4	341.3	241.2	494.1
80	56.1	53.5	0.5	0.5	4.97	9.53	0.1395	0.0727	531.1	757.2	554.3	937.3
400	98.1	102	3	3	9.93	9.21	0.0698	0.0752	1379	1824	1703	2368
600	153	185	1	0.5	7.08	8.31	0.0979	0.0834	1884	2971	2064	3785
Day 26												
20	32.1	31.2	1	0.5	5.30	14.4	0.1308	0.0482	293.0	434.2	304.1	628.6
80	62.8	62.7	1	0.5	5.30	6.93	0.1309	0.1000	564.5	829.1	587.7	961.1
400	108	111	1	4	4.38	14.6	0.1584	0.0473	1153	1628	1195	2421
600	137	149	1	4	6.64	19.8	0.1044	0.0351	1396	2393	1507	4105

Following oral dose administration, radioactivity was rapidly absorbed. The C_{max} of radioactivity in plasma and RBC occurred around 2 and 3 hr post dosing.

The $T_{½}$ of plasma [^{14}C]SC-58635 was 3.55 - 8.69 hr for ♂ animals and 6.18 - 13.6 hr for ♀ rats. The hepatic cytochrome P-450 content did not change with dose, but liver radioactivity increased proportionally with dose.

The main route of excretion was through feces and the radioactive dose was extensively abolished; approximately 86.6 % - 94.9% of radioactivity was eliminated over a period of 120 hr in both ♂ and ♀ rats at all dose levels. Elimination via urinary tract was 7.0% to 10.9%. Total radioactivity recovered was 95.1 - 105%. The rate, route and pattern of excretion following multiple dose administration was similar to the single dose administration.

3.4.1.4. Evaluation Of The Total Radioactivity Data In a 13-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635 (SA4346), Results Of Radioanalysis, Document No.: MRC95C-30-950232; Date: 09-Nov-1995 (Vol. 1.72, p. 257-369)

Report Nº: MRC95C-30-950232
Study Nº: SA4346/CHV 700-332 and CHW 6157-183
Study Aim: To identify toxic effects of SC-58635 when administered orally by gavage to rats for at least 13 weeks.
Compound: SC-58635 (Lot Nº 94K014-A4A), [^{14}C]SC-58635 (Lot Nº GDS 4404-145, 7.68 µCi/mg)
Vehicle: 0.5% methylcellulose (w/v) + 0.1% Polysorbate 80 (Tween® 80) (w/v) in dist. H_2O
Dosage: 0, 20, 80, 400 mg/kg/day, 10 ml/kg po for ≥13 weeks
Animals: 388 (194/sex) Crl:CD®BR rats, ~6 wk old.
Study Location:
Study Date: March 16, 1995 - July 14, 1995
Radioanalysis: 22 March 1995 - 26 July 1995
Compliance with GLP/QAU: Yes

Main and Recovery[a] Study				Satellite PK Study			
Group	Dose (mg/kg/day)	Nº of Animals		Group	Dose (mg/kg/day)	Nº of Animals	
		♂	♀			♂	♀
1	0 (MC)	25	25				
2	20 (Low)	25	25	5	20 (Low)	18	18
3	80 (Mid)	25	25	6	80 (Mid)	18	18
4	400 (High)	25	25	7	400 (High)	18	18

[a] The recovery group comprised of 10/sex/group.

Experimental Design: Rats were given SC-58635, 0, 20, 80 or 400 mg/kg/day via oral gavage once daily for at least 13 weeks; dosing continued through the day prior to terminal sacrifice (Days 93/94). Recovery animals were kept without treatment for an additional 4 weeks. Rats in the satellite PK study group received [^{14}C]SC-58635 on Days 1, 37, 86 and received nonradiolabeled SC-58635 on other days during the study. Blood samples were collected at 0.5, 1, 2, 4, 6, 8, and 24 hr following dosing with radiolabeled SC-58635. Urine and feces were collected at 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hr after radiolabeled dose administration. Plasma, red blood cells, urine, and feces were analyzed for content of radioactivity

Results:

- Radioactivity in Plasma and RBC - The following table shows C_{max} and T_{max} values for radioactivity in plasma and RBC following oral administration of [^{14}C] SC-58635 on Days 1, 37 and 86. Concentrations of radioactivity in the cellular fraction of blood were much higher than in plasma. The C_{max} values were higher in ♀ than ♂.

Sample	PK Parameters	Sampling Day	20 mg/kg		80 mg/kg		400 mg/kg	
			♂	♀	♂	♀	♂	♀
Plasma	C_{max} (μg eq/g)	1	3.45	3.72	5.90	6.81	9.54	11.3
		37	2.06	2.86	3.09	6.53	5.04	6.50
		86	1.84	2.03	2.77	4.12	4.97	7.54
	T_{max} (hr)	1	3	3	6	6	6	6
		37	3	3	4	3	8	3
		86	3	6	4	6	8	6
RBC	C_{max} (μg eq/g)	1	11.7	13.0	16.1	22.4	18.8	23.4
		37	12.5	13.5	16.3	19.7	20.5	22.8
		86	13.4	13.2	17.0	16.2	21.5	25.6
	T_{max} (hr)	1	3	8	4, 6	6	2	6
		37	3	3, 3	3	3	4	6
		86	3	6	8	3	6	6

- Excretion of Radioactivity- The major route of excretion of radioactivity was through the feces. Following administration of 20, 80, and 400 mg/kg of [^{14}C] SC-58635 on Day 1 and Weeks 6 and 13, the percentage of the dosed radioactivity excreted in the feces ranged from 72.1% to 92.2% over the 168-hour collection period with urinary excretion accounting for 1.51% to 9.18%. As the dose increased, the percentage of dosed radioactivity excreted in the feces generally increased. No changes were observed in the excretion pattern following Day 1, Week 6 and Week 13 of the dosing regimen. The following table reveals mean cumulative % radioactive dose in urine, feces, cage rinse and total radioactivity excreted during 0-168 hr period postdose with [^{14}C] SC-58635 on Day 1, Weeks 6 and 13.

