

Species	Study N ^o	NOEL (mg/kg/day)	Analyte	Exposure in Animals AUC ₀₋₂₄ (μg•hr/ml)	Ratio of Animal Exposure/Human Exposure ^a at MRHD (20 mg/day)
FERTILITY , EARLY EMBRYONIC DEVELOPMENT→IMPLANTATION					
Rat	SA4578	0.2	SC-65872	0.52	0.18
			SC-66905	0	-
EMBRYO-FETAL DEVELOPMENTAL					
Rat	SA4487	10	SC-65872	57.2	19.32
			SC-66905	5.32	23.13
	SA4963	12.5 ^b	SC-65872	51.0	17.23
			SC-66905	6.84	29.74
Rabbit	SA4528	10	SC-65872	23.2	7.84
			SC-66905	5.58	24.26
	SA4992	10	SC-65872	5.94	2.01
			SC-66905	5.64	24.5
PRE AND POST NATAL DEVELOPMENT					
Rat	SA4776	2	SC-65872	8.92 ^c	3.01
			SC-66905	1.36	5.91

^a Estimated mean exposure AUC₀₋₂₄ values for SC-65872 and SC-66905 at MRHD in young adults were 2.96 and 0.23 µg•hr/ml, respectively.

^b Animals were treated with SC-69124A (Parecoxib) at 0, 3, 6.25, 12.5, and 25 mg/kg/day iv bid.

^c The exposure of SC-65872 and SC-66905 were not determined in this study. Exposure data (2 mg/kg/day on GD 17) presented here were extracted from Study N° SA4487.

5.2.5. GENETIC TOXICOLOGY

The mutagenic potentials of SC-65872 and its active metabolite, SC-66905, were evaluated in both *in vitro* and *in vivo* systems and results are summarized in the following table.

Assay System	Indicator Cells	Compound Concentrations	Findings
Ames	<i>Salmonella typhimurium</i> strains (histidine auxotrophs) - TA97a, TA98, TA100, TA102, and TA1535	SC-65872 - 10, 50, 100, 500, 1000, and 5000 µg/plate	Not mutagenic.
		SC-66905 - 10, 50, 100, 500, 1000, and 5000 µg/plate	Not mutagenic.
CHO/HGRT Mutation	CHO cells (subline K1-BH ₄)	SC-65872 - -S9: 12.5, 25, 50, and 100 µg/ml +S9: 50, 100, and 200 µg/ml	Not mutagenic.
Chromosome Aberration	CHO-WBL cells	SC-65872 - -S9: 39, 58, and 117 µg/ml, 4 hr exposure; 25, 50, and 75 µg/ml, 24 hr exposure +S9: 39, 58, and 117 µg/ml	Not clastogenic.
		SC-66905 - -S9: 11.7, 35, 116.7, and 350 µg/ml, 4 hr exposure; 11.7, 35, and 116.7 µg/ml, 24 hrs exposure +S9: 35, 116.67, and 350 µg/ml	Not clastogenic.
Micronucleus Assay	♂ & ♀ CD(SD)BR Rats, 5/sex/group - Bone Marrow Cells	SC-65872 - 0, 6.25, 12.5, and 25 mg/kg/dose po bid 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 valdecoxib were evaluated and the observations are summarized in the following table.

Testing System	Species	Dose/Route	Observations/Comments
LOCAL TOLERANCE/IMMUNOGENICITY (DERMAL SENSITIZATION)			
Primary Dermal Irritation	Hra:(NZW)SPF Rabbits	SC-65872 - 0.5 g with 1.0 ml H ₂ O dermal occlusion	No dermal irritation.
Primary Eye Irritation	Hra:(NZW)SPF Rabbits	SC-65872 - 22 mg (0.1 ml wt equivalent) lower everted eye lid	Minimal ocular irritant.
Muscular and vascular Irritation	♂ New Zealand White rabbits	SC-65872 - 0.2 mg/ml Vehicle - 15 mg/ml Tween 80 + 9 mg/ml NaCl im - 1 ml/site; iv - 0.71 ml/site	SC-65872: slight→mild irritant Vehicle: slight→moderate irritant
Guinea Pig Maximization Test	Crl:(HA)BR Albino Guinea Pigs	Sensitization: 5% in FCA/H ₂ O id; Induction and Challenge 25% in Petrolatum dermal topical	No reaction post challenge. No concurrent (+) control was performed. Therefore, the study was not valid.
EFFECTS ON SUSCEPTIBILITY TO BACTERIAL INFECTION AND WOUND HEALING			
Wound Healing in Skin <i>Strep.</i> and <i>Staph.</i> Inoculation Model	♀ Beagle Dogs (4-6 ♀/group)	SC-65872 - 0, 7 mg/kg bid po for 28-day	Severe swellings persisted for 8-13 days at <i>Strep.</i> inoculation sites that subsequently developed into large open sores and delayed wound healing by 2-3 days in SC-65872 treated group.
Exploratory Range Finding in <i>Strep.</i> Inoculation Model	Beagle Dogs (N=3/sex)	SC-65872 - 0.15, 0.5, 1.5, 3 mg/kg bid po for 28-day or 7 mg/kg bid po for 7-day with 3-wk recovery	≥3 mg/kg/day: dose-dependent ↑ in incidence and severity of cellulitis/skin ulceration; ↓ PGE ₂ levels in exudate @ 14 mg/kg/day.
Exploratory Skin <i>Strep.</i> Inoculation Model	Beagle Dogs (N=3/sex)	SC-65872 - 0, 7 mg/kg bid po for 20-day	↑ incidence of skin ulceration/cellulitis in SC-65872 treated dogs.
Exploratory Skin <i>Strep.</i> Inoculation Model	Beagle Dogs (N=3/sex)	Valdecoxib (SC-65872) - 7 mg/kg SC-66791 - 20 mg/kg SC-70245 - 20 mg/kg SC-69340 - 20 mg/kg Naproxen Sodium - 5, 25 mg/kg Meloxicam - 1.5 mg/kg po bid for 14-16 days	Skin ulcers and GI injury in dogs treated with valdecoxib, SC-66791, SC-70245, Naproxen and meloxicam but not SC-69340 (positional isomer of valdecoxib); ↓ urine Na and Cl excretion and renal papillary necrosis in 50 mg/kg/day of naproxen and meloxicam groups; tubular atrophy and fibrosis @ 50 mg/kg/day of naproxen; ↓ levels of PGE ₂ and 6-keto-PGF-1α in exudate of all treated groups;
EFFECTS ON RENAL FUNCTIONS			
Exploratory Renal Function	♂ Beagle Dogs (N=6)	0, 14 mg/kg/day po bid for 42-day Switch to low sodium diet (~0.05% Na) from Day 15	GI (jejunal/ileal ulceration/erosion) and renal toxicity (↑BUN, tubular epithelial atrophy and fibrosis in the outer renal cortex, and alterations in renal hemodynamics) @ 14 mg/kg/day
Exploratory Renal Function	♂ Beagle Dogs (N=3)	SC-65872 - 14 mg/kg/day during Day 1-8 then 28 mg/kg/day during Day 9-42 bid po Naproxen Na - 5.0 mg/kg/day during Day 23-36 then 30 mg/kg/day during Day 36-48 bid po	SC-65872 - GI ulceration, ↓ GFR up to 42%, and ↓ urine output (42-72%) and urinary excretion of sodium, chloride, and calcium (45-86%) Naproxen - GI lesions (pyloric ulceration w/ peritonitis), ↓ urine output by 57%, ↓ urinary excretion of Na and Cl (87-89%), and kidney lesions of renal papillary degeneration/necrosis and multifocal tubular epithelial degeneration and atrophy in the outer cortex.
Renal Function	Cynomolgus Monkeys (N=3/sex)	SC-65872 - 12 mg/kg/day po bid for 42-day Naproxen Na - 150 mg/kg/day po bid for 42-day Switch to low sodium diet (~0.057% Na) from Day 15	SC-65872 - well tolerated Naproxen - ↓ food consumption, GI ulceration and morphologic alterations in the kidney with changes in renal functions secondary to obstructive nephropathy
IN VITRO COMPATIBILITY WITH HUMAN BLOOD			
Hemolytic Assay	Human Blood (N=4)	SC-65872 - 50 and 250 µl at 0.2 mg/ml	Non-hemolytic.

FCA = Freund's Complete Adjuvant; id = intradermal injection

5.3. ADME

5.3.1. ABSORPTION (BIOAVAILABILITY) AND TOXICOKINETICS

5.3.1.1. Single Dose Studies

Assessment of the pharmacokinetics of valdecoxib was conducted in various species.

• Single IV Administration -

Species	Dose (mg/kg)	T _{1/2} (hr)		Vd (l/kg)		CL (ml/hr•kg)		AUC _{0-∞} (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀
Mouse	5	0.76	0.33	1.56	1.23	23.6	43.2	3.87	2.55
Rat	1.1	2.76	4.17	2.56	2.30	10.8	6.65	1.78	2.92
	10	2.13	-	1.90	-	9.98	-	16.7	-
Guinea Pig	2	0.280	-	1.88	-	78.4	-	0.444	-
	10	0.279	-	1.35	-	59.0	-	2.95	-
Rabbit	5.11	-	1.07	-	0.521	-	8.70	-	14.2
Dog	2	1.48	-	1.38	-	12.2	-	3.21	-
	5	2.15	1.82	0.867	0.610	5.15	3.83	22.5	22.0
	10	-	2.76	-	1.01	-	4.33	-	38.7
Monkey	5	-	1.83	-	0.913	-	5.97	-	15.7

• Single Oral Administration -

Species	Dose (mg/kg)	Formulation	T _{max} (hr)		C _{max} (μg/ml)		AUC _{0-∞} (μg•hr/ml)		BA (%)	
			♂	♀	♂	♀	♂	♀	♂	♀
Mouse	5	Sol	0.25	0.25	2.25	2.35	3.20	1.99	89.8	106
		Susp	0.50	0.25	1.99	1.66	2.55	2.15	70.9	100
Rat	1.1	Susp	2.67	2.67	0.31	0.32	1.89	2.94	106	101
		10	Sol	1.50		3.15		16.2		96.5
Rabbit	5	Sol		0.5		0.53		1.98		14.0
		Susp		0.5		0.54		1.73		12.9
Dog	5	Sol	1.58	1.75	4.14	4.20	20.1	15.3	85.4	69.2
		Capsule	2.17	2.50	2.23	2.94	12.1	12.4	55.1	56.4
	10	Sol		0.5		7.33		31.6		81.0
		Capsule		9.67		1.52		20.7		48.0
Monkey	5	Susp		1.83		1.39		8.23		56.8

Formulation: Sol = PEG 400:H₂O solution; Susp = 0.5% methylcellulose (w/v) + 0.1% polysorbate 80 (v/v) aqueous suspension; Capsule = Gelatin capsule with micronized compound

- The pharmacokinetics of SC-66905, a pharmacologically active metabolite of valdecoxib, was studied in rats and dogs. The elimination T_{1/2} of SC-66905 in ♂ rat was 2.65 hr as listed in the following table. In dogs, the clearance of SC-66905 was slower than that of valdecoxib and its elimination T_{1/2} (5.11 hr) was longer than that of valdecoxib (1.48-2.76 hr).

