

Sample	PK Parameters	Sampling Day	20 mg/kg		80 mg/kg		400 mg/kg	
			♂	♀	♂	♀	♂	♀
Plasma	C <sub>max</sub> (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 <sub>max</sub> (hr)	1	3	3	6	6	6	6
		37	3	3	4	3	8	3
		86	3	6	4	6	8	6
RBC	C <sub>max</sub> (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 <sub>max</sub> (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 [<sup>14</sup>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 [<sup>14</sup>C] SC-58635 on Day 1, Weeks 6 and 13.

	Dose mg/kg	% of Radioactive Dose							
		Urine		Feces		Cage Rinse		Total	
		♂	♀	♂	♀	♂	♀	♂	♀
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 N<sup>o</sup>: MRC95C-30-950233  
 Study N<sup>o</sup>: 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 N<sup>o</sup> 94K014-A2B), [<sup>14</sup>C]SC-58635 (Lot N<sup>o</sup> GDS4021-68, specific activity 7.68 μCi/mg & Lot N<sup>o</sup> 4404-145, specific activity 143 μCi/mg)  
 Control Vehicle: 0.5% (w/v) methylcellulose and 0.1% Polysorbate 80 in distilled H<sub>2</sub>O  
 Dose & Route: 0, 20, 80, 400 mg/kg/day po by gavage  
 Animals: Sprague-Dawley rats, Crl:CD<sup>o</sup>(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: (b)(4)(CC)

Compliance with GMP/QAC: Yes

Study Date (In-Life): 03/06/95 - 10/12/95

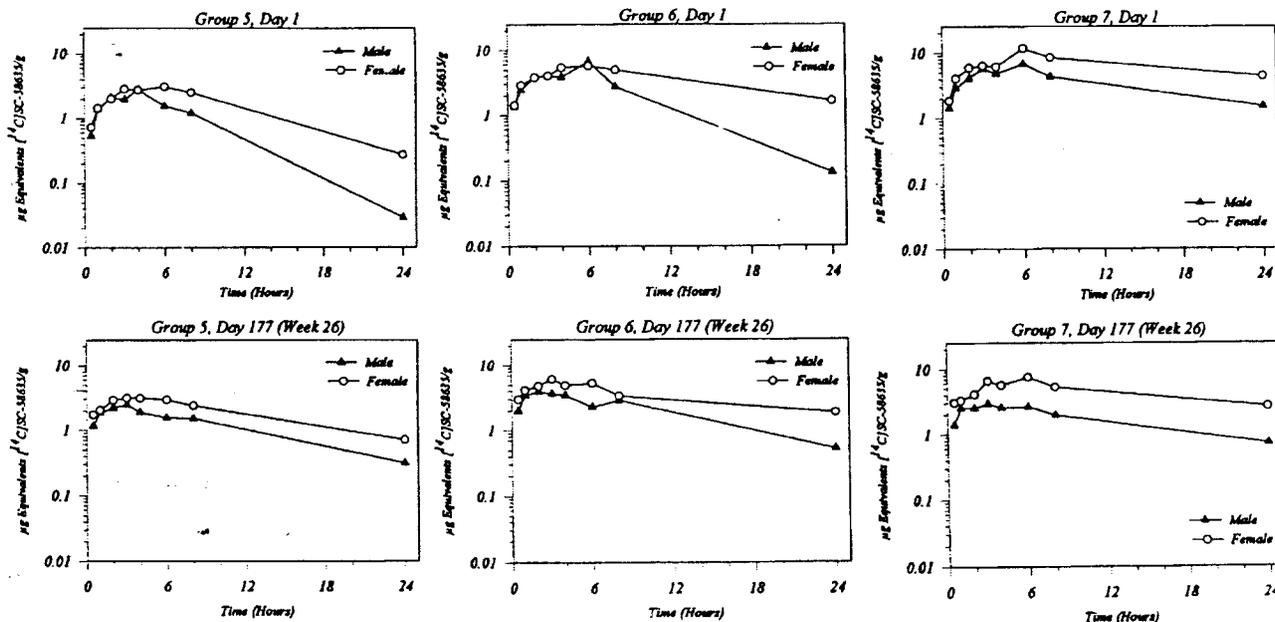
Study Design: Animals were given SC-58635, 0, 25, 80, or 400 mg/kg/day by oral gavage once daily for at least 26 weeks. Ten rats/sex from groups 1-4 were allowed to have a 4-week recovery period after the last dosing. Animal group designation and dosing levels are shown in the following table. On Days 1 and 177, [<sup>14</sup>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 dosing from 3 rats/sex/time point. Urine and fecal samples were collected over 168 hr after dosing with [<sup>14</sup>C] SC-58635 (Days 1 and 177) in 24 hr intervals. Plasma, red blood cells, urine, and feces were analyzed for content of radioactivity by liquid scintillation counting at the (b)(4)(CC)

Main and Recovery <sup>a</sup> Study				Satellite PK Study			
Group	Dose (mg/kg/day)	N <sup>o</sup> of Animals		Group	Dose (mg/kg/day)	N <sup>o</sup> 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	*The recovery group comprised of 10/sex/group			

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**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.

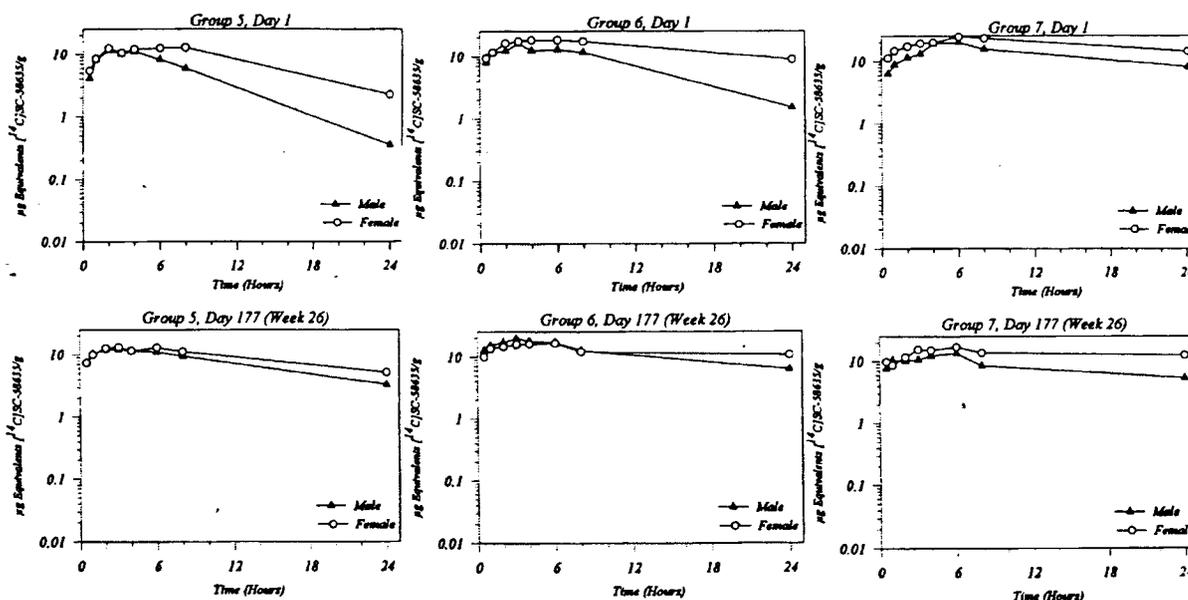


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The following table shows C<sub>max</sub> and T<sub>max</sub> values for radioactivity in plasma and RBC following oral administration of [<sup>14</sup>C] SC-58635 on Days 1 and 177.

Sample	PK Parameters	Sampling Day	20 mg/kg		80 mg/kg		400 mg/kg	
			♂	♀	♂	♀	♂	♀
Plasma	C <sub>max</sub> (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 <sub>max</sub> (hr)	1	4	3	6	6	6	6
		177	3	3	2	3	3	6
RBC	C <sub>max</sub> (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 <sub>max</sub> (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 excretion route was via feces. Mean cumulative and total percent radioactivity excreted in feces and urine during 0-168 hr following oral administration of [<sup>14</sup>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

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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; [<sup>14</sup>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♀ Sprague-Dawley 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)	N° 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

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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 ethoxycoumarin 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

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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 N<sup>o</sup>: M3096266  
 Study Aim: To determine if the glucuronide conjugate of SC-62807 is a urinary metabolite of [<sup>14</sup>C]SC-58635 in mouse, rat, rabbit or dog. Due to the instability of glucuronide conjugates in alkaline pH 7, following the administration of [<sup>14</sup>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: [<sup>14</sup>C]SC-58635 (Lot N<sup>o</sup> GDS-4671-84, 141 μCi/mg) and SC-58635 (Lot N<sup>o</sup>: 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 Sprague Dawley 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

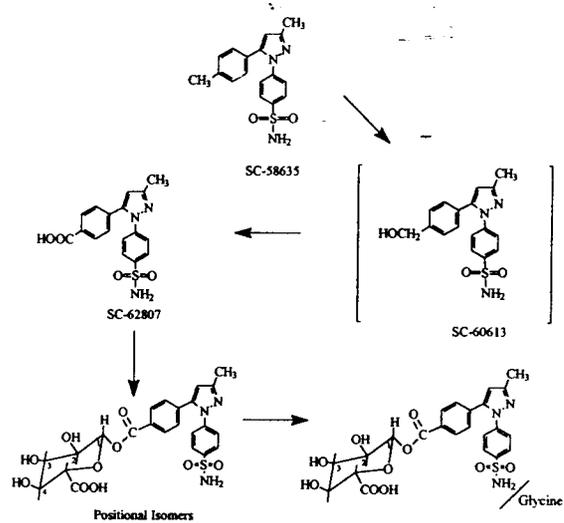
Sample Determination: The distribution of radioactivity in urine from each species dosed was determined by (b)(4)(CC) . The identification of the metabolites in rabbit urine was confirmed by (b)(4)(CC) (b)(4)(CC)

**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 (b)(4)(CC) 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 (b)(4)(CC) 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 - Four metabolites, SC-62807, two glucuronide conjugates and a glucuronide/glycine conjugates of SC-62807 (a dual conjugate of SC-62807), were identified in the urine by (b)(4)(CC). The position of the conjugation at the carboxylic acid moiety of SC-62807 was determined by (b)(4)(CC) Data showed that the two acid glucuronide conjugates of SC-62807 were likely positional isomers generated by acyl migration. The majority (92.3%) of the radioactivity in the urine collected in buffer at pH 5.0 was SC-62807 where only a minor portion of the radioactivity (<3%) in urine were conjugates of SC-62807. The proposed metabolic pathway in rabbit urine is depicted in the right figure.



Proposed Metabolic Pathway of SC-58635 in Rabbit Urine

Dog - the majority of the radioactivity in the (b)(4)(CC) 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.

(b)(4)(CC) distribution of radioactivity in the urine collected after the intravenous administration of [<sup>14</sup>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 HPLRC Chromatogram Present at			
			6-10.5 min (Tr=SC-62807)	10.5-11.0 min	11.0-19.5min	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 N°: MRC95S-0104

Study N<sup>o</sup>: 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: (b)(4)(CC)  
 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 from 14.5 to 19.9 mg/g of liver in males and 17.4 to 22.4 mg of protein/g 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 from 0.384 to 0.623 nmol /mg protein and was similar for both clearance rate groups and sexes. Results from this study were similar to those in Report N<sup>o</sup> MRC-95C-100-950295

3.4.3.2. The *In Vitro* Metabolism of [<sup>14</sup>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 N<sup>o</sup>: MRC-94S-0168  
 Study Aim: To evaluate the metabolism rate of [<sup>14</sup>C]SC-58635 in vitro and the metabolic profile of SC-58635 in rat, dog and human liver S9  
 Compound: [<sup>14</sup>C]SC-58635, 100,000 dpm/0.5 :1 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 [<sup>14</sup>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 (b)(4)(CC)

**Results:**

K<sub>m</sub> and V<sub>max</sub> values for [<sup>14</sup>C]SC-58635 metabolism in rat, dog and human liver S9 were present in the following table.

Species	K <sub>m</sub> (µg/ml)		V <sub>max</sub> (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

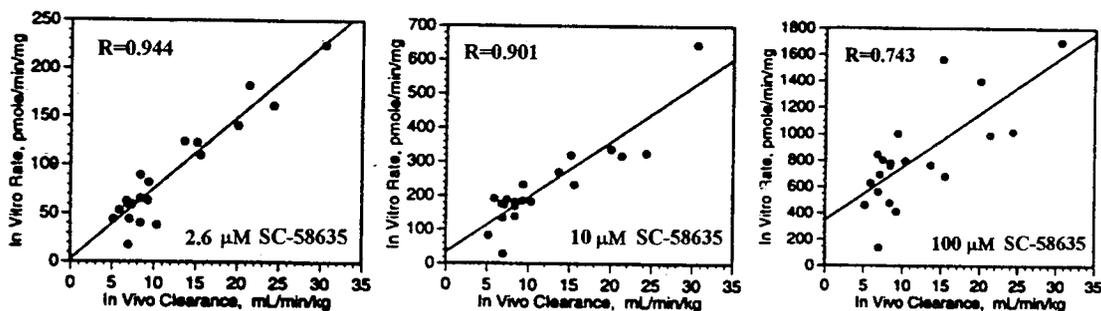
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The data showed that male rat liver metabolized [<sup>14</sup>C]SC-58635 greater than female rats. There was a tremendous variation (7x) in the metabolic rate of [<sup>14</sup>C]SC-58635 in different human liver S9 preparations (N=7). The liver S9 preparation from one human donor did not show any metabolic activity for [<sup>14</sup>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 (Vol. 1.73, p. 284-319)

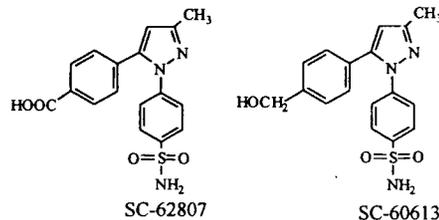
Report N<sup>o</sup>: M3095157  
 Study Aims: To establish that the slow and fast phenotypes correlate with hepatic P450 mediated metabolism and to determine which enzymes are involved.  
 Compound: SC-58635 and [<sup>14</sup>C]SC-58635  
 Specimens: Liver microsomes were isolated from 10 beagle dogs 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  $\mu$ M (1.0, 3.8 and 38  $\mu$ g/ml), respectively as shown in below figures.



The major metabolites of SC-58635 generated by dog liver microsomes were SC-60613 and SC-62807 which are the same as the major (unconjugated) metabolites *in vivo*. The *in vitro* metabolism of SC-58635 was NADPH-dependent, and was prohibited by carbon monoxide (CO), an inhibitor of cytochrome P450 (CYP) enzymes. Separate studies showed that human recombinant CYP2C9, CYP2C19 and CYP3A4 but not CYP2D6 metabolized SC-58635 and CYP2C9 was responsible for the major portion of SC-58635 metabolism by human liver microsomes. A series experiment with recombinant canine P450 isozymes to determine which isozymes contribute to SC-58635 metabolism showed that isoforms in the CYP2D subfamily had high activity for the oxidative metabolism of SC-58635, whereas CYP2B11, CYP2C21 and CYP3A12 had low activities activity for the oxidative metabolism of SC-58635.

Bufuralol, a putative marker substrate for CYP2D, was readily metabolized by 4 CYP2D15 isoforms and to lesser extent by CYP2B11, CYP2C21 and CYP3A12. Bufuralol hydroxylase activity was highly correlated ( $r=0.961$ ) with SC-58635 metabolism with recombinant protein. Furthermore, microsomes from both fast and slow dogs were significantly inhibited by quinidine, a potent CYP2D inhibitor. Altogether, these results suggest CYP2D15 is the major P450 responsible for SC-58635 metabolism in the dog. The complexity of the canine CYP2D15 system, with the presence of several variants, might be attributable to the differences in the rate of SC-58635 metabolism in the populations of slow and fast dogs.



3.4.3.4. Analysis Of Plasma, Urine And Fecal Samples From Dogs Dosed With [<sup>14</sup>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 (Vol. 1.74, p. 1-125)

Study N<sup>o</sup>: SA4260  
 Report N<sup>o</sup>: 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 [<sup>14</sup>C]SC-58635 and evidence for sex-related differences in any pharmacokinetic parameters.  
 Compound: SC-58553 (Lot N<sup>o</sup> 94K014-A1B) and [<sup>14</sup>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). [<sup>14</sup>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 [<sup>14</sup>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 <sup>14</sup>C by a Liquid Scintillation Counting (LSC) 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 high performance liquid radiochromatographic (HPLRC) procedure.

Group	Dose (mg/kg)	N <sup>o</sup> Animals /Sex/Group	N <sup>o</sup> 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 [<sup>14</sup>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.

- <sup>14</sup>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<sub>max</sub> and AUC values were noted on Day 28. The mean C<sub>max</sub> and AUC values for SC-58635 were higher in female dogs than male dogs.

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SC-58635 Concentration (µg eq/ ml)								
Time (hr)	25 mg/ kg				100 mg/ kg			
	Day 1		Day 28		Day 1		Day 15	
	♂	♀	♂	♀	♂	♀	♂	♀
<b>PLASMA</b>								
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
<b>RBC</b>								
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
<b>WHOLE BLOOD</b>								
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
<b>PK PARAMETERS</b>								
T <sub>max</sub> (hr)	1.5	1.5	2	5	24	7	2	2.5
C <sub>max</sub> (µg eq/ml)	1.42	1.66	1.38	3.50	9.93	24.7	3.47	6.14
AUC <sub>0-24</sub> (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		Day 1		Day 15	
	♂	♀	♂	♀	♂	♀	♂	♀
T <sub>max</sub> (hr)	1.5	1.25	2	3.25	13.75	6	1.5	2
C <sub>max</sub> (µg/ml)	1.24	1.525	1.835	3.167	9.335	20.65	7.305	13.5
AUC <sub>0-24</sub> (µg•hr/ml)	10.57	12.33	23.401	42.049	160.812	374.449	113.788	236.855

- Metabolic Profiles in Plasma - HPLRC 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 HPLRC 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 <sup>a</sup>	0.0142 ± 0.00442	0.0321 ± 0.0156	0.0383 ± 0.0125	0.0374 ± 0.0217

NP = No peak present in (b)(4)(C) profile in the SC-60613 position.

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

- Total <sup>14</sup>C in Urinary and Fecal Excretion - The majority (greater 90%) of the recovered dose was excreted in the feces as [<sup>14</sup>C]SC-58635 and [<sup>14</sup>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 N<sup>o</sup>: MRC95S-30-950263  
 Study N<sup>o</sup>: 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 N<sup>o</sup> 94K014-A2B) and [<sup>14</sup>C]SC-58635 (Lot N<sup>o</sup> GDS 4404-164, 2.13 μCi/mg & GDS 4404-165, 1.07 μCi/mg) in gelatin 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 <sup>a</sup> Study				Satellite PK Study			
Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	N <sup>o</sup> of Animals	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	N <sup>o</sup> of Animals
1 <sup>a</sup>	0	0	6/sex <sup>c</sup>	6 <sup>ab</sup>	7.5	15	3/sex
2 <sup>a</sup>	7.5	15	4/sex	7 <sup>ab</sup>	12.5	25	3/sex
3 <sup>a</sup>	12.5	25	4/sex	<sup>a</sup> Animals in Group 1-4, 6 and 7 were dosed twice daily at 12-hr intervals for ≥13 weeks.			
4 <sup>a</sup>	17.5	35	6/sex <sup>c</sup>	<sup>b</sup> 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 <sup>c</sup>	<sup>c</sup> Animals in group 6 and 7 received [ <sup>14</sup> C]SC-58635 at the first daily dose on day 1 and once during weeks 6 and 13.			

Study Location: (b)(4)(CC)

(b)(4)(CC) J.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 [<sup>14</sup>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  $^{14}\text{C}$  by a Liquid Scintillation Counting (LSC) method. The concentrations of SC-58635 in plasma were determined using a validated (b)(4)(C) procedure. The metabolic profiles of selected plasma, urine and fecal samples were determined using a (b)(4)(CC) procedure.

**Results:** In this report, the results of the (b)(4)(CC) 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 [ $^{14}\text{C}$ ]SC-58635 with values ranging from 62% to 100%. [ $^{14}\text{C}$ ]SC-60613, the hydroxylated metabolite of [ $^{14}\text{C}$ ]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 [ $^{14}\text{C}$ ]SC-58635 and [ $^{14}\text{C}$ ]SC-62807. There were no differences between sex, dose or duration of dosing in the fecal excretion profile. The following table shows mean ( $\pm$ SEM) percent of dose excreted in feces (0-72 hours) as SC-58635 and SC-62807 during Weeks 1, 6 and 13 in  $\sigma$  and  $\eta$  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-62807			
	7.5 mg/kg bid		12.5 mg/kg bid		7.5 mg/kg bid		12.5 mg/kg bid	
	$\sigma$	$\eta$	$\sigma$	$\eta$	$\sigma$	$\eta$	$\sigma$	$\eta$
1	75.6 $\pm$ 9.9	87.1 $\pm$ 3.8	77.4 $\pm$ 4.6	62.6 $\pm$ 13.6	19.4 $\pm$ 9.5	17.1 $\pm$ 10.8	11.5 $\pm$ 0.7	27.9 $\pm$ 13.9
6	65.6 $\pm$ 12.0	69.7 $\pm$ 12.5	75.8 $\pm$ 2.7	68.4 $\pm$ 9.5	24.0 $\pm$ 9.6	22.3 $\pm$ 12.2	14.6 $\pm$ 2.8	25.6 $\pm$ 17.2
13	78.2 $\pm$ 11.5	70.5 $\pm$ 7.8	77.3 $\pm$ 12.7	63.7 $\pm$ 10.4	15.6 $\pm$ 10.4	19.9 $\pm$ 7.6	14.3 $\pm$ 11.1	26.1 $\pm$ 9.9
	Fast	Slow	Fast	Slow	Fast	Slow	Fast	Slow
1	78.0 $\pm$ 11.5	84.7 $\pm$ 1.63	82.9 $\pm$ 1.0	57.1 $\pm$ 9.7	26.7 $\pm$ 10.8	9.78 $\pm$ 4.4	10.3 $\pm$ 1.5	29.2 $\pm$ 13.0
6	68.9 $\pm$ 13.2	66.4 $\pm$ 11.2	75.5 $\pm$ 2.6	68.8 $\pm$ 9.7	20.9 $\pm$ 10.8	25.4 $\pm$ 10.9	13.7 $\pm$ 3.4	26.5 $\pm$ 16.8
13	70.7 $\pm$ 7.7	78.0 $\pm$ 11.7	68.9 $\pm$ 12.0	72.0 $\pm$ 13.0	20.6 $\pm$ 8.2	14.9 $\pm$ 9.7	21.4 $\pm$ 10.5	19.1 $\pm$ 12.0

Mean ( $\pm$ SEM) percent of SC-58635 and SC-60613 in dog liver microsomes from  $\sigma$  and  $\eta$  dogs or from dogs characterized as having fast or slow SC-58635 clearance incubated with [ $^{14}\text{C}$ ]SC-58635 are tabulated as follows. The percentage of [ $^{14}\text{C}$ ]SC-58635 converted to [ $^{14}\text{C}$ ]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			
	$\sigma$	$\eta$	Fast	Slow	$\sigma$	$\eta$	Fast	Slow
Control	14.6 $\pm$ 4.4	14.0 $\pm$ 1.4	16.1 $\pm$ 2.5	9.00	71.3 $\pm$ 6.0	78.1 $\pm$ 1.7	73.7 $\pm$ 4.0	77.7
15	15.5 $\pm$ 5.3	14.8 $\pm$ 4.6	22.4 $\pm$ 3.7	7.88 $\pm$ 0.62	77.9 $\pm$ 5.7	84.5 $\pm$ 4.7	73.7 $\pm$ 4.3	88.7 $\pm$ 2.1
30	19.7 $\pm$ 6.7	10.8 $\pm$ 1.2	22.1 $\pm$ 5.3	8.45 $\pm$ 0.28	79.6 $\pm$ 6.7	88.9 $\pm$ 1.2	77.4 $\pm$ 5.4	91.2 $\pm$ 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 N<sup>o</sup>: CHV 700-338/SA4425  
Report N<sup>o</sup>: M3097112

Study Aim: To determine the metabolic profiles in plasma, urine and feces.  
 Compound: SC-58635 (Lot N<sup>o</sup> 94K014-A2B); [<sup>14</sup>C]SC-58635 (Lot N<sup>o</sup> 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)	N <sup>o</sup> of Animals/Sex	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	N <sup>o</sup> 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 [ <sup>14</sup> C]SC-58635 as 1 <sup>st</sup> daily dose on Day1 and Weeks 26 and 52.			