	% of Radioactive Dose								
	Dose	Urine		Feces		Cage Rinse		Total	
	mg/kg	♂	♀	♂	♀	♂	♀	♂	♀
Day 1	20	5.48 ± 2.45	7.59 ± 3.70	87.7 ± 3.42	72.1 ± 11.7	5.66 ± 3.69	15.4 ± 11.6	99.2 ± 0.90	95.9 ± 0.05
	80	3.34 ± 0.42	3.66 ± 1.15	81.5 ± 22.5	80.9 ± 8.48	12.2 ± 17.2	10.6 ± 8.2	98.0 ± 4.77	95.4 ± 1.66
	400	2.11 ± 1.83	1.69 ± 0.87	79.7 ± 17.4	87.4 ± 6.02	9.12 ± 12.5	5.25 ± 2.34	91.5 ± 2.88	94.8 ± 3.11
Week 6	20	9.18 ± 3.10	6.70 ± 1.74	88.5 ± 2.01	78.7 ± 12.9	1.59 ± 0.49	9.37 ± 7.40	99.9 ± 1.98	97.3 ± 2.47
	80	4.90 ± 3.67	3.42 ± 0.91	84.8 ± 2.53	83.3 ± 7.87	4.80 ± 4.32	5.35 ± 2.95	95.1 ± 0.31	93.5 ± 5.45
	400	1.51 ± 0.47	1.71 ± 0.21	90.2 ± 1.92	90.5 ± 6.47	1.62 ±2.25	4.05 ± 0.85	93.6 ± 1.74	97.1 ± 5.57
Week 13	20	9.06 ± 5.39	4.74 ± 1.98	82.4 ± 1.80	83.8 ± 3.49	1.79 ± 1.19	3.09 ± 1.97	94.1 ± 3.96	92.5 ± 2.32
	80	2.69 ± 1.34	3.28 ± 0.65	88.5 ± 3.90	85.7 ± 6.20	1.89 ± 2.26	3.34 ± 2.23	93.7 ± 3.61	94.2 ± 1.04
	400	1.93 ± 0.83	1.56 ± 0.96	90.6 ± 6.87	92.2 ± 4.74	3.93 ± 5.12	3.47 ± 2.85	96.5 ± 1.11	97.5 ± 1.17

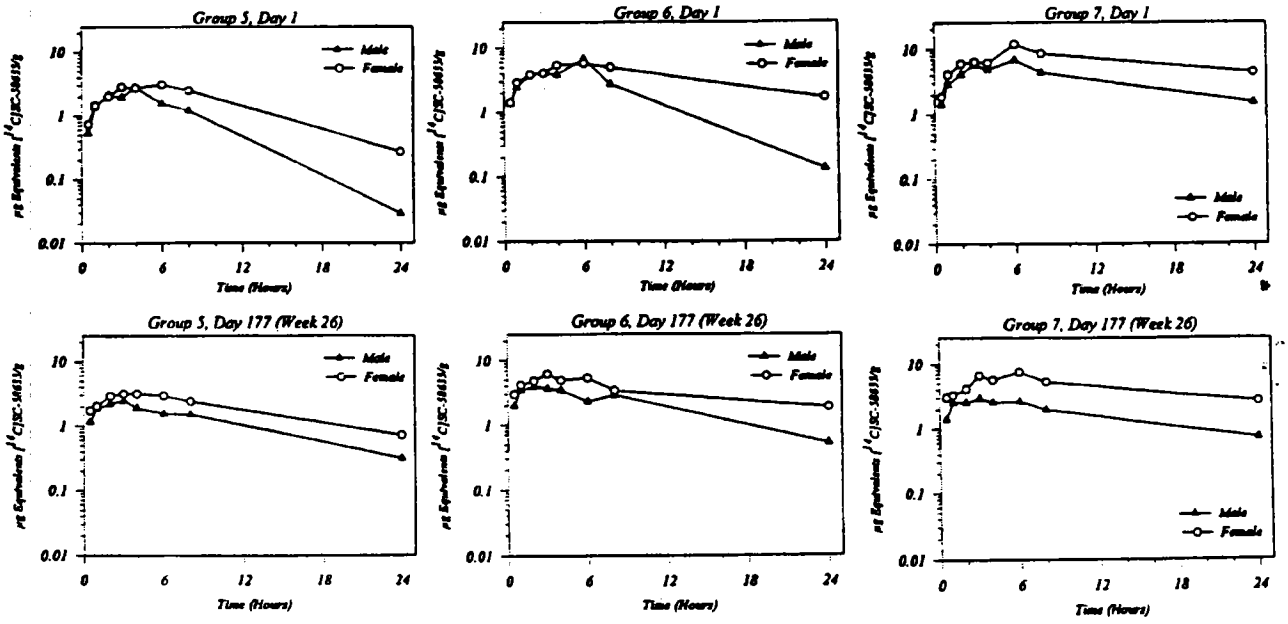
3.4.1.5. 26-Week Repeated Dose Oral Gavage Toxicity Study In Rats With SC-58635, SA4366, Document No.: MRC95C-30-950233; Date: 23-Feb-1996 (Vol. 1.73, p.1-71)

Report Nº: MRC95C-30-950233
Study Nº: SA4366/CHV 700-331 and CHW 6157-192
Study Aim: To evaluate the chronic toxicity of SC-58635 in rats following a daily oral gavage administration for ≥26 weeks.
Compound: SC-58635 (Lot Nº 94K014-A2B), [^{14}C]SC-58635 (Lot Nº GDS4021-68, specific activity 7.68 μCi/mg & Lot Nº 4404-145, specific activity 143 μCi/mg)
Control Vehicle: 0.5% (w/v) methylcellulose and 0.1% Polysorbate 80 in distilled H_2O
Dose & Route: 0, 20, 80, 400 mg/kg/day po by gavage
Animals: rats, Crl:CD®(SD)BR, ~6 weeks of age, weighing 194-268 g for ♂ and 131-192 g for ♀, 25/sex/group for main (15/sex/group) and recovery (10/sex/group) studies, 18/sex/group for satellite PK study.
Study Location:
Compliance with GLP/QAU: Yes
Study Date (In-Life): 03/06/95 - 10/12/95
Study Design: Animals were given SC-58635, 0, 25, 80, or 400 mg/kg/day by oral gavage once daily for at least 26 weeks. Ten rats/sex from groups 1-4 were allowed to have a 4-week recovery period after the last dosing. Animal group designation and dosing levels are shown in the following table. On Days 1 and 177, [^{14}C] SC-58635 was given to Groups 5, 6, and 7 animals. Blood samples were collected at 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, and 24 hr post doing from 3 rats/sex/time point. Urine and fecal samples were collected over 168 hr after dosing with [^{14}C] SC-58635 (Days 1 and 177) in 24 hr intervals. Plasma, red blood cells, urine, and feces were analyzed for content of radioactivity

