358) and received nonradiolabeled SC-58635 on other days during the study. Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 7, 12, 13, 14, 15, 18 and 24 hr following the ingestion of radiolabeled [^{14}C]SC-58635. Urine and fecal samples were collected for 168 hr after each radiolabeled dose approximate 24-hr intervals. Necropsies were performed on all animals at the end of the study. The metabolic profiles of selected plasma, urine and fecal samples were determined using a procedure.

Results: This report summarized the metabolic profile data from plasma, urine, and feces. The majority of the radioactivity circulating in plasma samples collected 4 and 18 hours post radiolabel dose administration on Days 1, 176 and 358 was parent drug. The hydroxyl, [^{14}C]SC-60613, and carboxyl, [^{14}C]SC-62807, metabolites of [^{14}C]SC-58635, also circulated in plasma at lower levels. Group 7 dogs with a fast SC-58635 clearance had ≥75% of SC-60613 in the circulation at Week 52. The following table presents the percent of SC-58635, SC-62807 and SC-60613 in profiles of pooled plasma samples.

Group	Week	Time hr	% SC-58635				% SC-60613				% SC-62807			
			slow		fast		slow		fast		slow		fast	
			♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
6	1	4	87.2	100 d	98.5	a	12.8	b, d	1.50	a	b	b, d	b	a
7	1	4	87.1	100 c	69.0 c	68.0	12.9	b, c	31.0 c	28.8	b	b, c	b, c	3.21
6	1	18	100 d	100 d	95.6	a	b, d	b, d	4.39	a	b, d	b, d	b	a
7	1	18	50.7 d	a	100 d	a	49.3 d	a	b, d	a	b, d	a	b, d	a
6	26	4	61.0 d	98.1 d	100 d	53.8 d	b, d	1.94 d	b, d	40.0 d	b, d	b, d	b, d	6.15 d
7	26	4	78.3 c	100c	100 d	65.6 d	21.7 c	b, c	b, d	34.4 d	b, c	b, c	b, d	b, d
6	26	18	91.0	100	100 d	100 d	9.03	b, d	b, d	b, d	b	b, d	b, d	b, d
7	26	18	93.4	100 d	100 c	a	6.56	b, d	b, c	a	b	b, d	b, c	a
6	52	4	100 d	a	a	75.0 d	b, d	a	a	25.0 d	b, d	a	a	b, d
7	52	4	100 c	78.0	86.8 c	74.5	b, c	14.4	13.2 c	16.7	b, c	7.68	b, c	8.79
6	52	18	74.2	a	a	78.1	7.59	a	a	4.14	15.1	a	a	17.8
7	52	18	48.2	62.1	12.2	23.2	46.0	36.7	83.6	76.8	2.20	b	1.31	b

[a] Plasma samples with radioactivity levels less than 1000 DPM/ml were not analyzed.
[b] No peak detected.

Due to < 2% of the dose was excreted in urine from 0 - 168 hours, urine samples were not profiled by The radioactivity excreted in the feces was mostly SC-58635 and SC-62807 with the mean percent of dose excreted 0 - 72 hr post-dose ranging respectively. The % of dose excreted in pooled fecal homogenates (0-72 hr) as SC-58635 and SC-62807 on Weeks 1, 26 and 52 in dogs characterized as having a fast or slow SC-58635 clearance are shown in the following table.

Group	Week	% of dose excreted as SC-58635				% of dose excreted as SC-62807			
		Fast SC-58635 Clearance		Slow SC-58635 Clearance		Fast SC-58635 Clearance		Slow SC-58635 Clearance	
		♂	♀	♂	♀	♂	♀	♂	♀
6	1	64.4	27.9	46.3	24.6	22.4	59.0	38.1	62.8
7	1	43.5	41.7	72.9	45.2	45.9	131	15.8	45.7
6	26	71.2	81.1	43.1	83.1	18.3	9.95	41.9	8.00
7	26	68.4	55.8	42.9	84.9	14.4	7.19	38.9	5.85
6	52	82.3	73.6	64.4	79.6	5.84	15.1	22.8	11.4
7	52	69.4	38.5	67.4	69.8	20.5	46.6	17.8	17.0

3.4.4. *HUMAN IN VITRO*

3.4.4.1. *In Vitro* Metabolism Of [^{14}C]Celecoxib ([^{14}C]SC-58635) By Human Liver Microsomes And Cytochrome P450, Document No.: M3095130; Date: 26-Feb-1998 (Vol. 1.74, p. 226-257)

The *in vitro* metabolism of [^{14}C]Celecoxib was Investigated using human liver microsomes and cDNA-expressed human cytochrome P450 enzymes.

Results:

- The major metabolites, SC-60613 and SC-62807, of celecoxib generated by human liver microsomes were similar to the major unconjugated metabolites found *in vivo*. The apparent K_m ($K_{m(app)}$) for celecoxib metabolism by a pool of human liver microsomes was 49.3 μM (~18.8 μg/ml).
- Human recombinant CYP2C9, CYP2C19, and CYP3A4 but not CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 and CYP3A5 were able to metabolize [^{14}C]celecoxib to [^{14}C]SC-60613 in vitro.

- In addition, sulfaphenazole, a potent and specific CYP2C9 inhibitor, inhibited both [^{14}C]celecoxib and tolbutamide to the same extent (80-90%) in a series of individual human microsome samples.

Therefore, human recombinant CYP2C9, CYP3A4, and CYP2C19 were capable of metabolizing [^{14}C]celecoxib. CYP2C9 was found to be most important in human metabolism of celecoxib based on correlation analysis using a series of characterized human microsome samples, and by the effect of isoform-specific inhibitors of P450 metabolism *in vitro*.

3.4.4.2. *In Vitro* Inhibition Of Cytochrome P450 Marker Activities In Human Liver Microsomes By Celecoxib (SC-58635): Determination Of Potential For Drug-Drug Interaction, Document No.: M3097243; Date: 13-Feb-1998 (Vol. 1.74, p. 258-301)

This study was to examine the ability of SC58635 to inhibit cytochrome P450 (CYP) isoform specific catalytic activities associated with CYP2C9, CYP2C19, CYP2D6 and CYP3A4. *In vitro* interactions were conducted by incubating marker substrates with human liver microsomes in the presence of SC58635 or CYP isoform-selective chemical inhibitors to furnish initial predictive information on the potential for drug-drug interactions.

Results: The following table shows the inhibitory effects of celecoxib (SC-58635) and selective CYP inhibitors on the CYP isoenzyme activities expressed as K_i values.

Based on the data presented, celecoxib was not a potent *in vitro* inhibitor of CYP2C9, CYP2C19 or CYP3A4, and had little effect on the metabolism of substrates mediated by these cytochrome P450s.

3.4.4.3. In Vitro Metabolism Of Celecoxib By Human Liver Microsomes: Determination Of Potential For Pharmacokinetic Interactions Between Celecoxib And Glyburide, Document No.: M3096335, Date: 27-Feb-1998 (Vol. 1.74, p. 302-336)

In vitro metabolism of Celecoxib (0.3 - 10 μg/ml) and glyburide (0.025 - 1.25 μg/ml) by human liver microsomes was determined. Glyburide metabolism by human recombinant CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and the effect of celecoxib on this metabolism, was also determined.

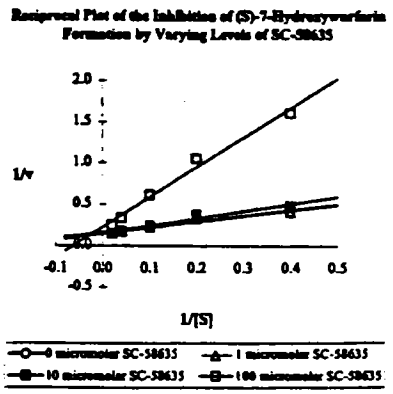
Results:

- At concentrations of 0.025-1.25 μg/ml, the rate of glyburide metabolism by human liver microsomes was approximately linear, indicating the human microsomal apparent K_m ($K_{m(app)}$) for glyburide was > 1.25 μg/ml.
- At the highest concentration, 10 μg/ml, celecoxib inhibited glyburide metabolism by 24%, indicating that celecoxib was a weak noncompetitive inhibitor of glyburide metabolism. Glyburide was readily metabolized by human recombinant CYP3A4, CYP2C19, but not by CYP2C9 or CYP2D6. Metabolism of glyburide by recombinant human CYP3A4 in Sf9 microsomes was inhibited by celecoxib.
- Glyburide (0.025-1.25 μg/ml) had little or no effect on human microsomal metabolism of celecoxib (0.3 - 10 μg/ml).The apparent K_m for celecoxib metabolism by the human liver microsomes was 7.29 μg/ml (19.1 μM).

3.4.4.4. In Vitro Drug-Drug Interaction Of SC-58635 And Warfarin At
Document No.: M2097288; Date: 18-Sep-1997 (Vol. 1.74, p. 337-357)

Report Nº:	M2097288
Study Aims:	To identify potential clinically significant drug-drug interactions of SC-58635 with warfarin using pooled human microsomes.
Compound:	(S)-Warfarin, 2.5, 5, 10, 25, and 50 μM; SC 58635, 0, 1.0, 10, and 100 μM.
Study Site:	
GLP/AUC Compliance:	Yes

Study Design: The metabolism of SC-58635 was shown to be mediated in part by CYP2C9 (see 3.4.4.1: Report Nº M3095130), which metabolizes warfarin to 7-hydroxywarfarin. Warfarin, at levels of 2.5, 5, 10, 25, and 50 μM, was incubated with pooled human microsomes (0.5-1.0 mg protein) in the presence of SC-58635, 0, 1.0, 10, and 100 μM. Both the depletion of racemic warfarin and the formation of (S)-7-hydroxywarfarin *in vitro* were measured. Warfarin and 7-hydroxywarfarin in *in vitro* buffer were extracted and analyzed by



Results: Increasing concentrations of SC-58635 had increasing effect on the disappearance of warfarin and formation of 7-hydroywarfarin with an apparent K_i value of 21.6 μM as illustrated in the figure.

3.5. EXCRETION PATTERN

3.5.1. DOG

3.5.1.1. Evaluation Of The Total 14-Carbon Analyses And Liver Microsomal And Postmitochondrial Supernatant Preparation In A 13-Week Capsule Toxicity Study With SC-58635 In Dogs (SA4324), Document No.: MRC95C-30-950253; Date: 27-Nov-1995 (Vol. 1.75, p. 1-130)

Study Nº: HWI 6127-233/SA4324
Study Aim: To obtain information on the absorption and excretion of the radiolabeled test material, determine the relationship of plasma and erythrocyte concentrations of the radiolabeled test material with dosage and duration of dosing, and evaluate evidence for sex-related differences in the absorption and elimination data.
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 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)	m of Animals/Sex	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals
1[a]	0	0	6[c]	6[a,b]	7.5	15	3
2[a]	7.5	15	4	7[a,b]	12.5	25	3
3[a]	12.5	25	4	[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[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[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:
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. Microsomes and postmitochondrial supernatants were prepared from liver samples from selected animals in Groups 1-5 and analyzed to determine total protein concentrations and cytochrome P450 enzyme content.

Results: This report contained the results of the radioanalytical portion of this study, liver microsome and postmitochondrial supernatant preparation, results of microsomal analysis for total protein and cytochrome P450 enzyme concentrations, and analysis of the postmitochondrial supernatant for total protein concentration. Following oral administration of [^{14}C]SC-58635 to male and female dogs at dose levels of 7.5 and 12.5 mg/kg, individual plasma and erythrocyte total radioactivity concentrations were highly variable which could be attributed to polymorphism in the metabolism of SC-58635. Double peak concentrations were observed in plasma and erythrocyte total radioactivity concentrations-time profiles. The first peak occurred between 1 and 5 hours, and the second peak occurred between 12 and 24 hours. Erythrocyte concentrations were ~2x of the plasma concentrations, an indicative of high partitioning into erythrocytes. The following table shows mean (±SD) C_{max} , T_{max}, and AUC_{0-t} radioactivity in plasma and RBC on Day 1 and during Weeks 6 and 13 after a single oral dose of [^{14}C]SC-58635. C_{max} values appeared to be higher in females; this difference might be as the result of differences in the rate of elimination by fast and slow metabolizers.