Study Location: (b)(4)(CC) 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 [<sup>14</sup>C]SC-58635 on Day 1, and Weeks 26 (Day 176) & 52 (Day 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 [<sup>14</sup>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 (b)(4)(CC) 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, [<sup>14</sup>C]SC-60613, and carboxyl, [<sup>14</sup>C]SC-62807, metabolites of [<sup>14</sup>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 (b)(4)(CC) profiles of pooled plasma samples.

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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

- <sup>a</sup> Plasma samples with radioactivity levels less than 1000 DPM/ml were not analyzed.
- <sup>b</sup> No peak detected.
- <sup>c</sup> The amount of radioactivity injected onto the (b)(4) (was < 500 DPM).
- <sup>d</sup> The amount of radioactivity injected onto the (b)(4) (was < 200 DPM).

Due to < 2% of the dose was excreted in urine from 0 - 168 hours, urine samples were not profiled by (b)(4)(CC). 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 from 27.8-93.6% and 6.45-71.2%, 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 [<sup>14</sup>C]Celecoxib ([<sup>14</sup>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 [<sup>14</sup>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  $\mu M$  (~18.8  $\mu g/ml$ ).
- Human recombinant CYP2C9, CY152C19, and CYP3A4 but not CYP1A2, CYP2A6, CYP21B6, CYP2D6, CYP2E1 and CYP3A5 were able to metabolize [<sup>14</sup>C]celecoxib to [<sup>14</sup>C]SC-60613 *in vitro*.
- Results from the comparison analysis of specific enzymatic activities for [<sup>14</sup>C]celecoxib metabolism by human microsome samples (N=16) with the known (phenotyped) specific

enzymatic activities of the same microsomes for a series of cytochrome P450 isoform specific substrates are shown in the following table.

P450 Isoform (Substrate)	Celecoxib @ 2.6 $\mu$ M		Celecoxib @ 10 $\mu$ M	
	Regression ( $r^2$ )	Correlation (r)	Regression ( $r^2$ )	Correlation (r)
CYP1A2 (Ethoxyresorufin)	0.315*	-0.561	0.223	-0.472
CYP2A6 (Ethoxycoumarin)	0.078	0.279	0.018	0.135
CYP2C9 (Tolbutamide)	0.616**	0.785	0.560**	0.748
CYP2C19 (Mephenytoin)	0.005	0.072	0.005	0.069
CYP2D6 (Bufuralol)	0.010	0.102	0.051	-0.225
CYP2E1 (Chlorzoxazone)	0.093	0.305	0.326*	0.571
CYP3A4/5 (Testosterone)	0.259*	0.509	0.186	0.432
CYP3A4 (Dextromethorphan)	0.253*	0.503	0.137	0.370
CYP4A9/11 (Lauric Acid)	0.021	-0.143	0.114	-0.338

\* $p \leq 0.05$ ; \*\* $p \leq 0.001$

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- 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.

P450 Isoforms	Marker	$K_i$ ( $\mu$ M)				
		Celecoxib	sulfaphenazole	omeprazole	quinidine	ketoconazole
CYP2C9	tolbutamide 4-hydroxylation	44.4	0.585	-	-	-
CYP2C19	(S)-mephenytoin 4'-hydroxylation	17.8	-	5.64	-	-
CYP2D6	(±)-bufuralol 1'-hydroxylation	4.19	-	-	0.466	-
CYP3A4	testosterone 6 $\beta$ -hydroxylation	106	-	-	-	0.0483

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  $\mu$ g/ml) and glyburide (0.025 - 1.25  $\mu$ g/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  $\mu\text{g/ml}$ , the rate of glyburide metabolism by human liver microsomes was approximately linear, indicating the human microsomal apparent  $K_m$  ( $K_m(\text{app})$ ) for glyburide was  $> 1.25 \mu\text{g/ml}$ .
- At the highest concentration, 10  $\mu\text{g/ml}$ , 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  $\mu\text{g/ml}$ ) had little or no effect on human microsomal metabolism of celecoxib (0.3 - 10  $\mu\text{g/ml}$ ). The apparent  $K_m$  for celecoxib metabolism by the human liver microsomes was 7.29  $\mu\text{g/ml}$  (19.1  $\mu\text{M}$ ).

#### 3.4.4.4. In Vitro Drug-Drug Interaction Of SC-58635 And Warfarin (b)(4)(CC)

Document No.: M2097288; Date: 18-Sep-1997 (Vol. 1.74, p. 337-357)

Report N<sup>o</sup>: 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  $\mu\text{M}$ ; SC 58635, 0, 1.0, 10, and 100  $\mu\text{M}$ .

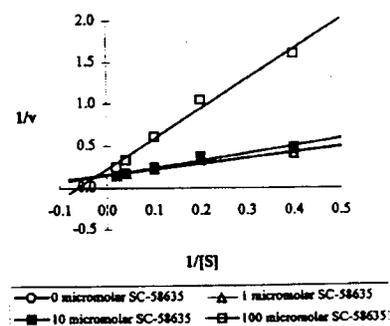
Study Site: (b)(4)(CC)

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 N<sup>o</sup> M3095130), which metabolizes warfarin to 7-hydroxywarfarin. Warfarin, at levels of 2.5, 5, 10, 25, and 50  $\mu\text{M}$ , was incubated with pooled human microsomes (0.5-1.0 mg protein) in the presence of SC-58635, 0, 1.0, 10, and 100  $\mu\text{M}$ . 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 (b)(4)(CC)

**Results:** Increasing concentrations of SC-58635 had increasing effect on the disappearance of warfarin and formation of 7-hydroxywarfarin with an apparent  $K_i$  value of 21.6  $\mu\text{M}$  as illustrated in the figure.

Reciprocal Plot of the Inhibition of (S)-7-Hydroxywarfarin Formation by Varying Levels of SC-58635



### 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 N<sup>o</sup>: 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 N<sup>o</sup> 94K014-A2B) and [<sup>14</sup>C]SC-58635 (Lot N<sup>o</sup> GDS 4404-164, 2.13  $\mu$ Ci/mg & GDS 4404-165, 1.07  $\mu$ Ci/mg) in gelatin capsule  
 Vehicle: Empty gelatin capsule  
 Dosage: 0, 15, 25, and 35 mg/kg/day po for  $\geq$  13 weeks  
 Animals: 30 $\sigma$  & 30 $\varphi$  beagle dogs, ~7-9 months old. Weighing 8.2-12.2 kg

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 <sup>o</sup> of Animals
1 <sup>a</sup>	0	0	6 <sup>c</sup>	6 <sup>ab</sup>	7.5	15	3
2 <sup>a</sup>	7.5	15	4	7 <sup>ab</sup>	12.5	25	3
3 <sup>a</sup>	12.5	25	4	<sup>a</sup> Animals in Group 1-4, 6 and 7 were dosed twice daily at 12-hr intervals for 13 weeks.			
4 <sup>a</sup>	17.5	35	6 <sup>c</sup>				
5	25	25	4 <sup>c</sup>	<sup>b</sup> Two animals/sex in group 1, 4, and 5 had a recovery phase for 28 days after a 13-week treatment.			
				<sup>c</sup> Animals in group 6 and 7 received [ <sup>14</sup> C]SC-58635 at the first daily dose on Day 1 and once during weeks 6 and 13.			

Study Location: (b)(4)(CC)

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 [<sup>14</sup>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 [<sup>14</sup>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 ( $\pm$ SD) C<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-t</sub> radioactivity in plasma and RBC on Day 1 and during Weeks 6 and 13 after a single oral dose of [<sup>14</sup>C]SC-58635. C<sub>max</sub> 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.

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	Dose mg/kg	PK Parameters	Day 1		Week 6		Week 13	
			♂	♀	♂	♀	♂	♀
Plasma	7.5	C <sub>max</sub> (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 <sub>max</sub> (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 <sub>0-4</sub> (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 <sub>max</sub> (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 <sub>max</sub> (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 <sub>0-4</sub> (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 <sub>max</sub> (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 <sub>max</sub> (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 <sub>0-4</sub> (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 <sub>max</sub> (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 <sub>max</sub> (hr)	5.9 ± 5	4.3 ± 1.2	5.3 ± 13	9.7 ± 5.8	5.0 ± 6.1	9.7 ± 5.8
		AUC <sub>0-4</sub> (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<sub>max</sub>, T<sub>max</sub>, and AUC of plasma and erythrocyte radioactivity concentrations following a single oral dose of [<sup>14</sup>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 mg/kg/day	Duration	C <sub>max</sub> (μg eq/g)		T <sub>max</sub> (hr)		AUC <sub>0-4</sub> (μg eq•hr/g)	
			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

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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 [<sup>14</sup>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

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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 from 0.577 to 0.688 nmole/mg 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 <sup>a</sup>	Control	0.641 ± 0.0526 <sup>b</sup>	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

<sup>a</sup> 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.

<sup>b</sup> 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 N<sup>o</sup>: CHV 700-338/SA4425

Report N<sup>o</sup>: 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 N<sup>o</sup> 94K014-A2B), [<sup>14</sup>C]SC-58635 (Lot N<sup>o</sup> 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)	N <sup>o</sup> of Animals/Sex	Group	Dose (mg/kg/dose)	Dose (mg/kg/day)	N <sup>o</sup> 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 [ <sup>14</sup> C]SC-58635 as 1 <sup>st</sup> daily dose on Day 1 and Weeks 26 and 52.			

Study Location: (b)(4)(CC)

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 [<sup>14</sup>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

[<sup>14</sup>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 [<sup>14</sup>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 1 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 [<sup>14</sup>C]SC-58635 showed concentrations in slow metabolizing animals to be higher than fast metabolizers.

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Sampling Time (hr)	Concentration of Radioactivity ( $\mu\text{g}$ 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	
	$\sigma$	$\phi$	$\sigma$	$\phi$	$\sigma$	$\phi$	$\sigma$	$\phi$
<b>Day 1</b>								
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
<b>Day 176</b>								
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
<b>Day 358</b>								
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 ( $\leq 2x$  background)

**APPEARS THIS WAY  
ON ORIGINAL**

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
<b>Day 1</b>								
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
<b>Day 176</b>								
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	ND	0.022±0.022	0.043±0.031	ND	ND
96	ND	ND	ND	ND	ND	ND	ND	ND
<b>Day 358</b>								
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 ( $\leq 2x$  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 [<sup>14</sup>C]SC-58635, 7.5 or 17.5 mg/kg, on Days 1, 176 and 358 are presented in the following table.

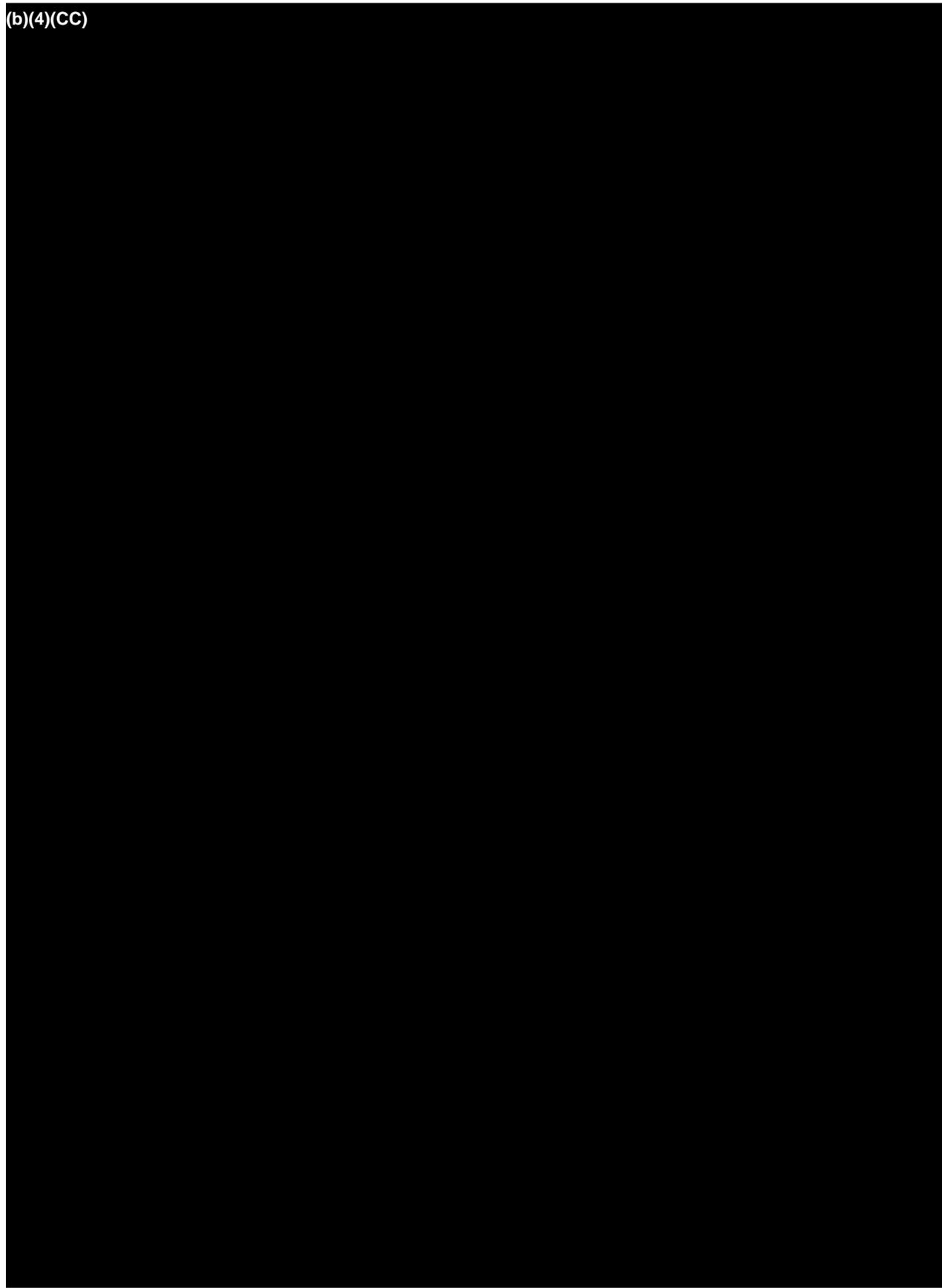
% RADIOACTIVE DOSE										
Dose mg/kg	Collection Time (hr)	URINE		FECES		PAN RINSE		Collection Time (hr)	CAGE WASH, CAGE/URINE WIPE	
		♂	♀	♂	♀	♂	♀		♀	♂
<b>DAY I</b>										
7.5	0-24	0.44±0.01	0.58±0.16	57.9±16.6	78.7±5.25	0.10±0.01	0.26±0.15	168 <sup>a</sup>	<0.005	0.11±0.08
	24-48	0.30±0.14	0.20±0.07	24.7±14.0	8.03±2.56	0.12±0.07	0.14±0.10	168 <sup>b</sup>	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 <sup>c</sup>	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 <sup>d</sup>	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	-	-			
	<b>Subtotal</b>	<b>0.88±0.21</b>	<b>0.99±0.21</b>	<b>88.8±0.32</b>	<b>89.5±1.54</b>	<b>0.25±0.08</b>	<b>0.59±0.37</b>	<b>Total<sup>e</sup></b>	<b>90.0±0.61</b>	<b>91.4±0.97</b>
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 <sup>a</sup>	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 <sup>b</sup>	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 <sup>c</sup>	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 <sup>d</sup>	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	-	-			
	<b>Subtotal</b>	<b>0.96±0.26</b>	<b>0.66±0.11</b>	<b>91.8±0.49</b>	<b>76.1±18.9</b>	<b>0.31±0.08</b>	<b>0.30±0.06</b>	<b>Total<sup>e</sup></b>	<b>93.4±0.49</b>	<b>77.3±18.8</b>
<b>DAY 176</b>										
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 <sup>a</sup>	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 <sup>b</sup>	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 <sup>c</sup>	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 <sup>d</sup>	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					
	<b>Subtotal</b>	<b>0.37±0.11</b>	<b>0.35±0.10</b>	<b>88.2±1.43</b>	<b>91.7±11.64</b>	<b>0.17±0.07</b>	<b>0.17±0.06</b>	<b>Total<sup>e</sup></b>	<b>88.8±1.34</b>	<b>92.3±1.60</b>
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 <sup>a</sup>	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 <sup>b</sup>	<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 <sup>c</sup>	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 <sup>d</sup>	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					
	<b>Subtotal</b>	<b>0.49±0.17</b>	<b>0.26±0.06</b>	<b>87.8±1.63</b>	<b>77.5±14.0</b>	<b>0.47±0.12</b>	<b>1.93±1.76</b>	<b>Total<sup>e</sup></b>	<b>88.8±1.43</b>	<b>80.0±11.9</b>
<b>DAY 358</b>										
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 <sup>a</sup>	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 <sup>b</sup>	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 <sup>c</sup>	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 <sup>d</sup>	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					
	<b>Subtotal</b>	<b>0.26±0.11</b>	<b>0.34±0.03</b>	<b>89.3±3.18</b>	<b>90.0±1.79</b>	<b>0.35±0.15</b>	<b>0.22±0.06</b>	<b>Total<sup>e</sup></b>	<b>92.0±1.69</b>	<b>91.0±1.70</b>
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 <sup>a</sup>	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 <sup>b</sup>	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 <sup>c</sup>	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 <sup>d</sup>	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					
	<b>Subtotal</b>	<b>0.40±0.07</b>	<b>1.05±0.39</b>	<b>88.2±1.65</b>	<b>87.1±1.99</b>	<b>0.31±0.11</b>	<b>0.20±0.06</b>	<b>Total<sup>e</sup></b>	<b>91.0±1.43</b>	<b>91.0±1.43</b>

ND = Not detectable; < 2x background; <sup>a</sup> Cage wash (MeOH); <sup>b</sup> Cage wash (TSP); <sup>c</sup> Cage wipe; <sup>d</sup> Urine wipe; <sup>e</sup> 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.

(b)(4)(CC)



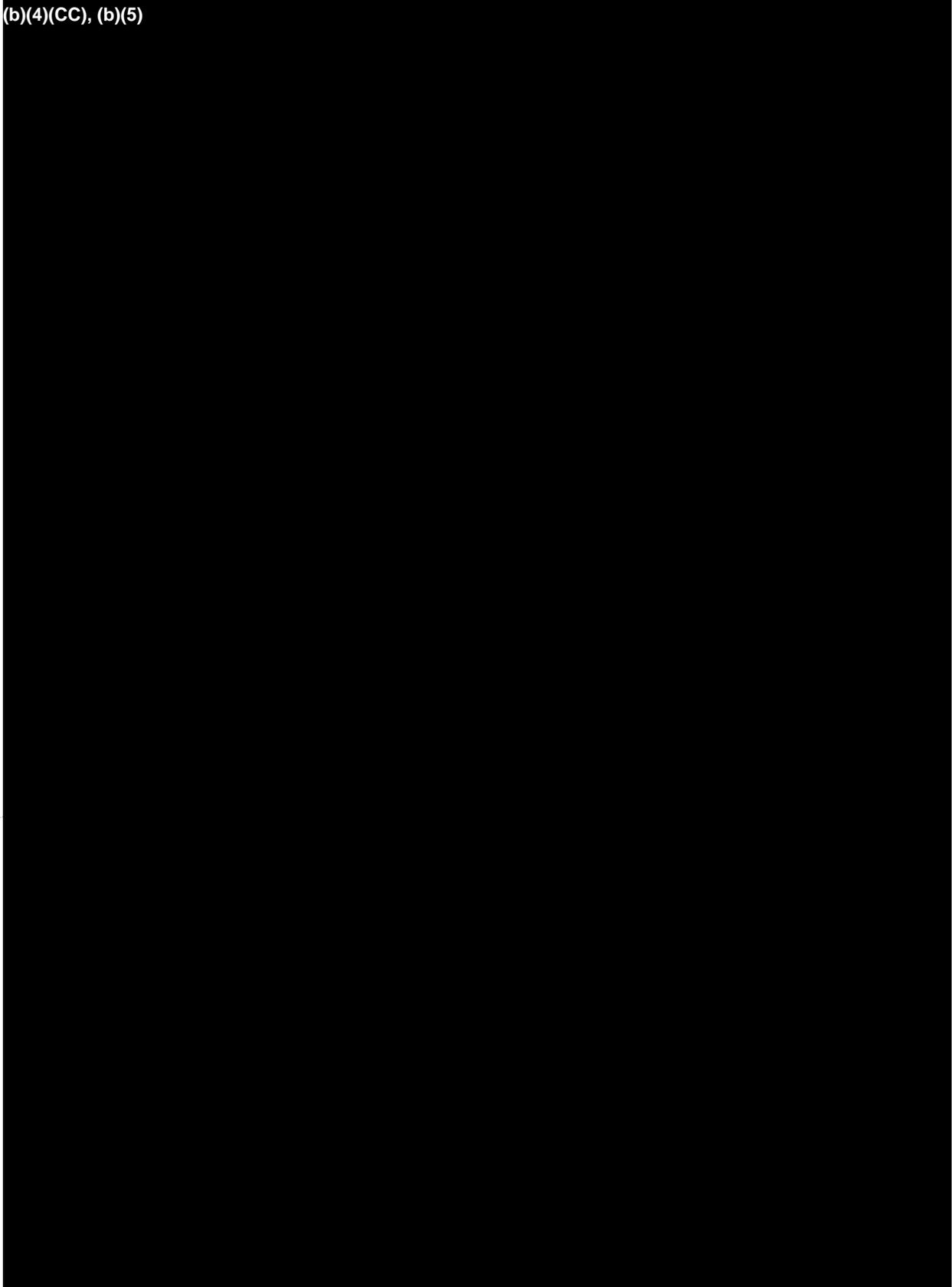
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**4. LABELING REVIEW:**

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## 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<sub>2</sub> 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<sub>50</sub> value of  $7 \pm 1$  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<sub>50</sub> value of  $0.3 \pm 0.1$  mg/kg; and
  - (3) carrageenan-induced air pouch in rats by the inhibition of PGE<sub>2</sub> and 6-keto PGE<sub>1α</sub> with an ED<sub>50</sub> value of  $0.2 \pm 0.1$  mg/kg.
- Analgesic Activity - SC58635 was effective in the following animal models.
  - (1) Hargreaves' hyperalgesia model with an ED<sub>50</sub> value of 0.35 mg/kg;
  - (2) formalin induced hyperalgesia in the mouse hindpaw model;
  - (3) peryl-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<sup>14</sup>. It has been demonstrated that colorectal tumors have elevated levels of COX-2<sup>15,16</sup>. The mechanism of chemoprevention by NSAIDs is not clear. However, NSAIDs induced apoptosis in human colorectal cancer cells has been demonstrated<sup>17</sup>.