Main and Recovery[a] Study				Satellite PK Study			
Group	Dose (mg/kg/day)	Nº of Animals		Group	Dose (mg/kg/day)	Nº of Animals	
		♂	♀			♂	♀
1	0 (MC)	25	25	5	20 (Low)	18	18
2	20 (Low)	25	25	6	80 (Mid)	18	18
3	80 (Mid)	25	25	7	400 (High)	18	18
4	400 (High)	25	25	[a]The recovery group comprised of 10/sex/group			

Results:

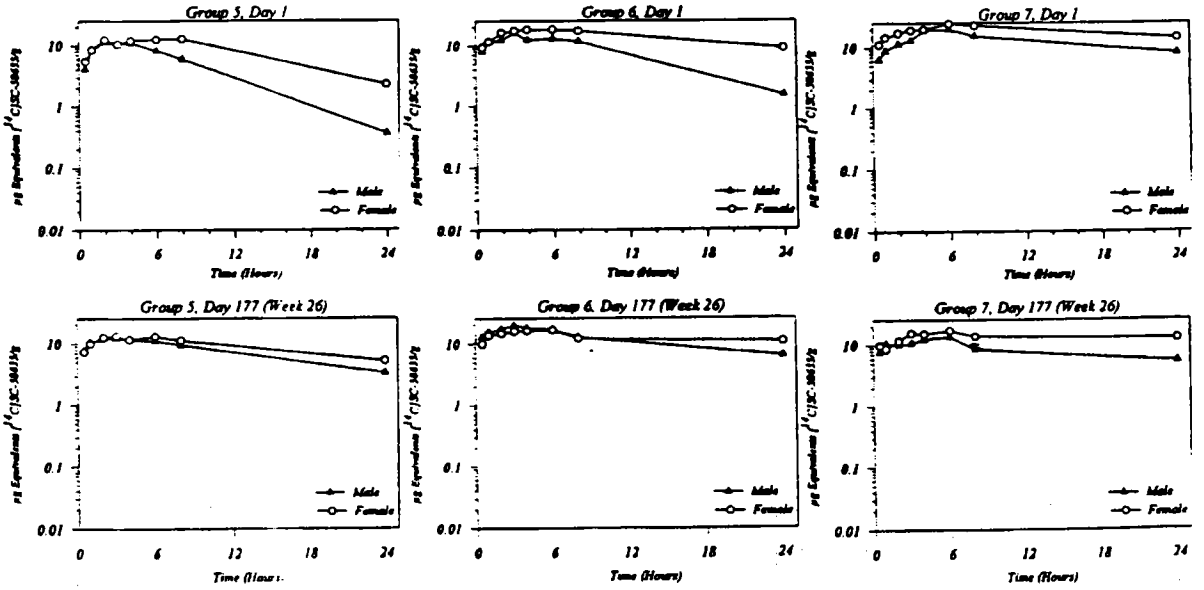
- Radioactivity in Plasma and RBC- Mean concentrations of radioactivity in plasma on Days 1 and 177 for rats receiving 20, 80, and 400 mg/kg/day are shown in the following graphs.



The following table shows C_{max} and T_{max} values for radioactivity in plasma and RBC following oral administration of [^{14}C] SC-58635 on Days 1 and 177.

Sample	PK Parameters	Sampling Day	20 mg/kg		80 mg/kg		400 mg/kg	
			♂	♀	♂	♀	♂	♀
Plasma	C_{max} (μg eq/g)	1	2.79	2.84	6.79	5.73	6.75	11.6
		177	2.46	3.13	3.90	6.15	2.95	7.15
	T_{max} (hr)	1	4	3	6	6	6	6
		177	3	3	2	3	3	6
RBC	C_{max} (μg eq/g)	1	11.2	12.8	16.1	18.2	19.8	24.5
		177	12.1	13.2	19.7	16.3	13.4	17.0
	T_{max} (hr)	1	2	8	3	6	6	6
		177	3	3	3	6	6	6

Mean concentrations of radioactivity in plasma on Days 1 and 177 for rats receiving 20, 80, and 400 mg/kg/day are shown in the following graphs.



- Excretion of Radioactivity in Urine and Feces - The primary radioactivity execration route was via feces. Mean cumulative and total percent radioactivity excreted in feces and urine during 0-168 hr following oral administration of [^{14}C]SC-58635 on Days 1 and 177 are summarized in the following table.

Dose mg/kg	Sampling Day	Feces		Urine		Cage Rinse		Total Excretion	
		♂	♀	♂	♀	♂	♀	♂	♀
20	1	81.7	83.7	3.98	4.91	9.17	4.48	95.3	93.4
	177	85.9	81.0	9.18	8.74	0.32	3.06	95.6	93.4
80	1	88.5	73.5	2.12	4.35	7.69	17.2	98.6	96.2
	177	83.7	83.6	6.11	7.29	2.49	3.34	93.2	94.7
400	1	89.1	86.4	1.74	2.91	5.54	4.18	96.8	94.0
	177	89.8	89.3	1.31	1.20	0.51	0.90	92.0	91.5

3.4.1.6. Effect Of SC-58635 Oral Administration On Liver Microsomal Enzyme Activities And Cytochrome P-450 Content In Male And Female Rats, Document No.: MRC-94S-0088; Date: 16-May-1995 (Vol. 1.73, 72-155)

Report Nº: MRC-94S-0088

Study Aim: (1) To examine the time course of induction by SC-58635 of its own metabolism.
(2) To evaluate the potential effect of SC-58635 on metabolism of concurrently administered drugs by determining its effects on metabolism of several in vitro substrates.

Compound: SC-58635 suspension in 1.5% methylcellulose and 0.1% Tween 80, 20 mg/ml for oral administration; [^{14}C]SC-58635, 100,000 dpm/0.5 µl DMSO for in vitro study

Dose & Route: 200 and 400 mg/kg, po (by gavage)

Animals: 16♂ & 16♀ rats, Crl:CD(SD)BR, 8-12 wk old, 6 and 10/sex/group

Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077 & 800 N. Lindberg, St. Louis, MO 63167

Compliance with GLP/QAU: N/A

Study Design: Animal grouping, dose of administration, and sampling schedule were presented in the following table.