	Dose	PK Parameters	Day 1		Week 6		Week 13	
	mg/kg		♂	♀	♂	♀	♂	♀
Plasma	7.5	C_{max} (μg eq/ml)	0.370 ± 0.180	0.226 ± 0.099	0.331 ± 0.188	0.311 ± 0.293	0.248 ± 0.118	0.338 ± 0.319
		T_{max} (hr)	5.7 ± 5.5	12.7 ± 9.2	9.7 ± 6.7	6.0 ± 6.1	5.7 ± 6.4	5.7 ± 6.4
		AUC_{0-t} (μg eq•hr/ml)	3.40 ± 1.96	1.87 ± 1.07	3.32 ± 1.35	3.16 ± 3.22	2.19 ± 1.38	3.30 ± 3.43
	12.5	C_{max} (μg eq/ml)	0.390 ± 0.242	1.14 ± 0.902	0.212 ± 0.032	0.812 ± 0.834	0.270 ± 0.164	0.851 ± 0.412
		T_{max} (hr)	9.3 ± 5.5	4.0 ± 1.7	7.0 ± 5.3	10.0 ± 6.1	5.0 ± 6.1	9.7 ± 6.7
		AUC_{0-t} (μg eq•hr/ml)	4.42 ± 4.38	10.0 ± 8.55	2.52 ± 1.09	7.98 ± 8.28	2.26 ± 1.85	7.63 ± 5.41
RBC	7.5	C_{max} (μg eq/ml)	0.768 ± 0.362	0.504 ± 0.114	0.677 ± 0.529	0.659 ± 0.531	0.521 ± 0.367	0.727± 0.570
		T_{max} (hr)	5.7 ± 5.5	12.7 ± 9.2	9.7 ± 6.7	6.0 ± 6.1	5.7 ± 6.4	13.0 ± 11.0
		AUC_{0-t} (μg eq•hr/ml)	7.78 ± 5.14	4.87 ± 3.71	7.16 ± 4.33	6.22 ± 5.29	5.09 ± 4.26	6.70 ± 5.86
	12.5	C_{max} (μg eq/ml)	0.440 ± 2.53	2.73 ± 0.774	0.066 ± 0.619	1.38 ± 1.17	0.664 ± 0.465	1.61 ± 0.825
		T_{max} (hr)	5.9 ± 5	4.3 ± 1.2	5.3 ± 13	9.7 ± 5.8	5.0 ± 6.1	9.7 ± 5.8
		AUC_{0-t} (μg eq•hr/ml)	7.35 ± 3.54	19.5 ± 15.2	1.80 ± 4.37	13.9 ± 13.1	4.99 ± 4.06	14 .4 ± 8.46

Summary of C_{max}, T_{max}, and AUC of plasma and erythrocyte radioactivity concentrations following a single oral dose of [^{14}C]SC-58635 on Day 1, and During Weeks 6 and 13 of a 13-week dosing regimen in dogs classified as fast or slow metabolizers of SC-58635 are showed in the following table. Plasma AUC values were higher in slow metabolizers compared to the fast metabolizers at both the 7.5 and 12.5 mg/kg dose levels on Day 1, and during Weeks 6 and 13.

Sample	Dose	Duration	C_{max} (μg eq/g)		T_{max} (hr)		AUC_{0-t} (μg eq.•hr/g)	
	mg/kg/day		Fast	Slow	Fast	Slow	Fast	Slow
Plasma	7.5	Day 1	0.322	0.274	10.7	7.7	2.40	2.87
		Week 6	0.270	0.373	6.0	9.7	2.39	4.09
		Week 13	0.231	0.350	5.7	5.7	2.12	3.37
	12.50	Day 1	0.213	1.310	5.7	7.7	1.42	13.00
		Week 6	0.214	0.809	9.7	7.3	1.99	8.51
		Week 13	0.444	0.677	8.7	6.0	3.01	6.88
RBC	7.50	Day 1	0.771	0.501	10.7	7.7	7.37	5.27
		Week 6	0.652	0.684	6.0	9.7	5.99	7.40
		Week 13	0.581	0.667	13.0	5.7	5.60	6.20
	12.50	Day 1	1.230	2.320	6.7	7.3	5.16	24.60
		Week 6	0.561	1.320	9.7	7.0	5.14	14.50
		Week 13	1.180	1.100	8.7	6.0	7.51	11.90

The radioactive dose was excreted rapidly following oral dosing. Greater than 80% of the dose was excreted in the first 48 hours after dosing. The primary route of elimination of total radioactivity was fecal excretion. Approximately 90.3% - 105% of the dose was excreted via the feces suggesting extensive biliary and/or intestinal secretion of radioactivity. The total recovery of the radioactive dose in urine and feces combined ranged from 91.3% to 106% at 168 hours postdose. No sex differences were noted in the excretion total radioactivity. Summary of the percent of radioactive dose excreted in urine and feces of dogs (Groups 6 and 7) following a single oral dose of [^{14}C]SC-58635 on Day 1, and during Weeks 6 and 13 are presented in the below table.

Dose mg/kg/day	Dosing Interval	% Radioactive Dose					
		Urine		Feces		Total	
		♂	♀	♂	♀	♂	♀
7.50	Day 1	0.49	0.56	96.2	105	96.9	106
	Week 6	0.77	0.73	91.8	92.2	92.8	93.2
	Week 13	0.41	0.87	94.1	90.9	94.8	92.4
12.50	Day 1	0.64	1.25	93.9	92.5	95.1	94
	Week 6	0.43	1.06	90.8	96.4	91.3	97.9
	Week 13	0.37	1.35	92.2	90.3	93.3	92.3

There was no apparent induction of microsomal cytochrome P450 following the daily oral administration of SC-58635 for 13 weeks to male and female dogs. The mean microsomal cytochrome P450 contents from males ranged protein and were not dose-dependent. The mean microsomal cytochrome P450 contents in females ranged from 0.586 to 0.653 nmole/mg protein and were also not dose-dependent. The following table shows total Cytochrome P450 Content, microsomes and total protein yield of dog liver, following oral administration of SC-58635 for 13 weeks.

Group	Dose mg/kg/day	P450 (nmole/mg protein)		Microsome Yield (mg/g liver)		Total Protein Yield	
		Male	Female	Male	Female	Male	Female
1[a]	Control	0.641 ± 0.0526[b]	0.606 ± 0.0387	14.5 ± 0.96	17.0 ± 1.52	99.8 ± 7.19	97.3 ± 5.91
2	15	0.577 ± 0.0659	0.613 ± 0.0668	17.9 ± 1.94	15.3 ± 2.42	107 ± 4.79	95.7 ± 8.93
3	25	0.620 ± 0.0313	0.586 ± 0.0400	16.9 ± 2.01	17.5 ± 1.31	103 ± 8.33	112 ± 6.60
4	35	0.619 ± 0.0780	0.597 ± 0.0410	18.2 ± 3.34	15.2 ± 2.33	109 ± 7.02	101± 7.87
5	25	0.69	0.65	15.10	16.90	105	107

[a] Total daily dose administered. Animals in Groups 1 through 4 were dosed twice daily for at least 13 weeks. Animals in Group 5 were dosed once daily for at least 13 weeks.

[b] Mean ± SD.

3.5.1.2. Evaluation Of Total Radioactivity Data For A 52-Week Capsule Toxicity Study With SC-58635 In Dogs, SA4425, Document No.: M2096056; Date: 09-Apr-1997 (Vol. 1.75, p. 131-254)

Study Nº: CHV 700-338/SA4425

Report Nº: M2096056

Study Aim: (1) To identify toxic effects of SC-58635 when administered orally to dogs for at least 26 or 52 weeks and (2) to assess the reversibility of any toxic effects of the test compound following a 4-week recovery period; (3) To determine the relationship of plasma concentration of test material to the duration of dosing; and (4) To evaluate evidence for sex-related differences in PK parameters.

Compound: SC-58635 (Lot Nº 94K014-A2B), [^{14}C]SC-58635 (Lot Nº GDS 4671-90, 2.08 μCi/mg).

Vehicle: Empty 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)	N° of Animals/Sex	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	N° 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:

for the in-life portion of study and
for radioanalysis procedures.

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 Days 1, 176 & 358 and received nonradiolabeled SC-58635 on other days during the study. Blood samples were collected at 0.5, 1, 2, 3, 4, 5, 7, 12, 13, 14, 15, 18, 24 and 96 hr following the ingestion of radiolabeled [^{14}C]SC-58635. Urine and fecal samples were collected for 168 hr after each radiolabeled dose approximate 24-hr intervals.

Results: In the current report, information on plasma and RBC radioactivity concentrations and excretion data following [^{14}C]SC-58635 administration to Groups 6 and 7 dogs on Days 1, 176 and 358 was included.

- Plasma and RBC Radioactivity - The concentrations of radioactivity in the cellular fraction of blood were higher than in plasma. Plasma T_{max} on Day 1 was 2 to 4 hours postdose in both males and females. Plasma T_{max} on Days 176 and 358 was 14 hours postdose in ♂ and 2 to 4 hours postdose in ♀. The time versus concentration profiles show an initial absorption and elimination phase followed by a second increase in concentrations of radioactivity subsequent to the p.m. dose of nonradiolabeled SC-58635. In males, this second increase in plasma concentration was higher than the initial increase on Days 176 and 358, accounting for the delayed C_{max} values in males. The plasma C_{max} values for radioactivity were higher in ♂ than ♀ on Days 1 and 176 but not Day 358. The plasma C_{max} values increased with increasing dose.
  RBC T_{max} on Day 1 occurred from 2 to 4 hours postdose in both ♂ and ♀. On Days 176 and 358 it occurred from 13 to 14 hours postdose in ♂ and from 2 to 4 hours postdose in ♀. The red blood cell C_{max} values for radioactivity were higher in ♂ than ♀ on Days I and 176. The red blood cell C_{max} values increased with increasing dose.
  A comparison of plasma and red blood cell concentrations from animals identified phenotypically as slow or fast metabolizers of [^{14}C]SC-58635 showed concentrations in slow metabolizing animals to be higher than fast metabolizers.