Species	Dose (mg/kg)	Route	Sex	T _{1/2} (hr)	Vd (l/kg)	CL (ml/hr•kg)	AUC _{0-∞} (μg•hr/ml)
Rat	10	iv	♂	2.65	1.78	7.86	21.2
Dog	10	iv	♀	5.11	0.346	0.794	210 ^a

^a AUC₀₋₂₄

- Effects of on Plasma SC-65872 Levels in Dogs - Fat contents in the diets caused increases in T_{max} values of SC-65872 and SC-66905 and AUC value of SC-66905.

5.3.1.2. Repeated-Dose Toxicity Studies (Toxicokinetics)

- Toxicokinetics of Parecoxib in Mouse Studies - The following table summarizes PK/TK parameters obtained from 2- and 13-week toxicity as well as carcinogenicity studies in mice.

Sampling (Day)	Dose		SC-58672 Parameters				SC-66905 Parameters			
			C_{max} ($\mu\text{g/ml}$)		AUC_{0-24} ($\mu\text{g}\cdot\text{hr/ml}$)		C_{max} ($\mu\text{g/ml}$)		AUC_{0-24} ($\mu\text{g}\cdot\text{hr/ml}$)	
	σ	f	σ	f	σ	f	σ	f	σ	f
2-Week Range-Finding Dietary Admix Toxicity Study										
14	30		1.95	0.805	8.17	3.90	0.914	0.892	4.95	5.86
	100		1.09	0.530	15.5	6.82	0.663	1.09	9.47	11.7
	300		3.77	0.984	27.5	14.1	1.78	1.52	15.0	23.3
	1000		11.3	2.38	95.5	34.9	7.78	3.86	68.6	55.2
13-Week Range-Finding Dietary Admix Toxicity Study										
7	30	60	0.202	0.195	3.94	3.18	0.117	0.345	1.53	4.45
	100	200	0.519	0.603	7.68	7.08	0.321	0.607	3.63	11.1
	300	600	1.09	1.62	17.2	17.9	0.679	1.45	11.1	24.1
	600	1000	1.72	1.57	23.9	21.5	0.940	2.18	17.8	35.1
28	30	60	0.351	0.169	5.55	1.86	0.167	0.243	2.69	4.69
	100	200	0.729	0.532	11.4	7.9	0.304	0.666	5.35	11.2
	300	600	1.87	1.99	24.3	17.9	0.678	1.66	12.3	24.1
	600	1000	2.29	1.53	27.1	24.8	1.09	1.78	17.8	36.3
87	30	60	0.264	0.162	4.59	3.03	0.141	0.280	2.63	5.70
	100	200	0.846	0.593	9.66	7.92	0.489	0.661	5.49	12.5
	300	600	1.26	1.39	14.3	ID ^a	0.751	1.22	9.69	ID
	600	1000	NA ^b	NA	NA	NA	NA	NA	NA	NA
2-Year Dietary Admix Carcinogenicity Study										
5	12.5	25	0.142	0.189	2.16	2.34	0.0730	0.247	0.672	3.54
	25	50	0.224	0.237	3.30	3.67	0.162	0.322	1.63	6.43
	50	100	0.306	0.440	5.14	5.60	0.360	0.519	4.52	9.31
202	6.25	12.5	0.107	0.119	1.42	1.79	0.0728	0.175	0.839	2.69
	12.5	25	0.150	0.173	2.67	2.41	0.110	0.220	1.62	3.92
	25	50	0.282	0.360	3.17	3.74	0.179	0.293	1.94	5.06
363	6.25	12.5	0.149	0.0343 ^c	1.86	- ^d	0.0827	0.203	0.729	1.62
	12.5	25	0.321	0.105	3.80	1.47	0.126	0.165	1.79	2.32
	25	50	0.804	0.196	9.80	2.48	0.295	0.198	4.34	3.96

^a ID = Insufficient samples, data were not calculated.

^b NA = Not available, animals sacrificed at an interim date.

^c This C_{max} value was a mean of one valid concentration (0.103 $\mu\text{g/ml}$) and two 0.0 $\mu\text{g/ml}$ values. The 0.0 $\mu\text{g/ml}$ concentration values were the result from plasma sample analyses with raised sensitivities and they were set to 0 in the calculation.

^d For this dose group, 4 out of 6 mean plasma concentrations used in AUC calculation were less than the sensitivity limits (they were set to 0.0 $\mu\text{g/ml}$ in calculations). The calculated AUC_{0-24} value of 0.305 $\mu\text{g}\cdot\text{hr/ml}$ was not used.

- Toxicokinetics of Valdecoxib in Rat Studies - The following table summarizes PK/TK parameters obtained from 2-, 4-, and 13-week toxicity studies in rats. Female rats had higher exposure to SC-65872 than σ rats. This observation is in agreement with the findings from single dose pharmacokinetic studies. Accumulation of SC-65872 and SC-66905 occurred in the female rats after repeated dosing.

Day	Dose (mg/kg/day)	SC-58672 Parameters						SC-66905 Parameters					
		T _{max} (hr)		C _{max} (μg/ml)		AUC ₀₋₂₄ (μg•hr/ml)		T _{max} (hr)		C _{max} (μg/ml)		AUC ₀₋₂₄ (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
2-Week Range-Finding Dietary Admix Toxicity Study													
6	10	24	0	0.562	1.51	8.47	26.4	0	0	0.266	0.294	3.82	3.53
	30	0	0	2.24	7.95	27.1	119	0	5	0.961	0.814	12.3	14.5
	100	5	24	8.64	28.8	144	408	5	5	9.57	5.77	105	92.1
	300	20	11	22.8	29.1	329	616	24	20	16	20.3	258	-
14	10	0	5	0.783	2.18	10.8	37.3	24	0	0.253	0.276	3.86	3.93
	30	24	0	2.28	8.76	34.6	133	24	5	1	1.09	14.8	17.8
	100	24	5	9.25	32.6	140	501	24	5	6.72	11.5	90.4	163
Day	Dose (mg/kg/day)	SC-58672 Parameters						SC-66905 Parameters					
		T _{max} (hr)		C _{max} (μg/ml)		AUC ₀₋₁₂ (μg•hr/ml)		T _{max} (hr)		C _{max} (μg/ml)		AUC ₀₋₁₂ (μg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
2-Week Range-Finding Oral Toxicity Study (po bid by gavage)													
1	1	1.0	2.0	0.095	0.126	0.466	0.841	4.0	7.0	0.024	0.007	0.116	0.027
	10	2.0	2.0	1.260	1.680	6.150	10.8	4.0	7.0	0.258	0.192	1.980	1.600
	50	2.0	2.0	5.500	9.950	29.800	74.7	4.0	2.0	1.970	0.855	16.50	8.360
14	1	1.0	1.0	0.092	0.170	0.424	0.970	4.0	4.0	0.008	0.007	0.020	0.017
	10	1.0	4.0	1.280	3.050	5.350	19.4	1.0	4.0	0.238	0.531	1.970	3.140
	50	1.0	1.0	6.140	9.810	26.500	77.3	1.0	4.0	1.400	1.640	12.40	15.30
4-Week Oral Toxicity Study (po bid by gavage)													
1	2.5	-	1.5	-	0.356	-	2.11	-	5.0	-	0.0392	-	0.312
	5	1.5	1.5	0.610	0.864	2.66	5.27	7.0	3.0	0.0949	0.0926	0.820	0.610
	10	1.5	1.5	1.29	1.97	5.68	11.3	1.5	7.0	0.261	0.192	1.79	1.49
	25	1.5	1.0	5.39	5.20	17.1	34.1	1.5	3.0	1.03	0.617	5.92	4.04
	50	1.5	-	6.98	-	32.9	-	5.0	-	2.52	-	16.5	-
25	2.5	-	0.5	-	0.560	-	3.04	-	7.0	-	0.0877	-	0.453
	5	1.5	1.5	0.696	1.19	2.50	7.48	1.5	0	0.130	0.233	0.904	1.19
	10	1.5	1.0	1.54	3.74	4.62	17.3	1.5	5.0	0.373	0.207	1.76	1.75
	25	1.5	1.0	4.53	8.35	14.1	54.2	1.5	5.0	1.28	0.646	8.00	6.00
	50	1.5	-	9.19	-	33.8	-	7.0	-	2.35	-	13.9	-
13-Week Oral Toxicity Study (po bid by gavage)													
1	1.25	-	2	-	0.595	-	3.94	-	7	-	0.0536	-	0.455
	2.5	1	1	0.48	0.819	2.58	4.53	2	4	0.124	0.0703	0.862	0.541
	5	2	2	0.908	1.46	5.71	9.45	2	2	0.237	0.14	1.65	1.28
	12.5	2	2	3.35	5.42	17.7	36.1	4	2	0.769	0.431	6.18	3.78
	25	2	-	5.92	-	37.5	-	2	-	1.67	-	14.1	-
	50	4	-	10.7	-	71.1	-	4	-	3.89	-	34.3	-
28	1.25	-	1	-	0.56	-	3.75	-	4	-	0.0351	-	0.333
	2.5	1	2	0.714	1.09	3.18	8.27	4	4	0.151	0.0953	0.992	0.737
	5	1	2	1.53	3.02	7.04	21.9	4	2	0.339	0.2	2.37	1.9
	12.5	1	2	4.75	10.6	26	77.6	4	2	1.15	0.983	8.34	7.44
	25	2	-	8.66	-	47.2	-	2	-	2.7	-	18.1	-
	50	1	-	12	-	84.8	-	7	-	6.13	-	51.7	-
80/ 90	1.25	-	2	-	0.58	-	4.15	-	7	-	0.0303	-	0.336
	2.5	2	1	0.646	1.33	3.75	10.3	4	4	0.156	0.104	1.08	0.864
	5	1	2	1.43	3.52	8.68	24.2	7	7	0.251	0.218	2.23	2.19
	12.5	2	2	6.71	12.3	42.2	98.6	4	7	1.4	1.06	11.3	9.57
	25	2	-	9.55	-	58.6	-	7	-	2.86	-	25.8	-
	50	3	-	11.1	-	94.9	-	7	-	7.20	-	54.6	-

The following table summarizes PK/TK parameters for valdecocixib and SC-66905 obtained from 26-week toxicity and carcinogenicity studies in rats.