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<sup>14</sup> Thun, MJ, 1995. Gastroenterol Clin North Am. 25: 333-348.

<sup>15</sup> Tsujii, M. and Bubois, RN, 1995. Cell 83: 493-501

<sup>16</sup> Morin, PJ, Vogelstein, B and Kinzler, KW, 1996. Proc. Natl. Acad. Sci. USA 93: 7950-4820.

<sup>17</sup> 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	
<b>Effect on General Activity and Behavior</b>				
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 1/3 mice.	
<b>Effect on Central Nervous System</b>				
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			Synergistic	≥150 mg/kg: slightly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected.
			Antagonistic	↓ incidences of tonic convulsions dose-dependently, the incidences of clonic and mortality were not affected.
Chemical-Induced Convulsions			Synergistic	≥150 mg/kg: significantly ↓ the incidences of clonic convulsions, the incidences of tonic and mortality were not affected.
	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)	
<b>Effect on Autonomic Nervous System and Smooth Muscle</b>				
Spontaneous Motility	Guinea Pig	4x10 <sup>-8</sup> to	≥4x10 <sup>-6</sup> : significantly ↓ the amplitude of spontaneous motility	
Agonist-induced Contraction	Isolated Ileum	4x10 <sup>-5</sup> M	≥4x10 <sup>-7</sup> M: ↓ BaCl <sub>2</sub> -induced contractions; ≥4x10 <sup>-6</sup> M: ↓ 5-HT-induced contractions; ≥4x10 <sup>-5</sup> 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 <sub>2</sub> , 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 <sup>+</sup> , Cl <sup>-</sup> excretion; ↑ urinary osmolarity significantly; ↔ on K <sup>+</sup> 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 <sub>2</sub> ↓ kidney PGE <sub>2</sub>	
	♀ Rat, 8/group	600 mg/kg/day x3 or x7	↔ urine volume, urinary PGE <sub>2</sub>	

5.2. TOXICOLOGY

5.2.1. ACUTE (SINGLE-DOSE)

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

Species N° 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

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## 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 N <sup>o</sup> 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 Determinable ♀: 150
CrI: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.	
CrI: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 pyelonephritis in ♂); statistically significant ↑ absolute liver weights and liver/body weight ratios without corresponding microscopic findings were identified for ♀ @ 400 or 600 mg/kg.	♂: 80 ♀: 400
CrI: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
CrI: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 <sub>2</sub> were present in the stomach and colon. SC-58635 caused ↓ in blood TBX and PGE <sub>2</sub> 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 incidence of interdigital pyoderma and subcutis abscess was 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 assessed 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

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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  $\geq 400$  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 was no treatment-induced increases in the tumor incidence rates. The exposure to SC-58635 in the high dose ♀ rats, as measure by AUC<sub>0-24</sub> 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*	0	0	0	0
1	25	12.5	50	25	25
2	50	25	100	50	50
3	75	37.5	150	75	150

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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 ♀ mice 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.

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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)
<b>FERTILITY, EARLY EMBRYONIC DEVELOPMENT → IMPLANTATION</b>				
♂ & ♀ Rats CrI: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 CrI: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 CrI:CD*(SD)BR	0, 60, 300	14-day followed by a 14-day reversal period before mating	No effects.	300
<b>TERATOLOGY- EMBRYO-FETAL DEVELOPMENT</b>				
♀ CD Rats VAF	0, 10, 30, 100	Gestation Days 6 → 17	100 mg/kg: slight ↓ live fetuses. ≥30 mg/kg: ↑ incidence of wavy ribs	30
♀ Rats CrI:CD*(SD)BR	0, 10, 30, 100	Gestation Days 6 → 17	≥30 mg/kg: ↑ incidence of diaphragmatic hernia, 5 <sup>th</sup> sternbrae 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 ↑ sternbrae fused and sternbrae misshapen 300 mg/kg: slight ↑ rib fused; ↑ post- implantation loss; ↓ live fetuses.	60
<b>PERINATAL/POST NATAL DEVELOPMENT</b>				
♀ Rats CrI:CD*(SD)BR	0, 10, 30, 100	Gestation Day 6 → Days 21-23 post partum	F <sub>0</sub> - ≥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 <sub>1</sub> & F <sub>2</sub> - Normal.	10

A comparison of exposure to SC-58635 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			
		C <sub>max</sub> (µg/ml)	AUC <sub>0-24</sub> (µg•hr/ml)	200 mg/day <sup>a</sup>		400 mg/day <sup>a</sup>	
				C <sub>max</sub>	AUC <sub>0-24hr</sub>	C <sub>max</sub>	AUC <sub>0-24</sub>
<b>Embryo-Fetal Developmental</b>							
Rat	10	3.20	47.6	4.7	5.7	2.4	2.8
Rabbit	60	2.37	41.5	3.5	4.9	1.8	2.5
<b>Pre-Mating and Early Pregnancy</b>							
Rat	30	5.17	63.3	7.7	7.5	3.8	3.8

<sup>a</sup> The mean C<sub>max</sub> and AUC<sub>0-24</sub> values for the 200 mg/day dose were 0.675 µg/ml and 8.40 µg•hr/ml, respectively and the mean C<sub>max</sub> and AUC<sub>0-24</sub> 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<sub>0-24hr</sub> or C<sub>max</sub> values by respective human values.

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### 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	<i>Salmonella typhimurim</i> strains (histidine auxotrophs) TA97a, TA98, TA100, TA1535 and TA1538	10, 50, 100, 500, 1000, and 5000 $\mu\text{g}/\text{plate}$	Toxic at concentrations of $\geq 500$ $\mu\text{g}/\text{plate}$ Not mutagenic at concentrations up to 500 $\mu\text{g}/\text{plate}$
CHO/HGRT Mutation	CHO cells (subline K1-BH4)	Range-Finding: 0.08 - 800.0 $\mu\text{g}/\text{ml}$ -S9: 4, 8, 12, and 16 $\mu\text{g}/\text{ml}$ +S9: 15, 30, 45, and 60 $\mu\text{g}/\text{ml}$	Not mutagenic at doses up to 16 $\mu\text{g}/\text{ml}$ and 45 $\mu\text{g}/\text{ml}$ in the absence and presence of S9 activation, respectively.
Chromosome Aberration	CHO-WBL cells	Range-Finding: 0.08 - 800.0 $\mu\text{g}/\text{ml}$ -/+ S9: 10, 20, and 40 $\mu\text{g}/\text{ml}$	+S9: $\uparrow$ frequency in cell endoreduplication. Slight but not significant $\uparrow$ in % cells with aberration.
Micronucleus Assay	$\sigma$ & $\text{♀}$ CrI:CD <sup>0</sup> (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
<b>ANTIGENIC PROPERTY</b>			
ASA, HmPCA (4 hr), and HtPCA Rxns <sup>a</sup>	$\sigma$ Guinea Pigs	Sensitization: 5, 25 po or 25 mg/kg sc Challenge: 5 mg/kg iv	Not antigenic.
<b>SKIN CONTACT SENSITIVITY/DERMAL/OCULAR IRRITATION</b>			
Guinea Pig Maximization Test	CrI:(HA)BR Albino Guinea Pigs	Sensitization: 5% in FCA/H <sub>2</sub> O id <sup>b</sup> Induction and Challenge 25% in Petrolatum dermal topical	No concurrent + control was performed. Therefore, the study was not valid.
Primary Skin Irritation	$\sigma$ Hra:(NZW)SPF Rabbits	0.5 g dermal occlusion	No dermal irritation.
Primary Eye Irritation	$\sigma$ Hra:(NZW)SPF Rabbits	0.011 g (0.1 ml wt equivalent) lower everted eye lid	Minimal ocular irritation.

<sup>a</sup> ASA = Active Systemic Anaphylaxis; HmPCA = Homologous Passive Cutaneous Anaphylaxis; HtPCA = Heterologous Passive Cutaneous Anaphylaxis; Rxns = Reactions.

<sup>b</sup> FCA = Freund's Complete Adjuvant; id = intradermal injection

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5.2.7. TOXICITY RELATED TO THE STATING MATERIAL (SC-70986, 4-SULFONAMIDOPHENYL HYDRAZINE HYDROCHLORIDE) FOR SYNTHESIS OF SC-58635

The following table shows the summary of toxicological findings for the stating material (SC-70986, 4-sulfonamidophenyl hydrazine hydrochloride) in various studies.

Testing System	Species/Indicator	SC-70986 Dose/Route	Findings
Acute Toxicity	♂ & ♀ Rats CrI:CD*(SD)BR	250, 500, 1000, and 2000 mg/kg/ ml po	LD <sub>50</sub> : ♂, 1000 (558-1792); ♀, 707 (483-1036). Clinical Signs: Hyporeactivity, staggered gait, absence of gasping/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	Unflushed: 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 <sub>2</sub> O applied to skin directly	Slight skin irritant.
Dermal Sensitivity (Guinea Pig Maximization Test)	guinea pigs CrI:(HA)BR	Sensitization: 5% in H <sub>2</sub> O or FCA/H <sub>2</sub> O id <sup>b</sup> Induction and Challenge: 25% in Petrolatum, dermal topical	<b>Extreme dermal sensitizer:</b> 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/microbial Ames Assay	Salmonella typhimurium: histidine auxotrophs TA97a, TA98, TA100, TA102, and TA1535	10-5000 µg/plate	<b>Mutagenic:</b> ≥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

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##### 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 <sub>1/2</sub> (hr)		Vd <sub>area</sub> (l/kg)		Vd <sub>ss</sub> (l/kg)		Cl (ml/min/kg)		AUC <sub>0-∞</sub> (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 <sub>max</sub> (hr)	C <sub>max</sub> (μg/ml)	AUC <sub>0-∞</sub> (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.

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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 <sub>max</sub> (hr)		C <sub>max</sub> (μg/ml)		AUC <sub>0-24</sub> (μg•hr/ml)	
			♂	♀	♂	♀	♂	♀
10 n=4	IG <sup>a</sup>	Fasted		0.688 ± 0.277		1.62 ± 0.36		10.3 ± 2.0
	Duodenum <sup>a</sup>			1.13 ± 0.63		1.46 ± 0.20		9.69 ± 1.57
	Jejunum <sup>a</sup>			2.25 ± 1.92		1.06 ± 0.21		9.37 ± 0.97
	Colon <sup>a</sup>			8.50 ± 2.02		0.789 ± 0.118		10.0 ± 0.9
5 n=3/sex	IG <sup>b</sup>	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

<sup>a</sup>SC-58635 was administered as a solution in PEG:H<sub>2</sub>O, 2:1, (v/v) or in PEG:Saline, 2:1, (v/v).

<sup>b</sup>SC-58635 was administered as neat chemical in a gelatin capsule.

Med. Fat = Medium Fat ; IG = Intragastrically.

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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 <sub>max</sub> (µg/ml)						AUC <sub>0-21</sub> (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 <sub>max</sub> (µg/ml)						AUC <sub>0-∞</sub> (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 <sub>max</sub> (µg/ml)		AUC <sub>0-24</sub> (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				

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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 <sub>max</sub> (µg/ml)								AUC <sub>0-24</sub> (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 (mg/kg)	C <sub>max</sub> (µg/ml)								AUC <sub>0-24</sub> (µg•hr/ml)							
	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	C <sub>max</sub> (µg/ml)	1.93	2.65	2.16	3.41	2.00	4.75	1.45	1.11						
	5															
	80		3.42	5.63	3.09	7.46	2.88	7.44	0.893	2.00						
Mid	10															
	400	6.09	10.1	4.62		4.71		4.28								
High	200				7.93		9.47		13.0							
	20	AUC <sub>0-24</sub> (µg•hr/ml)	18.7	39.1	22.6	51.6	24.8	72.8	20.8	17.9						
5																
80	42.6		81.2	39.0	111	38.2	114	11.6	27.7							
Mid	10															
	400	95.1	163	56.8		73.4		66.7								
High	200				118		158		132							

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

Pre-Mating and Early Pregnancy Study in Rats				
Dose (mg/kg)	C <sub>max</sub> (µg/ml)		AUC <sub>0-24</sub> (µg•hr/ml)	
	Day 1 <sup>a</sup>	Day 23 <sup>b</sup>	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
<sup>a</sup> 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.				
<sup>b</sup> Gestation Day 7				
Embryo-Fetal Development Toxicity Studies in Rat (n=6/dose)				
Dose (mg/kg)	C <sub>max</sub> (µg/ml)		AUC <sub>0-24</sub> (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)				
Dose (mg/kg)	Gestation Day 7	Gestation Day 19	Gestation Day 7	Gestation Day 19
	C <sub>max</sub> (µg/ml)	C <sub>max</sub> (µg/ml)	AUC <sub>0-24</sub> (µg•hr/ml)	AUC <sub>0-24</sub> (µg•hr/ml)
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

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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) <sup>a</sup>	C <sub>max</sub> (µg/ml)			AUC <sub>0-24</sub> (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

<sup>a</sup> 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.

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13-Week Oral Safety Assessment Study in the Dog (SA4324)							
Dose (mg/kg)	Phenotype <sup>b</sup>	C <sub>max</sub> (µg/ml) <sup>a</sup>			AUC <sub>0-24</sub> (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 <sub>max</sub> (µg/ml) <sup>b</sup>			AUC <sub>0-24</sub> (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

<sup>a</sup> The C<sub>max</sub> value reported is the maximal plasma SC-58635 concentration obtained over a 24 hour dosing day.  
<sup>b</sup> 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 <sup>b</sup>	NOEL (mg/kg)	Animal Exposure (Last Day of Dosing)		Animal/Human Exposure Ratio <sup>a</sup>			
				C <sub>max</sub> (µg/ml)	AUC <sub>0-24</sub> (µg•hr/ml)	200 mg/day		400 mg/day	
						C <sub>max</sub>	AUC <sub>0-24</sub>	C <sub>max</sub>	AUC <sub>0-24</sub>
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

<sup>a</sup> The mean C<sub>max</sub> and AUC<sub>0-24</sub> values for the 200 mg/day dose were 0.675 µg/ml and 8.40 µg•hr/ml, respectively. The mean C<sub>max</sub> and AUC<sub>0-24hr</sub> 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<sub>0-24</sub> or C<sub>max</sub> values by respective human values.  
<sup>b</sup> 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 [<sup>14</sup>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

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partitioning of celecoxib and/or its metabolites into skin. The concentrations of radioactivity in pigmented and nonpigmented 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 [<sup>14</sup>C]celecoxib at 2 mg/kg followed by a 5-hour IV infusion dose of [<sup>14</sup>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). Hydroxylation of the aromatic methyl group of celecoxib to form SC-60613 was the initial step in the metabolism of SC-58635. Then, the hydroxyl group of SC-60613 was further oxidized to a carboxyl to form SC-62807. SC-60613 and SC-62807 were metabolites produced by rat, dog, cynomolgus monkey and rhesus monkey. The glucuronide conjugates of SC-60613 and SC-62807 were present in bile of rat. The glucuronide conjugate of SC-62807 and the dual glucuronide glycine conjugate 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. hydroxylation of celecoxib to SC-60613 and further oxidation to the carboxylic acid, SC-62807. The *l*-O-glucuronide 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 and CYP3A4 were the most important cytochrome enzymes 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 95% 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 [<sup>14</sup>C]SC-58635 obtained from *in vitro* protein binding studies.

[ <sup>14</sup> C]SC-58635 (µg/ml)	Method	Mouse Plasma	Rat Plasma	Dog Plasma	Human Plasma	Human Albumin (40 mg/ml) <sup>a</sup>	Human AAG (1.8 mg/ml) <sup>a</sup>
0.1	(b)(4)(CC)	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		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 =  $\alpha_1$  acid glycoprotein.

<sup>a</sup> 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 by the evidence of little or no unchanged drug 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 [<sup>14</sup>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 [<sup>14</sup>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.

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**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 low incidence of interdigital pyoderma/subcutis abscess were observed in dogs treated with doses  $\geq 50$  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. Therefore, close monitoring of adverse events of microbial infections 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. Therefore, the observations of these changes may be attributable to drug-caused toxicity. 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 constitutively expressed in the pancreatic tissue (HIT-T15 cells, Syrian hamster islets and human pancreatic islets) under basal and stimulated condition<sup>18</sup>. Thus, the pharmacological or undesirable toxicological effects of SC-58635 on  $\beta$ -cells and blood glucose levels following long term use need to be addressed.

Approval of Celebrex™ is recommended.

**APPEARS THIS WAY  
ON ORIGINAL**

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W.C. Josie Yang, Ph.D.

Concur by team leader: Yes  No

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Andrea Weir, Ph.D.

**APPEARS THIS WAY  
ON ORIGINAL**

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<sup>18</sup> Sorli CH, et al., 1998. Proc. Natl. Acad. Sci. USA 95: 1788-1793.

cc:

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/JYang

/AWeir

/JWitter

/MAverbuch

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HFD-345

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ON ORIGINAL**

**7. APPENDIX:**

**1. Executive CAC Recommendations and Conclusions on Carcinogenicity Studies**

**Executive CAC**  
**October 27, 1998**

**Committee:** Joseph DeGeorge, Ph.D., HFD024, Chair  
Joseph Contrera, Ph.D., HFD-900, Member  
Barry Rosloff, Ph.D., HFD-120, Alternate Member  
Josie Yang, Ph.D., HFD-550, Presenting Reviewer  
Andrea Weir, Ph.D., HFD-550, Division Team Leader

**Author of Draft:** Josie W. C. Yang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

**NDA 20-998**

**Name of Drug:** Celecoxib; Celebrex™; SC-58635  
**Sponsor:** G.D. Searle & Co

**Background:** Celecoxib (SC-58635 - C17H14F3N3O2S), a newly developed cyclooxygenase-2 (COX-2) inhibitor, is a diarylsubstituted pyrazole compound. Celecoxib is proposed for the treatment of the signs and symptoms of RA and OA, and for the management of acute and chronic pain. Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an in vivo micronucleus test in rat bone marrow.

**Mouse Carcinogenicity 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*	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). Non-dose dependent pyelonephritis was only observed in drug-treated ♂ with low incidence rates. The GI injury was the most common cause of death in high-dose animals. No treatment-induced increases in the tumor incidence rates were identified.

**Rat Carcinogenicity 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.

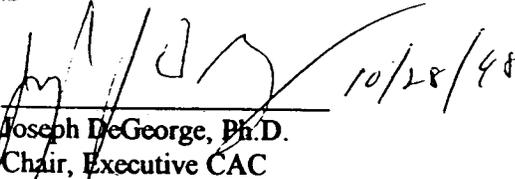
Group	Dose mg/kg/day				
	Wk 1-17	Wk 18-77		Wk 78-104	
	♂ & ♀	♂	♀	♂	♀
1 (Control)	0	0	0	0	0
2 (Low)	20	20	20	20	5
3 (Mid)	80	80	80	80	10
4 (High)	400	400	200	200	200

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  $\geq 400$  mg/kg/day for  $\sigma$  rats [ $AUC_{0-24}$  ( $\mu\text{g}\cdot\text{hr}/\text{ml}$ ) for 400 and 600 mg/kg  $\sigma$ : 195.9 and 97.6 on Day 1 and 60.7 and 58.2 on Day 26, respectively] and deaths were seen at 600 mg/kg/day for  $\text{f}$  rats. Treatment-related deaths increased with dose and occurred in the mid- and high-dose  $\sigma$  and all treated female groups (Group 2: 4 $\text{f}$ ; Group 3: 4 $\sigma$  & 20 $\text{f}$ ; Group 4: 19 $\sigma$  & 31 $\text{f}$ ). Due to excessive toxicity, high dose females were sacrificed at Week 79. The major non-neoplastic findings were dose-dependent increased incidence of GI necrosis/perforation/inflammation with secondary peritonitis and pyelonephritis ( $\sigma$  only). No treatment-induced increases in the tumor incidence rates were identified.

#### Executive CAC Recommendations and Conclusions

1. The Committee found that both rat and mouse carcinogenicity studies were acceptable.
2. Based on observed GI and kidney toxicity findings as well as mortality, the MTD was reached for both mouse and rat studies.
3. Celecoxib was not carcinogenic in rats or mice.