Group	Treatment	Dose (mg/kg)	Dose (Days)	Nº Animals	Sampling Day	
					Blood	Liver
1A	Control	0	4	3/sex	None	5
1B	Control	0	10	3/sex	None	11
2A	SC-58635	200x2	4	3/sex	5	5
2B	SC-58635	200x2	7	3/sex	8	8
2C	SC-58635	200x2	10	4/sex	2, 5, 8, 10, 11	11

Animal received the indicated dose twice per day, at 8 A.M. and 4 P.M. for 4, 7, or 10 days. Selected rats were sacrificed on days 5, 8, and 11. Plasma concentration of SC-58635 were determined for C_{max} at 3 hr post dose on days 2, 4, 8 and 10, and for C_{min} on days 5, 8, and 11 just prior to sacrifice. Liver microsomes were prepared from SC-58635 treated and control rats and analyzed for protein, cytochrome P-450 content and activity using different substrates.

Results: Treatment with SC-58635 at 400 mg/kg for 4, 7, or 10 days did not affect liver weights, liver weight/body weight ratios, or microsomal protein/g liver, but induced a significant increase in cytochrome P-450/mg microsomal protein in male rats.

The microsomal enzyme activities/mg microsomal protein which included ethoxyxoumarin o-deethylase (ECOD), p-nitroanisole o-demethylase (NADO), p-nitrophenol hydroxylase (NPH), pentoxyresorufin o-dealkylase (PROD; Day 10), testosterone 6-β hydroxylase and testosterone 16-β hydroxylase (Day 4 only) were significantly increased by SC-58635 treatment in male rats at both days 4 &10 unless otherwise indicated.

SC-58635 plasma C_{max} dropped ~60% between day 2 and day 10 in both ♂ & ♀ during repeated daily dosing. Male C_{max} appeared to be near steady state by Day 4, while female C_{max} did not reach steady state until Day 8. Mean plasma levels of SC-58635 (C_{max} & C_{min}) during daily oral administration of 400 mg/kg to both ♂ & ♀ rats are summarized in the table listed below.

Group (N)	Day	Time (hr)	SC-58635 Concentration (μg/ml)	
			♂	♀
2C (4)	2	3 (for C_{max})	9.33 ± 1.09	28.2 ± 3.3
	4		5.18 ± 0.24	21.3 ± 5.4
	8		4.15 ± 0.65	12.0 ± 1.7
	10		3.78 ± 0.17	11.1 ± 1.5
2A (3)	5	0 (for C_{min})	1.17 ± 0.26	10.1 ± 1.5
2B (3)	8		2.83 ± 1.53	11.4 ± 1.4
2C (4)	11		0.53 ± 0.05	7.74 ± 1.08

No significant increases in female microsomal enzyme activities/mg microsomal protein were observed on Day 4, but the activities of ECOD, PROD, benzyloxy resorufin o-dealkylase and testosterone 6-β and 16-β hydroxylase were increased significantly on Day 10.

CYP2B but not CYP1A, or CYP2A or CYP3A1 was demonstrated to be increased in both male and female rat microsomes by Day 4 of SC-58635 treatment.

3.4.2. MOUSE/RAT/DOG/RABBIT

3.4.2.1. The Metabolism Of SC-58635 In The Mouse, Rat, Rabbit And The Dog, Document No.: M3096266; Date: 02-Dec-1997 (Vol. 1.73, 156-207)

Report Nº: M3096266

Study Aim: To determine if the glucuronide conjugate of SC-62807 is a urinary metabolite of [^{14}C]SC-58635 in mouse, rat, rabbit or dog. Due to the instability of glucuronide conjugates in alkaline pH 7, following the administration of [^{14}C]SC-58635 to mouse, rat, rabbit and dog, the urine was collected at a pH of 5.0 or below to insure the stabilization of any acyl glucuronides that might be present.

Compound: [^{14}C]SC-58635 ((Lot Nº GDS-4671-84, 141 μCi/mg) and SC-58635 (Lot Nº: 94-031-A74 & 94L-013-A1A) in the polyethylene glycol (PEG) 400:saline (2:1) at a concentration of 5 mg/ml.

Dose & Route: 5 or 10 mg/2 ml/kg iv

Animals: 3♀ Charles River CD-1 mice, weighing 20.1 - 23.2 g
2♂ male rats, weighing 296 - 336 g
1♂ New Zealand White rabbit, weighing 3.6 kg
1♂ pure-bred Beagle dog, weighing 11.3 kg

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

Compliance with GLP/QAU: N/A

Urine Sampling: The urine was collected over 48 hr from the mouse, rat, rabbit and dog by free catch into containers packed in dry ice containing 0.1M sodium acetate buffer, pH 5.0 to stabilize any glucuronide conjugates that may be formed. The urine samples were thawed in an ice bath and 0.1M sodium acetate buffer, pH 5.0, was

added to adjust the pH to approximately 5.0. The following table shows the sampling times and the doses for each species.

Species	Mouse	Rat	Rabbit	Dog
Dose/Route	10 mg/2 ml/kg iv	10 mg/2 ml/kg iv	5 mg/2 ml/kg iv	5 mg/2 ml/kg iv
Time of Urine Collection	0-24 & 24-48 hr	0-24 & 24-48 hr and 0-4, 4-24, and 24-48 hr	0-24 & 24-48 hr	0-4, 4-24, and 24-48 hr

Sample Determination: The distribution of radioactivity in urine from each species dosed was determined The identification of the metabolites in rabbit urine was confirmed

Results: SC-58635 is metabolized through a single pathway in all species examined. The aromatic methyl group of SC-58635 is oxidized first to a hydroxyl methylene group (SC-60613) followed by complete oxidation to the carboxyl moiety (SC-62807).

Mouse - 100% of the radioactivity in the profiles of urine collected in buffer at pH 5.0 was at the same retention time as SC-62807 indicating that SC-62807 was a major urine metabolite.

Rat - Approximately 92.3% and 2.60% of the radioactivity in the profiles of urine collected in buffer at pH 5.0 was at the same retention time as SC-62807 and SC-58635, respectively. These results indicate that SC-62807 was the major urine metabolite of SC-58635 in the rat.

Rabbit -

Dog - the majority of the radioactivity in the profiles of urine collected in buffer at pH 5.0 was at the same retention time as authentic SC-62807, indicating that SC-62807 was the major urine metabolite of SC-58635 in the dog.

distribution of radioactivity in the urine collected after the intravenous administration of [^{14}C]SC-58635 to the mouse, rat, rabbit and dog is enlisted in the following table.