Day	Dose (mg/kg/day)		SC-58672 Parameters						SC-66905 Parameters					
			T_{max} (hr)		C_{max} (μ g/ml)		AUC_{0-24} (μ g•hr/ml)		T_{max} (hr)		C_{max} (μ g/ml)		AUC_{0-24} (μ g•hr/ml)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
26-Week Oral Toxicity Study (po qd by gavage)														
1	5	2.5	0.5	1	1.21	0.627	6.07	3.92	2	4	0.305	0.0787	2.28	0.793
	12.5	5	1	1	3.31	1.44	18.6	9.45	4	4	0.928	0.187	7.36	1.63
	25	10	1	1	6.06	2.69	39.5	21.6	4	4	2.04	0.526	17.7	4.53
78	5	2.5	0.5	1	1.33	1.03	7.29	9.84	4	4	0.292	0.0994	2.33	0.774
	12.5	5	2	4	3.90	2.20	34.3	18.1	4	4	1.07	0.182	12.1	1.89
	25	10	2	2	6.01	4.42	51.3	42.1	7	4	2.37	0.500	22.3	5.42
169	5	2.5	1	0.5	1.54	1.17	8.71	12.1	4	7	0.275	0.0782	2.59	0.986
	12.5	5	2	2	7.99	2.89	39.0	25.8	2	2	1.30	0.161	15.0	2.31
	25	5	2	2	7.33	2.86	55.7	23.7	7	2	1.86	0.207	17.6	2.46
2-Year Carcinogenicity Study (po qd by gavage)														
1	2.5	1.25	2	2	0.704	0.373	4.10	2.58	2	6	0.118	0.055	1.45	0.736
	5	2.5	1	2	1.62	0.889	7.98	5.58	6	6	0.255	0.095	2.61	1.04
	12.5	5	1	1	4.30	1.62	21.7	11.3	2	2	0.734	0.179	7.11	2.18
117	2.5	0.5	0.5	0.5	0.744	0.210	5.12	1.40	6	0	0.116	0	1.31	0
	5	1	2	0.5	1.79	0.500	11.6	3.95	6	0.5	0.229	0.020	3.15	0.105
	7.5	1.5	1	2	2.93	1.51	41.4	8.36	6	2	0.356	0.091	5.20	0.656
359	2.5	0.5	2	2	0.987	0.274	8.80	2.16	6	2	0.127	0.012	1.39	0.148
	5	1	1	1	2.01	0.524	16.9	5.07	6	6	0.256	0.032	3.29	0.445
	7.5	1.5	1	2	3.04	0.807	23.8	7.70	6	2	0.517	0.051	6.29	0.757

- Toxicokinetics of Valdecoxib in Dog Studies - Plasma concentrations of valdecoxib and SC-66905 increased nearly proportionally to dose. Accumulation of valdecoxib was observed in the combined 26-/52-week toxicity study. However, accumulation of plasma concentrations of SC-66905 was noted in all repeated dose studies. There were no apparent sex-differences in PK parameters for SC-658725 and SC-66905. The following table summarizes PK/TK parameters obtained from 2- 13-, and 26-/52-week toxicity studies.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Day	Dose (mg/kg/day) bid	SC-65872 Parameters						SC-66905 Parameters					
		T _{max} (hr)		C _{max} (μg/ml)		AUC _{0-12hr} (hr•μg/ml)		T _{max} (hr)		C _{max} (μg/ml)		AUC _{0-12hr} (hr•μg/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
2-Week Oral Capsule Toxicity Study													
1	5	1.75	1.25	0.934	1.58	2.96	4.74	3.5	3.0	0.447	0.623	2.68	3.05
	15	2.25	1.25	1.42	2.09	4.14	6.57	2.5	2.5	0.690	1.26	3.42	7.03
	30	1.50	2.00	1.38	3.07	5.30	9.09	2.25	2.0	0.740	1.63	4.07	8.38
15	5	1.25	2.00	0.632	1.43	2.93	5.66	2.88	2.75	0.768	1.04	5.20	6.57
	15	3.25	2.25	2.70	1.91	16.7	8.89	2.0	1.75	2.87	2.90	22.1	20.0
	30	1.00	2.30	2.59	3.08	16.0	19.5	1.0	1.75	3.34	3.70	22.9	28.5
4-Week Oral Capsule Toxicity Study													
1	1.0	2.00	1.00	0.405	0.444	1.20	1.26	3.00	3.00	0.262	0.361	1.27	1.69
	2.5	1.00	1.00	1.360	1.120	4.67	3.41	3.00	2.00	0.595	0.706	3.33	3.47
	5.0	2.00	1.00	1.980	1.580	7.36	5.58	12.0	3.00	1.550	1.310	5.71	6.15
29	1.0	2.00	1.00	0.384	0.291	1.13	0.85	2.00	2.00	0.382	0.420	1.99	2.06
	2.5	2.00	2.00	1.020	0.787	3.76	2.94	2.00	3.00	0.734	1.000	4.45	5.54
	5.0	2.00	2.00	2.180	1.420	9.64	5.83	2.00	3.00	1.950	1.720	12.6	10.7
13-Week Oral Capsule Toxicity Study													
1	1.0	2	1	0.193	0.151	0.380	0.357	2	2	0.119	0.099	0.567	0.631
	2.0	2	2	0.433	0.410	0.938	0.911	2	3	0.279	0.293	1.45	1.71
	4.0	1	1	0.729	0.470	2.37	1.47	2	2	0.597	0.416	2.55	2.5
28	1.0	1	1	0.127	0.194	0.335	0.350	1	1	0.108	0.142	0.896	0.959
	2.0	1	2	0.334	0.278	0.946	0.938	2	3	0.353	0.335	2.79	2.28
	4.0	1	2	0.457	0.472	2.19	1.89	1	3	0.591	0.760	5.04	7.19
49	1.0	1	0.5	0.153	0.159	0.377	0.338	2	2	0.138	0.141	1.02	0.773
	2.0	1	2	0.340	0.311	1.01	0.825	3	2	0.370	0.335	2.93	2.32
	4.0	2	1	0.518	0.640	2.81	1.95	5	2	0.593	0.750	5.88	7.25
91	1.0	1	1	0.200	0.145	0.507	0.333	2	2	0.206	0.175	1.01	0.800
	2.0	2	2	0.441	0.253	1.25	0.773	2	2	0.523	0.304	3.21	2.32
	4.0	2	2	0.573	0.571	2.64	2.20	2	2	0.535	0.941	4.36	7.01
26/52-Week Oral Capsule Toxicity Study													
1	3.0	2	2	0.643	0.667	1.47	1.37	2	2	0.526	0.609	1.96	1.79
	6.0	2	2	1.36	1.13	3.42	2.99	2	2	0.888	0.726	3.68	4.17
	14.0	2	2	2.02	1.41	5.92	4.02	2	2	1.47	1.15	8.00	5.91
14	3.0	1	2	0.588	0.378	1.55	1.02	2	2	0.633	0.431	3.10	2.79
	6.0	2	2	1.77	1.45	5.01	6.47	2	2	1.48	1.68	9.08	13.5
	14.0	2	2	2.42	1.79	13.5	8.17	1	2	4.20	2.66	35.8	20.3
30	3.0	1	2	0.516	0.388	1.48	1.06	4	4	0.531	0.312	3.34	2.65
	6.0	2	2	1.16	1.07	4.35	4.79	4	4	1.26	1.00	9.33	9.79
	14.0	2	2	1.94	2.10	11.4	10.9	2	2	2.99	2.77	29.6	21.4
182	3.0	1	2	0.717	0.584	2.39	1.69	2	2	0.622	0.506	3.77	4.17
	6.0	2	2	1.42	1.22	6.05	5.58	2	2	1.27	1.43	9.81	12.5
	14.0	2	2	3.56	2.71	20.9	16.6	2	2	3.60	3.31	28.5	28.5

- Toxicokinetics of Valdecocixib in Monkey Studies - The following table summarizes PK/TK parameters obtained from 2-, 4-, and 52-week toxicity studies in monkeys. Accumulation of SC-65872 and SC-66905 occurred after repeated dosing. No apparent sex-differences in PK parameters for SC-658725 and SC-66905 were noted.

Day	Dose (mg/kg/day) bid	SC-65872 Parameters						SC-66905 Parameters					
		T _{max} (hr)		C _{max} (µg/ml)		AUC ₀₋₁₂ (µg•hr/ml)		T _{max} (hr)		C _{max} (µg/ml)		AUC ₀₋₁₂ (µg•hr/ml)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
2-Week Oral Range-Finding Toxicity Study													
1	30	2	1	8.94	6.22	44.9	28.8	1	1	0.983	0.592	3.26	2.22
	60	2	2	10.2	15.1	78.6	81.9	2	2	0.465	1.16	2.74	4.17
	120	2	2	9.87	20.9	77.1	177	2	2	1.87	1.53	7.63	8.86
14	30	2	2	14.9	13.7	118	107	3	2	0.508	0.471	3.10	2.80
	60	3	2	29.9	23.4	308	230	3	3	0.892	1.40	6.83	8.28
	120	2	1	44.4	44.2	479	437	2	2	2.01	1.41	20.3	13.4
4-Week Oral Toxicity Study													
1	6	1	1	1.13	1.48	4.21	4.42	1	1	0.0630	0.0965	0.242	0.356
	14	2	2	1.45	2.75	5.82	10.7	2	2	0.107	0.309	0.477	1.37
	28	3	2	3.91	3.80	21.3	15.2	5	2	0.350	0.469	2.44	2.02
28	6	2	1	1.14	1.51	6.06	5.03	2	1	0.0495	0.212	0.230	1.06
	14	0.5	3	3.24	3.25	11.8	16.2	0.5	2	0.144	0.249	0.705	1.35
	28	2	2	8.03	12.0	49.2	81.0	3	3	0.366	0.461	2.60	3.04
1-Year Oral Toxicity Study													
1	5	1.67	1.42	0.535	0.846	1.86	2.78	1.83	1.83	0.0398	0.0492	0.140	0.126
	15	1.50	2.00	1.99	2.57	6.42	8.66	2.00	2.83	0.254	0.211	0.778	0.744
	45	2.00	2.60	4.55	4.60	22.0	22.1	2.10	2.40	0.355	0.480	1.36	1.89
90	5	1.08	0.80	0.740	1.06	2.50	2.83	1.67	1.40	0.0604	0.0612	0.216	0.131
	15	1.25	1.83	2.15	2.89	9.68	15.2	2.00	1.92	0.121	0.177	0.493	0.927
	45	2.70	3.50	11.1	10.0	78.9	78.2	2.60	4.40	0.392	0.254	2.56	1.94
180	5	1.83	1.50	1.15	1.22	3.57	3.60	1.83	1.83	0.0773	0.0683	0.203	0.198
	15	2.33	3.00	4.63	3.30	19.0	22.5	2.67	3.50	0.233	0.165	0.928	0.999
	45	2.25	2.40	10.6	11.9	85.0	101	2.50	2.40	0.223	0.191	1.29	1.40
360	5	0.83	1.00	0.767	0.758	2.84	2.39	0.50	1.33	0.0221	0.0242	0.0441	0.0901
	15	1.83	2.00	2.93	3.24	15.7	17.1	1.83	1.25	0.122	0.230	0.619	1.26
	45 ^a	3.00	2.60	7.30	5.74	45.7	43.8	2.00	1.50	0.162	0.135	0.819	0.838

^a The actual dose of this high dose group in Week 52 was estimated to be approximately 75% of targeted dose.