Sampling Time (hr)	Concentration of Radioactivity (μg equivalents/g)							
	PLASMA				RED BLOOD CELLS			
	7.5 mg/kg/dose		17.5 mg/kg/dose		7.5 mg/kg/dose		17.5 mg/kg/dose	
	♂	♀	♂	♀	♂	♀	♂	♀
	Day 1							
0.5	0.010±0.006	0.027±0.017	0.040±0.026	0.011±0.011	0.013±0.013	0.087±0.055	0.113±0.071	0.036±0.036
1	0.115±0.034	0.191±0.035	0.203±0.101	0.106±0.057	0.306±0.079	0.533±0.154	0.529±0.240	0.275±0.140
2	0.382±0.098	0.307±0.052	0.614±0.308	0.305±0.068	0.901±0.152	0.916±0.276	1.460±0.585	0.825±0.216
4	0.413±0.170	0.188±0.025	0.952±0.354	0.445±0.138	0.957±0.302	0.587±0.095	2.130±0.576	1.040±0.232
7	0.226±0.116	0.079±0.020	0.429±0.130	0.234±0.092	0.575±0.278	0.286±0.049	1.320±0.290	0.566±0.171
12	0.127±0.079	0.053±0.037	0.149±0.041	0.320±0.219	0.336±0.200	0.127±0.069	0.481±0.088	0.793±0.539
13	0.129±0.084	0.078±0.063	0.145±0.030	0.397±0.291	0.355±0.221	0.178±0.134	0.434±0.113	0.873±0.669
14	0.140±0.087	0.086±0.070	0.142±0.022	0.325±0.243	0.313±0.189	0.168±0.118	0.529±0.101	0.696±0.526
15	0.205±0.120	0.075±0.064	0.142±0.022	0.288±0.214	0.450±0.262	0.145±0.119	0.338±0.072	0.650±0.505
18	0.253±0.153	0.069±0.052	0.102±0.010	0.210±0.165	0.544±0.339	0.138±0.096	0.248±0.037	0.521±0.423
24	0.117±0.068	0.059±0.052	0.053±0.013	0.175±0.148	0.296±0.174	0.110±0.093	0.138±0.021	0.356±0.305
48	0.014±0.008	0.010±0.010	ND	0.013±0.013	0.027±0.016	0.017±0.017	ND	0.032±0.032
96	ND	ND	ND	ND	ND	ND	ND	ND
	Day 176							
0.5	0.029±0.014	0.009±0.009	0.030±0.016	0.020±0.020	0.075±0.051	0.042±0.025	0.078±0.040	0.029±0.029
1	0.090±0.034	0.088±0.018	0.118±0.052	0.124±0.054	0.251±0.115	0.269±0.048	0.321±0.136	0.217±0.062
2	0.085±0.014	0.153±0.039	0.140±0.034	0.315±0.055	0.254±0.039	0.435±0.093	0.384±0.112	0.615±0.106
4	0.057±0.013	0.123±0.036	0.150±0.059	0.243±0.070	0.144±0.024	0.411±0.168	0.352±0.095	0.520±0.074
7	0.025±0.015	0.069±0.018	0.377±0.327	0.152±0.067	0.085±0.037	0.234±0.087	0.913±0.752	0.296±0.103
12	0.164±0.131	0.044±0.020	0.541±0.276	0.077±0.042	0.467±0.340	0.123±0.044	1.520±0.667	0.151±0.090
13	0.245±0.110	0.045±0.022	0.586±0.339	0.063±0.038	0.724±0.292	0.120±0.045	1.630±0.769	0.143±0.087
14	0.307±0.125	0.047±0.025	0.605±0.357	0.060±0.038	0.913±0.329	0.089±0.044	1.750±0.848	0.120±0.079
15	0.291±0.130	0.040±0.022	0.588±0.352	0.055±0.035	0.778±0.313	0.085±0.039	1.380±0.655	0.058±0.034
18	0.183±0.099	0.032±0.021	0.428±0.256	0.042±0.029	0.479±0.248	0.062±0.033	0.975±0.543	0.076±0.056
24	0.099±0.069	0.017±0.017	0.198±0.131	0.027±0.020	0.236±0.159	0.031±0.031	0.564±0.386	0.056±0.043
48	0.011±0.011	0.004±0.004	0.021±0.017	0.007±0.007	0.022±0.022	ND	0.033±0.033	0.011±0.011
96	ND	ND	ND	ND	ND	ND	ND	ND
	Day 358							
0.5	0.019±0.011	0.008±0.008	0.070±0.045	0.029±0.029	0.057±0.034	0.025±0.025	0.186±0.113	0.038±0.038
1	0.051±0.019	0.054±0.013	0.124±0.040	0.107±0.025	0.159±0.061	0.147±0.041	0.296±0.098	0.241±0.043
2	0.065±0.018	0.177±0.040	0.265±0.152	0.281±0.050	0.178±0.033	0.497±0.131	0.532±0.237	0.698±0.187
4	0.038±0.015	0.093±0.029	0.173±0.108	0.690±0.214	0.095±0.040	0.293±0.076	0.390±0.188	1.750±0.604
7	0.022±0.014	0.055±0.021	0.093±0.050	0.417±0.128	0.057±0.037	0.155±0.041	0.260±0.133	1.040±0.304
12	0.067±0.042	0.026±0.016	0.288±0.184	0.251±0.100	0.202±0.117	0.054±0.031	0.753±0.407	0.617±0.228
13	0.142±0.119	0.028±0.019	0.390±0.237	0.226±0.104	0.420±0.350	0.064±0.038	0.993±0.510	0.574±0.237
14	0.193±0.179	0.028±0.021	0.409±0.278	0.286±0.175	0.468±0.411	0.062±0.039	0.815±0.457	0.629±0.341
15	0.185±0.173	0.026±0.020	0.377±0.261	0.287±0.196	0.403±0.375	0.044±0.029	0.702±0.422	0.547±0.330
18	0.106±0.098	0.018±0.018	0.300±0.235	0.252±0.174	0.273±0.255	0.028±0.028	0.569±0.391	0.432±0.275
24	0.044±0.039	0.013±0.013	0.195±0.178	0.148±0.113	0.113±0.113	0.018±0.018	0.360±0.318	0.293±0.231
48	ND	ND	0.017±0.017	0.030±0.030	ND	ND	0.030±0.031	0.055±0.055
96	ND	ND	ND	ND	ND	ND	ND	ND

ND = Not Detectable (≤2x background)

Sampling Time (hr)	Concentration of Radioactivity							
	Plasma				Red Blood Cells			
	Slow Metabolizer		Fast Metabolizer		Slow Metabolizer		Fast Metabolizer	
	7.5 mg/kg	17.5 mg/kg	7.5 mg/kg	17.5 mg/kg	7.5 mg/kg	17.5 mg/kg	7.5 mg/kg	17.5 mg/kg
	Day 1							
0.5	0.015±0.010	0.025±0.014	0.022±0.016	0.027±0.027	0.030±0.030	0.076±0.044	0.071±0.055	0.074±0.074
1	0.169±0.033	0.151±0.053	0.138±0.045	0.158±0.110	0.395±0.092	0.387±0.145	0.445±0.172	0.418±0.259
2	0.374±0.104	0.286±0.053	0.316±0.043	0.634±0.305	0.806±0.202	0.680±0.124	1.010±0.227	1.600±0.546
4	0.464±0.141	0.650±0.275	0.138±0.016	0.749±0.332	1.020±0.274	1.330±0.481	0.526±0.090	1.840±0.556
7	0.263±0.097	0.375±0.115	0.042±0.01	0.289±0.131	0.711±0.200	0.951±0.289	0.150±0.031	0.931±0.351
12	0.181±0.055	0.386±0.196	ND	0.082±0.032	0.452±0.140	0.986±0.469	0.012±0.012	0.287±0.114
13	0.208±0.064	0.457±0.267	ND	0.083±0.030	0.534±0.145	1.020±0.618	ND	0.291±0.154
14	0.223±0.070	0.381±0.221	0.004±0.004	0.085±0.034	0.470±0.135	0.939±0.453	0.011±0.011	0.287±0.129
15	0.280±0.091	0.340±0.195	ND	0.091±0.040	0.596±0.198	0.764±0.464	ND	0.224±0.114
18	0.322±0.120	0.258±0.147	ND	0.054±0.032	0.673±0.277	0.610±0.391	0.009±0.009	0.160±0.081
24	0.176±0.052	0.204±0.137	ND	0.024±0.017	0.406±0.132	0.425±0.282	ND	0.070±0.045
48	0.024±0.008	0.013±0.013	ND	ND	0.044±0.015	0.033±0.033	ND	ND
96	ND	ND	ND	ND	ND	ND	ND	ND
	Day 176							
0.5	0.022±0.008	0.027±0.019	0.016±0.016	0.023±0.018	0.063±0.021	0.045±0.028	0.054±0.054	0.063±0.044
1	0.103±0.019	0.115±0.061	0.101±0.024	0.128±0.044	0.247±0.057	0.182±0.084	0.274±0.111	0.357±0.109
2	0.145±0.042	0.188±0.046	0.093±0.016	0.266±0.079	0.336±0.117	0.347±0.080	0.353±0.046	0.652±0.104
4	0.101±0.016	0.278±0.066	0.080±0.043	0.115±0.031	0.236±0.061	0.503±0.093	0.320±0.190	0.370±0.087
7	0.065±0.009	0.492±0.293	0.058±0.040	0.038±0.010	0.178±0.034	1.080±0.698	0.141±0.107	0.127±0.019
12	0.180±0.126	0.557±0.265	0.028±0.019	0.063±0.058	0.462±0.334	1.420±0.689	0.128±0.083	0.249±0.249
13	0.232±0.110	0.589±0.334	0.058±0.046	0.059±0.059	0.602±0.300	1.490±0.803	0.241±0.191	0.288±0.288
14	0.293±0.127	0.594±0.357	0.061±0.050	0.071±0.071	0.764±0.362	1.500±0.904	0.238±0.215	0.363±0.363
15	0.288±0.129	0.570±0.356	0.044±0.035	0.074±0.074	0.707±0.337	1.100±0.716	0.158±0.129	0.034±0.034
18	0.201±0.078	0.415±0.258	0.015±0.010	0.055±0.055	0.488±0.241	0.869±0.570	0.052±0.037	0.183±0.183
24	0.116±0.062	0.214±0.124	ND	0.011±0.011	0.267±0.147	0.564±0.383	ND	0.055±0.055
48	0.015±0.010	0.029±0.015	ND	N D	0.022±0.022	0.043±0.031	ND	ND
96	ND	ND	ND	N D	ND	ND	ND	ND
	Day 358							
0.5	0.011±0.011	0.029±0.029	0.017±0.010	0.070±0.045	0.025±0.025	0.038±0.038	0.058±0.034	0.186±0.113
1	0.043±0.017	0.124±0.029	0.062±0.013	0.107±0.038	0.100±0.047	0.226±0.058	0.206±0.036	0.311±0.086
2	0.142±0.051	0.326±0.141	0.099±0.032	0.221±0.063	0.301±0.115	0.563±0.246	0.374±0.145	0.666±0.182
4	0.095±0.029	0.384±0.175	0.036±0.012	0.479±0.264	0.233±0.085	0.730±0.336	0.155±0.076	1.410±0.719
7	0.065±0.016	0.276±0.140	0.011±0.006	0.312±0.144	0.157±0.044	0.582±0.264	0.055±0.032	0.955±0.404
12	0.085±0.035	0.389±0.173	0.008±0.008	0.151±0.069	0.219±0.107	0.852±0.397	0.037±0.037	0.519±0.212
13	0.164±0.112	0.437±0.228	0.006±0.006	0.181±0.096	0.466±0.335	0.950±0.487	0.020±0.020	0.618±0.300
14	0.222±0.170	0.549±0.280	ND	0.147±0.074	0.515±0.396	0.980±0.481	0.017±0.017	0.462±0.232
15	0.211±0.165	0.544±0.272	ND	0.121±0.062	0.448±0.361	0.913±0.454	ND	0.337±0.174
18	0.124±0.093	0.474±0.243	ND	0.079±0.029	0.302±0.247	0.793±0.408	ND	0.208±0.094
24	0.057±0.036	0.324±0.172	ND	0.020±0.008	0.131±0.108	0.603±0.322	ND	0.049±0.017
48	ND	0.046±0.029	ND	ND	ND	0.086±0.053	ND	ND
96	ND	ND	ND	ND	ND	ND	ND	ND

ND = Not Detectable (≤2x background).

- Excretion - The major route of excretion of radioactivity was via the feces. The percent of dosed radioactivity excreted in the feces ranged from 76.1 % to 91.8% over the 168-hour collection period with urinary excretion accounting for 0.26% to 1.05%. There were no apparent effects of dose, duration of dosing, or sex in the patterns of excretion on different days or at different dose levels. The mean total recoveries ranged from 77.3% to 93.4% for males and females at all dose levels on all dose days.

- Percent of radioactive dose in urine, feces, pan rinse, cage wash, cage wipe, and urine wipe at specified intervals postdose for ♂ and ♀ dogs following a single oral dose of [^{14}C]SC-58635, 7.5 or 17.5 mg/kg, on Days 1, 176 and 358 are presented in the following table.