  
Joseph DeGeorge, Ph.D.  
Chair, Executive CAC

cc:\

/Division File, HFD-550  
/JYang  
/AWeir  
/ASeifried, HFD-024

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**ADVISORY COMMITTEE: ARTHRITIS DRUGS  
ADVISORY COMMITTEE MEETING**

**DATE OF MEETING: 12/1/98**

Arthritis Advisory Committee  
Food and Drug Administration  
Center for Drug Evaluation and Research

Town Center Hotel, 8727 Colesville Road, Silver Spring, MD

December 1, 1998

NDA 20-998, Celebrex™ (celecoxib) Searle

**Agenda**

**8:00** Call to Order, Introductions: Steven Abramson, M.D.,  
Acting Chair, Arthritis Advisory Committee  
Meeting Statement: Kathleen Reedy, Executive Secretary  
Arthritis Advisory Committee  
Introductory Comments: Robert DeLap, M.D., Director, ODEV  
John Hyde, M.D., Acting Deputy Director  
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs

**8:30 Searle Presentation**

**Introduction:** Dr. P. Needleman, Ph.D., Co-President Searle  
Chief Scientist Monsanto

**Non-clinical Overview:** Dr. P. Isakson, Ph.D.

Executive Director and Senior Fellow COX-2 Technology

**Clinical PK:** Dr. A. Karim, Ph.D., ABCP Distinguished Scientist,  
Senior Director, Clinical Pharmacokinetics and Bioavailability

**Clinical:** Dr. G. Steven Geis, Ph.D., M.D, Vice President  
Celecoxib Clinical Development

**10:00 Break**

**10:15 FDA Presentation**

**Introduction, Osteoarthritis, Rheumatoid Arthritis:**

James Witter, M.D., Ph.D., Medical Officer,

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs

**Pain:** Mordechai Averbuch, M.D., Medical Officer,

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs

**Renal:** Douglas C. Throckmorton, M.D., Medical Officer,

Division of Cardio Renal Drug Products

**GI:** Lawrence Goldkind, M.D., Medical Officer,

Division of Gastro-Intestinal and Coagulation Drug Products

**Pharmacology/Toxicology:** Josie Yang, Ph.D.,

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs

**Pharmacokinetics:** Sue-Chih Lee, Ph.D.,

Office of Clinical Pharmacology and Biopharmaceutics

**Conclusion:** James Witter, M.D., Ph.D., Medical Officer,

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drugs

**11:15 Open Public Hearing**

**12:15 Lunch**

**1:30 Discussion and Questions**

**3:00 Break**

**5:00 Adjourn**

**ARTHRITIS ADVISORY COMMITTEE  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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Abramson, Steven B., M.D. 9/30/99  
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Brigham and Women's Hospital  
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**Arthritis Advisory Committee**

Food and Drug Administration  
Center for Drug Evaluation and Research

Town Center Hotel, 8727 Colesville Road, Silver Spring, MD

**December 1, 1998**

**NDA 20-998, Celebrex™ (celecoxib) Searle**

**Guest Experts, Non Voting**

Denis M. McCarthy, M.D.  
Professor of Medicine  
Chief, Division of Gastroenterology  
University of New Mexico Medical School  
Chief, Gastroenterology and Hepatology  
New Mexico Regional Federal Medical Center  
USHS/VA Medical Center-111F; Bldg 41, Rm 5B126  
1501 San Pedro SE  
Albuquerque, NM 87108

Earl D. Silverman, M.D., FRCPC  
Professor of Pediatrics and Immunology  
Director, Pediatric SLE Clinic  
Division of Rheumatology  
Hospitals for Sick Children  
Room 8253 Elm Wing  
555 University Avenue  
Toronto, Ontario M5G1X8

**Arthritis Advisory Committee**  
Food and Drug Administration  
Center for Drug Evaluation and Research

Town Center Hotel, 8727 Colesville Road, Silver Spring, MD

December 1, 1998

**NDA 20-998, Celebrex™ (celecoxib) Searle**

**Open Public Hearing**

1. **SmithKline Beecham Pharmaceuticals:**  
Robert H. Palmer, M.D., Group Director-Rheumatology  
Clinical Reserch and Development
2. **Whitehall-Robins:**  
Stephen A. Cooper, DMD, PhD, Vice President  
Clinical and Medical Affairs
3. **Nonprescription Drugs Manufacturing Association:**  
William Soller, Senior Vice President
4. **Bayer Corporation:**  
letter

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**ADVISORY COMMITTEE: ARTHRITIS DRUGS**  
**ADVISORY COMMITTEE MEETING**

**DATE OF MEETING: 12/1/98**

**QUESTIONS**

**Arthritis Advisory Committee**  
Food and Drug Administration, Center for Drug Evaluation and Research  
Town Center Hotel, 8727 Colesville Road, Silver Spring, MD

**December 1, 1998**

**NDA 20-998, Celebrex™ (celecoxib) Searle**

**Questions**

**Efficacy**

**1. Should celecoxib be approved for the indications of the treatment of the signs and symptoms of OA and RA?**

**2. For the Indication "Management of Acute Pain", the Division's usual requirement is replicated evidence of efficacy in at least two different types of pain models. Traditionally, one type should be a single-dose model (e.g. dental pain) while the other type should be a multiple-dose model (e.g. post-operative, dysmenorrhea, etc.) studying patients with short-term (usually several days) therapy. While the replicated dental pain studies in this NDA support the analgesic efficacy of celecoxib, the multiple-dose studies are inconclusive (failed studies). The trials in OA are felt to be only supportive of the analgesic acute efficacy of celecoxib. The Agency believes that additional data are needed to support the acute pain indication. Does the committee agree? If so, what additional evidence should be provided?**

**Gastrointestinal**

**3. At prior AAC meetings on this subject, endoscopic studies have been viewed as surrogates of clinically meaningful endpoints. Given that celecoxib, in these endoscopic studies, has demonstrated consistent statistical superiority to only two of the three NSAIDs studied, what comparisons (if any) should be allowed in the labeling between celecoxib and these NSAIDs? Can these data be extrapolated to make comparisons between celecoxib and all other NSAIDs as well?**

**4. An underlying concept of the celecoxib development program has been that COX-2 selectivity would provide enhanced GI safety. While the celecoxib studies completed to date suggest that endoscopically diagnosed ulcers may occur less frequently with celecoxib treatment compared to NSAID comparators, studies completed to date have not included definitive comparisons of clinically significant GI adverse events. Is the NSAID-warning template still appropriate, pending completion of appropriately powered trials to assess the incidence of significant GI events with celecoxib compared to one or more NSAID products? Or should qualifications be made to the NSAID GI warning template, while noting the limited experience with the new molecular entity?**

5. NSAID labeling currently recommends against concurrent use of aspirin and NSAIDs. In view of the apparent lack of antiplatelet effect and the limited data from controlled endoscopy studies, what recommendations, if any, should be made concerning use of prophylactic low dose aspirin concurrently with celecoxib?

#### **Renal**

6. The sponsor and the FDA have agreed that the overall renal effects of celecoxib, including the incidence of peripheral edema and other renal adverse effects, are similar to those of currently approved NSAIDs.

- a. Do you agree with this assessment?
- b. How should any conclusion be reflected in labeling?

7. The NDA did not collect data on serum bicarbonates. Given the other laboratory abnormalities noted in the NDA:

- a. Should additional safety studies be required?
- b. How should this absence be reflected in labeling?

#### **Other Issues**

8. Information obtained from pharmacokinetic studies indicates that elderly subjects have a 40% increase in C<sub>max</sub> and a 70% increase in AUC. The FDA proposed label calls for initiating therapy with the lowest dose and titrating up slowly. Does the committee agree?

9. Celecoxib is almost entirely dependent upon hepatic metabolism (via P450 2C9). In patients with mild or moderate hepatic insufficiency should the dose or dosage regimen be altered?

- Mild hepatic insufficiency (plasma celecoxib levels 1.3-1.4x normal)
- Moderate hepatic impairment (plasma celecoxib levels > 2x normal)

10. At the present time there are no studies in subjects with severe hepatic failure. Should the sponsor be required to do studies which monitor both pharmacokinetics and clinical outcome (i.e. adverse events) prior to making labeling recommendations for this patient population?

11. Please provide recommendations for any Phase 4 studies for Celebrex™.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**ADVISORY COMMITTEE: ARTHRITIS DRUGS ADVISORY  
COMMITTEE**

**DATE OF MEETING: 12/1/98**

**SLIDES**

Arthritis Advisory Committee  
Food and Drug Administration  
Center for Drug Evaluation and Research

December 1, 1998

NDA 20-998, Celebrex<sup>TM</sup> (Celecoxib) Searle

**CELEBREX™  
(celecoxib)  
Capsules**

**Indications**

1. Acute or Chronic use in the Treatment of the Signs and Symptoms of Osteoarthritis and Rheumatoid Arthritis
2. Management of Pain

**Agenda**

- |   |                      |
|---|----------------------|
| I. Introduction                           | Dr. Richard Spivey   |
| II. Overview                              | Dr. Philip Needleman |
| III. Discovery & Pre-Clinical Development | Dr. Peter Isakson    |
| IV. Pharmacokinetics/<br>Pharmacodynamics | Dr. Aziz Karim       |
| V. Clinical Efficacy                      | Dr. G. Steven Geis   |
| VI. Clinical Safety                       | Dr. G. Steven Geis   |
| VII. Summary                              | Dr. Philip Needleman |

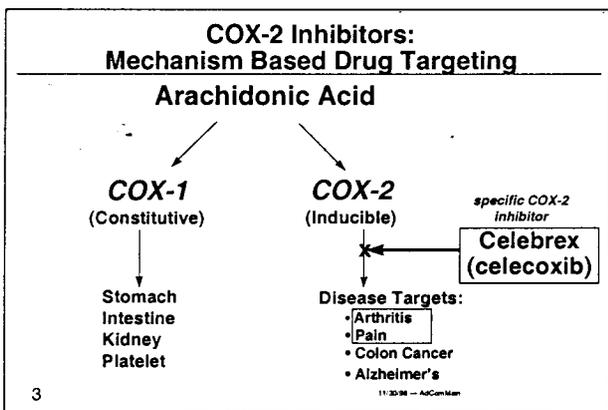
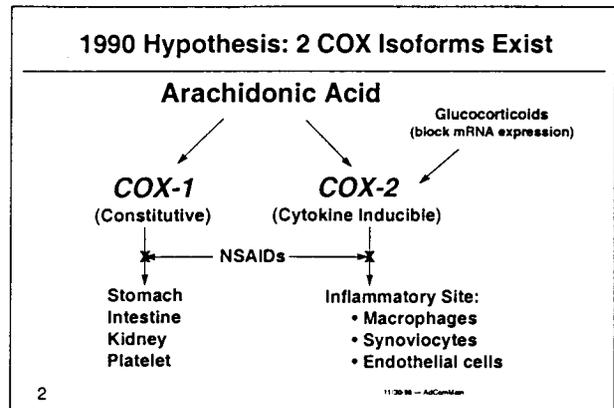
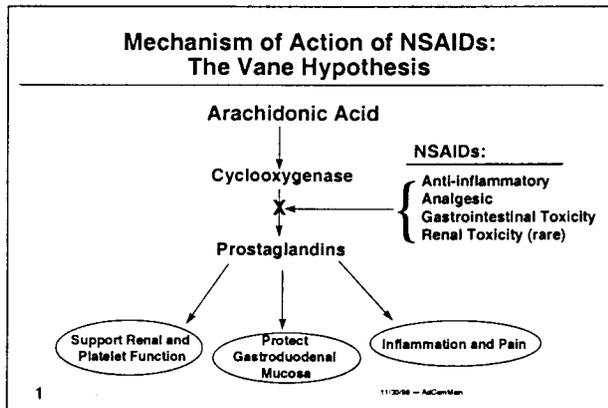
**Major Conclusions**

1. Celecoxib is effective in treating OA, RA, and Pain
2. In osteoarthritis, celecoxib given once daily or in divided doses is equally effective
3. Celecoxib is a specific COX-2 inhibitor that has an improved safety profile compared to mixed COX-1/COX-2 inhibitors
4. The clinically significant differences in GI effects compared to NSAIDs warrant specific changes in NSAID GI Class Labeling

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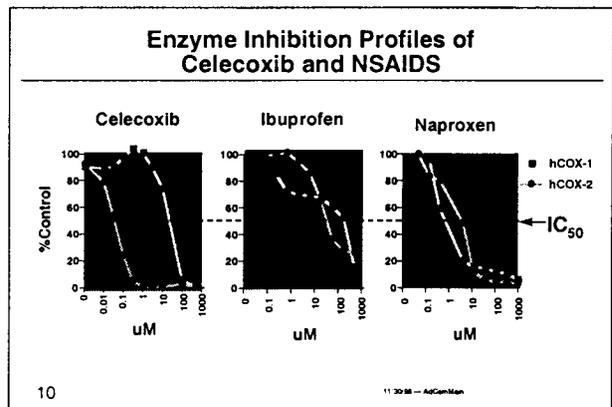
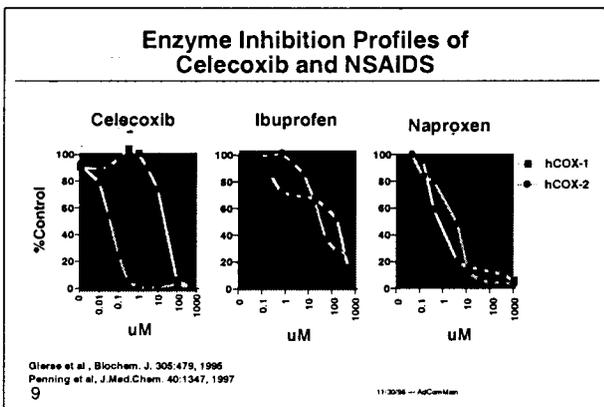
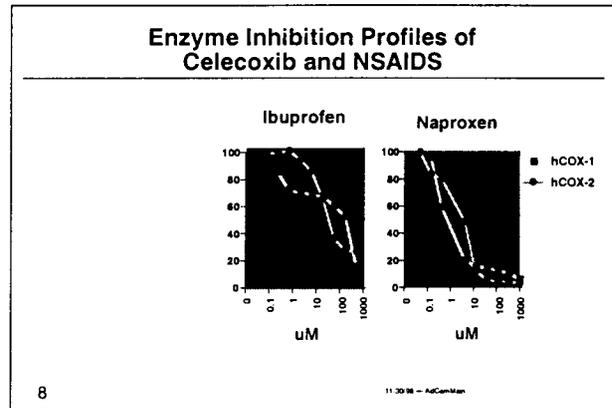
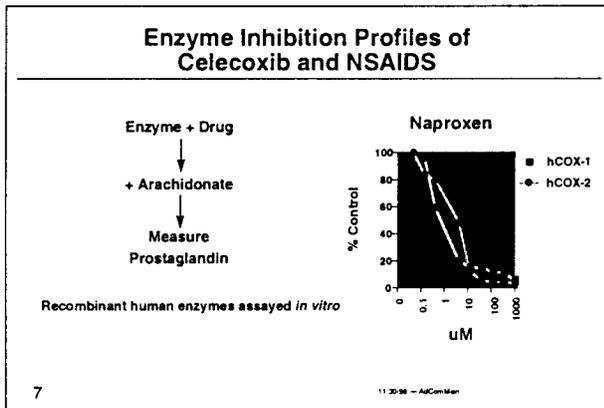
- ### Breakthroughs in Anti-Inflammatory Therapy
- 1897 Invention of aspirin
  - 1963 Development of NSAIDs
  - 1971 Mechanism of aspirin
  - 1990-91 Paradigm shift - Discovery of COX-2
  - 1992 Rational drug development begins
  - 1998 Delivery of a new class of drugs
    - Delivers the effectiveness of NSAIDs in arthritis and pain
    - Provides greater safety than the NSAIDs
    - Differentiated class with a clear therapeutic index
- 11/20/98 - AUCorMan

*Handwritten note:* Celebrex or NSAID Colon cancer target

- ### COX-2: Targeted Drug Discovery
- Scientific Objectives:**
- Mechanism of Specificity
  - Evaluation of the COX-2 Hypothesis
  - Efficacy and Safety Profile Consistent with COX-2 Specific Mechanism
- **Clinical Evaluation**
- 11/20/98 - AUCorMan

- ### Identification and Evaluation of COX-2 Inhibitors
- **In vitro** pharmacology
    - Recombinant human COX-1 and COX-2
    - Cells
  - **In vivo** pharmacology
    - Selectivity
    - Anti-inflammatory and analgesic activity
  - **Safety**
    - Acute and chronic
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### Inhibition of Cyclooxygenases *in vitro*

	IC <sub>50</sub> (μM)		
	COX-1	COX-2	COX-1/COX-2
Diclofenac	0.03	0.01	3
Etodolac	>100	54	>2
Ibuprofen	38	117	0.4
Nabumetone (6-MNA)	82	>1000	<0.1
Naproxen	32	235	0.1

11-30-98 - AdComMan

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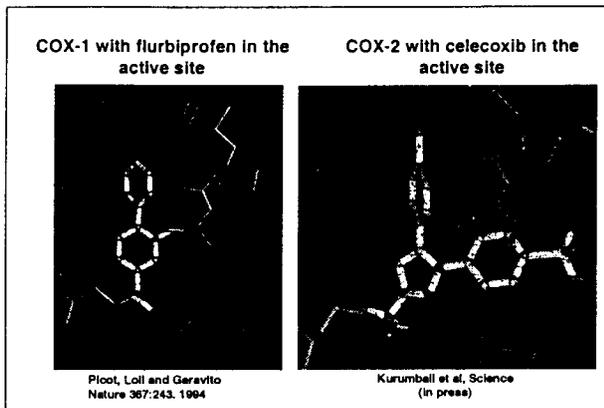
### Inhibition of Cyclooxygenases *in vitro*

	IC <sub>50</sub> (μM)		
	COX-1	COX-2	COX-1/COX-2
Celecoxib	15	0.04	375

11-30-98 - AdComMan

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### Mechanism of Celecoxib Enzyme Selectivity

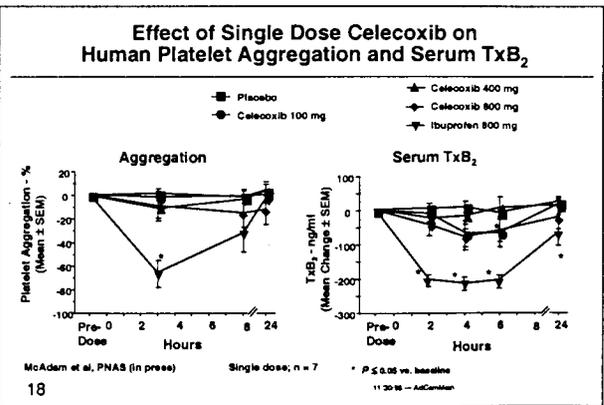
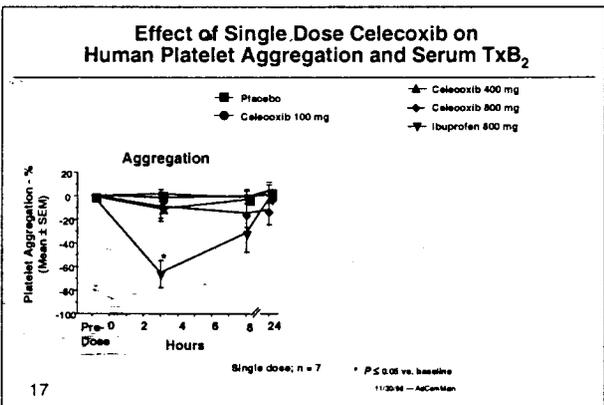
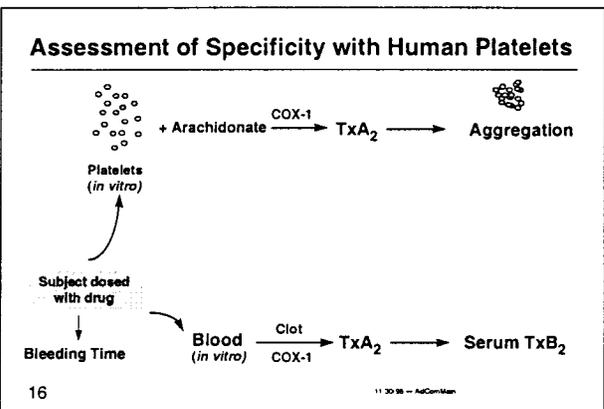
- Binds to a side pocket unique to the COX-2 active site
- Selectivity is due to a novel mechanism:
  - Low affinity, competitive inhibition of COX-1
  - High affinity, non-competitive inhibition of COX-2; very slowly reversible
- Duration of action longer than pharmacokinetic  $T_{1/2}$

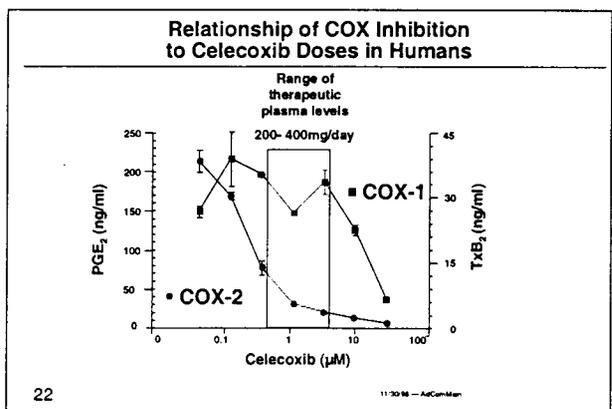
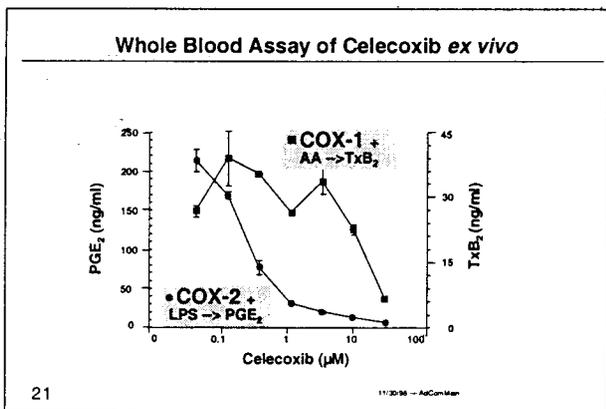
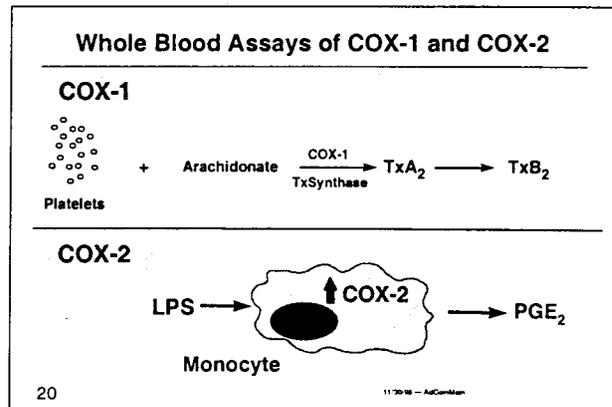
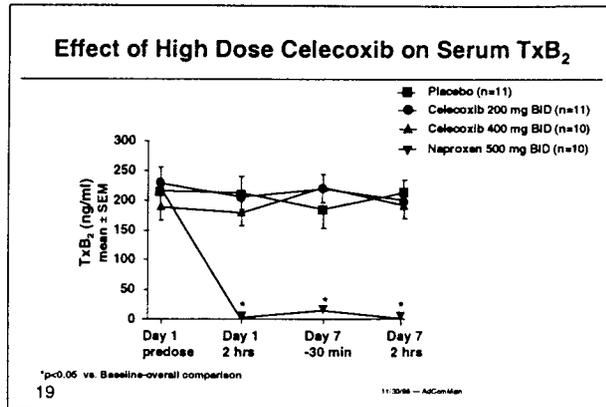
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### Identification and Evaluation of COX-2 Inhibitors

- *In vitro* pharmacology
  - Recombinant human COX-1 and COX-2
  - Cells
- *In vivo* pharmacology
  - Selectivity
  - Anti-inflammatory and analgesic activity
- Safety
  - Acute and chronic