- Toxicokinetics of Valdecocixib in Rat and Rabbit Reproductive Studies - The following table summarizes PK parameters obtained from ♀ animals in reproductive toxicity studies.

APPEARS THIS WAY
ON ORIGINAL

Sampling (GD)	Dose (mg/kg/day) bid	SC-65872			SC-66905		
		T _{max} (hr)	C _{max} (μg/ml)	AUC ₀₋₁₂ (μg•hr/ml)	T _{max} (hr)	C _{max} (μg/ml)	AUC ₀₋₁₂ (μg•hr/ml)
Fertility and Early Embryonic Development in Rats							
7	0.2	7	0.0274	0.260	0	0	0
	2	1	0.369	3.07	7	0.0333	0.226
	6	1	1.38	10.8	7	0.0886	0.829
Embryo-Fetal and Perinatal Toxicity Studies in Rats							
6	0.2	2	0.0209	0.107	12	0.00977	0.0391
	2.0	4	0.216	1.81	2	0.0148	0.0867
	6.0	4	0.825	6.67	4	0.084	0.677
	12.5	2	11.96	13.4	4	0.227	1.72
	25.0	2	4.27	35.6	4	0.462	3.60
17	0.2	1	0.0229	0.112	2	0.0147	0.0306
	2.0	2	0.332	2.14	2	0.0377	0.226
	6.0	1	1.45	11.5	4	0.154	1.32
	12.5	2	3.24	28.2	4	0.368	3.06
17	25.0	2	7.49	61.0	4	0.957	8.75
	2	2.0	0.666	4.32	7.0	0.0514	0.487
	6	2.0	1.77	12.2	7.0	0.162	1.46
	10	1.0	2.51	17.2	4.0	0.206	1.90
17	2	4.0	0.596	4.46	4.0	0.0690	0.682
	6	2.0	2.12	17.7	7.0	0.189	1.88
	10	1.0	3.67	28.6	4.0	0.251	2.66
6 ^a	3	0.5	0.344	1.78	1	0.0919	0.453
	6.25	1	0.937	4.79	0.5	0.260	1.26
	12.5	0.5	2.05	9.81	0.5	0.621	2.17
	25	0.5	4.12	24.1	0.5	1.13	5.36
17 ^a	3	1	0.622	4.08	1	0.0951	0.665
	6.25	0.5	1.32	9.14	1	0.208	1.35
	12.5	0.5	3.13	25.5	0.5	0.485	3.42
	25	1	7.95	59.6	1	0.910	5.73
Embryo-Fetal and Perinatal Toxicity Studies in Rabbits							
7	2	0.5	0.133	0.368	1	0.103	0.642
	10	0.5	0.757	2.07	1	0.685	2.99
	50	1.0	9.38	71.1	1	3.05	18.1
	100	3.0	36.5	382	3	8.88	76.7
19	2	0.5	0.268	0.356	1	0.856	1.38
	10	0.5	0.864	2.17	0.5	0.474	2.01
	50	1.0	11.3	54.7	1	3.23	16.5
	100	1.0	13.2	95.7	1	6.31	32.6
7	3	0.5	0.067	0.168	1	0.033	0.160
	10	1	0.384	1.42	1	0.365	1.61
	40	0.5	3.66	10.6	1	2.52	8.57
19	3	1	2.90	4.96	1	0.420	0.977
	10	1	1.75	11.6	1	0.602	2.79
	40	1	16.8	116	3	1.79	13.8
7	3	1.00	0.238	0.526	1.0	0.167	0.572
	10	0.33	0.423	1.26	1.0	0.697	2.52
	40	1.00	2.55	14.5	1.0	2.51	12.5
18	3	1.00	0.281	0.875	1.0	0.140	0.611
	10	0.33	1.02	2.97	1.0	0.677	2.82
	40	4.00	13.4	107	4.0	1.63	12.7

^a Rats received SC-69124A (parecoxib), a prodrug of SC-65872, at 0, 3.0, 6.25, 12.5, and 25 mg/2 ml/kg/day iv bid.

5.3.2. TISSUE DISTRIBUTION

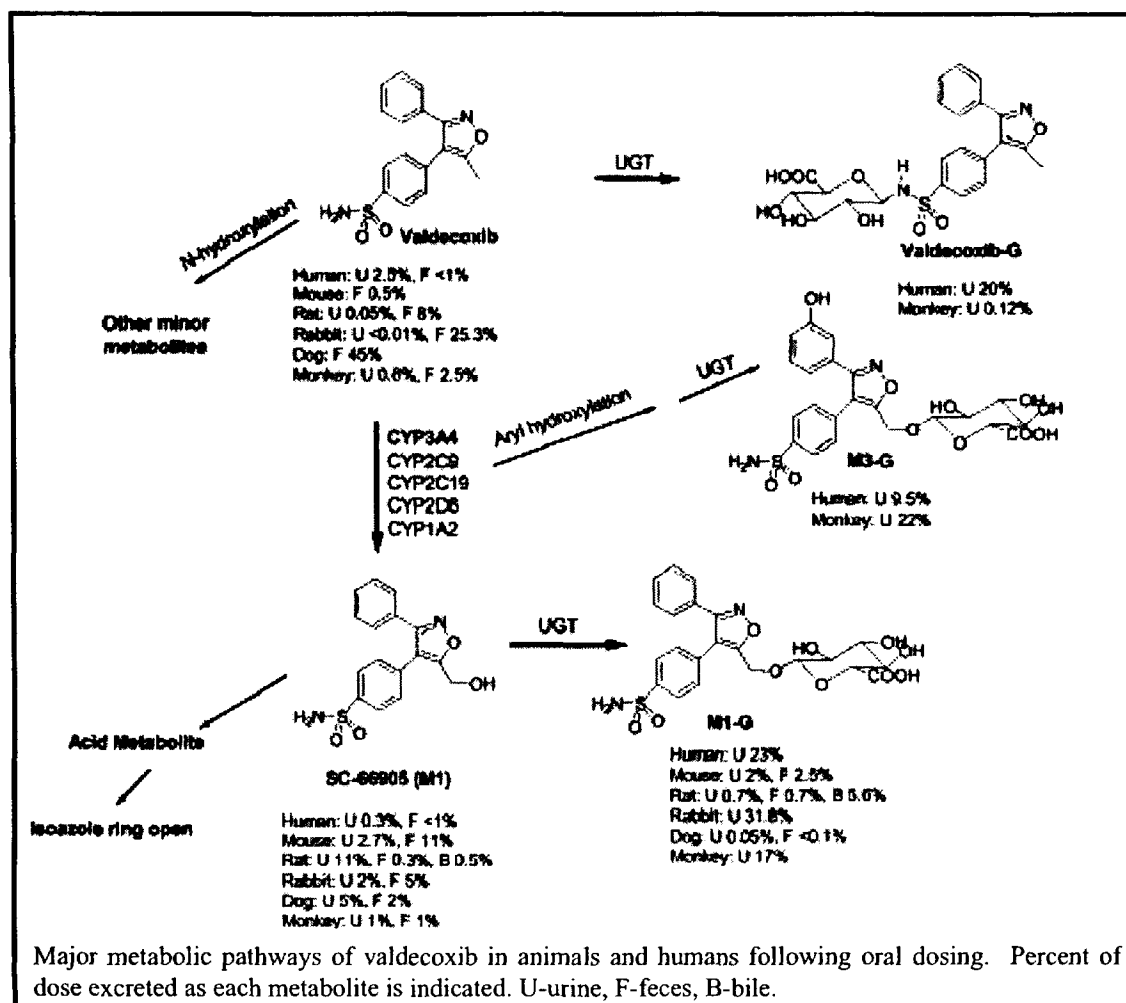
The tissue distribution of valdecocixib was also studied in the ♂ pigmented [redacted] rats by given an oral dose of 0.5 mg/kg [¹⁴C]valdecocixib. Results showed that the maximum mean tissue radioactivity was detected at approximately 1-2 hr post-dose. The T_{max} for subcutaneous fat, heart, stomach and vena cava was 0.5 hr and for eye lenses and GI was 4 and 8 hr, respectively with T_{1/2} values in most tissues ranged between 11.1-60.7 hr. Tissues with highest mean C_{max} values were RBC, blood, liver, bone marrow, and kidney. The C_{max} of the brain was 0.154 µg eq/g. By 48 hr post dosing, <0.05 µg eq/g of the radioactivity. Adrenals, aorta, urinary bladder, eye and subcutaneous fat had long terminal elimination half lives with values of 80-360 hr.

5.3.3. METABOLISM

5.3.3.1. In Vivo Metabolism

Valdecocixib and SC-66905 were the major circulating radioactive components in plasma following intravenous administration of [¹⁴C]valdecocixib sodium to the mouse, rat, rabbit, dog, and monkey. The main phase I metabolic pathway was the oxidation of the methyl group on the isoxazole ring to SC-66905, the corresponding carboxylic acid metabolite (SC-67817) and the isoxazole ring-opened metabolite. A sex-related difference in metabolism was observed in the mouse and rat. Male mice had lower plasma concentrations of SC-66905 than female mice. On the contrary, female rats had lower plasma concentrations of SC-66905 than male rats. Phase II metabolism involved the formation of various stable glucuronide conjugates of phase I metabolites. The N-glucuronide conjugate of valdecocixib, a non P-450-mediated pathway, was the major phase II metabolic pathway in humans (accounting for 20% of dose). Contrarily, the N-glucuronide conjugate of valdecocixib was a minor urinary metabolite in the monkey, accounting for 0.12% of dose. The major metabolic pathways of the mouse, rat, rabbit, dog, monkey, and human are illustrated in the following figure.

**APPEARS THIS WAY
ON ORIGINAL**



5.3.3.2. *In Vitro* Metabolism

Formation of SC-66905 was noted when [^{14} C]SC-65872 was incubated with rat, dog and human liver microsomes. Dog kidney microsomes were not able to metabolize [^{14} C]SC-65872 and [^{14} C]SC-66905 *in vitro*.

In vitro studies using recombinant cDNA expressed human P-450 isoforms showed that CYP1A1, 1A2, 2B6, 2C9, 2C19, 2D6 and 3A4 were all capable of metabolizing valdecoxib to SC-66905, while CYP2A6, 2C8 and 2E1 were inactive. In vitro studies using human liver microsomes indicated that the phase I metabolism of valdecoxib was mainly mediated by cytochrome P-450 CYP3A4. Metabolism of valdecoxib with human liver microsomes was significantly inhibited by ketoconazole (a CYP3A4 inhibitor), and less extensively by sulphaphenazole (a CYP2C9 inhibitor), tranilcypromine (a CYP2C19 and CYP2C9 inhibitor), quinidine (a CYP2D6 inhibitor), and furafylline (a CYP1A2 inhibitor).