% Radioactive Dose										
Dose	Collection	♂	♀	♂	♀	♂	♀	Collection	♀	♂
mg/kg	Time (hr)	Urine		Feces		Pan Rinse		Time (hr)	Cage Wash, Cage/Urine Wipe	
Day 1										
7.5	0-24	0.44±0.01	0.58±0.16	57.9±16.6	78.7±5.25	0.10±0.01	0.26±0.15	168[a]	<0.005	0.11±0.08
	24-48	0.30±0.14	0.20±0.07	24.7±14.0	8.03±2.56	0.12±0.07	0.14±0.10	168[b]	0.01±0.00	0.03±0.03
	48-72	0.10±0.05	0.10±0.06	5.10±2.88	2.42±1.28	0.03±0.01	0.04±0.02	168[c]	0.03±0.01	0.04±0.03
	72-96	0.03±0.02	0.04±0.03	0.89±0.61	0.19±0.13	0.01±0.01	0.04±0.02	168[d]	0.05±0.02	0.14±0.09
	96-120	0.01±0.01	0.05±0.04	0.09±0.06	0.12±0.12	<0.005	0.11±0.07			
	120-144	ND	0.01±0.01	0.01±0.01	0.04±0.03	ND	0.01±0.01			
	144-168	0.01±0.01	0.01±0.00	ND	0.03±0.03	-	-			
	Subtotal	0.88±0.21	0.99±0.21	88.8±0.32	89.5±1.54	0.25±0.08	0.59±0.37	Total[e]	90.0±0.61	91.4±0.97
17.5	0-24	0.58±0.21	0.33±0.09	78.7±3.70	66.1±17.9	0.21±0.07	0.12±0.03	168[a]	0.01±0.01	0.04±0.01
	24-48	0.24±0.07	0.21±0.07	10.6±3.26	8.87±4.25	0.06±0.01	0.10±0.04	168[b]	0.04±0.02	0.03±0.01
	48-72	0.05±0.01	0.07±0.04	1.85±1.06	0.73±0.36	0.02±0.00	0.02±0.01	168[c]	0.10±0.06	0.07±0.04
	72-96	0.03±0.01	0.02±0.01	0.52±0.40	0.27±0.19	0.02±0.00	0.02±0.01	168[d]	0.15±0.09	0.02±0.00
	96-120	0.02±0.01	0.02±0.01	0.04±0.02	0.05±0.02	<0.005	0.04±0.01			
	120-144	0.04±0.02	0.01±0.00	0.02±0.01	0.08±0.06	<0.005	0.01±0.00			
	144-168	<0.005	0.01±0.00	ND	0.07±0.07	-	-			
	Subtotal	0.96±0.26	0.66±0.11	91.8±0.49	76.1±18.9	0.31±0.08	0.30±0.06	Total[e]	93.4±0.49	77.3±18.8
Day 176										
7.5	0-24	0.17±0.06	0.22±0.08	59.0±12.9	87.3±1.71	0.03±0.01	0.07±0.02	168[a]	0.01±0.01	0.01±0.00
	24-48	0.12±0.06	0.10±0.04	25.6±10.8	3.94±0.75	0.05±0.03	0.04±0.02	168[b]	ND	ND
	48-72	0.03±0.01	0.02±0.01	2.72±0.92	0.35±0.16	0.04±0.01	0.03±0.02	168[c]	0.01±0.01	<0.005
	72-96	0.02±0.01	0.01±0.00	0.57±0.26	0.12±0.11	0.01±0.01	0.01±0.00	168[d]	0.03±0.01	0.01±0.00
	96-120	0.01±0.01	0.01±0.00	0.16±0.13	0.01±0.01	0.02±0.01	0.01±0.01			
	120-144	0.01±0.00	<0.005	0.03±0.03	0.01±0.01	0.02±0.01	0.01±0.00			
	144-168	<0.005	<0.005	0.01±0.01	ND					
	Subtotal	0.37±0.11	0.35±0.10	88.2±1.43	91.7±11.64	0.17±0.07	0.17±0.06	Total[e]	88.8±1.34	92.3±1.60
17.5	0-24	0.33±0.16	0.13±0.02	68.4±8.32	73.8±14.9	0.20±0.05	0.50±0.42	168[a]	0.01±0.00	0.11±0.11
	24-48	0.08±0.03	0.03±0.02	13.3±4.25	2.60±0.94	0.11±0.03	0.49±0.43	168[b]	<0.005	0.01±0.01
	48-72	0.04±0.01	0.02±0.01	4.71±3.16	0.34±0.16	0.10±0.04	0.38±0.37	168[c]	0.01±0.00	0.06±0.06
	72-96	0.02±0.01	0.02±0.01	1.13±1.04	0.35±0.18	0.02±0.01	0.08±0.06	168[d]	0.02±0.00	0.18±0.17
	96-120	0.01±0.00	0.04±0.03	0.12±0.09	0.13±0.10	0.04±0.01	0.21±0.20			
	120-144	<0.005	<0.005	0.02±0.01	0.05±0.05	0.01±0.00	0.28±0.27			
	144-168	<0.005	0.01±0.01	0.02±0.01	0.16±0.16					
	Subtotal	0.49±0.17	0.26±0.06	87.8±1.63	77.5±14.0	0.47±0.12	1.93±1.76	Total[e]	88.8±1.43	80.0±11.9
Day 358										
7.5	0-24	0.08±0.02	0.26±0.05	68.9±19.4	86.3±3.03	0.12±0.03	0.15±0.04	168[a]	0.03±0.01	0.02±0.01
	24-48	0.15±0.11	0.06±0.04	17.6±15.5	3.20±1.40	0.12±0.09	0.03±0.01	168[b]	0.01±0.00	ND
	48-72	0.01±0.01	0.02±0.01	1.19±0.99	0.40±0.28	0.03±0.02	0.02±0.01	168[c]	0.01±0.00	<0.005
	72-96	0.01±0.00	<0.005	0.23±0.14	0.14±0.12	0.03±0.02	0.01±0.01	168[d]	2.04±1.34	0.37±0.10
	96-120	0.01±0.00	ND	0.04±0.02	0.03±0.01	0.03±0.01	0.01±0.00			
	120-144	0.01±0.00	ND	0.03±0.02	ND	0.01±0.01	<0.005			
	144-168	ND	ND	0.01±0.01	0.01±0.01					
	Subtotal	0.26±0.11	0.34±0.03	89.3±3.18	90.0±1.79	0.35±0.15	0.22±0.06	Total[e]	92.0±1.69	91.0±1.70
17.5	0-24	0.16±0.04	0.74±0.34	73.0±7.72	59.4±11.4	0.16±0.07	0.13±0.05	168[a]	0.04±0.02	0.04±0.02
	24-48	0.16±0.06	0.22±0.07	12.1±5.06	25.6±12.8	0.10±0.04	0.03±0.01	168[b]	0.01±0.00	0.01±0.00
	48-72	0.04±0.02	0.06±0.03	2.48±1.42	1.25±0.41	0.03±0.02	0.02±0.01	168[c]	0.03±0.02	0.03±0.02
	72-96	0.02±0.01	0.02±0.01	0.52±0.46	0.61±0.52	0.01±0.00	0.01±0.00	168[d]	2.04±0.70	2.04±0.70
	96-120	0.01±0.00	0.01±0.00	0.05±0.03	0.17±0.09	0.01±0.00	0.01±0.00			
	120-144	0.01±0.00	0.01±0.00	0.04±0.02	0.05±0.03	<0.005	0.01±0.00			
	144-168	<0.005	<0.005	0.01±0.01	0.03±0.02					
	Subtotal	0.40±0.07	1.05±0.39	88.2±1.65	87.1±1.99	0.31±0.11	0.20±0.06	Total[e]	91.0±1.43	91.0±1.43

ND = Not detectable; < 2x background; [a] Cage wash (MeOH); [b] Cage wash (TSP); [c] Cage wipe; [d] Urine wipe; [e]Includes urine, feces, pan rinse, cage wash, cage wipe, and urine wipe.

3.6. Bioanalytical Procedures

The following study reports related to analytical method development and validation were submitted to the present NDA but were not reviewed.

3.6.1. MOUSE

1. The Method Development And Ruggedness Testing Of A Detection For SC-58635 In Mouse Plasma, Document No.: MRC-95S-0060; Date: 12-Apr-1995 (Vol. 1.76, p. 1-29)
2. Validation Of A Assay With Detection For SC-58635 In Mouse Plasma By Document No.: MRC-95S-0082; Date: 07-Nov-1995 (Vol. 1.76, p. 30-91)
3. The Method Development And Validation Of A Assay With Detection For SC-58635 In Mouse Plasma Supernatant For Searle At , Document No.: M2097057; Date: 30-Sep-1997 (Vol. 1.76, p. 92-179)

3.6.2. RAT

1. The Method Development And Validation Of A Assay With For SC-58635 In Rat Plasma, Document No.: MRC-94S-0119; Date: 14-Oct-1994 (Vol. 1.77, p. 1-70)
2. The Validation In Rat Plasma At Document No.: MRC-94S-0241; Date: 18-Sep-1995 (Vol. 1.77, p.71-125) Final Report Amendment No. 1: The Validation Of An Assay In Rat Plasma At Document No.: MRC-94-0241A; Date: 07-Nov-1995 (Vol. 1.77, p. 126-137)
3. The Method Development And Validation Of A Assay With Detection For SC-58635 In Rat Plasma Supernatant For Searle At Document No.: M2097056; Date: 29-Sep-1997 (Vol. 1.77, p. 138-225)
4. Validation Of An Assay For SC-58635 In Rat Serum At Document No.: M2097265; Date: 01-Dec-1997 (Vol. 1.77, p. 226-290)

3.6.3. RABBIT

The Validation Of A Assay With Detection For SC-58635 In Rabbit Plasma, Document No.: MRC-95S-0007; Date: 12-Apr-1995 (Vol. 1.77, p. 291-351)

3.6.4. DOG

1. The Method Development And Validation Of A Assay With Detection For SC-58635 In Dog Plasma, Document No.: MRC-94S-0117; Date: 16-Nov-1994 (Vol. 1.77, p. 352-413),
2. The Validation Of A Assay With Detection For SC-58635 In Dog Plasma By Document No.: MRC-94S-0235; Date: 06-Nov-1995 (Vol. 1.78, p. 1-71)
3. The Method Development and Validation Of A Assay With Detection For SC-58635 In Dog Plasma Supernatant For Searle At Document No.: M2097055; Date: 30-Sep-1997 (Vol. 1.78, p. 72-159)
4. Evaluation Of The Analytical Interference Of SC-58635 In The Clinical Chemistry Analyses Of Dog Serum , Document No.: MRC-94S-0187; Date: 10-Jul-1995 (Vol. 1.78, p. 160-181) Final Report Amendment No. 1: Evaluation Of The Analytical Interference Of SC-58635 In The Clinical Chemistry Analyses Of Dog Serum, Document No.: MRC-94S-31-0187; Date: 24-Jul-1995 (Vol. 1.78, p. 182)

3.6.5. HUMAN IN VITRO (QC REPORTS)

1. 7-Hydroxywarfarin: Validation Of An Assay In Vitro Incubation Buffer At Document No.: M2097289; Date: 18-Sep-1997 (Vol. 1.78, p. 183-244)
2. Warfarin: Validation Of An Assay In Vitro Incubation Buffer At (DCN #B6-140-04), Document No.: M2097290; Date: 17-Sep-1997 (Vol. 1.78, p. 245-308)
3. Project DBD - QC Report For The Assay Of Glyburide Microsomal Fraction Samples With Human Plasma Calibration Standards And Quality Controls By To Support G.D. Searle & Co., Document No.: M2097287; Date: 17-Sep-1997 (Vol. 1.78, p. 309-327)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

5. SUMMARY AND EVALUATION:

5.1. PHARMACOLOGY/PHARMACODYNAMICS

5.1.1. ACTION-RELATED PHARMACOLOGY

SC-58635 was demonstrated to have following properties.

5.1.1.1. *In Vitro* -

SC-58635 preferentially inhibited COX-2 mediated PGE_2 production by human whole blood and dog whole blood.

5.1.1.2. *In Vivo* -

- Anti-inflammatory Activity - SC58635 was effective in the following animal models.
  (1) carrageenan-induced rat paw edema model with an ED_{50} value of 7 ± 1 mg/kg;
  (2) adjuvant induced arthritis in rats by the inhibition of cartilage destruction, bone lysis, bone proliferation, soft tissues edema and synovial inflammation with an ED_{50} value of 0.3 ± 0.1 mg/kg; and
  (3) carrageenan-induced air pouch in rats by the inhibition of PGE_2 and 6-keto $PGE_{1\alpha}$ with an ED_{50} value of 0.2 ± 0.1 mg/kg.
- Analgesic Activity - SC58635 was effective in the following animal models.
  (1) Hargreaves' hyperalgesia model with an ED_{50} value of 35 mg/kg;
  (2) formalin induced hyperalgesia in the mose hindpaw model;
  (3) phenyl-benzoquinone induced doxoflexion in mice; and
  (4) acetic acid-induced writhing in mice.
- Anti-pyretic Activity - SC58635 was shown to reduce LPS-induced fever but did not alter normal temperature in rats.
- Chemoprevention Properties - Reports indicated that administration of SC58635 in the diet to rats at 1500 ppm inhibit azoxymethan-induced colonic aberrant cryptic foci and tumors. Reports show that NSAIDs use in the general population is associated with a reduced risk (40-50%) of colon cancer death[14]. It has been demonstrated that colorectal tumors have elevated levels of COX-2[15,16]. The mechanism of chemoprevention by NSAIDs is not clear. However, NSAIDs induced apoptosis in human colorectal cancer cells has been demonstrated[17].