Species (Animal #)	Dose (mg/kg)	Collection Period (Hours)	% Radioactivity in 6-10.5 min	10.5-11.0 min (Tr=SC-62807)	11.0-19.5min	Present at 19.5-20min (Tr=SC-58635)
Mouse #1	12.9	0-24	<1	100	<1	<1
Mouse #2	9.32	0-24	<1	100	<1	<1
Mouse #3	12.2	0-24	<1	100	<1	<1
Rat	10.0	0-24	NA	NA	NA	NA
Rat	10.0	24-48	NA	NA	NA	NA
Rat	10.6	0-4	<1-1.56	92.3	<1	2.60
Rat	10.6	4-24	NA	NA	NA	NA
Rat	10.6	24-48	NA	NA	NA	NA
Dog	5.24	0-4	1.11-3.18	86.1	<1-6.36	1.02
Dog	5.24	4-24	<1-1.63	95.5	1.00-1.58	<1
Dog	5.24	24-48	NA	NA	NA	NA
Rabbit	5.18	0-24	2.69-4.70	92.3	<1	<1
Rabbit	5.18	24-48	NA	NA	NA	NA

NA Not Analyzed

3.4.3. DOG

3.4.3.1. Preparation Of Postmitochondrial Supernatant And Microsomes From Dogs Known To Be Either Slow Or Fast Metabolizers Of SC-58635, Document No.: MRC-95S-0104; Date: 27-Nov-1995 (Vol. 1.73, p. 208-253)

Report Nº: MRC95S-0104
Study Nº: CHW 6127-245
Study Aims: To prepare microsomes and postmitochondrial supernatants from both slow and fast metabolizer dogs and analyze for total protein and P450 content.
Study Site:
Study Date: 4/9/95 - 4/10/95
Study Design: Seven male and eight female purebred beagles previously characterized as fast or slow metabolizers of SC-58635 were sacrificed, and livers and jejunal mucosa scrapings were collected from each animal. Liver microsomes and postmitochondrial supernatants were prepared. The liver microsomes were analyzed for total P450 content and total protein. The postmitochondrial supernatant was analyzed for total protein.

Results: Approximately one quarter of each liver was used for preparation of postmitochondrial supernatant and one quarter for microsomes. The protein yields of postmitochondrial supernatants ranged from 91.4 to 116 mg/g of liver and were similar regardless of the rate of clearance and sex. The protein yields of microsomes ranged of liver in males of liver in females. Similar yields were obtained from dogs with either fast or slow clearance rate groups within the same sex. The total microsomal P450 content ranged protein and was similar for both clearance rate groups and sexes. Results from this study were similar to those in Report Nº MRC-95C-100-950295

3.4.3.2. The *In Vitro* Metabolism of [^{14}C] SC-58635 In Rat, Human, Dog Liver S9 (A Pilot Study), Document No.: MRC-94S-0168; Date: 09-Jan-1995 (Vol. 1.73, p. 254-283)

Report Nº: MRC-94S-0168

Study Aim: To evaluate the metabolism rate of [^{14}C]SC-58635 in vitro and the metabolic profile of SC-58635 in rat, dog and human liver S9

Compound: [^{14}C]SC-58635, 100,000 dpm/0.5 :l DMSO

Study Location: G.D. Searle & Co, 4901 Searle Parkway, Skokie, IL 60077 & 800 N. Lindberg, St. Louis, MO 63167

Compliance with GLP/QAU: N/A

Study Design: Liver S9 fractions of ♂ & ♀ rats, dogs and humans were incubated with various concentrations of [^{14}C]SC-58635 and an NADPH-generating system with or without UDP-glucuronic acid for the appropriate times. Reactions were terminated by the addition of formic acid to the final concentration of 2.1%. Sample were then subjected to the analysis.

Results:

K_m and V_{max} values for [^{14}C]SC-58635 metabolism in rat, dog and human liver S9 were present in the following table.

Species	K_m (µg/ml)		V_{max} (ng/min/mg protein)	
	♂	♀	♂	♀
Rat	105	5.04	581	12.0
Dog	3.61	2.00	19.4	4.20
Human	17.2	3.98	56.0	2.60

The data showed that male rat liver metabolized [^{14}C]SC-58635 greater than female rats. There was a tremendous variation (7x) in the metabolic rate of [^{14}C]SC-58635 in different human liver S9 preparations (N=7). The liver S9 preparation from one human donor did not show any metabolic activity for [^{14}C]SC-58635.

3.4.3.3. *In Vitro* Metabolism Of SC-58635 By Dog Liver Microsomes And Cytochrome P450, Document No.: M3095157; Date: 08-Jan-1998 (V0l. 1.73, p. 284-319)

Report Nº: M3095157

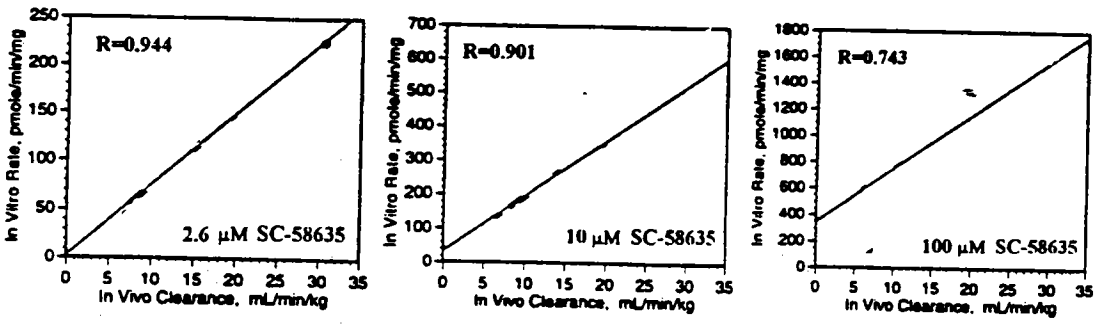
Study Aims: To establish that the slow and fast phenotypes correlate with hepatic P450 mediated metabolism and to determine which enzymes are involved.

Compound: SC-58635 and [^{14}C]SC-58635

Specimens: Liver microsomes were isolated from 10 beagle dogs known to be either fast or slow metabolizers of SC-58635.