5.3.4. PLASMA PROTEIN BINDING

The *in vitro* plasma protein binding of valdecocixib was determined in rat, dog, mouse, rabbit, monkey and human. Approximately 88.0-98.6% and 84.9-96.2% of valdecocixib was protein bound as determined by the ultrafiltration and ultracentrifugation, respectively. The following table summarizes results expressed as % binding of [¹⁴C]SC-65872 obtained from *in vitro* protein binding studies.

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

Method A = Ultrafiltration; Method B = Ultracentrifugation.

^a Therapeutically relevant concentrations are 1.48 µg/ml for valdecocixib and 0.087 µg/ml for SC-66905 at dosage of 40 mg, bid in human.

In addition, the *in vitro* plasma protein binding of SC-66905, an active metabolite, was also determined. The percentages of [¹⁴C]SC-66905 bound to various species plasma proteins and to purified human serum albumin and α1-acid glycoprotein are presented in the following table.

Species	Analysis Method	% Protein Bound [¹⁴ C]SC-66905			
		0.03	0.30	3.0	30.0
Mouse	Ultra-filtration	85.7	89.9	86.3	88.4
Rat	Ultra-filtration	87.5	90.4	83.7	90.5
Rabbit	Ultra-filtration	87.8	93.6	88.5	89.9
Dog	Ultra-filtration	91.1	95.2	90.9	94.3
Monkey	Ultra-filtration	~~81.9~~	82.7	~~77.8~~	~~80.8~~
Human	Ultra-filtration	88.4	90.7	87.2	88.9
HSA	Ultra-filtration	84.8	85.0	83.3	82.7
α1-AG	Ultra-filtration	56.5	55.6	44.7	22.3
α1-AG	Ultra-centrifugation	89.5	90.3	84.4	62.3

5.3.5. ERYTHROCYTE PARTITIONING

Valdecocixib were preferentially partitioned into erythrocytes in rat, dog and human whole blood. The ratio of valdecocixib concentrations in erythrocytes to those in plasma was 3.8:1 for the rat, 3.5:1 for the dog, and 2.5:1 for the human. The partitioning of valdecocixib into erythrocytes was reversible.

5.3.6. EXCRETIONS

Studies in the mouse, rat, rabbit, dog, and cynomolgus monkey, showed that biliary/intestinal excretion was the major route for the elimination of valdecocixib following a single oral or iv dose of [¹⁴C]valdecocixib with values of 47.2-61.8% for the mouse, 55.6-70.6% for the rat, 58.1% for the ♀ rabbit, 67.4-73.2% for the dog, and 42.2% for ♂ cynomolgus monkey. The remaining dose was eliminated through urine. The total recoveries of the radioactive dose in these species were high as shown in the following table.

Species	Sex	Route	Dose (mg/kg)	Urine (%)	Feces (%)	Total (%)
Mouse	♂	Oral	5	38.0	61.8	99.8
	♀	Oral	5	47.5	47.2	94.7
Rat	♂	Oral	0.33	29.0	70.6	100 ^a
	♀	Oral	0.33	40.3	58.5	100 ^a
	♂	IV	0.33	33.0	67.2	101 ^a
	♀	IV	0.33	44.4	55.6	101 ^a
Rabbit	♀	Oral	5	43.3	58.1	101
Dog	♂	Oral	0.2	17.8	73.1	91.7 ^a
	♀	Oral	0.2	23.6	67.4	92.5 ^a
	♂	IV	0.2	20.4	73.2	94.6 ^a
	♀	IV	0.2	23.6	69.5	94.5 ^a
Monkey	♂	Oral	5	42.5	42.2	103 ^b
Human	♂	Oral	0.7 ^c	76.1	18.0	94.1

^a Including a small amount of radioactivity recovered in cage washes and cage wipes at 168 hr.

^b Including 18.1% radioactivity recovered in the cage wash and cage wipe collected at the end of study.

^c Each subject (~ 70 kg body weight) received 50 mg valdecoxib.

In human healthy male subjects, the majority of radioactivity was recovered in urine (76.1%) after oral administration of [¹⁴C]valdecoxib. The remaining radioactivity was recovered in human feces (18.0%).

5.3.7. PLACENTAL TRANSFER AND MILK SECRETION

Milk secretion of valdecoxib was evaluated in the lactating SD rats (LD 11-14) by giving a single dose of 1.01 mg/kg of [¹⁴C]SC-65872 via oral gavage. The concentrations of [¹⁴C]SC-65872 and [¹⁴C]SC-66905 in maternal plasma and milk were similar, indicating that valdecoxib and its active metabolite, SC-66905, were distributed to milk and available to the neonate.

Placental transfer of SC-65872, valdecoxib, from maternal blood to amniotic fluid and fetuses was evaluated in 15 pregnant SD rats by given a single oral dose of 2.50 mg/kg of [¹⁴C]SC-65872 on GD 17. Results showed that radioactivity was rapidly distributed to the fetus with T_{max} of 3 hr and the highest concentration of radioactivity was detected in the fetal blood sample with C_{max} of 2.71 µg eq/g. The C_{max} of total radioactivity in fetal tissues examined ranged from 1.45 µg eq/g for the brain to 2.61 µg eq/g for the liver. This observation indicated that valdecoxib crossed the placenta and was available to the fetus.

6. CONCLUSION AND RECOMMENDATION:

Valdecoxib (SC-65872 - C₁₆H₁₄N₂O₃S), a highly selective cyclooxygenase-2 (COX-2) inhibitor, is a diarylsubstituted isoxazole compound and proposed for the following indications: management of acute pain in adults, treatment of primary dysmenorrhea, and relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis.

The toxicity profiles of the valdecoxib were evaluated in the non-clinical safety studies following oral dosing to the mouse, rat, rabbit, dog, and monkey. It appeared that GI, kidney, adrenal glands, liver, and skin were major target organs for valdecoxib induced toxicity. GI injury with lesions of hemorrhage, ulcer/perforation or necrosis was noted in the mouse, rat, rabbit, dog, and monkey. Renal toxicity of valdecoxib was observed in the dog and was characterized by an increase in BUN and histologic alterations of minimal-to-moderate tubular atrophy with interstitial fibrosis in outer renal cortex. These changes were enhanced by placing dogs on a Na depleted diet. Similar effects were seen in dogs treated with naproxen.

Valdecoxib induced adrenal toxicity including increased weights and cortical hypertrophy/hyperplasia (zona fasciculata) with some cellular degeneration/depletion were seen in rats, mice and monkeys. The observed effects on adrenal may be due to the involvement of prostaglandins in cortisol/corticosterone release from the adrenal gland via the hypothalamic-pituitary-adrenal axis. Increased adrenal weights and the incidence of adrenal cortical hypertrophy were also noted in animals treated with conventional NSAIDs or other COX-2 inhibitors.

In addition, a dose-dependent increase in the incidence of skin cellulitis was observed in dogs and monkeys. Similar findings of cutaneous lesions were observed in dogs treated with celecoxib and some other COX-2 inhibitors. Although these observations occurred in the dog and monkey but not in the mouse or rat, test-article caused toxicity by the mechanism of in situ inhibition of phagocytic cell functions could not be ruled out.

Transient antinatriuretic effects (decreases in urinary sodium excretion) by valdecoxib were observed in the rat 13-week and dog 6-week studies. Antinatriuresis, a common side effect caused by NSAIDs, was not associated with alterations in serum sodium or clinical signs.

Transient hepatopathy, characterized by increased liver weights and centrilobular hepatocyte hypertrophy with or without hepatic microsomal enzyme induction, was noted in mouse 2- and 13-week and rat 2-week oral toxicity studies.

Other pharmacologically caused effects included increased post-implantation losses with reduced live fetuses in rats at oral doses ≥ 0.2 mg/kg in a fertility and early embryonic development (Segment I) study and ≥ 10 mg/kg (equivalent to approximately human exposure at 20 mg QD as measured by the AUC_{0-24}) in embryo-fetal development (Segment II) studies. Similar observations were noted in rabbit embryo-fetal development studies at an oral dose of 40 mg/kg/day (equivalent to approximately 72x human exposure at 20 mg QD as measured by the AUC_{0-24}). Reduced relative and absolute ovary weights with reduced ovary size and numbers of corpora lutea were noted in a mouse 13-week oral toxicity study. A reduction in the numbers of corpora lutea was also observed in the rat fertility/early embryonic development reproductive toxicity study. The effect on ovulation was reversible. In addition, a slight increase in the incidence of fetuses with skeletal malformation and fetuses with semi-bipartite thoracic vertebra centra and fused sternbrae were observed in the rabbits at 40 mg/kg/day. Although, vertebral malformation with or without associated rib anomaly is a common skeletal malformation in NZW rabbits, similar observations were noted in a Segment II study with parecoxib, a prodrug of valdecoxib. In addition, parecoxib rapidly converted into valdecoxib. Thus, the relationship of observed malformations to treatment with valdecoxib could not be excluded and these observations of increased incidence of vertebral malformation with semi-bipartite thoracic vertebra centra and fused sternbrae should be reflected on the labeling.

Close monitoring of adverse events of microbial infections and renal complications in addition to GI injury in humans is highly recommended.

Approval of valdecoxib is recommended.

W.C. Josie Yang, DVM, Ph.D.

Concur by team leader: Yes

☐

No

☐

Robert Osterberg, Ph.D.

cc:

NDA 21-341

HFD-550/Division File

/JYang

/ROsterberg

/KJohnson

/CDeBellas

F/T by JYang, November 14, 2001

7. APPENDICES

7.1. EXECUTIVE CAC RECOMMENDATIONS AND CONCLUSIONS ON CARCINOGENICITY STUDIES

Executive CAC

August 21, 2001

Committee: Abby Jacobs, Ph.D., HFD-540, Acting Chair
Joseph Contrera, Ph.D., HFD-901, Member
Charles Resnick, Ph.D., HFD-110, Alternate Member
Conrad Chen, Ph.D., HFD-550, Acting Team Leader
Josie W.C. Yang, DVM, Ph.D., HFD-550, Presenting Reviewer

Author of Draft: Josie W. C. Yang

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 Nº 21-341

Name of Drug: Valdecoxib (SC-65872)

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

Background:

Valdecoxib (SC-65872 - $C_{16}H_{14}N_2O_3S$), a highly selective cyclooxygenase-2 (COX-2) inhibitor, is a diarylsubstituted isoxazole compound. Valdecoxib is proposed for the following indications: management of acute pain in adults, treatment of primary dysmenorrhea, and relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis. Valdecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO/HGPRT) cells or clastogenic in a chromosome aberration assay in CHO cells and an in vivo micronucleus test in rat bone marrow. Both rat and mouse carcinogenicity study protocols had not been previously presented to Executive CAC.