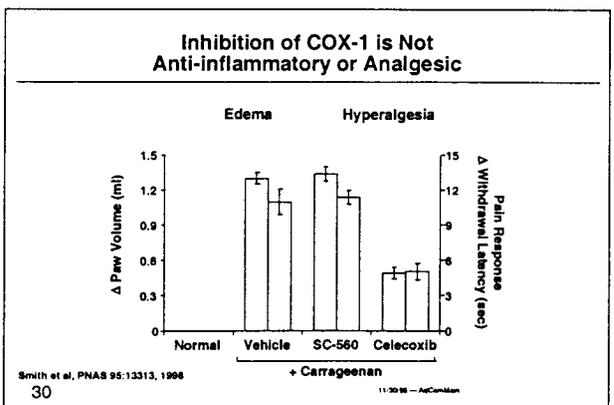
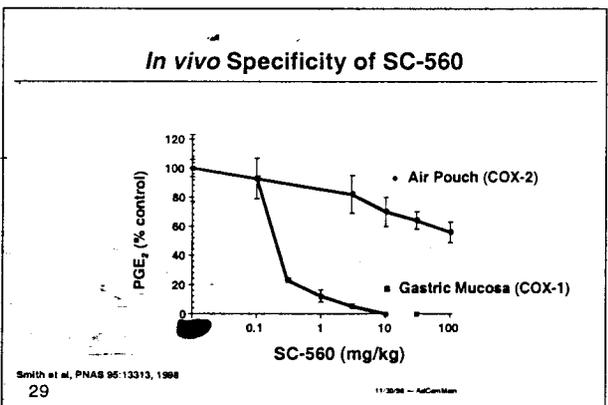
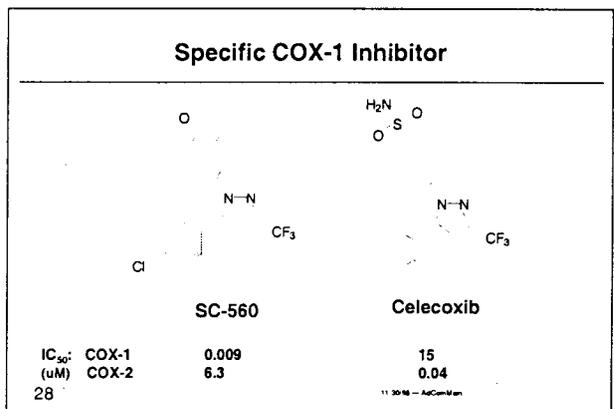
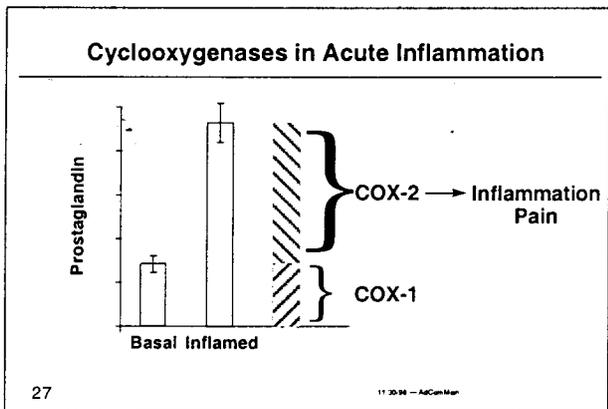
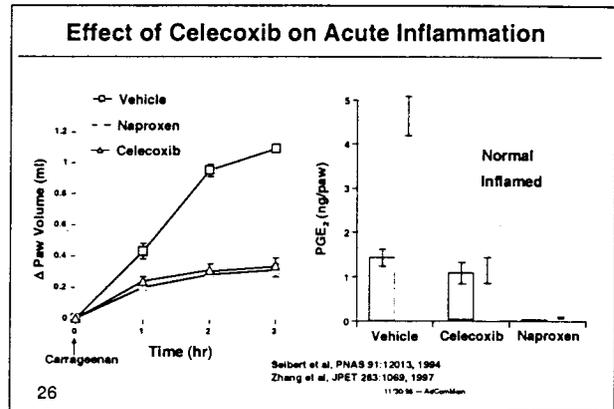
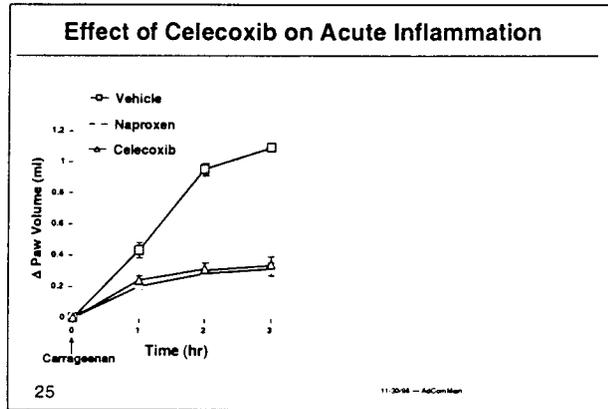
15 11/20/98 - AIC/Carlin



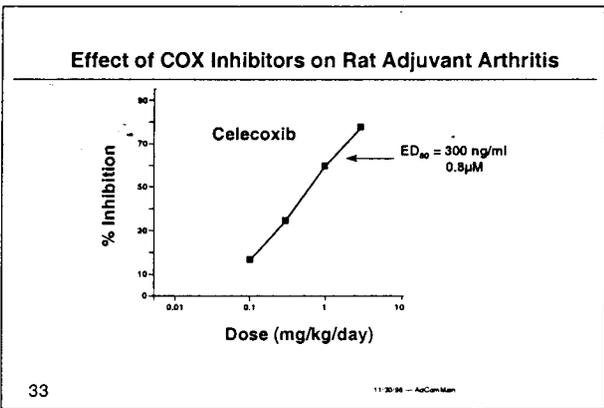
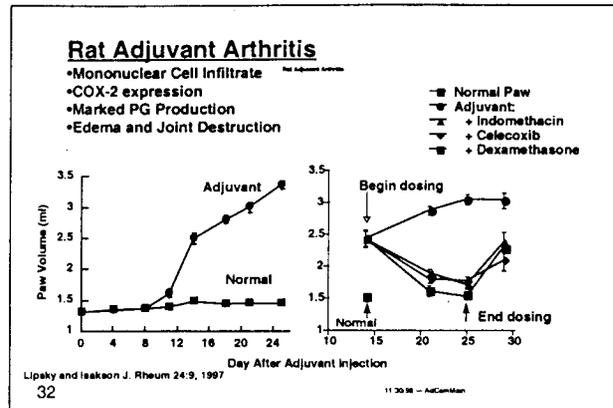
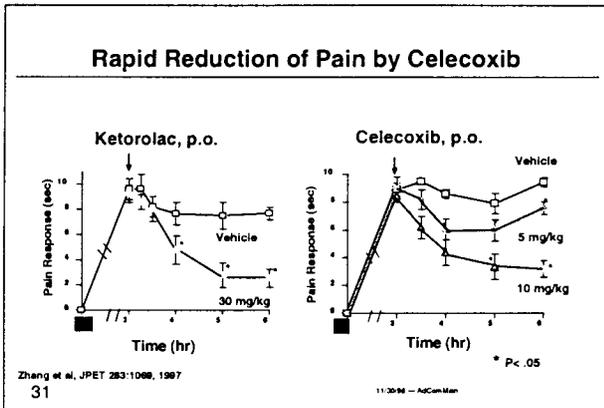


- ### Celecoxib Platelet Effects
- No effect of celecoxib at 2X the maximum therapeutic dose on:
    - Platelet aggregation
    - TxB<sub>2</sub> production
  - COX-1 sparing
- 23 11/30/98 - AdComMan

- ### Identification and Evaluation of COX-2 Inhibitors
- *In vitro* pharmacology
    - Recombinant human COX-1 and COX-2
    - Cells
  - *In vivo* pharmacology
    - Selectivity
    - Anti-inflammatory and analgesic activity
  - Safety
    - Acute and chronic
- 24 11/30/98 - AdComMan



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### Conclusions

- Specific inhibition of COX-2 by celecoxib results in the same maximal efficacy as inhibition of both COX-1 and COX-2 by NSAIDs
- Therefore, in animal models COX-2 is the therapeutic target for NSAIDs

34

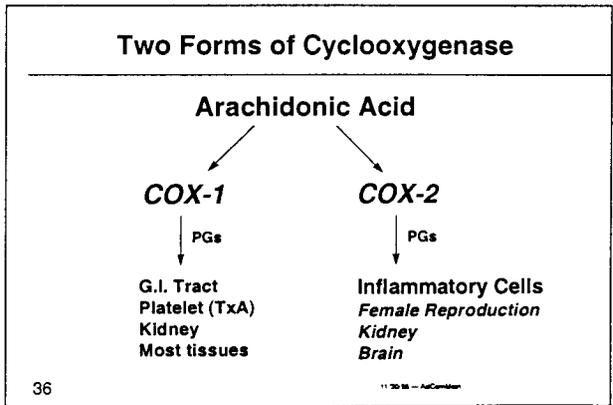
11/20/98 - AdComMan

### Identification and Evaluation of COX-2 Inhibitors

- **In vitro** pharmacology
  - Recombinant human COX-1 and COX-2
  - Cells
- **In vivo** pharmacology
  - Selectivity
  - Anti-inflammatory and analgesic activity
- **Safety**
  - Acute and chronic
    - Rat (6 months to 2 years)
    - Dog (1 year)

35

11/20/98 - AdComMan



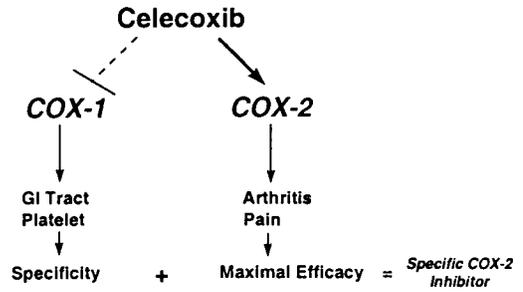
**Preclinical Toxicology of Celecoxib  
Relevant to Mechanism**

- **Pregnancy**
  - No effect on ovulation or fertility
  - Effects on embryo viability (implantation) at exposures 6-12 fold therapeutic
- **No adverse effects related to:**
  - Bleeding
  - CNS
- **Renal**
  - No renal papillary necrosis
  - Transient anti-natriuresis in rats
- **Gastrointestinal**
  - Chronic safety established at exposures 3 to 6 fold therapeutic in sensitive species (rat and dog)

37

11/20/98 - AUCorMan

**COX-2 Inhibitors:  
Mechanism Based Drug Targeting**



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**APPEARS THIS WAY  
ON ORIGINAL**

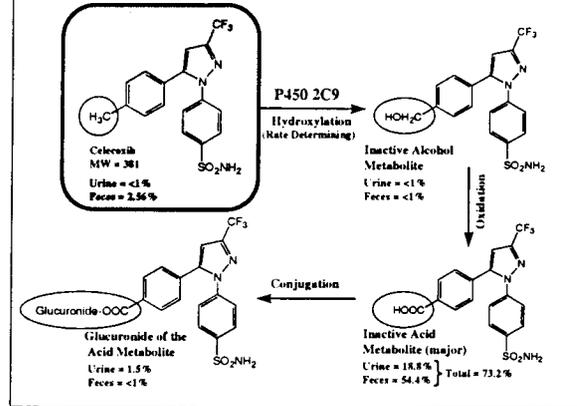
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## Celecoxib: Clinical PK

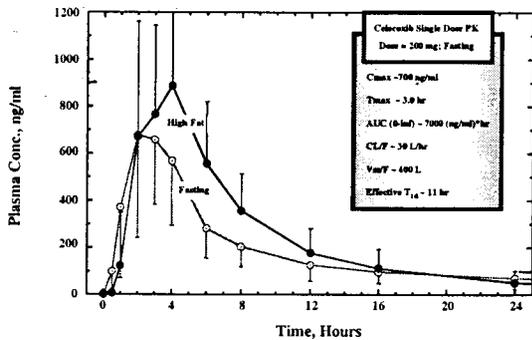
- ① Basic PK Profile
- ② PK in Special Populations
- ③ Drug-Drug Interactions
- ④ Population PK/PD Analysis of Pivotal Clinical Trial Data
- ⑤ Bioequivalency: Clinical Trial Batches vs. Commercial Formul.

Celecoxib PK  
Assessed In  
1566 Subjects  
From 32 Studies

### Metabolism of Celecoxib in Man



Mean (SD; N = 24) Plasma Concentrations of Celecoxib Following 200 mg Single Doses Given Under Fasting State or With High Fat Breakfast



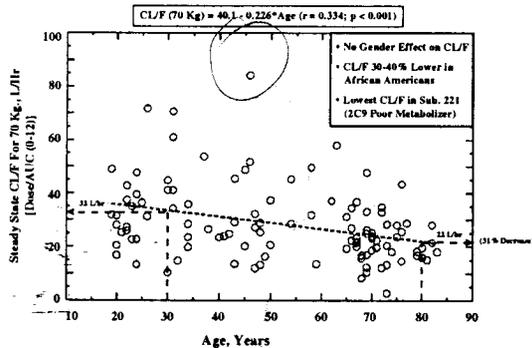
## Celecoxib: Clinical PK

### PK in Special Population

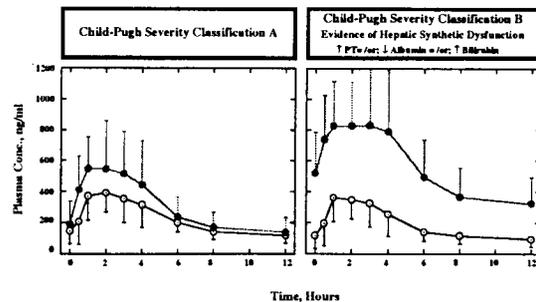
- ① Effect of Age, Gender, Weight and Race
- ② Effect of Hepatic Impairment
- ③ Effect of Chronic Renal Impairment
- ④ Effect of Diabetes (NIDDM)
- ⑤ Effect of Osteo- and Rheumatoid Arthritis

Relationship Between Celecoxib CL/F (Adjusted For 70 Kg) and Age (N=112)

[-0.10 Renal Elderly; -0.15 Young vs. Elderly PK; -0.17 MTX Interaction; -0.43 BID vs QD PK]



Mean (SD; N = 11-12) Steady State Plasma Conc.-Time Curves of Celecoxib in Hepatic Impaired Patients (●) and Matching Healthy Subjects (○) Following Celecoxib 100 mg BID



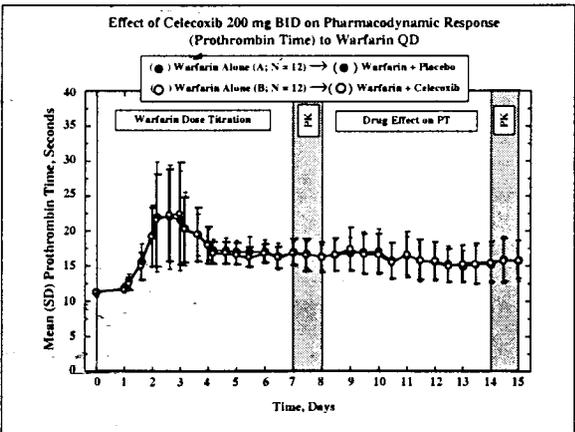
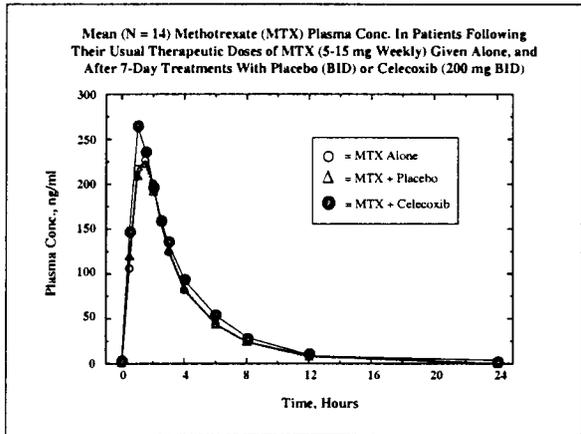
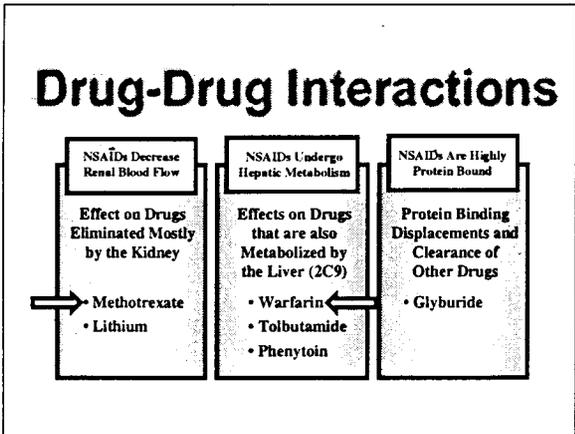
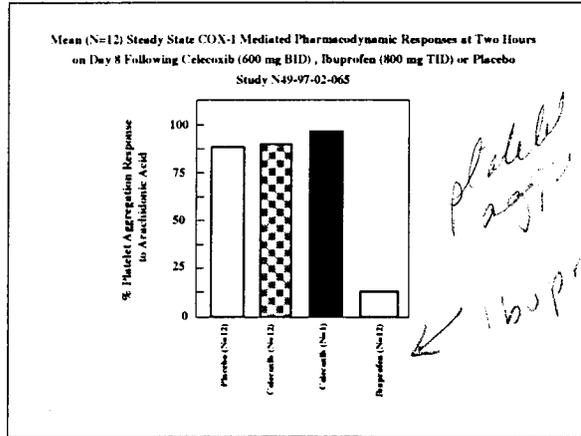
600-1.6 w/10-12h

12/21 = Same  
3/19/11

Six Subjects (Out of 1566) Showing Unusually High Exposure of Celecoxib

Subject	Study	Age (Years)	Weight (kg)	Sex	Race	Dose (mg BID)	AUC (0-12h)	CL/F (L/hr)	Dose/AUC
221	-015	73	74.9	F	Caucasian	200 (1 dose with food)	72.2	2.59	10.2
222	-015	68	79.3	F	Caucasian	200 (1 dose with food)	21.4	8.25	3.20
031	-072	33	70.1	M	Caucasian	200 (1 high dose)	54.6 (lpc)	3.66	2.84
827	-024	68	56.2	F	Afr. Amer.	100 (1 dose with food)	NA	NA	2.39
461	-024	80	71.9	F	Afr. Amer.	200 (1 dose with food)	NA	NA	5.97

Note: Subject #112, study -045 and subject #031, study -072 were the same subject participating in two different studies



- ### Celecoxib: PK Summary
- Achiral, Low-Solubility-High-Permeability Drug With Systemic Availability of ~73%
  - CL/F ~500 ml/min (~30 L/hr); Vss/F ~400 L; Effective T<sub>1/2</sub> ~11 hr; Extensive Hepatic Metabolism To Inactive Metabolites via P450 2C9; Protein Binding ~97% and Concentration Independent
  - Advantages of Dosing With or Without Food and Potential For Once a Day Dosing
  - Lower CL (higher AUC) in Elderly Women (Lower Body Weight), in Patients With Moderate to Severe Hepatic Impairment and in African Americans
  - Lack of Drug-Drug Interactions Commonly Encountered With NSAIDs (MTX, Lithium, Warfarin, Phenytoin, Glyburide, Tolbutamide)

# Celecoxib Clinical Efficacy and Safety

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## Hypothesis

Specific inhibitors of COX-2 will be  
anti-inflammatory and analgesic without  
the typical side-effects of NSAIDs

2

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## Celecoxib - Clinical Objectives

### Indications

- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

### Differentiation

- Gastrointestinal
- Platelet
- General Safety

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## Celecoxib Clinical Program Overview

- Studies: 51
- Patients/Subjects: 13,072
- Endoscopy: > 4,700 patients
- No. Patients with  $\geq 1$  Year Exposure:  
981 - NDA  
2,443 - Safety Update
- Patient Years: 3,283 - NDA  
5,005 - Safety Update

4

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## Celecoxib - Clinical Objectives

### Indications

- Osteoarthritis
- Rheumatoid Arthritis
- Management of Pain

### Differentiation

- Gastrointestinal
- Platelet
- General Safety

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## Pivotal OA Studies

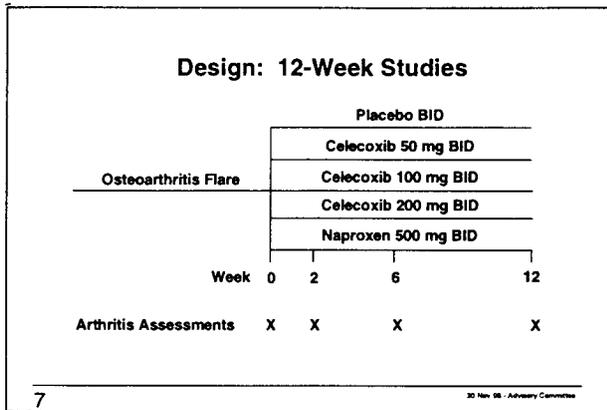
- 12-week studies  
-2 knee  
-1 hip
- 6-week studies  
-2 knee

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*Handwritten notes:*  
 1. 12-Week Studies  
 2. 12-Week Studies



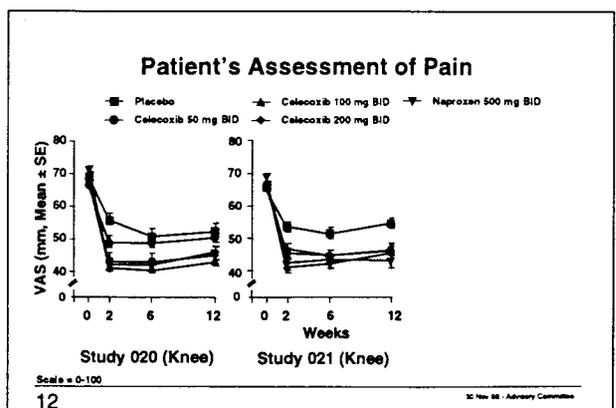
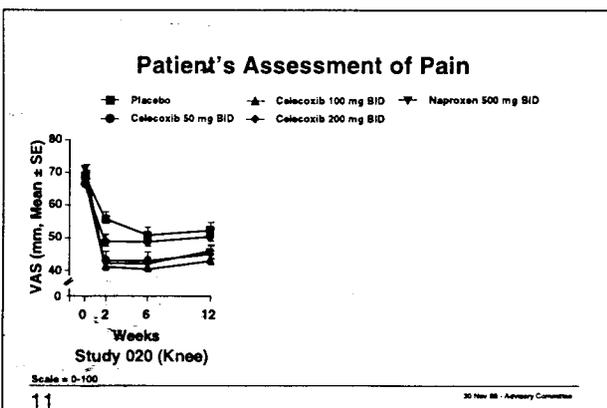
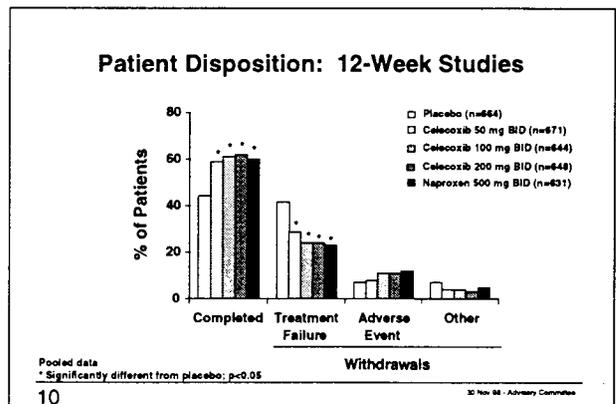
- ### Measures of OA Efficacy
- Patient's Assessment of Pain (VAS)
    - Pain
    - Function
    - Stiffness
  - Patient's Global Assessment
  - Physician's Global Assessment
  - SF-36 Health Survey
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### 12-Week OA Studies