GLP/QAC Compliance: N/A

Results: The *in vitro* metabolism of SC-58635 was investigated using liver microsomes isolated from two distinct populations of beagles that were either slow or fast elimination of SC-58635 *in vivo*. Hepatic microsomes from fast SC-58635 clearance dogs metabolized this drug at a higher rate than microsomes from slow clearance dogs. Correlation analysis of *in vitro* metabolism rates with in vivo clearance rates (N=20 dogs) showed that correlation coefficients (r) were of 0.944, 0.901 and 0.743 at in vitro SC-58635 substrate concentrations of 2.6, 10 and 100 µM (1.0. 3.8 and 38 µg/ml), respectively as shown in below figures.



3.4.3.4. Analysis Of Plasma, Urine And Fecal Samples From Dogs Dosed With [^{14}C]SC-58635 During A 4-Week Oral Toxicity Study Of SC-58635 In The Dog (SA4260), Document No.: MRC-94S-0144; Date: 29-Nov-1994 (V0l. 1.74, p. 1-125)

Study Nº:	SA4260
Report Nº:	PSA-94S-0144
Study Aim:	To determine absorption of the test article, the relationship of plasma concentrations of SC-58635 with dosage and duration of dosing, the metabolism of [^{14}C]SC-58635 and evidence for sex-related differences in any pharmacokinetic parameters.
Compound:	SC-58553 (Lot Nº 94K014-A1B) and [^{14}C]SC-58635 (38.4 μCi/mg) in gelatin capsule
Dose & Route:	20, 25, 50, 100 and 250 mg/kg/day in gelatin capsule po
Animals:	♂ & ♀ beagle dogs, 9 - 11 months old, weighing 9.5 to 14.3 kg, 4 or 8/sex/group
Study Location:	G.D. Searle, Skokie, IL
Compliance with GLP/QAU:	No

Study Design: SC-58635 was administered orally in a gelatin capsule to dogs at a dose of 25 mg SC-58635/kg/day for 28 days and at a dose of 100 mg SC-58635 /kg/day for 15 days (Groups 6 and 7). [^{14}C]SC-58635 was administered on Days 1 and 28 to the dogs @ 25 mg/kg (Group 6) and on Days 1 and 15 to the dogs @ 100 mg/kg (Group 7). The dogs were dosed with unlabelled SC-58635 on the intervening days. Blood was collected at 0.5, 1, 1.5, 2, 2.5, 3.5, 5, 7, and 24 hr on Days 1 and 15 from dogs @ 100 mg/kg group or on Day 28 from dogs @ 25 mg/kg. Urine and feces were collected over a 7 days period (-18-0, 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hr) following dosing with [^{14}C]SC-58635. Urine was collected by free-catch in containers surrounded by dry ice and feces were collected into Stomacher bags. Whole blood, plasma, red blood cells, urine and feces were analyzed for ^{14}C by a

method. The concentrations of SC-58635 in plasma were determined using a validated procedure. The metabolic profiles of selected plasma, urine and fecal samples were determined using a procedure.

Group		Dose (mg/kg)	Nº Animals /Sex/Group	Nº Animals/Sex Sacrificed	
				Day 17	Days 29-31
Toxicology Study	1	0	4 (4)*	-	8
	2	25	4	-	4
	3	50	4	-	4
	4	100	4 (4)*	4	4
	5	250	4 (4)*	4	4
PK Study**	6	25	2		
	7	100	2		

* The number in the parenthesis indicating the number of animals were used in the 2 week reversal phase study.
** Animals in group 6 & 7 were treated with [^{14}C]SC-58635.

Results: One female dog in Group 7 (100 mg/kg) was moribund and sacrificed on Day 12. This animal was not given a second dose of radiolabeled SC-58635 and a single 0 hour blood sample was collected for analysis for SC-58635.

- ^{14}C Concentrations in Plasma, Red Blood Cells and Whole Blood PK Parameters - SC-58635 was absorbed and systemically available. The exposures to SC-58635 increased with dose. Accumulation of SC-58635 might have occurred as higher C_{max} and AUC values were noted on Day 28. The mean Cmax and AUC values for SC-58635 were higher in female dogs than male dogs.

SC-58635 Concentration (μg eq/ ml)								
Time (hr)	25 mg/ kg				100 mg/ kg			
	Day 1		Day 28		Day 1		Day 15	
	♂	♀	♂	♀	♂	♀	♂	♀
PLASMA								
0.5	0.761	0.960	0.853	0.306	0.841	0.339	0.430	1.31
1	1.33	1.59	1.05	0.763	2.05	2.05	1.36	2.19
1.5	1.42	1.66	1.27	1.30	3.30	3.28	2.31	3.82
2	1.23	1.40	1.38	1.49	3.64	4.41	3.47	5.70
2.5	1.06	1.31	1.29	2.02	5.18	6.47	3.23	6.14
3.5	0.915	1.10	1.10	2.80	6.64	14.1	3.17	5.25
5	0.780	0.924	1.03	3.50	8.21	21.5	3.06	5.72
7	0.587	0.864	0.818	3.29	8.87	24.7	2.76	5.42
24	0.250	0.224	0.344	1.19	9.93	17.1	1.55	2.89
RBC								
0.5	1.43	2.16	1.37	0.625	1.40	0.603	0.564	1.40
1	2.49	3.30	1.61	1.34	3.91	3.32	1.38	1.88
1.5	2.13	3.25	1.65	1.78	4.39	4.62	2.50	2.66
2	2.03	3.07	1.88	2.25	5.58	5.66	3.53	4.04
2.5	1.96	3.01	1.87	2.68	7.33	8.44	3.04	4.34
3.5	1.85	2.47	1.78	3.44	8.30	12.5	3.22	3.95
5	1.40	2.07	1.49	3.69	9.48	18.5	3.38	4.19
7	1.01	1.57	1.39	3.41	10.3	19.7	3.32	3.99
24	0.466	0.402	0.508	1.51	8.24	15.0	2.46	2.84
WHOLE BLOOD								
0.5	1.23	1.58	1.16	0.474	1.34	0.733	0.387	0.993
1	2.01	2.38	1.30	1.06	3.10	2.56	1.13	1.78
1.5	2.02	2.42	1.46	1.56	4.03	4.33	2.13	2.96
2	1.69	2.28	1.69	1.97	5.00	5.26	3.25	4.51
2.5	1.61	2.15	1.65	3.25	6.25	7.39	3.17	5.10
3.5	1.73	1.79	-	-	8.30	13.9	3.19	4.59
5	1.13	1.53	1.27	3.75	8.81	22.0	2.87	4.66
7	1.71	1.19	1.20	3.31	9.48	22.5	2.79	4.46
24	0.433	0.324	0.438	1.34	8.81	16.3	1.87	2.79