[14] Thun, MJ, 1995. Gastroenterol Clin North Am. 25: 333-348.
[15] Tsujii, M. and Bubois, RN, 1995. Cell 83: 493-501
[16] Morin, PJ, Vogelstein, B and Kinzler, KW, 1996. Proc. Natl. Acad. Sci. USA 93: 7950-4820.
[17] Chan, TA, et al., 1998. Proc. Natl. Acad. Sci. USA 95: 681-686.

5.1.2. *SAFETY PHARMACOLOGY*

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

Study Type	Species	Dose/Route	Results
Effect on General Activity and Behavior			
General Activity and Behavior	Mice, 3/group	0, 50, 150, or 500 mg/kg po	50 & 150 mg/kg: slightly ↓ locomotive activities. 500 mg/kg: ↑ in locomotive activities in ⅓ mice.
Effect on Central Nervous System			
Spontaneous Locomotor Activity	Mice, 10/group	0, 50, 150, or 500 mg/kg po	500 mg/kg: significantly ↓ spontaneous locomotive activities by 87% as compared to control animals at 3 hr post dosing.
Effect on Hexobarbital-Induced Sleep			↑ hexobarbital-induced sleep dose-dependently
Electroshock-Induced Convulsions: Synergestic			≥150 mg/kg: slightly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected.
Electroshock-Induced Convulsions: Antagonistic			↓ incidences of tonic convulsions dose-dependently, the incidences of clonic and mortality were not affected.
Chemical-Induced Convulsions: Synergestic			≥150 mg/kg: significantly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected.
Chemical-Induced Convulsions: Antagonistic			dose-dependently ↓ the incidences of tonic convulsions and mortality, the incidences of clonic were not affected.
Analgesic Activity			Significantly ↓ acetic acid-induced writhing in dose-dependent fashion, but had no effect on tail pinch-induced pain.
Body Temperature	Rat, 8/group	0, 50, 150, or 500 mg/kg po	↔ (no effect)
Effect on Autonomic Nervous System and Smooth Muscle			
Spontaneous Motility	Guinea Pig Isolated Ileum	$4x10^{-4}$ to $4x10^{-5}$ M	$\geq 4x10^{-6}$: significantly ↓ the amplitude of spontaneous motility
Agonist-induced Contraction			$\geq 4x10^{-7}$ M: ↓ $BaCl_2$-induced contractions; $\geq 4x10^{-6}$ M: ↓5-HT-induced contractions; $\geq 4x10^{-5}$ M: ↓ ACh-, Histamine-induced contractions.
Effect on Digestive system	Mice, 10/group	0, 50, 150, or 500 mg/kg po	↔ on the rate passage of charcoal meal in small intestine.
Effect on Respiratory and Cardiovascular Systems	Dog, 3/group	0, 50, 100 or 200 mg/kg	200 mg/kg: ↑ blood flow significantly, ↔ on the ECG, and PR, QT, and QRS interval times, systolic, diastolic, and mean blood pressure, heart rate and respiratory pressure
Effect on Urine Volume, Urinary PGE_2, and Urinary Electrolytes Excretion	Rat, 8/group	0, 50, 150, or 500 mg/kg po	↓ urine volume significantly up to 6 hr postdose, and Na^+, Cl^- excretion; ↑ urinary osmolarity significantly; ↔ on K^+ excretion and pH.
		0, 5, 15, 50, mg/kg po	50 mg/kg: similar effects were obtained as previous test. 15 mg/kg: ↓ urine volume at 3 hr postdose; ↑ urinary osmolarity for 6 hr, excretion of urine electrolytes were not affected.
	♂ Rat, 6/group	600 mg/kg/day x7	↔ urine volume, urinary PGE_2 ↓ kidney PGE_2
	♀ Rat, 8/group	600 mg/kg/day x3 or x7	↔ urine volume, urinary PGE_2

5.2. TOXICOLOGY

5.2.1. *ACUTE (SINGLE-DOSE)*

Single-dose oral toxicity of celecoxib was accessed in the rat, dog and cynomolgus monkey. Results are listed in the following table.

Species Nº of Animal/Group	Dose (mg/kg)/Route	Length of Observation	Observations	NOAEL (mg/kg)
SPF Crj:CD(SD) Rats 5/sex/group	0, 1000, or 2000 po by gavage	2-Week	White stool was seen in ♂ & ♀ @ 2000 mg/kg on the day of dosing.	2000
♂ Beagle Dogs 2/group	1000 and 2000 po	2-Week	Vomiting and test article like substance in the stool were noted.	2000
♀ Cynomolgus Monkeys 3/group	25 and 250 po	2-Week	Watery stool was seen on Day 1 in one animal from each treatment group. The one receiving 25 mg/kg/day also showed blood in the stool on Day 2 but not on Days 3-14.	<25

5.2.2. *REPEATED-DOSE*

The repeated-dose toxicity of SC-58635 was evaluated in mice, rats, and dogs. Findings from each study are summarized as followings.

Species Nº of Animal	Dose (mg/kg)	Duration and Route	Findings	NOAEL (mg/kg)
CD-1 Mice 10/sex/group	0, 100, 300, 1000 & 3000 qd	2-Wk Diet Admix	≥1000: Deaths occurred with clinical signs of hunched posture, shivering, reduced activity and reduced fecal output; ↓ in body weights and food consumption; a slight ↑ (7 to 13%) in liver/body weight ratios; GI (perforated ulcers with secondary peritonitis) and kidney (renal tubule degeneration/regeneration) were the major target organs.	♂: 100 ♀: 300
CD-1 Mice 20/sex/group	♂: 0, 75, 150, 300 qd ♀: 0, 150, 300, & 1000 qd	13-Wk Diet Admix	Deaths (1♂ @ 75 mg/kg, one ♂ @ 150 mg/kg, 5♂ & 1♀ @ 300 mg/kg and 15♀ @ 1000 mg/kg) observed as a result of SC-58635 treatment related GI toxicity and secondary peritonitis; a significant ↓ in food consumption (85-94%) in ♀ @ 1000 mg/kg; a dose-dependent ↓ in serum triglycerides (♂ & ♀ @ ≥150 mg/kg); GI (perforated ulcers with secondary peritonitis) was the major target organ. Inconclusive nephropathy was noted.	♂: Not Determin-able ♀:150
Crl:CD®(SD)BR Rats 5/sex/group	100→ 200 →400→600 →800 qd	15-Day Dose Escalation (3-Day/Dose) Oral Gavage	mild→moderate liver enlargement; ↑ cytochrome P-450 content per mg protein (1.8x); slight mild hypertrophy of centrilobular hepatocytes.	
Crl:CD®(SD)BR VAF/Plus® Rats 10-15/sex/group	20, 40, 80, 400, & 600 qd	4-Wk with 4-Wk Recovery Oral Gavage	Deaths (1♀ @ 600 and 1♂ @ 400) occurred as a result of SC-58635 treatment related toxicity (perforation of Jejunum with peritonitis in ♀ and pyelonephritisin ♂); statistically significant ↑ absolute liver weights and liver/body weight ratios without corresponding microscopic findings were identified for ♀ @ 400 or 600 mg/kg.	♂: 80 ♀: 400
Crl:CD®(SD)BR Rats 25/sex/group	0, 20, 80, & 400 qd	13-Wk with 4-Wk Recovery Oral Gavage	Marked elevations in ALT (524 and 574 U/l, respectively), AST (640 and 815 U/l, respectively), and sorbitol dehydrogenase (SDH) (134 and 136, respectively) at Week 18 in 1♂ each at 20 and 80 mg/kg and ↑ALT, AST, and SDH (~2-3x relative to control values) in ♂ at Weeks 6 and/or 14 (1 @ 20, 2 @ 80 and 3 @ 400 mg/kg) without corresponding histopathological alterations were identified. Minimal→slight changes in the liver with centrilobular to midzonal hepatocellular enlargement was seen in both high dose ♂ and ♀ rats. Minimal or slight degeneration of the renal papilla was noted in 1♂ @ 80 mg/kg/day and 3♂ @ 400 mg/kg/day but not in ♀ or rats in recovery phase. There were no treatment-related microscopic changes in the GI tract.	♂: 400 ♀: 400
Crl:CD®(SD)BR Rats 25/sex/group	0, 20, 80, & 400 qd	26-Wk with 4-Wk Recovery Oral Gavage	Deaths (1♀ @ 80 and 6♀ @ 400) occurred as a result of SC-58635 treatment related GI injury (necrosis in jejunum with moderate→severe peritonitis).	♂: 400 ♀: 20
♂ & ♀Beagle Dogs 3/group	0, 15, 40 qd	7-Day iv	High levels of PGE_2 were present in the stomach and colon. SC-58635 caused ↓ in blood TBX and PGE_2 levels. GI lesions (pyloric-duodenal ulcer/erosion) in one dog @ 40 mg/kg after repeated iv dosing for 7 days.	15
Beagle Dogs 4-8/sex/group	0, 20, 25, 50, 100, & 250 qd	4-Wk with 4-Wk Recovery Oral	Treatment caused deaths (ulceration of pylorus, jejunum, duodenum, and ileum) were seen in dogs @ ≥50 mg/kg day. Low incidences of lesions with papillary necrosis/pyelitis and/or interstitial suppurative nephritis/fibrosis, and interdigital pyoderma/subcutis abscess were noted in dogs at @ ≥50 mg/kg/day. Inconclusive histopathological changes in the brain (mild→moderate periventricular/perivascular lymphocytic infiltration) were noted.	25
Beagle Dogs 4-8/sex/group	0, 7.5, 12.5, 17.5 bid & 25 qd	13-Wk with 4-Wk Recovery Oral	No remarkable findings were attributable to the treatment.	17.5 bid
Beagle Dogs 4-8/sex/group	0, 7.5, 12.5, 17.5 bid & 25 qd	52-Wk with 4-Wk Recovery Oral	Not remarkable.	17.5 bid

5.2.3. *CARCINOGENICITY*

The carcinogenic potentials of SC-58635 were accessed in rats and mice.

Rat Study - Groups of rats were given SC-58635 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	Dose mg/kg/day				
	Wk 1-17	Wk 18-77		Wk 78-104	
	♂ & ♀	♂	♀	♂	♀
1 (Control)	0	0	0	0	0
2 (Low)	20	20	20	20	5
3 (Mid)	80	80	80	80	10
4 (High)	400	400	200	200	200

The doses selected in this study were based on the results of a 4-week oral gavage study at doses of 0, 20, 80, 400 and 600 mg/kg in which it was shown that absorption of SC-58635 attained a plateau at dosages ≥400 mg/kg/day for ♂ rats and deaths were seen at 600 mg/kg/day for ♀ rats. Based on GI (necrosis/perforation/inflammation with secondary peritonitis) and kidney (pyelonephritis, ♂ only) toxicity findings as well as mortality observed in this study, MTD was reached for both ♂ and ♀. There were no treatment-induced increases in the tumor incidence rates. The exposure to SC-58635 in the high dose ♀ rats, as measure by AUC_{0-24} was ~20 and 10x of that observed in humans at the doses of 200 and 400 mg/day, respectively. The exposure of the high dose ♂ rats to SC-58635, was ~10 and 5x of that observed in humans at 200 and 400 mg/day, respectively. The NOAEL for ♂ was 20 mg/kg and was not perceptible for ♀.

Mouse Study - Groups of mice were given celecoxib at the doses shown in the following table via dietary admix.