Rat Carcinogenicity Study

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

**APPEARS THIS WAY
ON ORIGINAL**

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

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

The doses selected in this study were based on the results of a 13-week oral gavage study at doses of 0, 5, 10, 25, 50, and 100 mg/kg for ♂ and 0, 2.5, 5, 10, and 25 mg/kg for ♀ in which it was shown that NOAEL was 5 mg/kg for ♂ and 2.5 mg/kg for ♀.

Treatment-related deaths increased with dose and occurred in all SC-65872 treated groups. Due to excessive toxicity, the high dose females were sacrificed at Week 99. The major non-neoplastic findings were dose-dependent increased incidence of GI necrosis/perforation/inflammation with secondary peritonitis. Based on GI (necrosis/perforation/inflammation with secondary peritonitis) toxicity findings as well as mortality, the doses used in this study exceeded MTD for both ♂ and ♀. There were no treatment-induced increases in the tumor incidence rates. The exposure to SC-65872 in the high dose ♂ and ♀ rats, as measured by AUC₀₋₂₄, was ~2x and 6x of that observed in humans at the dose of 20 mg/day, respectively. The exposure to SC-66905, an active metabolite of SC-65872, in the high dose ♂ and ♀ rats, as measure by AUC₀₋₂₄, was ~2x and 20x of that observed in humans at 20 mg/day, respectively.

Mouse Carcinogenicity Study

Groups of mice were given valdecoxib at the doses shown in the following table via dietary admix.

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

The doses selected in this study were based on toxicity findings of a 13-week dietary admix (♂: 0, 30, 100, 300, and 600 mg/kg; ♀: 0, 60, 200, 600, and 1000 mg/kg).

Treatment-caused histopathological changes were limited to the GI tract (erosion/ulceration with associated chronic active inflammation in the glandular stomach, duodenum, jejunum, ileum, cecum, and colon at one or more sites). The GI injury was the most common cause of death in mid- and high-dose animals. Therefore, the MTD was reached. No treatment-induced increases in the tumor

incidence rates were identified. The exposure to SC-65872 and SC-66905, as measured by AUC_{0-24} , in the high dose ♂ and ♀ mice was equivalent to ~0.6-2x and 12-14x of values seen in humans (20 mg/day), respectively. The NOAEL for either ♂ or ♀ could not be determined for this study as treatment-induced toxicity was observed in all SC-65872 treated groups.

Executive CAC Recommendations and Conclusions:

1. The Committee found that both rat and mouse carcinogenicity studies were adequate.
2. The Committee agreed that there were no significant treatment-related tumor findings in both rat and mouse studies.

Abby Jacobs, Ph.D.,
HFD-540, Acting Chair

cc:\n
/Division File, HFD-550
/HFD-550 Pharm-Tox Team Leader/ROsterberg
/HFD-550 Pharm-Tox Review/JYang
/HFD-550 PM/SSchmidt
/ASeifried, HFD-024

7.2. SUMMARY TABLES FOR RAT AND MOUSE TUMOR DATA SUBMITTED BY THE SPONSOR

7.2.1. *MOUSE TUMOR SUMMARY TABLE*

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

TISSUE MORPHOLOGIC CHANGE	MALES												TREND P-VALUE(b)
	CONTROL			LOW DOSE			MID DOSE			HIGH DOSE			
	OBSD	EXPD	RATIO(a)	OBSD	EXPD	RATIO(a)	OBSD	EXPD	RATIO(a)	OBSD	EXPD	RATIO(a)	
Adrenals)		(N=99)			(N=100)			(N=99)			(N=99)		
1) #B - Adenoma, Subcapsular Cells	3	1.80	1.66	2	1.89	1.06	0	1.33	0.00	1	0.98	1.02	.84
2) #B - Cortical Adenoma	1	0.62	1.60	0	0.62	0.00	0	0.44	0.00	1	0.31	3.21	.47
3) #M -Cortical Carcinoma	0	0.30	0.00	1	0.30	3.31	0	0.23	0.00	0	0.17	0.00	.70
4) Combine #2 and #3	1	0.93	1.08	1	0.93	1.08	0	0.67	0.00	1	0.48	2.09	.53
Epididymis(ides)		(N=100)			(N=100)			(N=99)			(N=100)		
1) #B -Leiomyoma	0	0.31	0.00	0	0.30	0.00	1	0.23	4.41	0	0.16	0.00	.39
Gross Condition		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - Carcinoma, NOS	0	0.32	0.00	1	0.30	3.32	0	0.21	0.00	0	0.16	0.00	.68
2) #M - Hemangiosarcoma, Foot	0	0.28	0.00	1	0.34	2.90	0	0.23	0.00	0	0.15	0.00	.72
Harderian Gland		(N=100)			(N=100)			(N=99)			(N=100)		
1) #M - Adenocarcinoma	3	2.37	1.26	1	2.47	0.40	3	1.82	1.65	1	1.33	0.75	.52
2) #B - Adenoma	9	5.88	1.53	4	6.14	0.65	5	4.59	1.09	2	3.38	0.59	.89
3) Combine #1 and #2	12	8.26	1.45	5	8.62	0.58	8	6.42	1.25	3	4.71	0.64	.86
Hematopoietic System		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - Histiocytic Sarcoma	2	1.34	1.61	0	1.21	0.00	2	0.89	2.23	0	0.65	0.00	.74
2) #M - Leukemia, Granulocytic	1	1.18	0.85	1	1.29	0.78	2	0.94	2.12	0	0.60	0.00	.57
3) #M - Lymphoma	7	6.15	1.14	6	6.27	0.96	4	4.86	0.82	4	3.72	1.08	.59
Kidney(s)		(N=100)			(N=100)			(N=99)			(N=98)		
1) #B - Tubular Adenoma	2	0.94	2.13	1	0.92	1.09	0	0.66	0.00	0	0.48	0.00	.97
Large Intestine		(N=100)			(N=100)			(N=99)			(N=99)		
1) #M - Adenocarcinoma, Mucinous	0	0.32	0.00	0	0.31	0.00	1	0.21	4.86	0	0.16	0.00	.37
Liver		(N=100)			(N=100)			(N=99)			(N=99)		
1) #B - Hemangioma	0	0.31	0.00	1	0.31	3.18	0	0.21	0.00	0	0.16	0.00	.69
2) #M - Hemangiosarcoma	1	1.51	0.66	3	1.58	1.90	1	1.12	0.89	0	0.79	0.00	.75
3) #M - Hepatoblastoma	0	0.31	0.00	1	0.30	3.34	0	0.23	0.00	0	0.16	0.00	.69
4) #B - Hepatocellular Adenoma	9	10.8	0.84	10	11.2	0.89	11	8.12	1.36	6	5.88	1.02	.20
5) #M - Hepatocellular Carcinoma	6	9.70	0.62	11	9.98	1.10	4	7.24	0.55(d)	11	5.08	2.17	.016/.17(c)
6) Combine #1 and #2	1	1.79	0.56	4	1.89	2.11	1	1.35	0.74	0	0.96	0.00	.72
7) Combine #4 and #5	15	19.7	0.76	19	20.2	0.94	15	14.7	1.02(e)	16	10.3	1.55	.015/.093(c)

TISSUE MORPHOLOGIC CHANGE	MALES												TREND P-VALUE(b)
	CONTROL			LOW DOSE			MID DOSE			HIGH DOSE			
	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	
Lung(s)		(N=100)			(N=100)			(N=100)			(N=100)		
1) #B - Bronchiolar/Alveolar Adenoma	19	12.3	1.54	9	12.7	0.71	8	10.9	0.74	9	9.10	0.99	.93
2) #M - Bronchiolar/Alveolar Carcinoma	17	12.1	1.41	8	12.6	0.64	8	8.78	0.91	7	6.60	1.06	.78
3) Combine #1 and #2	34	23.0	1.48	17	24.8	0.69	16	19.2	0.83	15	15.0	1.00	.95
Pancreas		(N=100)			(N=100)			(N=99)			(N=97)		
1) #B - Islet Cell Adenoma	2	0.94	2.13	0	0.92	0.00	1	0.66	1.51	0	0.48	0.00	.88
Parathyroid(s)		(N=92)			(N=96)			(N=90)			(N=81)		
1) #B - Adenoma	0	0.31	0.00	1	0.31	3.24	0	0.22	0.00	0	0.16	0.00	.69
Pituitary		(N=98)			(N=99)			(N=98)			(N=98)		
1) #B - Adenoma, Pars Distalis	0	0.63	0.00	1	0.63	1.58	1	0.43	2.34	0	0.31	0.00	.47
2) #M - Carcinoma, Pars Distalis	0	0.31	0.00	1	0.30	3.34	0	0.23	0.00	0	0.16	0.00	.69
3) Combine #1 and #2	0	0.94	0.00	2	0.93	2.15	1	0.65	1.53	0	0.48	0.00	.52
Salivary Gland		(N=100)			(N=100)			(N=99)			(N=99)		
1) #M - Fibrous Histiocytoma	0	0.31	0.00	0	0.30	0.00	1	0.23	4.41	0	0.16	0.00	.39
Skeletal Muscle		(N=100)			(N=100)			(N=100)			(N=100)		
1) #B - Hemangioma	0	0.29	0.00	0	0.33	0.00	1	0.24	4.15	0	0.14	0.00	.38
Skin		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - Squamous Cell Carcinoma	0	0.59	0.00	0	0.59	0.00	0	0.45	0.00	2	0.37	5.41	0.34/.37(c)
Spleen		(N=100)			(N=100)			(N=99)			(N=97)		
1) #M - Hemangiosarcoma	0	0.67	0.00	2	1.15	1.74	0	0.74	0.00	1	0.44	2.28	.36
Subcutis		(N=100)			(N=100)			(N=100)			(N=100)		
1) #B - Fibroma	1	0.30	3.29	0	0.33	0.00	0	0.22	0.00	0	0.15	0.00	1.00
2) #M - Fibrosarcoma	0	0.31	0.00	0	0.29	0.00	0	0.22	0.00	1	0.17	5.82	.17
3) #M - Hemangiosarcoma	0	0.26	0.00	1	0.27	1.74	0	0.25	0.00	0	0.22	0.00	.74
4) Combine #1 and #2	1	0.62	1.62	0	0.62	0.00	0	0.44	0.00	1	0.32	3.11	.48

TISSUE MORPHOLOGIC CHANGE	MALES												TREND P-VALUE(b)
	CONTROL			LOW DOSE			MED DOSE			HIGH DOSE			
	OBSD	EXPD	RATIO(a)	OBSD	EXPD	RATIO(a)	OBSD	EXPD	RATIO(a)	OBSD	EXPD	RATIO(a)	
Testis(a)	(N=100)			(N=100)			(N=99)			(N=100)			
1) #B - Interstitial Cell Tumor	6	2.14	2.81	0	2.19	0.00	1	1.53	0.65	0	1.14	0.00	.99
Combinations Across All Tissues	(N=100)			(N=100)			(N=100)			(N=100)			
1) #B - All Hemangiomas	0	0.47	0.00	1	0.57	1.76	1	0.52	1.92	0	0.44	0.00	.61
2) #M - All Hemangiosarcomas	1	2.91	0.34	7	3.04	2.30	1	2.30	0.43	1	1.75	0.57	.61
3) Combine #1 and #2	1	3.43	0.29	8	3.56	2.25	2	2.81	0.71	1	2.21	0.45	.59