PK PARAMETERS								
T_{max} (hr)	1.5	1.5	2	5	24	7	2	2.5
C_{max} (μg eq/ml)	1.42	1.66	1.38	3.50	9.93	24.7	3.47	6.14
AUC_{0-24} (μg eq•hr/ml)	13.2	16.7	16.9	54.4	200	445	54.8	103

- Plasma SC-58635 PK Parameters -

PK Parameters	25 mg/kg				100 mg/kg			
	Day 1		Day 28		Day1		Day 15	
	♂	♀	♂	♀	♂	♀	♂	♀
Tmax (hr)	1.5	1.25	2	3.25	13.75	6	1.5	2
Cmax (μg/ml)	1.24	1.525	1.835	3.167	9.335	20.65	7.305	13.5
AUC_{0-24} (μg•hr/ml)	10.57	12.33	23.401	42.049	160.812	374.449	113.788	236.855

- Metabolic Profiles in Plasma - analysis showed that SC-58635 was the major (97.56 - 100%) circulating compound for both ♂ and ♀ @ 25 or 100 mg/kg on Days 1, 15 or 28 of dosing.
- Metabolite Profiles in Feces -

Metabolites (%)	Mean (± SEM) % Dose Excreted in Feces							
	25 mg/kg				100 mg/kg			
	Day 1		Day 28		Day 1		Day 15	
	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr	0-24 hr	24-48 hr
SC-58635	72.6 ± 2.0	0.54 ± 0.45	58.0 ± 14.8	0.86 ± 0.43	39.1 ± 14.8	14.7 ± 14.5	60.1 ± 5.7	11.3 ± 6.92
SC-60613	NP	NP	NP	NP	NP	NP	NP	NP
SC-62807	13.65 ± 5.2	5.94 ± 0.33	17.8 ± 6.7	18.9 ± 7.3	11.7 ± 2.9	32.4 ± 14.5	4.19 ± 2.21	8.28 ± 7.3

NP = No peak present in profile in the SC-60613 position.

- Metabolic Profiles in Urine -

Metabolites (%)	Mean (± SEM) % Dose Excreted in Urine (0-24 hr)			
	25 mg/kg		100 mg/kg	
	Day 1	Day 28	Day 1	Day 15
SC-58635	0.00482 ± 0.00280	0.00157 ± 0.00157	0.00196 ± 0.00196	0.0122 ± 0.0122
SC-60613	NP	NP	NP	NP
SC-62807	0.416 ± 0.114	0.662 ± 0.227	0.812 ± 0.313	0.635 ± 0.398
M1[a]	0.0142 ± 0.00442	0.0321 ± 0.0156	0.0383 ± 0.0125	0.0374 ± 0.0217

NP = No peak present in profile in the SC-60613 position.

[a] Radioactivity eluted as a position between [14C]SC-58635 and [14C]SC-62807.

- Total ^{14}C in Urinary and Fecal Excretion - The majority (greater 90%) of the recovered dose was excreted in the feces as [^{14}C]SC-58635 and [^{14}C]SC-62807 as shown in the following table.

Sample	Mean Cumulated (0-168 hr) % Radioactive Dose in Feces and Urine							
	25 mg/kg				100 mg/kg			
	Day 1		Day 28		Day 1		Day 15	
	♂	♀	♂	♀	♂	♀	♂	♀
Urine	0.523	0.979	0.525	2.71	2.20	5.63	1.38	2.82
Feces	85.5	103.5	99.7	101	116	102	85.9	97.3
Total	86.1	104	100	104	119	108	87	100

3.4.3.5. Metabolism Support For A 13-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4324, Document No.: MRC95S-30-950263; Date: 27-Nov-1995 (Vol. 1.74, p. 126-193)

Report Nº: MRC95S-30-950263

Study Nº: HWI 6127-233/SA4324

Study Aim: To determine PK, metabolism and excretion of SC-58635 during a 13-week oral capsule toxicity study in dogs.

Compound: SC-58635 (Lot Nº 94K014-A2B) and [^{14}C]SC-58635 (Lot Nº GDS 4404-164, 2.13 μCi/mg & GDS 4404-165, 1.07 μCi/mg) in capsule

Vehicle: Empty gelatin capsule
Dosage: 0, 15, 25, and 35 mg/kg/day po for ≥13 weeks
Animals: 30♂ & 30♀ beagle dogs, ~7-9 months old. Weighing 8.2-12.2 kg

Main and Recovery[a] Study				Satellite PK Study			
Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	N[a] of Animals	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	N[a] of Animals
1[a]	0	0	6/sex[c]	6[a,b]	7.5	15	3/sex
2[a]	7.5	15	4/sex	7[a,b]	12.5	25	3/sex
3[a]	12.5	25	4/sex	[a]Animals in Group 1-4, 6 and 7 were dosed twice daily at 12-hr intervals for ≥13 weeks.			
4[a]	17.5	35	6/sex[c]	[b]Two animals/sex in group 1, 4, and 5 had a recovery phase for 28 days after a 13-week treatment.			
5	25	25	4/sex[c]	[c]Animals in group 6 and 7 received [^{14}C]SC-58635 at the first daily dose on day 1 and once during weeks 6 and 13.			

Study Location: (In-Life) and G.D. Searle, Skokie, IL (PK analysis).
Study Date: March 10, 1995 - July 10, 1995
Compliance with GLP/QAU: Yes
Study Design: Three dogs /sex/group were administered SC-58635 at a dose level of 7.5 or 12.5 mg/kg bid for 13 weeks. A single dose of [^{14}C]SC-58635 was administered on Days 1, 39 (Week 6) and 87 (Week 13) and nonradiolabeled SC-58635 was given in the intervening days. Blood samples were collected at 30 min, 1, 2, 3, 5, 7, 12, 13, 14, 15, 18, and 24 hr post dose on Days 1, 39 and 88 for radioactivity determination. Urine and feces were collected at 24 hour intervals through 168 hours after each radiolabeled dose. Post-mitochondrial supernatant fractions and microsomes were prepared from the liver samples from selected animals in Group 1 (control), Group 2 (15 mg/kg/day), Group 3 (25 mg/kg/day), Group 4 (35 mg/kg/day) and Group 5 (25 mg/kg/day). Whole blood, plasma, red blood cells, urine and feces were analyzed for ^{14}C by a method. The concentrations of SC-58635 in plasma were determined using a validated HPLC procedure. The metabolic profiles of selected plasma, urine and fecal samples were determined using a procedure.