Group	Dose (mg/kg)				
	♂		♀		
	Wk1-18	Wk 19-104	Wk1-18	Wk19-22	Wk 23-104
N	0[a]	0	0	0	0
1	25	12.5	50	25	25
2	50	25	100	50	50
3	75	37.5	150	75	150

The doses selected in this study were based on toxicity findings of a 13-week dietary admix (♂: 0, 75, 150 and 300 mg/kg; ♀: 0, 150, 300 and 1000 mg/kg). Due to excessive toxicity, high dose group (♂ and ♀) was terminated at Week 80. 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). Low incidence of pyelonephritis was noted in the ♂ mice. The GI injury was the most common cause of death in high-dose animals. Therefore, the MTD was reached. No treatment-induced increases in the tumor incidence rates were identified. The exposure to SC-58635 in the high dose ♂ and ♀ mince was equivalent to ~2-3x of values seen in humans (200 or 400 mg/day). The NOAEL for either ♂ or ♀ could not be determined for this study as treatment-induced toxicity was observed in all SC-58635 treated groups.

5.2.4. *REPRODUCTIVE TOXICOLOGY*

The following table summarizes the effects of SC-58635 on fertility, reproductive functions, embryo-fetal development, and peri-/post-natal development.

Animals Species	Dose (mg/kg)	Duration of Treatment	Observations	NOAEL (mg/kg)
FERTILITY, EARLY EMBRYONIC DEVELOPMENT→IMPLANTATION				
♂ & ♀ Rats Crl:CD®(SD)BR	0, 60, 300, 600	♂: ≥28 days prior to mating → the end of study ♀: 14-day prior to mating→Gestation Day 7	≥ 60 mg/kg: ↓ live fetuses and implantation sites; ↑ preimplantation loss.	♂: 600 ♀: <60
♀ Rats Crl:CD®(SD)BR	0, 15, 30, 50, 300	14-day prior to mating→Gestation Day 7	≥50 mg/kg: ↓ live fetuses and implantation sites; ↑ pre- and post-implantation loss. 300 mg/kg: ↓ corpora lutea	30
♀ Rats Crl:CD®(SD)BR	0, 60, 300	14-day followed by a 14-day reversal period before mating	No effects.	300
TERATOLOGY- EMBRYO-FETAL DEVELOPMENT				
♀ CD Rats VAF	0, 10, 30, 100	Gestation Days 6→16/17	100 mg/kg: slight ↓ live fetuses. ≥30 mg/kg: ↑ incidence of wavy ribs	30
♀ Rats Crl:CD®(SD)BR	0, 10, 30, 100	Gestation Days 6→17	≥30 mg/kg: ↑ incidence of diaphragmatic hernia, 5th sternebrae incomplete ossification	10
♀ Rabbits Hra: (NZW)SPF	0, 6, 30, 60, 300, 600	Gestation Days 7→18	600 mg/kg: ↓ body weights and food intake; ↑post-implantation loss; ↓ live fetuses.	300
♀ Rabbits Hra: (NZW)SPF	200, 400, 600	Gestation Days 19/21→23/25	600 mg/kg: ↓ body weights (5%)	600 (?)
♀ Rabbits Hra: (NZW)SPF	0, 60, 150, 300	Gestation Days 7→18	≥150 mg/kg: slight ↑ sternebrae fused and sternebrae misshapen 300 mg/kg: slight ↑ rib fused; ↑ post-implantation loss; ↓ live fetuses.	60
PERINATAL/POST NATAL DEVELOPMENT				
♀ Rats Crl:CD®(SD)BR	0, 10, 30, 100	Gestation Day 6→Days 21-23 post partum	F_0 - ≥30 mg/kg: Deaths or Moribund (1 @ 30, 8 @ 100 mg/kg) with GI lesions; transient ↓ in food consumption (Gestation Days 6-9); ↓ live pups; ↑ dead pups. F_1 & F_2 - Normal.	10

A comparison of exposure to SC-56835 on the last day of dosing in rat and rabbit reproductive study to human clinical exposure is presented in the following table.

Species	NOEL (mg/kg)	Exposure in Animal		Ratio of Animal Exposure/Human Exposure to SC-58635			
				200 mg/day[a]		400 mg/day[a]	
		C_{max} (µg/ml)	AUC_{0-24} (µg•hr/ml)	C_{max}	AUC_{0-24hr}	C_{max}	AUC_{0-24}
Embryo-Fetal Developmental							
Rat	10	2.81[b]/3.20[c]	37.1[b]/47.6[b]	4.1/4.7	4.4/5.7	2.1/2.4	2.2/2.8
Rabbit	60	1.49	22.5	2.2	2.7	1.1	1.3
Pre-Mating and Early Pregnancy							
Rat	30	5.17	63.3	7.7	7.5	3.8	3.8

[a] The mean C_{max} and AUC_{0-24} values for the 200 mg/day dose were 0.675 µg/ml and 8.40 µg•hr/ml, respectively and the mean C_{max} and AUC_{0-24} values for the 400 mg/day dose were 1.35 µg/ml and 16.8 µg•hr/ml, respectively. Ratio was calculated by dividing animal Day last AUC_{0-24hr} or C_{max} values by respective human values.

[b] See Teratology Studies Section; Study №: 2.4.2.1, p. 64.

[c] See Teratology Studies Section; Study №: 2.4.2.2, p. 66.

5.2.5. *GENETIC TOXICOLOGY*

The mutagenic potentials of celecoxib were evaluated in both *in vitro* and *in vivo* systems and results are summarized in the following table.

Assay System	Indicator Cells	SC-58635 Conc.	Findings
Ames	*Salmonella typhimurim* strains (histidine auxotrophs) TA97a, TA98, TA100, TA1535 and TA1538	10, 50, 100, 500, 1000, and 5000 μg/plate	Toxic at concentrations of ≥500 μg/plate Not mutagenic at concentrations up to 500 μg/plate
CHO/HGRT Mutation	CHO cells (subline K1-BH4)	Range-Finding: 0.08 - 800.0 μg/ml -S9: 4, 8, 12, and 16 μg/ml +S9: 15, 30, 45, and 60 μg/ml	Not mutagenic at doses up to 16 μg/ml and 45 μg/ml in the absence and presence of S9 activation, respectively.
Chromosome Aberration	CHO-WBL cells	Range-Finding: 0.08 - 800.0 μg/ml -/+ S9: 10, 20, and 40 μg/ml	+S9: ↑ frequency in cell endoreduplication. Slight but not significant ↑ in % cells with aberration.
Micronucleus Assay	♂ & ♀ Crl:CD®(SD)BR Rats - Bone Marrow Cells	150, 300, and 600 mg/kg/day po for 3 days	Not clastogenic

5.2.6. *SPECIAL TOXICOLOGY*

The antigenic properties and the potentials to cause skin sensitivity, dermal or ocular irritations of celecoxib were evaluated and the observations are summarized in the following table.

Testing System	Species	SC-58635 (Dose/Route)	Observations/Comments
ANTIGENIC PROPERTY			
ASA, HmPCA (4 hr), and HtPCA Rxns[a]	♂ Guinea Pigs	Sensitization: 5, 25 po or 25 mg/kg sc Challenge: 5 mg/kg iv	Not antigenic.
SKIN CONTACT SENSITIVITY/DERMAL/OCULAR IRRITATION			
Guinea Pig Maximization Test	Crl:(HA)BR Albino Guinea Pigs	Sensitization: 5% in FCA/H_2O id[b] Induction and Challenge 25% in Petrolatum dermal topical	No concurrent + control was performed. Therefore, the study was not valid.
Primary Skin Irritation	♂ Hra:(NZW)SPF Rabbits	0.5 g dermal occlusion	No dermal irritation.
Primary Eye Irritation	♂ Hra:(NZW)SPF Rabbits	0.011 g (0.1 ml wt equivalent) lower everted eye lid	Minimal ocular irritation.

[a] ASA = Active Systemic Anaphylaxis; HmPCA = Homologous Passive Cutaneous Anaphylaxis; HtPCA = Heterologous Passive Cutaneous Anaphylaxis; Rxns = Reactions.

[b] FCA = Freund's Complete Adjuvant; id = intradermal injection

5.2.7. *TOXICITY RELATED TO THE STARTING MATERIAL (SC-70986, FOR SYNTHESIS OF SC-58635*

The following table shows the summary of toxicological findings for the starting material (SC-70986,) in various studies.

Testing System	Species/Indicator	SC-70986 Dose/Route	Findings
Acute Toxicity	♂ & ♀ Rats Crl:CD®(SD)BR	250, 500, 1000, and 2000 mg/kg/ ml po	LD_{50}: ♂, 1000 (558-1792); ♀, 707 (483-1036). Clinical Signs: Hyporeactivity, staggered gait, absence of grasping/righting reflex, prostration, clonic convulsions, thin appearance, hunched posture, red-stained face, excessive salivation, lacrimation, mydriasis, dyspnea, soft stool, wet and/or yellow-stained urogenital area
Primary Eye Irritation	Rabbits Hra:(NZW) SPF	73 mg lower eyelid	Unflashed: corneal and iridal involvement and moderate conjunctival irritation. Flushed: corneal involvement and slight conjunctival irritation.
Primary Dermal Irritation	Rabbits Hra:(NZW) SPF	0.5 g in 0.4 ml dist. H_2O applied to skin directly	Slight skin irritant.
Dermal Sensitivity (Guinea Pig Maximization Test)	guinea pigs Crl:(HA)BR	Sensitization: 5% in H_2O or FCA/H_2O id® Induction and Challenge: 25% in Petrolatum, dermal topical	**Extreme dermal sensitizer**: mild→intense skin reactions were noted in all animals in the test group; Some animals (12/20) in the test group showed subcutaneous hemorrhaging, necrosis, and desquamation in the test sites following challenge.
Salmonella/micro-somal Ames Assay	*Salmonella typhimurium*: histidine auxotrophs TA97a, TA98, TA100, TA102, and TA1535	10-5000 μg/plate	**Mutagenic**: ≥50 μg/plate, -S9 - TA97a and TA102 ≥100 μg/plate, + S9 - TA97a 5000 μg/plate, +/- S9 - TA98 and TA100

5.3. ADME

5.3.1. *ABSORPTION (BIOAVAILABILITY) AND TOXICOKINETICS*

5.3.1.1. Single IV Studies

Assessment of the intravenous (iv) pharmacokinetics of celecoxib was conducted in five species. The following table presents the summary of mean plasma PK parameters (SEM) following single dose iv administration of SC-58635.

Species	Dose (mg/kg)	$t_{1/2}$ (hr)		Vd_{ss} (l/kg)		Vd_{ss} (l/kg)		Cl (ml/min/kg)		$AUC_{0-\infty}$ (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Rat (N=3)	1	3.73	14.0	2.51	2.42	ND	ND	7.76	1.99	2.15	8.38
Rat (N=3)	10	3.49		1.86		ND	ND	5.81		28.7	
Guinea Pig (N=2)	6	1.16		1.98		ND	ND	20.5		5.49	
Dog (N=3)	1	3.92 (1.41)	4.09 (1.92)	2.30 (0.32)	2.30 (0.59)	ND	ND	10.0 (2.9)	7.98 (2.00)	2.00 (0.49)	2.52 (.52)
Dog (N=2)	5	8.84		2.42		ND	ND	3.08		31.2	
Dog (Fast) (N=3)	5	1.77 (0.25)	1.66 (0.16)	2.63 (0.43)	2.32 (0.15)	2.18 (0.20)	1.98 (0.05)	19.2 (2.2)	16.9 (1.6)	4.95 (0.47)	5.20 (0.47)
Dog (Slow) (N=3)	5	4.69 (0.44)	5.54 (0.36)	2.95 (0.21)	3.27 (0.21)	2.26 (0.09)	2.45 (0.09)	7.43 (0.44)	6.95 (0.45)	11.5 (0.7)	12.5 (0.7)
Cynomolgus Monkey (N=3)	1		1.66 (0.50)		3.58 (1.02)		3.22 (0.88)		22.7 (1.0)		0.736 (0.032)
Rhesus Monkey (N=3)	1		1.50 0.10)		2.73 (0.34)		2.34 (0.41)		17.8 (1.9)		0.957 (0.096)

ND = Not determined.
Fast = Dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate
Slow = Dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

5.3.1.2. Single Oral Studies

A summary of mean (SEM) plasma PK parameters for SC-58635 following single dose oral administration is shown in the following table.