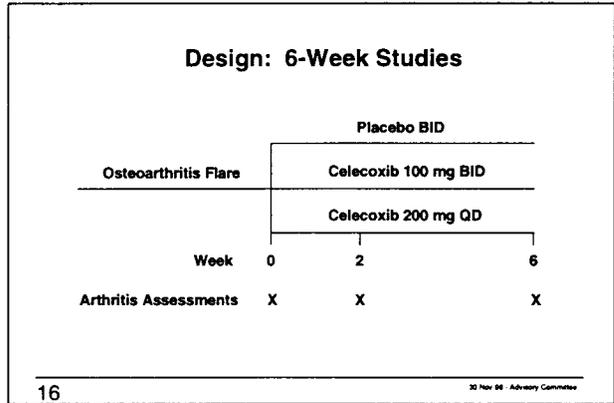
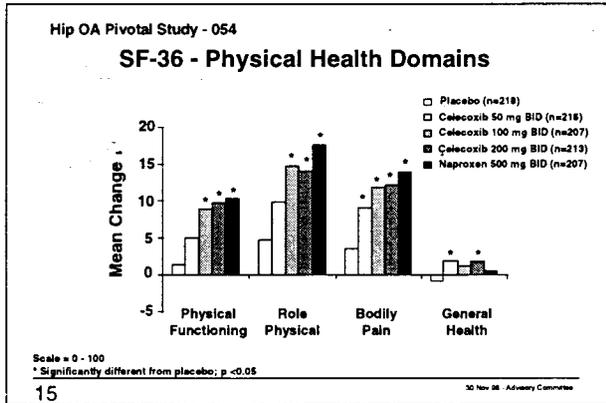
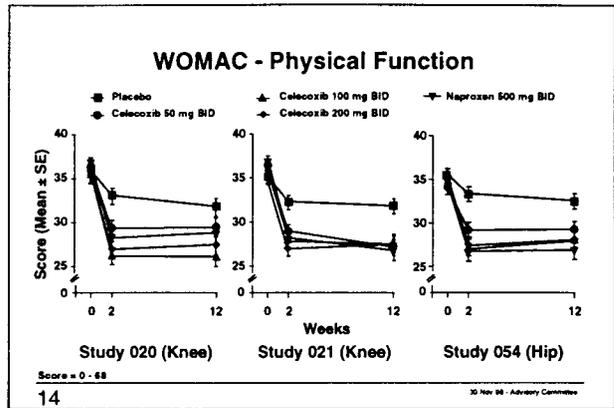
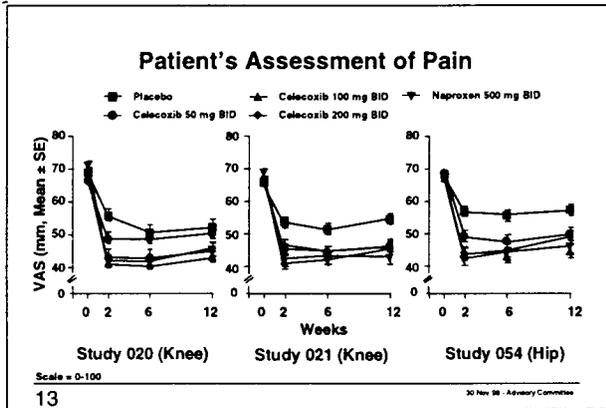
Index Joint	Study No.			Total
	020 Knee	021 Knee	054 Hip	
Treatment Group (n)				
Placebo	204	242	218	664
Celecoxib 50 mg BID	203	252	216	671
Celecoxib 100 mg BID	197	240	207	644
Celecoxib 200 mg BID	202	233	213	648
Naproxen 500 mg BID	198	226	207	631
<b>Total</b>	<b>1004</b>	<b>1193</b>	<b>1061</b>	<b>3258</b>

Planned sample size - 200/group

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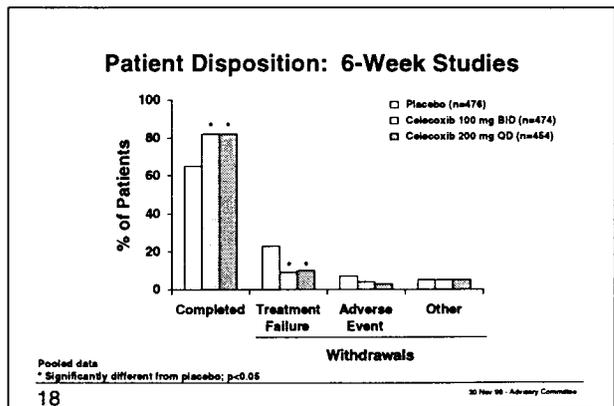
### 6-Week OA Studies

Index Joint	Study No.		Total
	060 Knee	087 Knee	
Treatment Group (n)			
Placebo	232	244	476
Celecoxib 100 mg BID	231	243	474
Celecoxib 200 mg QD	223	231	454
<b>Total</b>	<b>686</b>	<b>718</b>	<b>1404</b>

Planned sample size - 200/group

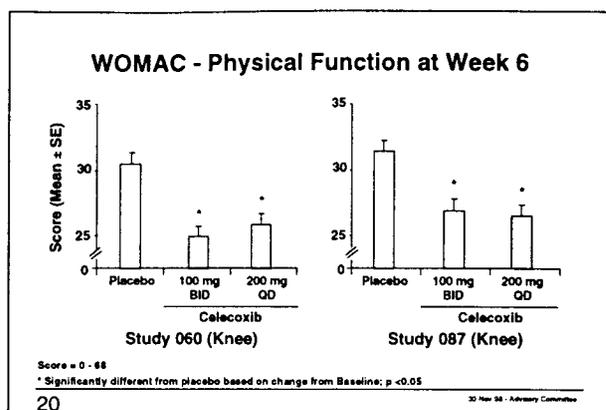
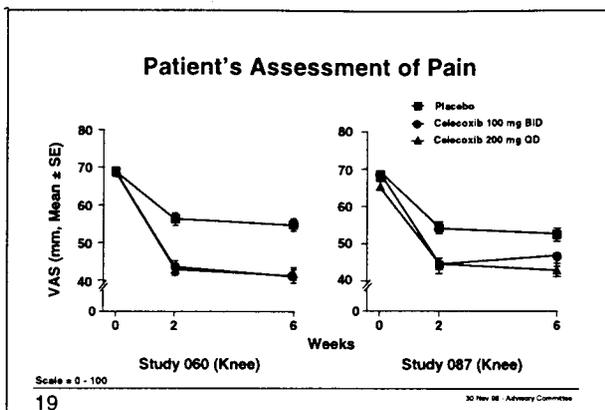
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**17**



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### Conclusions: Celecoxib in OA

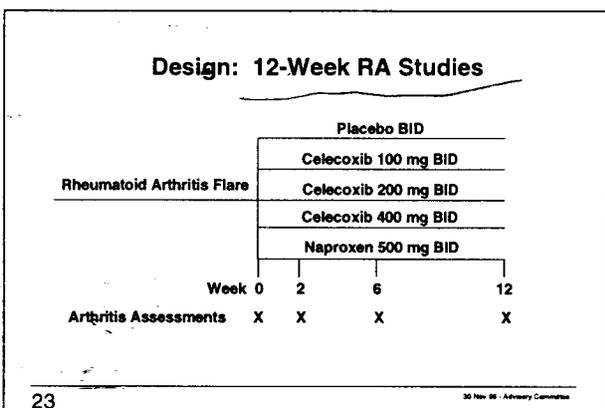
- Effective in OA
- Recommended dose
  - 200 mg per day
  - Can be administered in single or divided doses
- Efficacy similar to naproxen

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### Celecoxib - Clinical Objectives

<u>Indications</u>	<u>Differentiation</u>
• Osteoarthritis	• Gastrointestinal
• Rheumatoid Arthritis	• Platelet
• Management of Pain	• General Safety

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### Measures of RA Efficacy

- ACR-20
- Number of Swollen Joints
- Number of Tender/Painful Joints
- Patient's Global Assessment of Arthritis
- Physician's Global Assessment of Arthritis
- SF-36 Health Survey

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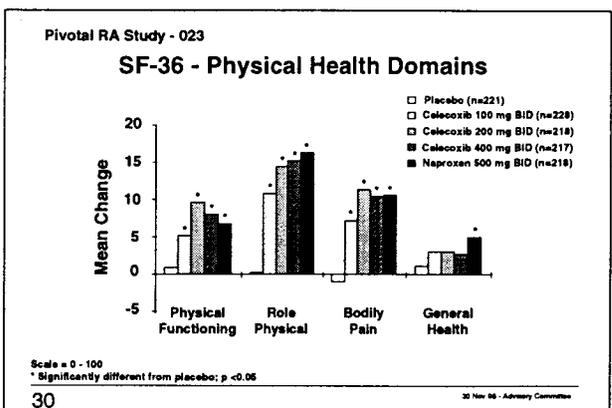
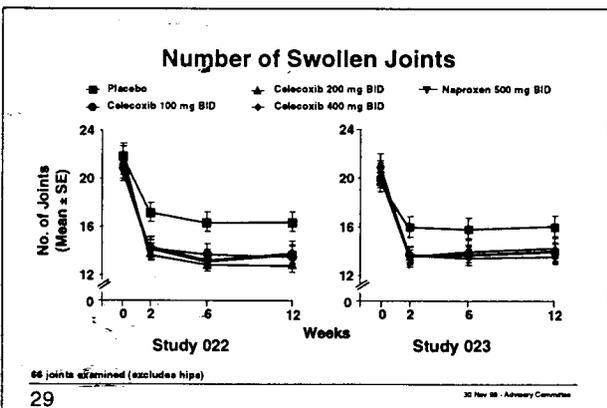
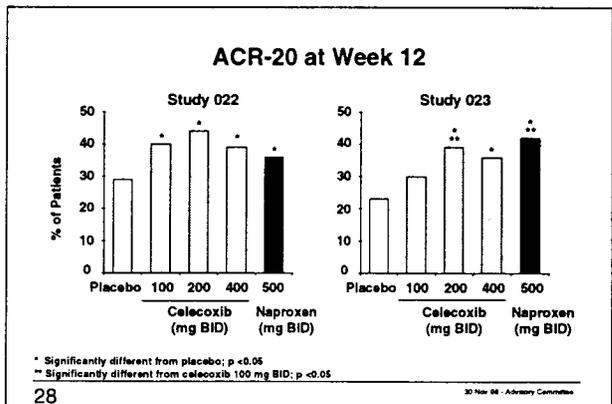
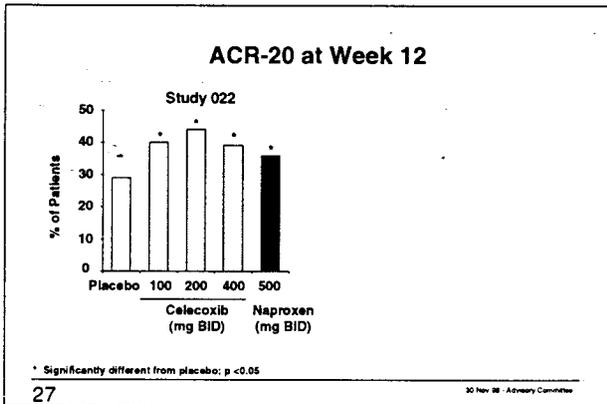
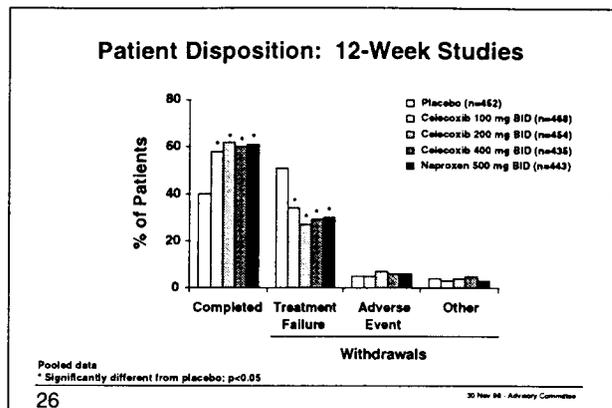
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### 12-Week RA Studies

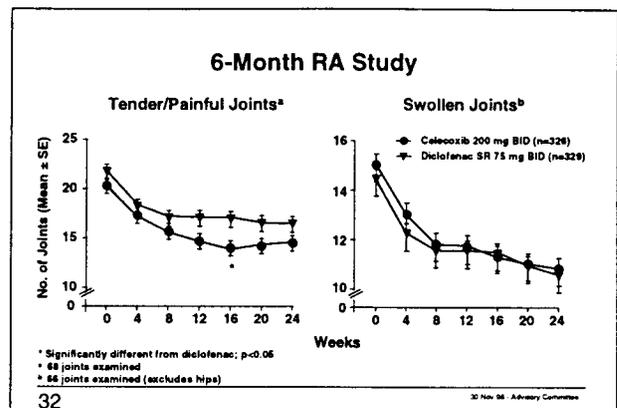
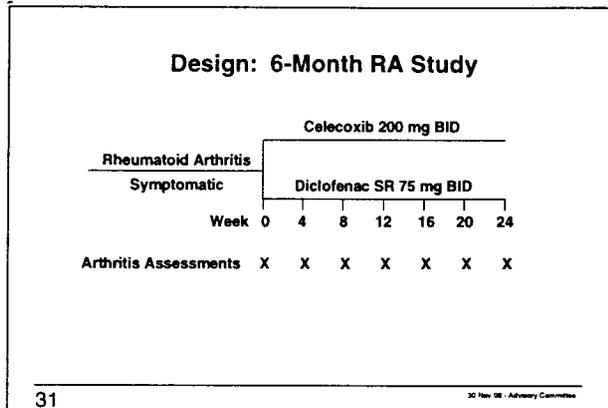
Treatment Group (n)	Study No.		Total
	022	023	
Placebo	231	221	452
Celecoxib 100 mg BID	240	228	468
Celecoxib 200 mg BID	235	219	454
Celecoxib 400 mg BID	218	217	435
Naproxen 500 mg BID	225	218	443
<b>Total</b>	<b>1149</b>	<b>1103</b>	<b>2252</b>

Planned sample size - 200/group

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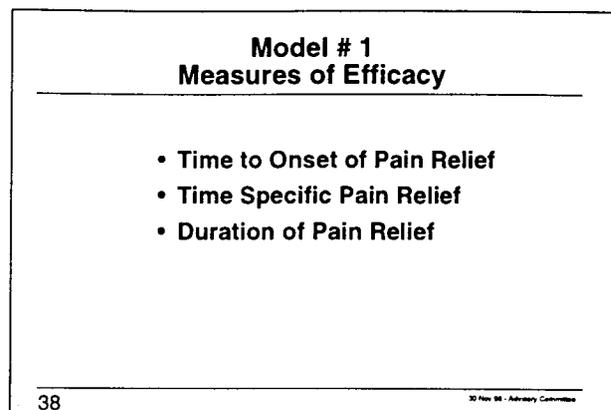
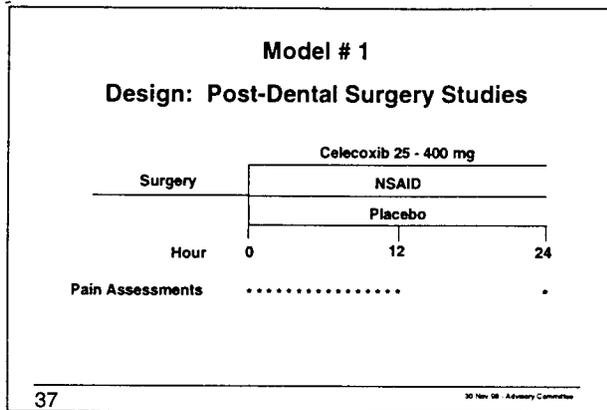
- ### Conclusions: Celecoxib in RA
- Effective in RA
  - Recommended dose
    - 100 mg BID
    - Some patients may benefit by increasing the dose to a maximum of 200 mg BID
  - Efficacy similar to naproxen
  - Sustained efficacy
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- ### Celecoxib - Clinical Objectives
- | Indications  | Differentiation    |
|--|--------------------|
| • Osteoarthritis   | • Gastrointestinal |
| • Rheumatoid Arthritis   | • Platelet         |
| • Management of Pain <ul style="list-style-type: none"> <li>- acute pain</li> <li>- short term pain</li> <li>- chronic arthritis pain</li> </ul> | • General Safety   |
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- ### Pain Program
- 
- Model # 1  
ACUTE PAIN  
(0 - 24 HOURS)**
- Post-dental surgery
    - 3 pivotal studies
      - single dose
  - Post-orthopedic surgery
    - 1 supporting study
      - repeat dose
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- ### Pain Program
- 
- |   |   |
|---|---|
| <p><b>Model # 1<br/>ACUTE PAIN<br/>(0 - 24 HOURS)</b></p> <ul style="list-style-type: none"> <li>• Post-dental surgery                             <ul style="list-style-type: none"> <li>- 3 pivotal studies                                     <ul style="list-style-type: none"> <li>- single dose</li> </ul> </li> </ul> </li> <li>• Post-orthopedic surgery                             <ul style="list-style-type: none"> <li>- 1 supporting study                                     <ul style="list-style-type: none"> <li>- repeat dose</li> </ul> </li> </ul> </li> </ul> | <p><b>Model # 2<br/>SHORT TERM PAIN<br/>(1 - 7 DAYS)</b></p> <ul style="list-style-type: none"> <li>• OA flare                             <ul style="list-style-type: none"> <li>- 3 pivotal studies                                     <ul style="list-style-type: none"> <li>- multiple dose</li> </ul> </li> </ul> </li> </ul> |
|---|---|
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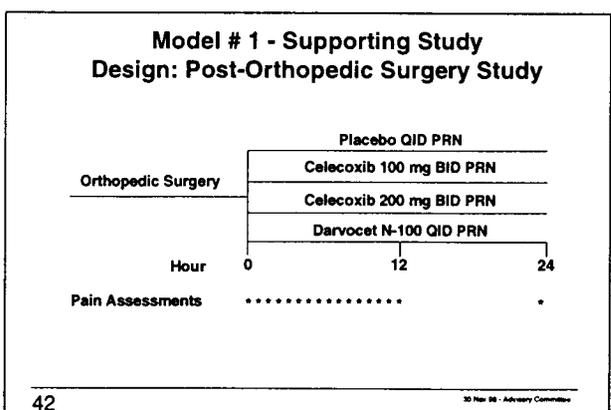
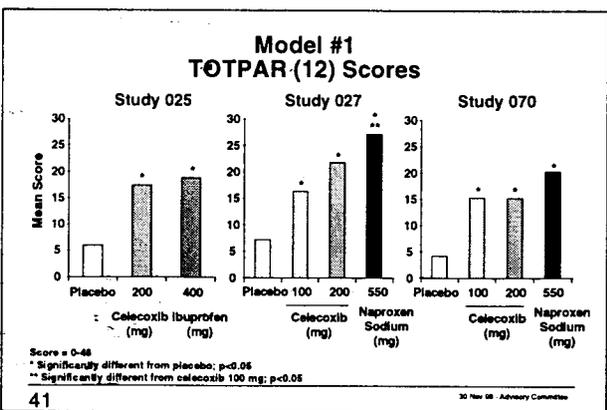
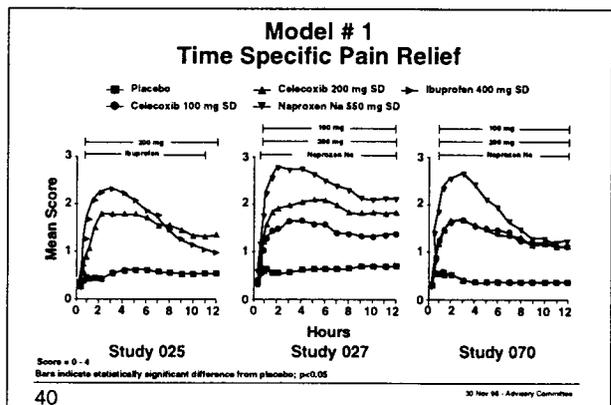


### Model # 1

#### Post-Dental Surgery Studies

Treatment Group (n)	Study No.			Total
	025	027	070	
Placebo	50	55	50	155
Celecoxib 100 mg	--	55	50	105
Celecoxib 200 mg	50	56	50	156
Ibuprofen 400 mg	50	--	--	50
Naproxen Na 550 mg	--	54	35	89

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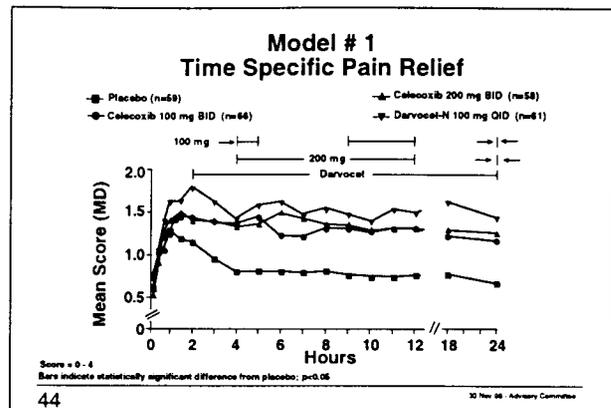
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**Model # 1**  
**Dosing Regimen: Post-Orthopedic Surgery Study**

	First Dose	Second Dose	Third Dose	Fourth Dose
Darvocet N-100	+	+	+	+
Celecoxib 200 mg	+	+	Pbo	Pbo
Celecoxib 100 mg	+	+	Pbo	Pbo
Placebo	Pbo	Pbo	Pbo	Pbo

Remedication was allowed  $\geq 4$  hours after the first dose of study medication

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**Pain Program**

Model # 1 ACUTE PAIN (0 - 24 HOURS)	Model # 2 SHORT TERM PAIN (1 - 7 DAYS)
<ul style="list-style-type: none"> <li>• Post-dental surgery                             <ul style="list-style-type: none"> <li>- 3 pivotal studies                                     <ul style="list-style-type: none"> <li>- single dose</li> </ul> </li> </ul> </li> <li>• Post-orthopedic surgery                             <ul style="list-style-type: none"> <li>- 1 supporting study                                     <ul style="list-style-type: none"> <li>- repeat dose</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• OA flare                             <ul style="list-style-type: none"> <li>- 3 pivotal studies                                     <ul style="list-style-type: none"> <li>- multiple dose</li> </ul> </li> </ul> </li> </ul>

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- Model # 2**  
**Rationale: OA Flare Pain Model**
- Pain is the primary symptom of OA
  - Non-anti-inflammatory analgesics (e.g., acetaminophen and opiates) are efficacious in treating OA pain
  - OA model has been used to evaluate the efficacy of a variety of analgesics including opiates and centrally acting analgesics
- Bradley, JD, Brandt, KD, *N Engl J Med* 1991; 325:87-91  
Jensen, EM, Ginsberg, F, *Drug Invest* 1994; 8:211-218
- 46 30 Nov 98 - Advisory Committee