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Trend through the high dose; values unadjusted for multiplicity unless footnoted otherwise

(c) Adjusted for multiplicity

(d) P = .50 for trend through this group

(e) P = .18 for trend through this group

APPEARS THIS WAY
ON ORIGINAL

TISSUE MORPHOLOGIC CHANGE	FEMALES												TREND P-VALUE(b)
	CONTROL			LOW DOSE			MID DOSE			HIGH DOSE			
	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	
Adrenal(s)		(N=100)			(N=100)			(N=100)			(N=100)		
1) #B - Adenoma, Subcapsular Cells	2	2.62	0.76	1	1.96	0.51	2	1.53	1.30	2	0.88	2.28	.11
2) #B - Pheochromocytoma	2	1.32	1.52	1	1.08	0.93	1	1.03	0.97	0	0.57	0.00	.87
3) #M - Pheochromocytoma	0	0.37	0.00	1	0.27	3.64	0	0.22	0.00	0	0.13	0.00	.63
4) Combine #2 and #3	2	1.62	1.23	2	1.38	1.45	1	1.31	0.76	0	0.69	0.00	.87
Gall Bladder		(N=100)			(N=99)			(N=99)			(N=96)		
1) #B - Adenoma	1	0.43	2.35	0	0.25	0.00	0	0.21	0.00	0	0.11	0.00	1.00
Ganglion, Gasiron		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - Schwannoma	1	0.36	2.80	0	0.29	0.00	0	0.23	0.00	0	0.12	0.00	1.00
Harderian Gland		(N=100)			(N=99)			(N=100)			(N=100)		
1) #B - Adenoma	1	3.01	0.33	3	2.50	1.20	4	2.14	1.87	1	1.34	0.75	.15
Hematopoietic System		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - Histiocytic Sarcoma	2	2.88	0.69	3	2.25	1.33	1	1.82	0.55	2	1.04	1.92	.25
2) #M - Leukemia, Granulocytic	1	1.39	0.72	1	1.14	0.88	0	0.93	0.00	2	0.55	3.67	.19
3) #M - Lymphoma	9	9.71	0.93	6	7.96	0.75	7	6.43	1.09	6	3.89	1.54	.16
Kidney(s)		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - Nephroblastoma	0	0.35	0.00	0	0.30	0.00	1	0.23	4.40	0	0.12	0.00	.35
Liver		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - Hemangiosarcoma	1	1.35	0.74	2	1.06	1.89	0	1.00	0.00	1	0.60	1.68	.55
2) #B - Hepatocellular Adenoma	2	2.37	0.84	2	1.98	1.01	3	1.65	1.82	0	1.01	0.00	.54
3) #M - Hepatocellular Carcinoma	1	1.10	0.91	0	0.86	0.00	1	0.65	1.53	1	0.39	2.58	.25
4) Combine #2 and #3	3	3.45	0.87	2	2.83	0.71	4	2.33	1.72	1	1.40	0.72	.34
Lung(s)		(N=100)			(N=100)			(N=100)			(N=99)		
1) #B - Bronchiolar/Alveolar Adenoma	11	13.2	0.83	15	11.7	1.29	13	10.2	1.27	3	6.89	0.44	.67
2) #M - Bronchiolar/Alveolar Carcinoma	6	5.37	1.12	4	4.48	0.89	2	3.80	0.53	4	2.34	1.71	.41
3) Combine #1 and #2	15	17.4	0.86	19	15.1	1.26	14	13.2	1.06	6	8.30	0.72	.58
Mammary Gland		(N=96)			(N=100)			(N=95)			(N=94)		
1) #M - Adenocarcinoma	4	3.53	1.13	2	2.96	0.68	2	2.27	0.88	2	1.24	1.62	.40

TISSUE MORPHOLOGIC CHANGE	FEMALES												TREND P-VALUE(b)
	CONTROL			LOW DOSE			MID DOSE			HIGH DOSE			
	OBSD	EXPD	RATIO(a)	OBSD	EXPD	RATIO(a)	OBSD	EXPD	RATIO(a)	OBSD	EXPD	RATIO(a)	
Mouth		(N=100)			(N=100)			(N=100)			(N=100)		
1) #B - Papilloma	0	0.42	0.00	0	0.26	0.00	1	0.21	4.74	0	0.11	0.00	.32
Ovary(ies)		(N=100)			(N=100)			(N=100)			(N=100)		
1) #B - Cystadenoma	3	2.63	1.14	2	1.96	1.02	2	1.53	1.31	0	0.87	0.00	.73
2) #B - Granulosa Cell Tumor	0	0.35	0.00	1	0.30	3.33	0	0.22	0.00	0	0.12	0.00	.65
3) #M - Granulosa Cell Tumor	0	0.77	0.00	1	0.55	1.83	1	0.44	2.27	0	0.34	0.00	.40
4) #B - Hemangioma	0	0.31	0.00	0	0.29	0.00	1	0.26	3.91	0	0.15	0.00	.41
5) #B - Luteoma	0	0.43	0.00	1	0.61	1.64	0	0.56	0.00	1	0.40	2.52	.35
6) #B - Teratoma	0	0.30	0.00	1	0.28	3.54	0	0.26	0.00	0	0.15	0.00	.70
7) Combine #2, #3, and #5	0	1.56	0.00	3	1.44	2.08	1	1.23	0.81	1	0.77	1.30	.29
Pancreas		(N=99)			(N=100)			(N=99)			(N=99)		
1) #B - Islet Cell Adenoma	0	0.68	0.00	1	0.60	1.66	1	0.44	2.26	0	0.28	0.00	.44
Pituitary		(N=97)			(N=97)			(N=99)			(N=99)		
1) #B - Adenoma, Pars Distalis	2	1.93	1.04	1	1.66	0.60	2	1.47	1.36	1	0.94	1.06	.41
2) #B - Adenoma, Pars Intermedia	0	0.41	0.00	0	0.27	0.00	0	0.21	0.00	1	0.12	8.62	.12
3) #M - Carcinoma, Pars Distalis	1	1.15	0.87	0	0.80	0.00	2	0.69	2.88	0	0.35	0.00	.43
4) Combine #1 and #3	3	3.00	1.00	1	2.52	0.40	4	2.19	1.83	1	1.30	0.77	.35
Skin		(N=100)			(N=100)			(N=99)			(N=99)		
1) #M - Fibrosarcoma	0	0.36	0.00	1	0.30	3.35	0	0.22	0.00	0	0.13	0.00	.64
2) #M - Neurofibrosarcoma	0	0.40	0.00	1	0.28	3.39	0	0.20	0.00	0	0.12	0.00	.60
3) #B - Squamous Papilloma	0	0.32	0.00	1	0.29	3.45	0	0.24	0.00	0	0.15	0.00	.68
Spleen		(N=100)			(N=100)			(N=99)			(N=100)		
1) #M - Hemangiosarcoma	2	0.84	2.37	0	0.51	0.00	0	0.42	0.00	0	0.22	0.00	1.00
Subcutis		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - Fibrosarcoma	1	0.37	2.73	0	0.29	0.00	0	0.21	0.00	0	0.13	0.00	1.00
2) #M - Fibrous Histiocytoma	0	0.25	0.00	1	0.25	3.98	0	0.25	0.00	0	0.24	0.00	.75
Thyroid(s)		(N=100)			(N=99)			(N=100)			(N=98)		
1) #B - Follicular Adenoma/Cystadenoma	0	0.38	0.00	1	0.28	3.63	0	0.23	0.00	0	0.12	0.00	.62
Tongue		(N=100)			(N=98)			(N=100)			(N=99)		
1) #M - Squamous Cell Carcinoma	1	0.39	2.56	0	0.26	0.00	0	0.23	0.00	0	0.11	0.00	1.00

TISSUE MORPHOLOGIC CHANGE	FEMALES												TREND P-VALUE(b)
	CONTROL			LOW DOSE			MID DOSE			HIGH DOSE			
	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	
Urinary Bladder		(N=100)			(N=100)			(N=100)			(N=100)		
10 #B - Mesenchymal Tumor	1	0.42	2.37	0	0.26	0.00	0	0.21	0.00	0	0.11	0.00	1.00
Uterus		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - Adenocarcinoma/Carcinoma	0	0.84	0.00	1	0.51	1.95	1	0.42	2.37	0	0.22	0.00	.36
2) #B - Fibroma	1	1.14	0.87	0	0.81	0.00	0	0.70	0.00	2	0.34	5.88	.11
3) #B - Hemangioma	0	0.42	0.00	1	0.26	3.89	0	0.21	0.00	0	0.11	0.00	.58
4) #M - Hemangiosarcoma	1	0.42	2.37	0	0.26	0.00	0	0.21	0.00	0	0.11	0.00	1.00
5) #B - Leiomyoma	4	2.53	1.58	2	1.54	1.30	0	1.27	0.00	0	0.66	0.00	.97
6) #M - Leiomyosarcoma	1	1.51	0.66	2	1.09	1.83	1	0.93	1.07	0	0.46	0.00	.64
7) #B - Mucosal Polyp	5	8.12	0.62	9	7.00	1.29	7	5.93	1.18	4	3.96	1.01	.19
8) #M - Schwannoma	1	0.42	2.37	0	0.26	0.00	0	0.21	0.00	0	0.11	0.00	1.00
9) #M - Stromal Sarcoma	1	2.48	0.40	3	1.97	1.52	1	1.61	0.62	2	0.94	2.14	.14
10) Combine #3 and #4	1	0.84	1.18	1	0.51	1.95	0	0.42	0.00	0	0.22	0.00	.82
11) Combine #5 and #6	5	4.03	1.24	4	2.71	1.47	1	2.08	0.48	0	1.17	0.00	.92
12) Combine #7 and #9	6	10.6	0.57	12	8.97	1.34	8	7.59	1.05	6	4.88	1.23	.099
Vagina		(N=100)			(N=100)			(N=100)			(N=100)		
1) #B - Leiomyoma	0	0.38	0.00	0	0.27	0.00	0	0.23	0.00	1	0.13	8.00	.13
Combinations Across All Tissues		(N=100)			(N=100)			(N=100)			(N=100)		
1) #M - All Fibrosarcomas	1	0.72	1.38	1	0.58	1.71	0	0.44	0.00	0	0.26	0.00	.87
2) All Fibromas(c) and Fibrosarcomas	2	1.94	1.03	1	1.35	0.74	0	1.14	0.00	2	0.57	3.49	.30
3) #B - All Hemangiomas	0	0.60	0.00	1	0.52	1.92	1	0.54	1.85	0	0.34	0.00	.53
4) #M - All Hemangiosarcomas	4	2.45	1.63	2	1.99	1.01	0	1.62	0.00	1	0.95	1.06	.87
5) Combine #3 and #4	4	2.99	1.34	3	2.53	1.18	1	2.14	0.47	1	1.33	0.75	.82
6) #B - All Leiomyomas	4	2.68	1.49	2	1.95	1.03	0	1.51	0.00	1	0.86	1.16	.83
7) All Leiomyomas and Leiomyosarcomas(d)	5	4.23	1.18	4	3.05	1.31	1	2.37	0.42	1	1.35	0.74	.80
8) #M - All Schwannomas	2	0.78	2.57	0	0.55	0.00	0	0.44	0.00	0	0.23	0.00	1.00