Species (N)	Dose (mg/kg)	Sex	T_{max} (hr)	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg•hr/ml)	BA %
Rat (3)	2	♂	3.00	0.599	ND	ND
Rat (3)	10	♂	3.00	2.01	18.5	64.5
Dog (3)	1	♂	1.00 (0.50)	0.309 (0.015)	1.57 (0.32)	74.4 (5.6)
Dog (3)	1	♀	0.667 (0.167)	0.553 (0.070)	2.12 (0.47)	85.9 (20.7)
Dog (2)	5	♀	0.500	2.19	16.2	57.1
Dog (2)	5	♀	3.00	0.517	4.80	16.9
Dog-Fast (3)	5	♂ & ♀	0.667 (0.167)	0.822 (0.219)	2.63 (0.59)	63.7 (10.5)
Dog-Slow (3)	5	♂ & ♀	0.500 (0)	1.54 (0.19)	10.5 (1.6)	88.0 (5.8)

ND = Not determined; N = The number of animals.
Fast = Dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate.
Slow = Dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

The following table presents the food effect on mean SC-58635 PK (±SEM) parameters in beagle dogs.

Site of Absorption and Food Effect Studies in Beagle Dogs								
Dose (mg/kg)	Route	Diet	T_{max} (hr)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
			♂	♀	♂	♀	♂	♀
10 n=4	IG[a]	Fasted		0.688 ± 0.277		1.62 ± 0.36		10.3 ± 2.0
	Duodenum[a]			1.13 ± 0.63		1.46 ± 0.20		9.69 ± 1.57
	Jejunum[a]			2.25 ± 1.92		1.06 ± 0.21		9.37 ± 0.97
	Colon[a]			8.50 ± 2.02		0.789 ± 0.118		10.0 ± 0.9
5 n=3/sex	IG[b]	Fasted	1.50 ± 0.29	7.50 ± 5.27	0.356 ± 0.163	0.364 ± 0.035	1.89 ± 1.01	3.32 ± 0.28
		Low Fat	3.00 ± 0.50	3.67 ± 1.17	0.712 ± 0.227	0.775 ± 0.064	5.63 ± 1.94	5.58 ± 1.09
		Med. Fat	5.33 ± 0.67	4.67 ± 0.67	0.706 ± 0.148	0.631 ± 0.080	5.07 ± 1.35	5.07 ± 0.83
		High Fat	6.00 ± 1.15	5.33 ± 1.76	0.737 ± 0.115	0.808 ± 1.06	6.64 ± 1.73	6.66 ± 1.34

[a]SC-58635 was administered as a solution in PEG:H_2O, 2:1, (v/v) or in PEG:Saline, 2:1, (v/v).
[b]SC-58635 was administered as neat chemical in a gelatin capsule.
Med. Fat = Medium Fat ; IG = Intragastrically.

5.3.1.3. Repeated-Dose Oral Toxicity Studies

Mouse Studies

The following table summarizes PK parameters obtained from 2-, 13-, and 104-week oral toxicity studies.

2-Week Diet Admix Study in Mice, EX4325

Dose (mg/kg)	C_{max} (μg/ml)		AUC_{0-21} (μg•hr/ml)	
	♂	♀	♂	♀
100	3.52	1.52	55.8	20.4
300	10.4	4.54	148	60.5
1000	19.7	10.6	288	162

13-Week Diet Admix Range-Finding Study in Mice, EX4357

Dose (mg/kg)		C_{max} (μg/ml)						$AUC_{0-\infty}$ (μg•hr/ml)					
♂	♀	♂			♀			♂			♀		
		Day 1	Day 45	Day 87	Day 1	Day 45	Day 87	Day 1	Day 45	Day 87	Day 1	Day 45	Day 87
75	150	2.78	2.00	2.44	2.99	1.92	2.04	38.7	32.2	39.6	42.1	24.2	30.8
150	300	6.71	4.62	3.79	6.22	2.79	3.55	84.7	70.7	57.2	85.3	47.0	48.0
300	1000	12.8	8.27	6.65	14.6	12.8	11.5	216	153	123	226	181	183

104-Week Diet Admix Carcinogenicity Study, SA4452

Week (Days)	Dose (mg/ kg)					C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
	Wk1-18	Wk 19-104	Wk1-18	Wk19-22	Wk 23-80				
	♂		♀			♂	♀	♂	♀
1 (3- 4)	25	12.5	50	25	25	0.973	0.807	11.1	12.3
	50	25	100	50	50	1.73	2.73	22.0	29.9
	75	37.5	150	75	150	2.55	2.65	34.7	33.8
19 (126- 127)	25	12.5	50	25	25	0. 865	0.555	13.5	7.05
	50	25	100	50	50	1.75	0. 815	32.8	14.3
	75	37.5	150	75	150	2.69	0.699	50.8	13.8
52 (357- 358)	25	12.5	50	25	25	0.328	0. 290	6.43	4.31
	50	25	100	50	50	0.723	0.558	13.2	8.14
	75	37.5	150	75	150	1.24	0.967	22.8	17.6
78 (540- 541)	25	12.5	50	25	25	0.479	0.335	9.22	5.99
	50	25	100	50	50	0.933	0.813	16.4	12.9
	75	37.5	150	75	150	1. 22	1.84	25.0	26.5

Rat Studies

The following table summarizes PK parameters obtained from 4-, 13-, 26-, and 104-week oral toxicity studies.

4-Week Oral Toxicity Study (SA4261)

Dose (mg/kg)	C_{max} (μg/ml)				AUC_{0-24} (μg•hr/ml)			
	Day 1		Day 26		Day 1		Day 26	
	♂	♀	♂	♀	♂	♀	♂	♀
20	2.60	3.44	1.57	2.63	30.3	41.8	19.2	36.0
80	5.19	7.64	3.09	5.55	73.2	118	29.7	82.0
400	10.3	12.3	5.85	9.60	196	245	60.7	159
600	6.71	13.9	5.53	16.2	97.6	276	58.2	315

13- and 26-Week Oral Toxicity Studies (SA4346 and SA4366*)

Dose	C_{max} (μg/ml)								AUC_{0-24} (μg•hr/ml)							
(mg/kg)	Day 1		Day 42		Day 91		Day 182*		Day 1		Day 42		Day 91		Day 182*	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
20	2.47	2.91	1.68	3.06	1.75	2.20	2.03	4.05	22.0	38.3	17.6	36.9	18.9	34.2	26.5	52.5
80	3.79	5.99	2.58	6.86	2.49	4.26	2.97	6.94	42.4	83.5	23.4	90.3	36.3	75.4	41.5	101
400	6.50	11.6	4.36	6.80	3.91	7.19	5.12	10.5	78.8	149	66.1	100	58.3	105	54.6	150

104-Week Carcinogenicity Study (SA4367)

Group	Dose mg/kg/day	PK Parameter	Day 1 (Wk1)		Day 180 (Wk 26)	Day 359 (Wk 52)		Day 541 (Wk 78)	
			♂	♀	♂	♀	♂	♀	♂	♀
Low	20 5	C_{max} (μg/ml)	1.93	2.65	2.16	3.41	2.00	4.75	1.45	1.11
Mid	80 10		3.42	5.63	3.09	7.46	2.88	7.44	0.893	2.00
High	400 200		6.09	10.1	4.62	7.93	4.71	9.47	4.28	13.0
Low	20 5	AUC_{0-24} (μg•hr/ml)	18.7	39.1	22.6	51.6	24.8	72.8	20.8	17.9
Mid	80 10		42.6	81.2	39.0	111	38.2	114	11.6	27.7
High	400 200		95.1	163	56.8	118	73.4	158	66.7	132

The following table summarizes PK parameters obtained from reproductive toxicity studies.

Pre-Mating and Early Pregnancy Study in Rats				
Dose (mg/kg)	C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
	Day 1[a]	Day 23[b]	Day 1	Day 23
5	1.84	1.63	25.6	23.3
15	3.59	3.35	57.6	47.2
30	3.96	5.17	70.6	63.3
50	5.93	5.25	95.7	90.9
[a] Animals were dosed 14 days prior to mating, throughout the mating period until day 7 of gestation. The total dosing period was approximately 23 days. [b] Gestation Day 7				
Embryo-Fetal Development Toxicity Studies in Rat (n=6/dose)				
Dose (mg/kg)	C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
	Gestation Day 6	Gestation Day 16/17	Gestation Day 6	Gestation Day 16/17
SA4362 - Animals were dosed once daily from day 6 to day 16 of gestation.				
10	1.79	2.81	20.3	37.1
30	3.01	5.03	43.9	67.0
100	6.37	7.45	134	115
SA4599 - Animals were dosed once daily from day 6 to day 17 of gestation.				
10	3.79	3.20	45.7	47.6
30	4.91	5.43	54.3	104
100	7.66	7.41	140	115
Embryo-Fetal Development Toxicity Studies in Rabbit, SA4342 (n=6/dose)				
	Gestation Day 7	Gestation Day 19	Gestation Day 7	Gestation Day 19
60	0.951	1.49	14.9	22.5
150	1.41	2.37	24.5	41.5
300	1.76	5.14	37.4	89.0

Dog Studies

Mean PK (±SEM) parameters for SC-58635 obtained from 4-, 13-, 26/52-week oral toxicity studies are summarized in the following tables.

4-Week Oral Safety Assessment Study in the Dog, SA4260							
Day of Dosing	Dose (mg/kg)[a]	C_{max} (μg/ml)			AUC_{0-24} (μg•hr/ml)		
		♂	♀	♂+♀	♂	♀	♂+♀
1	25 (n=4)	1.90 ± 0.79	1.72 ± 0.42	1.81 ± 0.42	21.7 ± 10.9	18.7 ± 6.7	20.2 ± 6.0
	50 (n=4)	4.15 ± 1.42	1.94 ± 0.66	3.04 ± 0.84	47.7 ± 13.3	25.4 ± 10.4	36.6 ± 8.9
	100 (n=8)	6.89 ± 1.54	3.96 ± 0.89	5.42 ± 0.94	104 ± 30	71.0 ± 19.9	87.3 ± 17.9
	250 (n=8)	10.3 ± 3.1	8.44 ± 2.05	9.37 ± 1.82	153 ± 53	120 ± 36	136 ± 31
15	100	8.35 ± 2.71	8.72 ± 3.34	8.51 ± 2.02	117 ± 41	104 ± 36	111 ± 27
	250	7.72 ± 2.98	12.0 ± 3.9	9.85 ± 2.43	135 ± 67	211 ± 80	173 ± 51
27	25	4.62 ± 2.58	2.27 ± 0.65	3.45 ± 1.31	71.5 ± 50.9	22.2 ± 7.8	46.9 ± 25.6
	50	6.77 ± 2.10	4.66 ± 2.04	5.86 ± 1.43	83.7 ± 30.2	60.6 ± 30.0	73.8 ± 20.3

[a] The 100 and 250 mg/kg dose groups were sacrificed on day 15 of dosing. The 25 and 50 mg/kg dose groups were sacrificed on day 27 of dosing. Reference: Document Number MRC-94S-0185.