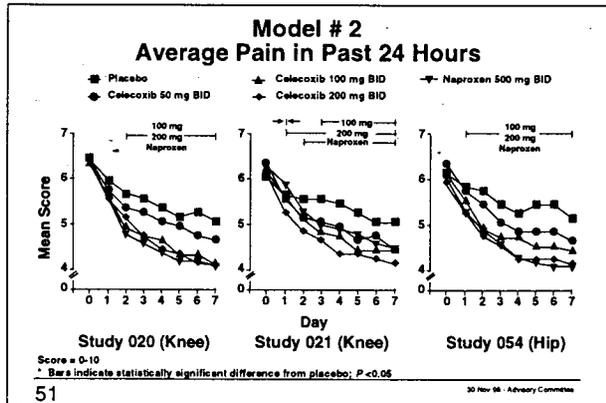
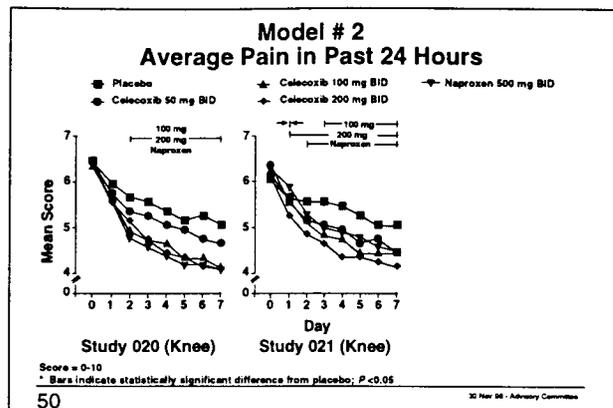
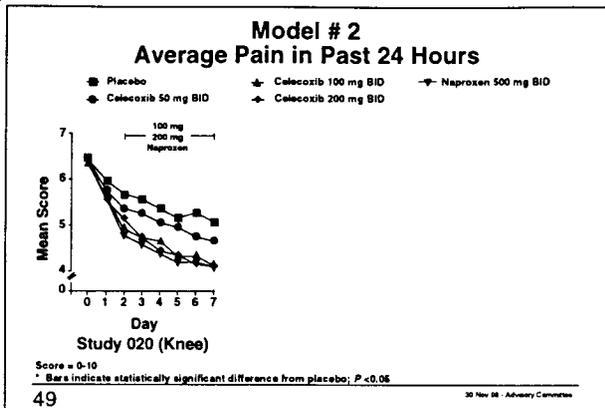
**Model # 2**  
**Design: Three Pivotal 12-Week OA Studies**

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Placebo BID								
Celecoxib 50 mg BID								
Celecoxib 100 mg BID								
Celecoxib 200 mg BID								
Naproxen 500 mg BID								
Osteoarthritis Flare								
APS pain measures	X	X	X	X	X	X	X	X

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- Model # 2**  
**American Pain Society (APS) Pain Measure**
1. Have you experienced any pain in the last 24 hrs?
  2. How much pain are you having right now?
  3. Indicate the worst pain you have had in the past 24 hrs.
  4. Indicate the average level of pain you have had in the past 24 hrs.
  5. Indicate how pain has interfered with function.
- JAMA, December 20, 1996, Vol. 274, No. 23
- 48 30 Nov 98 - Advisory Committee

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- Celecoxib in Analgesia**
- Efficacy was demonstrated by replicate studies:
    - Model # 1: acute pain - 3 post-dental surgery studies; single dose
    - Model # 2: short term pain - 3 OA flare studies; multiple dose over several days
  - Recommended dose:
    - 100 mg or 200 mg BID
    - For acute pain, the second dose may be administered as early as 4 hrs
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**Celecoxib - Clinical Objectives**

Indications	Differentiation
<ul style="list-style-type: none"> <li>Osteoarthritis</li> <li>Rheumatoid Arthritis</li> <li>Management of Pain</li> </ul>	<ul style="list-style-type: none"> <li>Gastrointestinal</li> <li>Platelet</li> <li>General Safety</li> </ul>

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**Safety Database**

	Placebo	Celecoxib	Active Control
Pharmacokinetic Studies	281	1,023	280
Analgesia Studies	305	748	295
North American Arthritis Trials	1,864	5,704	2,768
International Arthritis Trial	0	672	670
Long-term Open Label Arthritis	---	4,499	---
<b>Total</b>	<b>2,450</b>	<b>12,646</b>	<b>3,343</b>

\* 13,072 unique subjects/patients

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## General Safety Analyses

- Serious adverse events and deaths
- Incidence of adverse events and withdrawals:
  - North American Arthritis Trials
  - Long-term Open Label Arthritis Trial
- Laboratory results

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## Serious Adverse Events

	Placebo (n=2450)	Celecoxib* (n=12,646)	Active Control (n=3343)
SAEs Incidence, No. (%)	34 (1.4)	341 (2.7)	61 (1.8)
Events/100 patient-yrs	15.9	10.4	11.3
Gastrointestinal, No. (%)	6 (0.2)	39 (0.3)	10 (0.3)
Events/100 patient-yrs	2.8	1.2	1.9
Cardiovascular, No. (%)	7 (0.3)	53 (0.4)	4 (0.1)
Events/100 patient-yrs	3.3	1.6	0.7

\* All doses

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## Deaths

	Placebo (n=2450)	Celecoxib* (n=12,646)	Active Control (n=3343)
Deaths Incidence, No. (%)	0 (0.0)	22 (0.2)	4 (0.1)
Events/100 patient-yrs	0.0	0.5	0.7
Cardiovascular deaths, No. (%)	0 (0.0)	16 (0.1)	2 (0.1)
Events/100 patient-yrs	0.0	0.3	0.4

\* All doses

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## North American Arthritis Trials

### Adverse Events with $\geq 5\%$ Incidence in Any Treatment

Adverse Event	Placebo (n=1864)	Celecoxib* (n=4146)	Celecoxib 400 mg BID (n=615)	NSAID (n=2098)
Any Event	54.6	60.4*	60.2	66.7**
Headache	20.2	15.8*	14.5*	14.8*
Dyspepsia	6.2	8.8*	8.1*	12.0**
URTI	6.7	8.1*	7.0	9.9
Diarrhea	3.8	5.6*	6.5*	6.1
Sinusitis	4.3	5.0	5.4	4.6
Abdominal Pain	2.8	4.1	3.3	8.2**
Nausea	4.2	3.5	3.6	5.6**

\* Patients who received either celecoxib 100 mg BID, 200 mg BID or 200 mg QD

\*\* Significantly different from placebo, p<0.05

\*\*\* Significantly different from celecoxib 100 mg BID, 200 mg BID or 200 mg QD

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## North American Arthritis Trials

### Adverse Events Causing Withdrawal with Incidence $\geq 0.5\%$

Adverse Events	Placebo (n=1864)	Celecoxib* (n=4146)	Celecoxib 400 mg BID (n=615)	NSAID (n=2098)
Any Event	6.1	7.1	6.8	9.7*
Abdominal Pain	0.6	0.8	0.3	2.1**
Dyspepsia	0.6	0.8	0.8	1.6*
Rash	0.6	0.8	1.1	0.3**
Diarrhea	0.3	0.3	0.3	0.4
Nausea	0.6	0.5	0.3	0.9
Pruritis	0.2	0.2	0.5	0.0
Esophageal Ulceration	0.0	<0.1	0.0	0.6*

\* Patients who received either celecoxib 100 mg BID, 200 mg BID or 200 mg QD

\*\* Significantly different from placebo, p<0.05

\*\*\* Significantly different from celecoxib 100 mg BID, 200 mg BID or 200 mg QD

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## Adverse Events With an Incidence $\geq 5\%$

Adverse Event	Incidence, %	
	North American Arthritis Trials* (n=4146)	Long-term Open Label Trial (n=4499)
Headache	15.8	16.0
URTI	8.1	14.1
Dyspepsia	8.8	10.1
Sinusitis	5.0	9.2
Diarrhea	5.6	7.7
Accidental Injury	2.9	7.2
Abdominal Pain	4.1	5.5
Nausea	3.5	5.4

\* The column shows the incidence of adverse events for celecoxib 100 mg BID, 200 mg BID, and 200 mg QD

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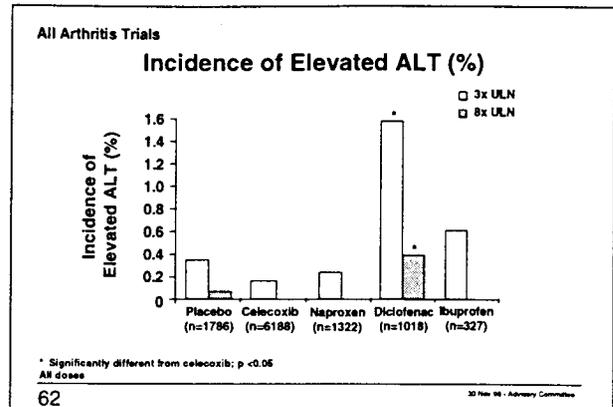
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### Laboratory Analyses

- Hepatic
- Renal

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### North American 12-Week Placebo and Active-Controlled Arthritis Trials Incidence of Abnormal Renal Lab Tests (%)

	Placebo	Celecoxib 100 and 200 mg BID	Naproxen 500 mg BID
<b>Creatinine</b>			
>1.8 mg/dL	0.1	0.1	0.0
>3.0 mg/dL	0.0	0.0	0.0
<b>Potassium</b>			
>5.5 mmol/L	0.3	0.4	0.8
>6.0 mmol/L	0.0	0.0	0.0
<b>Uric Acid</b>			
<148.7 μmol/L	0.5	0.8	0.7
<119 μmol/L	0.2	0.1	0.1

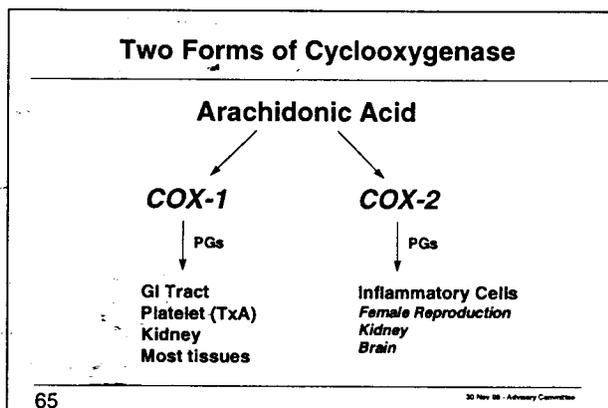
Placebo n = 1003 - 1080; celecoxib n = 2056 - 2149; naproxen n = 878 - 1072

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### Conclusions: General Safety of Celecoxib

- Well tolerated
- Similar short and long term safety profiles
- Incidence of adverse events
  - less than NSAIDs
  - higher than placebo
- Laboratory tests results similar to placebo
- Incidence of elevated liver function tests lower than with diclofenac

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### North American Arthritis Trials Incidence of CNS/Psychiatric Adverse Events ≥0.5%

Adverse Event	Placebo (n=1864)	Celecoxib* (n=4146)	NSAID (n=2098)
Any Event	28.4	25.4*	23.5*
Headache	20.2	15.8*	14.8*
Insomnia	2.3	2.3	2.3
Dizziness	1.7	2.0	2.3
Hypertonia	0.8	1.1**	0.2*
Anxiety	0.6	0.8	0.6
Migraine	1.1	0.7	0.7
Leg Cramps	0.5	0.7	0.9*
Somnolence	0.4	0.6	0.3
Paresthesia	0.4	0.5	0.3
Withdrawals:	0.7	1.1	0.7

\* doses of 100 mg BID, 200 mg QD and BID  
\* significantly different from placebo; p < 0.05 \*\* significantly different from NSAID; p < 0.05

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### Effects on Renal Function

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- Renal-related adverse events
- Effects on blood pressure
- Renal pharmacology studies
  - healthy elderly
  - chronic renal insufficiency

---

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### North American Arthritis Trials Incidence of Renal Adverse Events $\geq 0.5\%$

Adverse Event	Placebo (n=1864)	Celecoxib* (n=4146)	NSAID (n=2098)
Any renal event	2.5	4.3*	4.1*
Generalized Edema	0.0	0.1	0.5
Peripheral Edema	1.1	2.1*	2.1*
Hypertension	0.3	0.8	0.7
Aggravated Hypertension	0.4	0.6	0.3
Withdrawals	0.2	0.3	0.3

\* 100 mg BID and 200 mg QD or BID  
\* Significantly different from placebo; p < 0.05

---

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### Placebo- and Active-Controlled Arthritis Trials Effects on Blood Pressure in 12-Week Arthritis Trials

	n	Blood Pressure (mm Hg)	
		Baseline	Mean Change $\pm$ SE
Placebo	2194	132/79	-1.9 $\pm$ 0.3 / -1.0 $\pm$ 0.2
Celecoxib*	4410	132/79	-0.5 $\pm$ 0.3 / -0.4 $\pm$ 0.1
Naproxen	2150	133/79	-0.9 $\pm$ 0.3 / -0.5 $\pm$ 0.2

\* doses of 50-400 mg BID  
Treatments were not significantly different

---

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### Renal Pharmacology Studies

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- Objectives:
  - Assess effects vs. placebo and naproxen
- Design:
  - Healthy elderly and patients with chronic renal insufficiency
  - Duration - 7 to 10 days
- Results:
  - No effects on GFR
  - Transient reduction in sodium excretion (24-48 hrs) similar to naproxen

---

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### Conclusions: Celecoxib Renal Safety

---

- Renal adverse events - uncommon and similar to NSAIDs
- No effects on blood pressure
- Transient reduction in sodium excretion similar to naproxen
- Low incidence of edema
- No evidence of serious metabolic abnormalities with celecoxib or NSAIDs

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### Celecoxib - Clinical Objectives

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Indications	Differentiation
<ul style="list-style-type: none"> <li>• Osteoarthritis</li> <li>• Rheumatoid Arthritis</li> <li>• Management of Pain</li> </ul>	<ul style="list-style-type: none"> <li>• Gastrointestinal</li> <li>• Platelet</li> <li>• General Safety</li> </ul>

---

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## Effects on Platelet Function

---

- Bleeding-related adverse events
- Platelet studies
  - single dose
  - multiple dose

---

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### North American Arthritis Trials Incidence of Bleeding-Related Adverse Events $\geq 0.5\%$

Adverse Event	Placebo (n=1864)	Celecoxib* (n=4146)	NSAID (n=2098)
Any Bleeding-Related Event	1.6	1.8	3.8* **
Anemia	0.4	0.5	1.6* **
Ecchymosis	0.3	0.4	1.0* **
Withdrawals	0.0	<0.1	0.3

\* 100 mg BID and 200 mg QD or BID  
 \* Significantly different from placebo; p < 0.05  
 \*\* Significantly different from celecoxib; p < 0.05

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## Platelet Studies

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- Objectives:
  - Assess effects vs placebo and NSAIDs
- Design:
  - 5 studies in healthy volunteers
  - Duration - 1 to 10 days
- Results:
  - No effect at 2X the therapeutic dose:
    - platelet aggregation
    - Tx<sub>B2</sub> production
    - bleeding time

---

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## Conclusions: Celecoxib Effects on Platelet Function

---

- Bleeding-related adverse events - uncommon, significantly lower than NSAIDs and similar to placebo
- No effect on serum Tx<sub>B2</sub> levels, platelet function or bleeding time at 2X the therapeutic dose
- Platelet studies supported the COX-1 sparing effect of celecoxib

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## Celecoxib - Clinical Objectives

---

<h3 style="text-align: center;">Indications</h3> <ul style="list-style-type: none"> <li>• Osteoarthritis</li> <li>• Rheumatoid Arthritis</li> <li>• Management of Pain</li> </ul>	<h3 style="text-align: center;">Differentiation</h3> <ul style="list-style-type: none"> <li>• Gastrointestinal</li> <li>• Platelet</li> <li>• General Safety</li> </ul>
---	---

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## MUCOSA Trial

—■— Placebo + NSAIDs (n=4438)  
 —□— Misoprostol + NSAIDs (n=4404)

p = 0.031

Derived from Silverstein et al., Ann Intern Med 1995;123:241-249

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## Prospective Evaluation of GI Effects

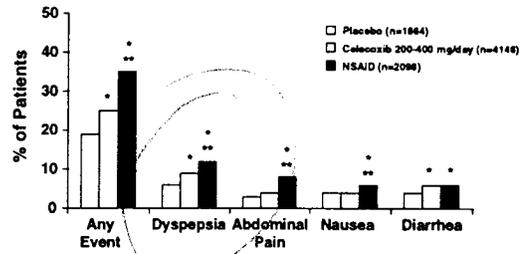
- GI symptoms
- Endoscopy findings
  - 5 arthritis trials
- Analyses of UGI ulcer complications

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## North American Arthritis Trials

### GI Adverse Events



\* Significantly different from placebo; p<0.05  
 \*\* Significantly different from celecoxib; p<0.05

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## North American Arthritis Trials

### GI Adverse Events Causing Withdrawal with an Incidence $\geq 0.5\%$

Adverse Event	Treatment Group		
	Placebo (n=1864)	Celecoxib <sup>a</sup> (n=4146)	NSAID (n=2098)
Any GI Event	2.0	2.7	6.3**
Abdominal Pain	0.6	1.0	2.1* **
Dyspepsia	0.6	0.8	1.6*
Diarrhea	0.3	0.3	0.4
Nausea	0.6	0.5	0.9
Esophageal Ulceration	0.0	<0.1	0.6**

<sup>a</sup> Patients who received either celecoxib 100 mg BID, 200 mg BID or 200 mg QD  
 \* Significantly different from placebo; p<0.05  
 \*\* Significantly different from celecoxib; p<0.05

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## Prospective Evaluation of GI Effects

- GI symptoms
- Endoscopy findings
  - 5 arthritis trials
- Analyses of UGI ulcer complications

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## Endoscopic Ulcers are Surrogates for UGI Ulcer Complications

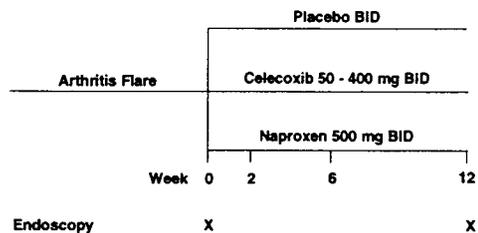
- Rationale:
  - NSAIDs reduce mucosal prostaglandins and cause ulcers
  - Ulcers can result in bleeding, perforation or outlet obstruction
  - Exogenous prostaglandins reduce both endoscopic ulcers and ulcer complications by ~50% over six months<sup>a,b</sup>

<sup>a</sup> Agrawal et al., Dig Dis Sci 1985; 40:1125-1131  
<sup>b</sup> Silverstein et al., Ann Intern Med 1995; 123:241-249

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## Design: 12-Week Studies



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## Mucosal Grading Scale

Grade	Description
0	No visible lesions (normal mucosa)
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions*
4	6-10 erosions
5	11-25 erosions
6	>25 erosions
7	Ulcer**

\* An erosion is defined as any break in the mucosa without depth  
 \*\* An ulcer is defined as any break in the mucosa at least 3 mm in diameter with unequival depth

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## 12-Week Endoscopy Studies

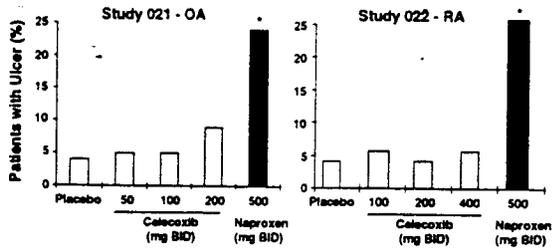
Treatment Group (n)	Study No.		Total
	021	022	
Placebo	247	231	478
Celecoxib 50 mg BID	258	-	258
Celecoxib 100 mg BID	240	240	480
Celecoxib 200 mg BID	237	235	472
Celecoxib 400 mg BID	-	218	218
Naproxen 500 mg BID	233	225	458
<b>Total</b>	<b>1215</b>	<b>1149</b>	<b>2364</b>

Planned sample size - 200/group

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## Incidence of Gastroduodenal Ulcers 12-Week Studies



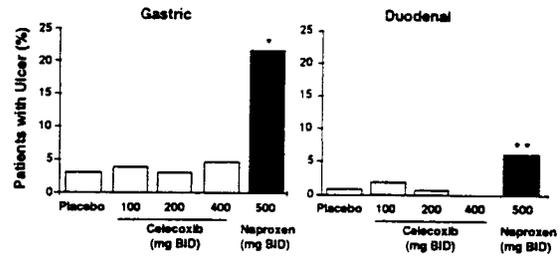
\* Significantly different from all other treatments: p < 0.001

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## RA and UGI Safety Study - 022

### Incidence of Ulcers



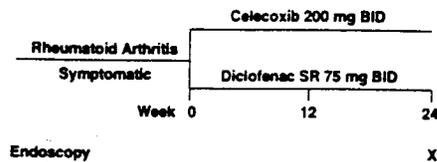
\* Significantly different from all other treatments: p < 0.026

\*\* Significantly different from placebo and celecoxib 200 and 400 mg BID: p < 0.033

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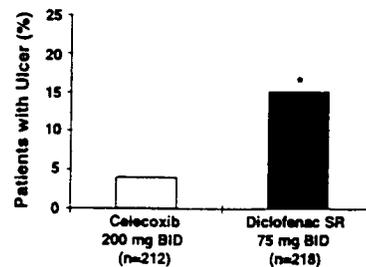
## Design: 6-Month RA Study



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## Incidence of Gastroduodenal Ulcers 6-Month Study



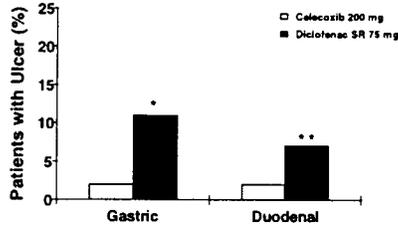
\* Significantly different from celecoxib: p < 0.001

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## Incidence of Ulcers 6-Month Study



\* Significantly different from celecoxib;  $P=0.002$

\*\* Significantly different from celecoxib;  $P=0.003$

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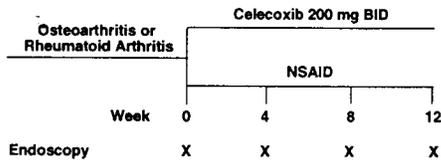
## Rationale for Serial Endoscopy Trials

- Asymptomatic ulcers may form and reheel without detection (with long intervals between endoscopies)
- Serial endoscopies might better estimate the true incidence of ulcers

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## Design: 12-Week Serial Endoscopy Studies



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## 12-Week Serial Endoscopy Studies

Treatment Group (n)	Study No.		Total
	062	071	
Celecoxib 200 mg BID	270	366	636
Naproxen 500 mg BID	267	--	267
Diclofenac 75 mg BID	--	387	387
Ibuprofen 800 mg TID	--	346	346
<b>Total</b>	<b>537</b>	<b>1099</b>	<b>1636</b>