Results: In this report, the results of the profiles of plasma, urine and fecal samples and in vitro incubations of liver microsomes were presented.
The majority of the radioactivity circulating in plasma was [^{14}C]SC-58635 with values ranging from 62% to 100%. [^{14}C]SC-60613, the hydroxylated metabolite of [^{14}C]SC-58635, also circulated in plasma, but at lower levels (0-28.7%). The metabolic profile of SC-58635 in plasma differed in dogs characterized as having fast and slow SC-58635 clearances. Higher plasma levels of SC-60613 were found in fast SC-58635 clearance dogs than dogs with a slow SC-58635 clearance. The majority of the urine (0-48 hr) radioactivity was excreted as SC-62807. SC-58635 was also excreted in urine (0-48 hours), but at low levels on Days 1 and 39. No parent compound was excreted in urine on Day 88. There were no differences between sex and dose in the urine excretion profile.
The majority of the radioactivity excreted in the feces was [^{14}C]SC-58635 and [^{14}C]SC-62807. There were no differences between sex, dose or duration of dosing in the fecal excretion profile. The following table shows mean (±SEM) percent of dose excreted in feces (0-72 hours) as SC-58635 and SC-62807 during Weeks 1, 6 and 13 in ♂ and ♀ dogs or in dogs characterized as having a fast or slow SC-58635 clearance.

Week	% of dose excreted as SC-58635				% of dose excreted as SC SC-62807			
	7.5 mg/kg bid		12.5 mg/kg bid		7.5 mg/kg bid		12.5 mg/kg bid	
	♂	♀	♂	♀	♂	♀	♂	♀
1	75.6 ± 9.9	87.1 ± 3.8	77.4 ± 4.6	62.6 ± 13.6	19.4 ± 9.5	17.1 ± 10.8	11.5 ± 0.7	27.9 ± 13.9
6	65.6 ± 12.0	69.7 ± 12.5	75.8 ± 2 .7	68.4 ± 9.5	24.0 ± 9.6	22. 3 ± 12.2	14.6 ± 2.8	25.6 ± 17.2
13	78.2 ± 11.5	70.5 ± 7.8	77.3 ± 12.7	63 .7 ± 10.4	15.6 ± 10.4	19.9 ± 7.6	14.3 ± 11.1	26.1 ± 9. 9
	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow
1	78.0 ± 11.5	84 .7 ± 1.63	82.9 ± 1.0	57.1 ± 9.7	26.7 ± 10.8	9.78 ± 4.4	10.3 ± 1.5	29 .2 ± 13.0
6	68.9 ± 13.2	66.4 ± 11.2	75.5 ± 2.6	68.8 ± 9 .7	20.9 ± 10.8	25.4 ± 10.9	13.7 ± 3.4	26.5 ± 16.8
13	70 .7 ± 7.7	78.0 ± 11.7	68.9 ± 12.0	72.0 ± 13.0	20.6 ± 8.2	14.9 ± 9.7	21.4 ± 10.5	19.1 ± 12.0

Mean (±SEM) percent of SC-58635 and SC-60613 in dog liver microsomes from ♂ and ♀ dogs or from dogs characterized as having fast or slow SC-58635 clearance incubated with [^{14}C]SC-58635 are tabulated as follows. The percentage of [^{14}C]SC-58635 converted to [^{14}C]SC-60613 was greater in liver microsomes from dogs characterized as having a fast SC-58635 clearance than in liver microsomes from dogs characterized as having a slow SC-58635 clearance.

Dose (mg/kg/day)	% SC SC-62813				% SC-58635			
	♂	♀	Fast	Slow	♂	♀	Fast	Slow
Control	14.6 ± 4.4	14.0 ± 1.4	16.1 ± 2.5	9.00	71.3 ± 6.0	78.1 ± 1.7	73.7 ± 4.0	77.7
15	15.5 ± 5.3	14.8 ± 4.6	22.4 ± 3.7	7.88 ± 0.62	77.9 ± 5.7	84.5 ± 4.7	73.7 ± 4.3	88.7 ± 2.1
30	19.7 ± 6.7	10.8 ± 1.2	22.1 ± 5.3	8.45 ± 0.28	79.6 ± 6.7	88.9 ± 1.2	77.4 ± 5.4	91.2 ± 0.3

3.4.3.6. Metabolism Support For A 52-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4425, Document No.: M3097112; Date: 17-Jun-1997 (Vol. 1.74, p. 194-225)

Study Nº: CHV 700-338/SA4425
Report Nº: M3097112
Study Aim: To determine the metabolic profiles in plasma, urine and feces.
Compound: SC-58635 (Lot Nº 94K014-A2B); [^{14}C]SC-58635 (Lot Nº GDS 4671-90, 2.08 μCi/mg)
Vehicle: Empty gelatin capsule
Dosage: 0, 15, 25, and 35 mg/kg/day po for 52 weeks
Animals: 56 & 56 beagle dogs, ~7 months old, weighing 6.6-10.4 kg for the ♂ and 4.8-9.3 kg for the ♀.

Main and Recovery Study				Satellite PK Study			
Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals/Sex	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals/Sex
1	0	0	12	6	7.5	15	4
2	7.5	15	8	7	17.5	35	4
3	12.5	25	8	4/sex from Groups 1-5 were sacrificed at Week 26.			
4	17.5	35	12	Dogs in Groups 1-4 & 6-7 received SC-58635 2x/day.			
5	25.0	25	8	Dogs in Groups 6 & 7 received [^{14}C]SC-58635 as 1st daily dose on Day1 and Weeks 26 and 52.			

Study Location: G. D. Searle, Skokie, IL for metabolic profile determination.
Compliance with GLP/QAU: Yes
Experimental Design:
Dogs were given SC-58635, 0, 7.5x2, 12.5x2, 17.5x2 or 25x1 mg/kg/day in gelatin capsule orally gavage for at least 52 weeks; dosing continued through the day before terminal sacrifice (Weeks 52). Recovery animals were kept without treatment for an additional 4 weeks. Dogs in the companion PK study group received [^{14}C]SC-58635 on Day 1, and Weeks 26 (Day 176) & 52 (Day