13-Week Oral Safety Assessment Study in the Dog (SA4324)							
Dose (mg/kg)	Phenotype[b]	C_{max} (μg/ml)[a]			AUC_{0-24} (μg•hr/ml)		
		Day 1	Day 39	Day 88	Day 1	Day 39	Day 88
7.5 (bid)	Fast	1.04 ± 0.11	1.03 ± 0.11	0.802 ± 0.251	6.88 ± 1.33	5.79 ± 1.13	7.11 ± 2.70
	Slow	2.19 ± 0.36	1.75 ± 0.23	2.19 ± 0.32	17.3 ± 2.9	19.3 ± 2.5	21.0 ± 3.0
12.5 (bid)	Fast	1.75 ± 0.32	1.55 ± 0.14	1.33 ± 0.15	10.1 ± 1.0	12.6 ± 0.6	11.0 ± 1.7
	Slow	1.81 ± 0.49	2.39 ± 0.15	2.13 ± 0.35	15.2 ± 4.6	24.8 5.0	22.9 ± 5.5
17.5 (bid)	Fast	1.53 ± 0.26	2.16 ± 0.41	2.12 ± 0.41	12.8 ± 2.2	17.3 ± 3.4	17.0 ± 3.9
	Slow	2.76 ± 0.43	3.74 ± 0.40	3.14 ± 0.43	25.8 ± 3.5	43.0 ± 4.7	38.0 ± 4.4
25 (qd)	Fast	0.800 ± 0.329	0.326 ± 0.119	0.490 ± 0.046	6.18 ± 2.54	2.77 ± 1.52	3.18 ± 0.74
	Slow	0.916 ± 0.215	0.846 ± 0.182	0.860 ± 0.316	7.27 ± 1.52	9.41 ± 3.67	10.9 ± 5.1
26/52-Week Oral Safety Assessment Study in the Dog (SA4324)							
Dose (mg/kg)	Phenotype	C_{max} (μg/ml)[b]			AUC_{0-24} (μg•hr/ml)		
		Day 1	Day 178	Day 360	Day 1	Day 178	Day 360
7.5 (bid)	Fast	0.917 ± 0.238	0.832± 0.091	0.725 ± 0.083	5.16 ± 0.96	5.89 ± 0.63	5.61 ± 1.39
	Slow	2.01 ± 0.36	1.91 ± 0.38	1.91 ± 0.12	18.2 ± 2.1	21.2 ± 4.6	22.8 ± 4.7
12.5 (bid)	Fast	1.14 ± 0.28	2.15 ± 0.32	1.79 ± 0.36	9.22 ± 2.29	15.6 ± 3.9	15.1 ± 5.2
	Slow	2.04 ± 0.30	2.86 ± 0.39	2.53 ± 0.36	20.1 ± 3.4	30.9 ± 3.2	33.4 ± 6.5
17.5 (bid)	Fast	1.07 ± 0.13	1.76 ± 0.23	1.47 ± 0.20	8.92 ± 1.42	11.4 ± 1.3	11.8 ± 1.7
	Slow	2.61 ± 0.40	3.61 ± 0.19	3.11 ± 0.29	28.7 ± 5.3	40.6 ± 3.1	37.2 ± 5.0
25 (qd)	Fast	0.774 ± 0.254	0.537 ± 0.160	0.651 ± 0.235	4.00 ± 2.02	2.98 ± 0.88	3.86 ± 2.02
	Slow	1.94 ± 0.56	0.951 ± 0.186	0.886 ± 0.153	23.7 ± 7.4	10.6 ± 3.9	7.38 ± 1.28

[a] The C_{max} value reported is the maximal plasma SC-58635 concentration obtained over a 24 hour dosing day.

[b] Phenotype: Fast are dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate. Slow are dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

The following table shows the comparison of exposures to SC-58635 on last day of dosing in rat and dog toxicity studies to clinical human exposures at 200 and 400 mg/day.

Species	Duration	Sex/ Pheno-type[b]	NOEL (mg/kg)	Animal Exposure (Last Day of Dosing)		Animal/Human Exposure Ratio[a]			
				C_{max} (μg/ml)	AUC_{0-24} (μg•hr/ml)	200 mg/day		400 mg/day	
						C_{max}	AUC_{0-24}	C_{max}	AUC_{0-24}
Rat	4-Wk	♂	80						
		♀	400	9.60	159	14.2	18.9	7.1	9.5
Rat	13-Wk	♂	20	1.75	18.9	2.6	2.3	1.3	1.1
		♀	20	2.20	34.2	3.3	4.1	1.6	2.0
Rat	6-Mon	♂	20	2.03	26.5	3.0	3.2	1.5	1.6
		♀	20	4.05	52.5	6.0	6.3	3.0	3.1
Dog	4-Wk	♂	25	2.27	22.2	3.4	2.6	1.7	1.3
		♀	25	4.62	71.5	6.8	8.5	3.4	4.3
Dog	13-Wk	Fast (♂ & ♀)	35	2.12	17.0	3.1	2.0	1.6	1.0
		Slow (♂ & ♀)	35	3.14	38.0	4.7	4.5	2.3	2.3
Dog	6-Mon	Fast (♂ & ♀)	35	1.76	11.4	2.6	1.4	1.3	0.7
		Slow (♂ & ♀)	35	3.61	40.6	5.3	4.8	2.7	2.4
Dog	1-Year	Fast (♂ & ♀)	35	1.47	11.8	2.2	1.4	1.1	0.7
		Slow (♂ & ♀)	35	3.11	37.2	4.6	4.4	2.3	2.2

[a] The mean C_{max} and AUC_{0-24} values for the 200 mg/day dose were 0.675 μg/ml and 8.40 μg•hr/ml, respectively. The mean C_{max} and AUC_{0-24hr} values for the 400 mg/day dose were 1.35 μg/ml and 16.8 μg•hr/ml, respectively. Ratio was calculated by dividing animal Day last AUC_{0-24} or C_{max} values by respective human values.

[b] Phenotype: Fast are dogs of the phenotype that eliminate SC-58635 from plasma at a fast rate. Slow are dogs of the phenotype that eliminate SC-58635 from plasma at a slow rate.

5.3.2. *TISSUE DISTRIBUTION*

Celecoxib was well distributed into the majority of tissues as demonstrated by a rat tissue distribution study. Following an oral dose of 2 mg/kg [^{14}C]celecoxib, the gastrointestinal tract tissues contained the highest concentrations of radioactivity, with high levels of radioactivity also found in liver, red blood cells, adrenal glands, lacrimal glands and bone marrow. The concentrations of radioactivity in skin were the same as that of plasma, indicating that there was no preferential

partitioning of celecoxib and/or its metabolites into skin. The concentrations of radioactivity in pigmented and non-pigmented skin were similar and decreased at similar rates, indicating no irreversible or extensive binding of celecoxib to melanin. By 96 hours post dose, concentrations of radioactivity in most tissues were below the limit of detection.

Data from the whole-body autoradiography study (iv bolus loading dose of [^{14}C]celecoxib at 2 mg/kg followed by a 5-hour IV infusion dose of [^{14}C]celecoxib at 0.4 mg/kg/hr) showed that highly perfused tissues, namely liver, heart, lungs, and kidney, and intestinal contents contained the largest amounts of radioactivity. Smaller levels of radioactivity were observed in the stomach, lining of the cecum and intestines, harderian gland, adrenal gland, pancreas, bone marrow, blood, brain, spinal cord, testes, skin and hair follicles.

5.3.3. *METABOLISM*

Celecoxib was metabolized by a single metabolic pathway in all species studied (mouse, rat, dog, rabbit, and monkey). celecoxib to form SC-60613 was the initial step in the metabolism of SC-58635. Then, the of SC-60613 was further to form SC-62807. SC-60613 and SC-62807 were metabolites produced by rat, dog, cynomolgus monkey and rhesus monkey. The of SC-60613 and SC-62807 were present in bile of rat. The of SC-62807 and the of SC-62807 were present in rabbit urine. SC-60613 and SC-62807 have been synthesized and shown not to have any inhibitory activity to COX-1 or COX-2. The metabolism of celecoxib by the animal species studied was similar to that for human, i.e. of celecoxib to SC-60613 and further , SC-62807. The of SC-62907 is a minor metabolite in human.

In vitro metabolism of celecoxib was studied in the rat, dog, and human. Data showed that (1) celecoxib was a mild inducer of CYP2B but not CYP3A in the rat; (2) CYP2D15 was important for the metabolism of celecoxib in the dog; and (3) CYP2C9, which was the most import one, with CYP3A4 and CYP2C19 were involved in the metabolism of celecoxib in the human.

5.3.4. *PLASMA PROTEIN BINDING*

The plasma protein binding of SC-58635 was evaluated *in vivo*. Approximately 98-99% of celecoxib bound to plasma protein following oral administration to the mouse, rat and dog. Similar data were noted in the *in vitro* studies. The following table summarizes results expressed as % binding of [^{14}C]SC-58635 obtained from *in vitro* protein binding studies.

[^{14}C]SC-58635 (μg/ml)	Method	Mouse Plasma	Rat Plasma	Dog Plasma	Human Plasma	Human Albumin (40 mg/ml)[a]	Human AAG (1.8 mg/ml)[a]
0.1	Ultracentrifugation	94.4	98.4	98.2	98.2	100	92.4
0.3		ND	94.3	96.7	97.9	100	91.6
1		ND	91.4	97.0	96.5	99.8	91.0
3		ND	95.9	97.0	96.7	99.9	88.4
10		93.5	84.2	97.1	96.3	99.8	78.6
0.3	Charcoal	ND	95.6	ND	97.3	ND	ND
1		ND	85.3	ND	ND	ND	ND
3		ND	88.3	ND	90.6	ND	ND

ND - Not Determined.
AAG = α_1 acid glycoprotein.
[a] These concentrations reflect values in normal human.

5.3.5. *EXCRETIONS*

Studies in the rat, dog, cynomolgus monkey, and Rhesus monkey showed that biliary/intestinal excretion was the major route for the elimination of celecoxib following a single iv dose with values of 90%, 90%, 65%, and 80%, respectively. The remaining dose was eliminated through urine. SC-62807, the carboxylic acid metabolite, was the major metabolite excreted in both urine and feces. Celecoxib was metabolized extensively in all species studied as little or no unchanged drug was excreted in urine or bile.

5.3.6. *PLACENTAL TRANSFER AND MILK SECRETION*

Secretion of celecoxib through milk was evaluated in the lactating SD rats by given a single oral dose of 5 mg [^{14}C]SC-58635 via gavage. The concentrations of celecoxib in maternal plasma and milk were similar, indicating that celecoxib was distributed to milk and available to the neonate. In addition, celecoxib was present in plasma of neonates from dams that were administered the test article.

Placental transfer of celecoxib was studied by giving a single oral dose mg/kg [^{14}C]celecoxib to pregnant rats (n=18) at approximately day 18 of gestation. Results showed that the concentrations of celecoxib in maternal plasma and fetuses were similar, indicating that celecoxib crossed the placenta and was available to the fetus.

6. CONCLUSION AND RECOMMENDATION:

It appeared that GI and kidney were major target organs for SC-58635 induced toxicity following repeated oral administration to the mouse and rat.

GI injury with a low incidence of interdigital pyoderma/subcutis abscess was observed in dogs treated with doses ≥50 mg/kg/day (equivalent to 1.3-4.4x of human exposure at 400 mg/day dose as measured by AUC_{0-24}) for 4-week. **Similar findings of cutaneous lesions were observed in dogs treated with other COX-2 inhibitors. Although these observations occurred at low incidence and did not appear to be dose-dependent, test-article caused toxicity through the mechanism by inhibiting phagocytic cell functions could not be ruled out. Pathological lesions of papillary necrosis/pyelitis or interstitial suppurative nephritis/fibrosis were also identified in dogs receiving ≥50 mg/kg/day with a low frequency. Therefore, close monitoring of adverse events of microbial infections and renal complications in addition to GI injury in humans is highly recommended.** Additionally, there were lesions with slight→mild chronic multifocal perivascular/periventricular lymphocytic infiltrate identified in a dog 4-week toxicity study. These pathological changes within brain are often seen in dogs with viral infection with CNS involvement. Information from a rat study implied that SC-58635 could pass blood-brain-barrier (BBB) and rapidly distribute into CNS tissues as the levels of SC-58635 in CNS were higher than blood following an oral administration of 10 mg/kg (see **1.5.17; Document Nº BRD97D1852**). In addition, positive radioactivity was located in the brain and spinal cord in a microautoradioagraphic study (see **3.3.1.4, p.117**). Therefore, the observations of these changes may be attributable to drug-caused toxicity. Recent reports indicate that COX-2 is expressed by neuron in certain regions of the brain and the expression increases during neuron activity[18,19]. It would be beneficial to conduct additional studies to distinguish whether such lesions are drug-induced or due to underlying viral inflammatory diseases of the CNS or other causes.

The effects of SC-58635 on pancreatic functions were not investigated in the current submission. It has been shown that COX-2 is constitutively expressed in the pancreatic tissue (HIT-T15 cells, Syrian hamster islets and human pancreatic islets) under basal and stimulated condition[20]. Thus, the pharmacological or undesirable toxicological effects of SC-58635 on β-cells and blood glucose levels following long term use need to be addressed.

Approval of Celebrex™ is recommended.

Josie Yang 11/24/98
W.C. Josie Yang, Ph.D.

Concur by team leader: Yes ☒ No ☐

Andrea Weir 12-3-98
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cc:
HFD-550/Division File
/JYang
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