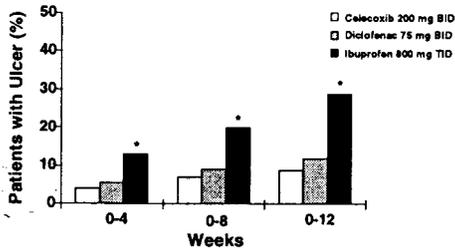
Planned sample size - 200 to 240/group

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## UGI Safety vs Diclofenac and Ibuprofen Study - 071

### Cumulative Incidence of Gastroduodenal Ulcers



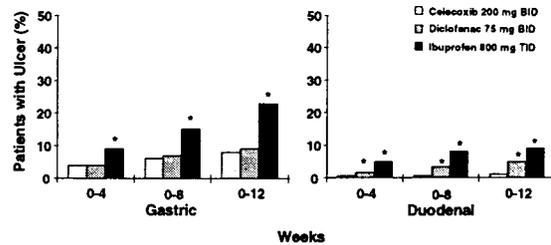
\* Significantly different from celecoxib and diclofenac;  $p < 0.001$

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## UGI Safety vs Diclofenac and Ibuprofen Study - 071

### Cumulative Incidence of Gastric & Duodenal Ulcers

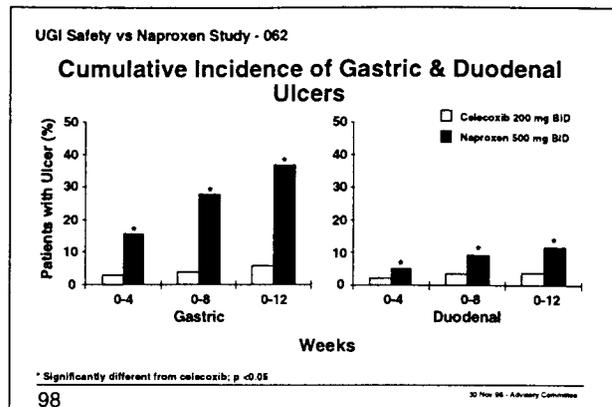
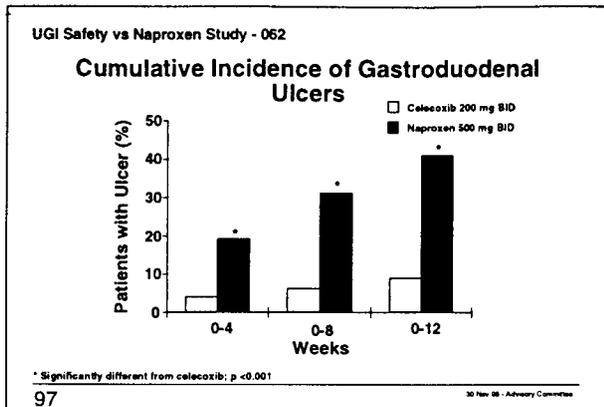


\* Significantly different from celecoxib;  $p < 0.05$

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- ### Celecoxib Endoscopy Studies
- Endoscopies in over 4,700 arthritis patients
  - Incidence of UGI ulcers
    - similar to placebo in replicate studies
    - statistically lower compared to:
      - naproxen
      - diclofenac
      - ibuprofen
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- ### Prospective Evaluation of GI Effects
- GI symptoms
  - Endoscopy findings
    - 5 arthritis trials
  - Analyses of UGI ulcer complications
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- ### Identifying UGI Ulcer Complications
- External Committee prospectively defined UGI ulcer complications
  - Investigators reported potential cases from OA and RA trials
  - Committee reviewed and adjudicated cases
  - Committee was blinded to patient, study and treatment
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- ### UGI Ulcer Complications Committee
- Fred Silverstein, M.D.
  - Naurang Agrawal, M.D.
  - Jay Goldstein, M.D.
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## Categories of UGI Ulcer Complications

- Bleeding
- Perforation
- Gastric Outlet Obstruction

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## UGI Ulcer Complications Program Overview

	Controlled Trials	Open Label Trial	
		NDA	Safety Update
No. Studies	14	1	-
No. Patients	11,008	4499	5155
No. Patient-Years	1763	2672	5002

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## UGI Ulcer Complications Controlled Trials

Treatment	No. Patients	No. Events	K-M Est.*	Patient Years	Events/ 100 Pt. Yrs.	Annual Incidence
Placebo	1864	0	0	208	0	0.00%
Celecoxib	6376	2	0.036%	1020	0.20	0.20%
NSAIDs	2768	9	0.393%	535	1.68	1.68%**

\* Estimates of cumulative event rate through 12 Weeks  
 \*\* Significantly different from celecoxib and placebo;  $p < 0.05$

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## UGI Ulcer Complications Celecoxib Open-Label Study

	No. Patients	No. Events	K-M Est.*	Patient Years	Events/ 100 Pt. Yrs.	Annual Incidence
NDA	4499	7	0.219%	2672	0.26	0.26%
Safety Update	5155	9	0.226%	5002	0.18	0.18%

\* Estimates of cumulative event rate through 18 Months

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## UGI Ulcer Complications

	No. Patients	No. Events	K-M Est.*	Patient Years	Events/ 100 Pt. Yrs.	Annual Incidence
NDA	4499	7	0.219%	2672	0.26	0.26%
Safety Update	5155	9	0.226%	5002	0.18	0.18%
<b>CONTROLLED TRIALS</b>						
Celecoxib	6376	2	0.036%	1020	0.20	0.20%

\* Estimates of cumulative event rate through 18 Months

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## Conclusions: GI Effects of Celecoxib

- NSAID GI class labeling is obviated:
  - similar to placebo:
    - UGI ulcers
    - ulcer complications
  - compared to NSAIDs showed a significant reduction in:
    - GI symptoms
    - UGI ulcers
    - ulcer complications

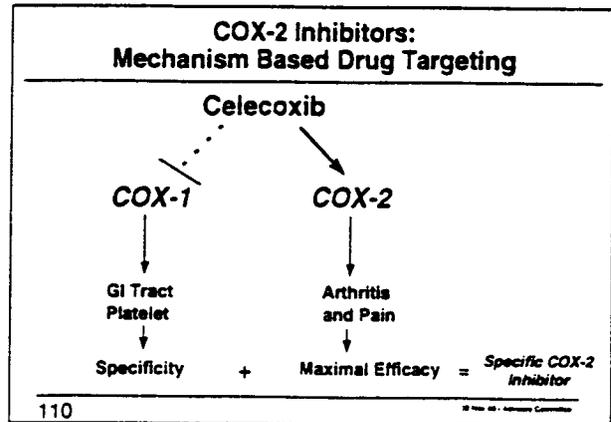
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Celecoxib - Differentiation Summary	
NSAIDs	Celecoxib
<b>Gastrointestinal</b>	<b>Gastrointestinal</b>
<ul style="list-style-type: none"> <li>- Ulcers</li> <li>- Complications</li> <li>- Symptoms</li> </ul>	<ul style="list-style-type: none"> <li>- Ulcers and complications similar to placebo</li> <li>- Reduction in ulcers and complications</li> <li>- Reduction in symptoms</li> </ul>
<b>Hemostasis</b>	<b>Hemostasis</b>
<ul style="list-style-type: none"> <li>- Inhibit platelets</li> </ul>	<ul style="list-style-type: none"> <li>- No effect on platelet function</li> </ul>
<b>Hepatic</b>	<b>Hepatic</b>
<ul style="list-style-type: none"> <li>- Elevated LFTs</li> </ul>	<ul style="list-style-type: none"> <li>- No elevation in LFTs</li> </ul>

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APPEARS THIS WAY  
ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**ADVISORY COMMITTEE: ARTHRITIS DRUGS ADVISORY  
COMMITTEE**

**DATE OF MEETING: 12/1/98**

**BRIEFING PACKAGE**

**EVALUATION OF THE ROLE OF  
COX-2 IN ANIMALS AND MAN: FOCUS  
ON THE POTENTIAL IMPACT OF  
SELECTIVE COX-2 INHIBITION**

Prepared by:

(b)(4)(CC)

Prepared for:

SmithKline Beecham Pharmaceuticals  
Philadelphia, Pennsylvania

November 6, 1998

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## **EXECUTIVE SUMMARY: OVERVIEW OF THE ROLES AND DISTRIBUTIONS OF COX-1 AND COX-2 IN ANIMALS AND MAN AND POTENTIAL IMPLICATIONS FOR SELECTIVE COX-2 INHIBITION**

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When aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) initially were developed, it was thought that all NSAIDs produced anti-inflammatory effects by inhibiting a single cyclooxygenase enzyme. NSAID-mediated inhibition of prostaglandin production led to a variety of promising anti-inflammatory, antiphlogistic, and analgesic effects, although it soon became apparent that not all NSAID-mediated effects were beneficial. Inhibition of prostaglandin synthesis in the gastrointestinal (GI) tract had deleterious effects on gastric mucosal protection and, in the kidney, led to decreased renal blood flow under certain conditions (see review by Donnelly and Hawkey, 1997). (It is recognized, however, that there are a number of other factors that may contribute to the deleterious effects of NSAIDs.)

Since the discovery of two isoforms of cyclooxygenase (COX), COX-1 generally has been considered to be expressed constitutively and is responsible for production of prostaglandins that participate in normal physiologic processes and protective functions (eg, maintaining integrity of GI mucosa, mediating normal platelet function, regulating renal blood flow and sodium resorption). In contrast, COX-2 was considered to be rapidly inducible in response to inflammation (Crofford, 1997; DeWitt et al, 1993; Donnelly and Hawkey, 1997; Jouzeau et al, 1997; Smith and DeWitt, 1995) and to produce prostaglandins involved in inflammation. It was hypothesized that inhibition of the "housekeeping" COX-1 enzyme resulted in many of the adverse effects associated with the use of NSAIDs and that COX-2 inhibition led to anti-inflammatory and analgesic effects.

This simplified view now appears to be misleading based on the following information:

- COX-1 is not just constitutive, but also is inducible.
- COX-1 has a role in certain types of inflammation.
  - Data from COX-1 and COX-2 knockout mice suggest that COX-1 plays a role in inflammation, and that COX-2 is not obligatory for an inflammatory effect. The relative importance of COX-1 and COX-2 in inflammation may depend, in part, on whether the inflammation is acute or chronic.
- COX-1 is not essential in preserving GI integrity and may not necessarily be involved in the development of GI toxicity associated with NSAIDs.
  - The role of COX-1 in homeostasis may have been overstated because COX-1 knockout mice do not exhibit excessive GI damage and remain susceptible to gastric damage with indomethacin (Langenbach et al, 1995; Mahmud et al, 1996). There are effects of NSAIDs unrelated to cyclooxygenase inhibition (eg, effects on mitochondria) that may be important (Chavez et al, 1993; Somasundaram et al, 1997).
- COX-2 is expressed constitutively in several tissues.
  - Although COX-2 is expressed in response to inflammatory stimuli, such as lipopolysaccharide and interleukins (Donnelly and Hawkey, 1997), it also can be detected in a variety of normal animal and human tissues.

- COX-2 has important physiologic activities, in addition to its role in inflammation.
  - COX-2 appears to be involved in a variety of physiologic or homeostatic functions, including:
    - Gastric cytoprotection
    - Ulcer healing and repair of mucosal injury
    - GI epithelial integrity and resistance to infection (peritonitis)
    - Renal salt and water homeostasis
    - Cardiovascular repair following injury
    - Pulmonary repair following injury
    - Central nervous system function
    - Reproduction (ovulation, fertilization, implantation, maintenance of pregnancy, parturition), and
    - Normal organogenesis in the fetus.

A more specific summary of the expression and roles of COX-1 and COX-2 in various body systems follows.

## **ROLE OF COX-1 AND COX-2 IN INFLAMMATION**

During inflammation, COX-2 clearly is upregulated (Anderson et al, 1996; Crofford, 1997; Sano et al, 1992). Although COX-1 was not thought to be directly involved in inflammation, recent studies have demonstrated that both cyclooxygenase isoforms are detected in synovial cells from inflammatory joints (Crofford et al, 1994; Gilroy et al, 1998; Iñiguez et al, 1998). In vitro analyses of cultured human synovial tissues show that macrophage, fibroblast, endothelial, and mononuclear inflammatory cells express both COX-1 and COX-2. In addition, in studies of COX-2 knockout mice, experimental challenges with inflammatory agents resulted in inflammatory responses that did not differ significantly from those in wild-type animals (Dinchuk et al, 1995; Morham et al, 1995). Thus, the presence of the

COX-2 enzyme is not essential for inflammation to occur. In contrast to findings in COX-2-deficient mice, inflammatory challenge in COX-1 knockout mice resulted in reduced inflammatory response (Langenbach et al, 1995). These findings are contrary to established views that COX-1 is a constitutive, housekeeping enzyme responsible only for maintaining normal cell function and that COX-2 is inducible and solely responsible for inflammatory response.

## **GASTROINTESTINAL TRACT**

In the GI tract, COX-1 is expressed constitutively in almost all tissues (Kargman et al, 1996). However, COX-2 is also expressed constitutively (to a much lesser extent), with highest concentrations found in the cecum and distal intestine in rats (Kargman et al, 1996). In rats, COX-2 is expressed in gastric epithelial cells (Sasaki et al, 1998) and is necessary for proliferation (Sawaoka et al, 1997).

In humans, constitutive COX-2 was found in intestinal mucosa (Mahida et al, 1997). In patients with ulcerative colitis, COX-2 is upregulated in colonic apical epithelial cells (Singer et al, 1998).

COX-2 appears to have an important role, which was previously attributed only to COX-1, in preventing or repairing GI mucosal damage. In COX-1 knockout mice, the absence of COX-1, which is purported to provide the majority of cytoprotective prostaglandins, did not cause spontaneous GI ulceration (Langenbach et al, 1995), indicating that compensatory protective mechanisms (possibly COX-2-mediated) must be involved. In addition, these mice remained susceptible to NSAID-induced damage, which could not have been COX-1-mediated. (Other explanations, unrelated to cyclooxygenase inhibition, for NSAID-induced damage to the GI tract have been proposed, including local, physicochemical effects [Lichtenberger et al, 1995] and effects on mitochondrial function [Chavez et al, 1993; Somasundaram et al, 1997]). Selective COX-2 inhibitors increase ischemia/reperfusion injury (Maricic

et al, 1998) and decrease adaptive cytoprotection (Brzozowski et al, 1998; Ehrlich et al, 1997; Gretzer et al, 1998a). Studies in rats and mice indicate that specific inhibition of COX-2 may delay ulcer healing (Mizuno et al, 1997; Schmassmann et al, 1998; Shigeta et al, 1998; Tsuji et al, 1997).

In the colon, COX-2 may protect against invasive bacteria because COX-2 knockout mice develop peritonitis (Morham et al, 1995; Morteau et al, 1997a). In addition, selective COX-2 inhibitors exacerbate experimental colitis in rats, with resultant septicemia (Reuter et al, 1996), and COX-2 stimulates fluid secretion by colonic epithelial cells (Blume et al, 1998; Eckmann et al, 1997).

Inhibition of COX-2 enhances apoptosis, which may inhibit tissue repair (Von Knethen and Brüne, 1997). This effect may be advantageous in preventing colonic polyps but may be disadvantageous in normal GI mucosa that is subject to repeated toxic insult and is characterized by one of the highest turnover rates of all body tissues.

## **KIDNEY**

In the kidney, COX-1 activity occurs primarily in medullary collecting ducts and interstitial cells. However, COX-2 also is expressed constitutively in the kidney and has an important role in renal homeostasis (Harris et al, 1994). In the human kidney, COX-2 is present in endothelial cells, smooth muscle cells, and glomerular podocytes (Kömhoff et al, 1997). Under basal conditions, COX-2 has been located in the renal cortex (Seibert et al, 1994). The presence of COX-2 in the macula densa of the juxtaglomerular apparatus and ascending limb of Henle suggests that COX-2 expression may correlate with volume expansion or contraction. Chronic volume depletion increases renal COX-2 expression in rats (Harris et al, 1994).

A recent study confirms that selective COX-2 inhibitors affect renal function in man (Rossat et al, 1998). The role of COX-2 in human renal homeostasis, and its importance relative to COX-1 inhibition, will need to be delineated by studies on the effects of specific COX-2 inhibitors in patients with conditions in which COX-2 is upregulated.

## **REPRODUCTIVE TRACT**

In the reproductive tract, both cyclooxygenase isoenzymes are expressed at various times during pregnancy (Vane et al, 1998). During early pregnancy, expression of COX-2 is necessary for ovulation, fertilization, implantation, and decidualization. COX-2 appears to be necessary for delivery of the fetus, and COX-2 levels increase significantly before and after labor (Gibb and Sun, 1996). Studies in COX-2 knockout mice indicate that females lacking COX-2 have reproductive defects and are infertile (Dinchuk et al, 1995; Lim et al, 1997). Although ovarian follicular development was normal, ovaries were small because of absence of corpora lutea (Dinchuk et al, 1995). COX-2 knockout mice also have impaired oocyte maturation, defective implantation of blastocysts in the uterus, and failed decidualization of the uterus (Lim et al, 1997). In contrast, both male and female COX-1 knockout mice remained fertile in the absence of COX-1, although the newborns were not always viable (Langenbach et al, 1995).

Development of luteinized unruptured follicles associated with infertility has been reported in women taking NSAIDs and could be associated with COX-2 inhibition (Smith et al, 1996). These data suggest that constitutive COX-2 is absolutely necessary for maintaining fertility. The potential long-term consequences of inhibiting normal luteal function, with consequent hyperestrogenemia, on endocrine-sensitive tissues need to be explored.

## **CENTRAL NERVOUS SYSTEM**

The human brain contains equal amounts of messenger ribonucleic acid (mRNA) for COX-1 and COX-2 (O'Neill and Ford-Hutchinson, 1993). Although the exact function of COX-1 and COX-2 in the brain remains to be determined, it is important to note that both isoenzymes are expressed constitutively.

## **CARDIOVASCULAR AND PULMONARY SYSTEMS**

In cardiovascular tissue, COX-2 knockout mice develop diffuse myocardial fibrosis (Dinchuk et al, 1995), and COX-2 is found in fibrotic cardiac tissue of patients with dilated cardiomyopathy (Wong et al, 1998). In pulmonary tissue, COX-2 also is expressed constitutively in rat lung (Brannon et al, 1998; Charette et al, 1995; Ermert et al, 1998) and is responsible for maintaining intrinsic tone in the guinea pig trachea (Charette et al, 1995); inhibition of tone may be greater with a selective COX-2 inhibitor than with a nonselective COX-1/COX-2 inhibitor (Charette et al, 1995). Patients with idiopathic pulmonary fibrosis are unable to induce COX-2 (Wilborn et al, 1995), suggesting that COX-2-mediated prostaglandin formation may be important in healing lesions and preventing fibrosis from occurring. This may be particularly relevant when selective COX-2 inhibitors are used to treat patients with rheumatoid arthritis, in whom the incidence of interstitial fibrosis is already increased (Anderson, 1993).

## **SUMMARY AND CONCLUSIONS**

The view that COX-1 is purely a constitutive enzyme functioning in housekeeping roles (such that inhibition of COX-1 is necessarily bad), whereas COX-2 is purely an isoenzyme induced during inflammation (such that inhibiting COX-2 only suppresses inflammation and is therefore necessarily good) is, clearly, an

oversimplification. COX-2 has important physiologic functions, and the potential impact of inhibiting these functions should be considered carefully.

A common theme surrounding the known roles of COX-2 and the known effects of selective COX-2 inhibitors is that COX-2-mediated prostaglandins participate in cellular proliferation in inflammatory cells, angiogenesis, tissue repair (in the GI, cardiovascular, and respiratory systems), neoplasia, reproduction, and osteogenesis (Majerus, 1998; Majima et al, 1997; Onoe et al, 1996; Sarrazin and de Brum-Fernandes, 1998; Sato et al, 1997; Stenson, 1997; Tsuji and DuBois, 1995; Vane et al, 1998). As stated by William Stenson, MD, in a recent *Gastroenterology* editorial (1997), it may well be that "...inflammation and wound healing form a seamless continuum; drugs that inhibit inflammation may also retard healing."

It should be noted that the effects of inhibiting COX-2 are not necessarily restricted to selective COX-2 inhibitors. Indeed, many typical adverse effects associated with nonselective NSAIDs (such as impairment of ulcer healing, effects on renal function, effects on fertility) may be due to inhibition of COX-2. Therefore, selective COX-2 inhibitors should be considered similar to nonselective NSAIDs in sharing these typical adverse effects.

In contrast, it is not self-evident that sparing COX-1 will have no effects other than obviating toxicity mediated by COX-1. Selective COX-2 inhibitors may exhibit diminished therapeutic activity for certain applications because they lack associated COX-1 inhibition. Furthermore, the complex relationship between COX-1 and COX-2, and connections between the cyclooxygenase system and inducible nitric oxide synthase or other intracellular pathways, make it difficult or impossible to predict what effects will be associated with unopposed suppression of COX-2.

Finally, not all of the beneficial or detrimental effects of NSAIDs are necessarily associated with cyclooxygenase inhibition. NSAIDs, through effects on divalent cation translocation, have important effects on mitochondrial function that are independent of any effect on cyclooxygenase function (Chavez et al, 1993; Somasundaram et al, 1997); and this may be more important than inhibition of cyclooxygenase in GI toxicity. Another physicochemical effect of NSAIDs, unrelated to cyclooxygenase inhibition, involves alterations in hydrophobicity of the phospholipid barrier in the gastric mucosa (Lichtenberger et al, 1995; Lugea et al, 1997). NSAIDs (both nonselective and COX-2-specific) may have important effects on apoptosis and polyp regression that are independent of effects on cyclooxygenase (Piazza et al, 1997) or on prostaglandin formation (Chan et al, 1998).

In view of the evolving science in this area, the following points need to be considered when evaluating more highly selective COX-2 inhibitors:

- COX-1 and COX-2 have overlapping functions. It is unlikely that the pharmacodynamic profile of a drug can be predicted by knowledge of its effects on these isoenzymes.
- Because COX-1, as well as COX-2, is involved in inflammation, it is not immediately apparent that inhibition of COX-2 alone will provide optimal anti-inflammatory activity. However, because of the variability inherent in clinical trials designed to compare active agents, definitive differences in relative efficacy will be difficult to demonstrate.
- Because the functions of the cyclooxygenase isoenzymes are interrelated with each other, and with other intracellular pathways, the effects of isolated inhibition of one of the isoenzymes (ie, COX-2) cannot easily be predicted. It cannot be assumed that an agent that does not inhibit COX-1 is either completely safe or has a safety profile that can be predicted.

- In addition to any effects or lack of effects on prostaglandins produced by COX-1 or COX-2, NSAIDs have other pharmacologic properties that may affect their safety profile.
- Because inhibition of COX-2 by both conventional NSAIDs and selective COX-2 inhibitors contributes to their efficacy and side-effect profiles, selective COX-2 inhibitors should be considered NSAIDs. As with other NSAIDs, the individual safety and efficacy profiles of selective COX-2 inhibitors should be determined by clinical trials and clinical experience.

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