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Trend through the high dose; values unadjusted for multiplicity unless footnoted otherwise

(c) Fibromas appeared in only one tissue (uterus) and hence were not combined across tissues

(d) Leiomyosarcomas appeared in only one tissue (uterus) and hence were not combined across tissues

7.2.2. *RAT TUMOR SUMMARY TABLE*

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MALES														
TISUE	MORPHOLOGIC CHANGE	CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE			TREND P-VALUE(b)
		OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	
Adrenal(s)		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #B - Cortex, Adenoma	1	0.50	1.98	1	0.82	1.81	0	0.46	0.00	0	0.42	0.00	.94
	2) #B - Pheochromocytoma(c)	25	18.2	1.38	16	18.2	0.88	12	13.0	0.92	5	8.62	0.58	.98
	3) #M - Pheochromocytoma	2	0.90	2.23	0	0.82	0.00	0	0.68	0.00	1	0.51	1.97	.75
	4) Combine #2 and #3	27	18.8	1.43	16	19.2	0.83	12	13.8	0.87	6	9.17	0.65	.88
Brain		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #M - Astrocytoma	1	2.78	0.35	2	2.90	0.69	4	1.97	2.03	2	1.38	1.47	.051
	2) #B - Granular Cell Tumor	1	1.80	0.55	2	1.84	1.09	2	1.39	1.44	1	0.98	1.04	.28
	3) #B - Meningioma	0	0.31	0.00	0	0.38	0.00	1	0.17	6.08	0	0.14	0.00	.31
	4) #M - Meningioma	0	0.34	0.00	0	0.34	0.00	1	0.19	5.33	0	0.13	0.00	.31
	5) #M - Pilocytosis	0	0.24	0.00	0	0.26	0.00	0	0.26	0.00	1	0.24	4.13	.24
	6) Combine #3 and #4	0	0.65	0.00	0	0.72	0.00	2	0.35	5.65	0	0.27	0.00	.19
Ear		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #B - Amelanotic Melanoma	0	0.63	0.00	0	0.68	0.00	1	0.40	2.48	1	0.29	3.44	.080
	2) #M - Carcinoma, Zymba's Gland	0	0.60	0.00	1	0.60	1.67	1	0.46	2.16	0	0.33	0.00	.50
Epididymis(ides)		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #B - Mesothelioma	0	0.34	0.00	1	0.36	2.82	0	0.19	0.00	0	0.12	0.00	.86
Harderian Gland		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #M - Carcinoma	0	0.28	0.00	1	0.31	3.26	0	0.23	0.00	0	0.18	0.00	.72

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Trend through the high dose; values unadjusted for multiplicity unless footnoted otherwise

(c) Includes multiple pheochromocytomas

TISSUE	MORPHOLOGIC CHANGE	MALES												TREND P-VALUE ^(b)
		CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE			
		OBS ^(a)	EXP ^(a)	RATIO ^(a)	OBS ^(a)	EXP ^(a)	RATIO ^(a)	OBS ^(a)	EXP ^(a)	RATIO ^(a)	OBS ^(a)	EXP ^(a)	RATIO ^(a)	
Heart		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #M - Atrial/vent Mesothelioma	1	0.32	3.13	0	0.29	0.00	0	0.23	0.00	0	0.16	0.00	1.00
	2) #B - Endocardial Schwannoma	0	0.31	0.00	1	0.31	3.23	0	0.22	0.00	0	0.16	0.00	.69
	3) #M - Endocardial Schwannoma	1	0.34	2.97	0	0.35	0.00	0	0.17	0.00	0	0.13	0.00	1.00
	4) #B - Hemangioma	0	0.62	0.00	1	0.75	1.31	1	0.33	3.00	0	0.29	0.00	.42
	5) Combine #2 and #3	1	0.64	1.55	1	0.67	1.49	0	0.39	0.00	0	0.29	0.00	.90
Hematopoietic System		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #M - Histocytic Sarcoma	3	2.16	1.37	2	2.17	0.92	2	1.59	1.26	0	1.05	0.00	.62
	2) #M - Lymphoma	0	0.62	0.00	1	0.99	1.01	1	0.61	1.64	1	0.58	1.73	.20
	3) #M - Mononuclear Cell Leukemia	1	0.35	2.88	0	0.36	0.00	0	0.17	0.00	0	0.13	0.00	1.00
Kidney(s)		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #B - Lipoma	0	0.31	0.00	1	0.38	2.63	0	0.17	0.00	0	0.14	0.00	.69
	2) #M - Mesenchymal Tumor	1	0.32	3.15	0	0.30	0.00	0	0.23	0.00	0	0.16	0.00	1.00
	3) #B - Tubular Adenoma	1	1.97	0.51	2	2.06	0.97	3	1.67	1.80	1	1.30	0.77	.27
	4) #M - Tubular Carcinoma	0	0.33	0.00	1	0.34	2.89	0	0.22	0.00	0	0.12	0.00	.68
	5) Combine #3 and #4	1	2.28	0.44	3	2.37	1.25	3	1.89	1.69	1	1.45	0.69	.30
Liver		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #B - Hepatocellular Adenoma ^(c)	7	3.57	1.96	2	3.65	0.55	2	2.77	0.72	1	2.00	0.50	.96
	2) #M - Hepatocellular Carcinoma	1	1.73	0.58	2	1.77	1.13	1	1.42	0.70	2	1.08	1.86	.20
	3) Combine #1 and #2	8	5.31	1.51	4	5.39	0.74	3	4.20	0.71	3	3.08	0.97	.83
Lung(s)		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #B-Bronchiolar/Alveolar Adenoma	0	0.79	0.00	1	0.79	1.27	1	0.79	1.27	1	0.64	1.86	.27
	2) #M - Sarcoma, NOS	0	0.33	0.00	1	0.33	3.00	0	0.22	0.00	0	0.12	0.00	.67

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Trend through the high dose; values unadjusted for multiplicity unless footnoted otherwise

(c) Includes multiple adenomas

TISUE	MORPHOLOGIC CHANGE	MALES												TREND P-VALUE ^(b)
		CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE			
		OBS'D	EXP'D	RATIO ^(a)	OBS'D	EXP'D	RATIO ^(a)	OBS'D	EXP'D	RATIO ^(a)	OBS'D	EXP'D	RATIO ^(a)	
Lymph Node, Mesenteric		(N=107)			(N=120)			(N=118)			(N=113)			
	1) #B - Hemangioma	1	0.52	1.94	1	0.44	2.25	0	0.51	0.00	0	0.43	0.00	.84
	2) #M - Hemangiosarcoma	0	0.54	0.00	1	0.85	1.53	1	0.42	2.37	0	0.29	0.00	.45
	3) #B - Lymphangioma	0	0.31	0.00	1	0.38	2.63	0	0.17	0.00	0	0.14	0.00	.89
	4) Combine #1 and #2	1	1.10	0.91	2	1.14	1.75	1	0.99	1.01	0	0.77	0.00	.81
Mammary Gland		(N=108)			(N=120)			(N=119)			(N=113)			
	1) #B - Adenoma	0	0.33	0.00	0	0.30	0.00	0	0.24	0.00	1	0.13	7.66	.13
	2) #B - Fibroadenoma	2	1.52	1.32	3	1.55	1.94	0	1.13	0.00	0	0.81	0.00	.95
Nasal Turbinate		(N=108)			(N=120)			(N=118)			(N=111)			
	1) #M - Schwannoma	1	0.32	3.12	0	0.30	0.00	0	0.22	0.00	0	0.16	0.00	1.00
Oral Cavity		(N=108)			(N=120)			(N=119)			(N=113)			
	1) #M - Squamous Cell Carcinoma	0	0.31	0.00	1	0.38	2.63	0	0.17	0.00	0	0.14	0.00	.89
Pancreas		(N=108)			(N=120)			(N=119)			(N=113)			
	1) #B - Acinar Cell Adenoma(c)	3	3.82	0.83	3	3.68	0.82	3	2.75	1.09	3	1.95	1.53	.30
	2) #M - Acinar Cell Carcinoma	1	0.33	3.02	0	0.33	0.00	0	0.23	0.00	0	0.11	0.00	1.00
	3) #B - Islet Cell Adenoma (c)	18	11.9	1.51	11	11.9	0.92	8	8.52	0.94	1	5.82	0.18	1.00
	4) #M - Islet Cell Carcinoma	0	0.95	0.00	2	0.79	2.53	0	0.81	0.00	1	0.45	2.22	.34
	5) Combine #1 and #2	4	3.93	1.02	3	3.99	0.75	3	2.98	1.01	3	2.10	1.43	.32
	6) Combine #3 and #4	18	12.6	1.43	13	12.6	1.03	8	8.97	0.89	1	5.90	0.17	1.00
Parathyroid(s)		(N=84)			(N=101)			(N=100)			(N=88)			
	1) #B - Adenoma	2	1.47	1.36	1	1.24	0.81	1	1.45	0.69	1	0.94	1.19	.88

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Trend through the high dose; values unadjusted for multiplicity unless footnoted otherwise

(c) Includes multiple adenomas

TISSUE	MORPHOLOGIC CHANGE	CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE			TREND P-VALUE(b)
		OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	
Pituitary		(N=108)			(N=120)			(N=118)			(N=112)			
	1) #B - Pars Distalis, Adenoma(c)	57	49.3	1.16	56	59.1	0.95	47	46.7	1.01	31	36.0	0.86	.94
	2) #M - Pars Distalis, Carcinoma	0	0.33	0.00	1	0.34	2.90	0	0.21	0.00	0	0.11	0.00	.67
	3) #M - Schwannoma	0	0.38	0.00	1	0.31	3.26	0	0.23	0.00	0	0.18	0.00	.72
	4) Combine #1 and #2	57	49.8	1.14	57	59.0	0.97	47	47.0	1.00	31	36.2	0.86	.94
Prostate		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #B - Adenoma	2	2.25	0.89	4	2.36	1.70	2	1.91	1.05	0	1.49	0.00	.82
	2) #M - Carcinoma	0	0.33	0.00	0	0.34	0.00	1	0.22	4.56	0	0.12	0.00	.34
	3) Combine #1 and #2	2	2.59	0.77	4	2.69	1.48	3	2.10	1.43	0	1.62	0.00	.71
Skeletal Muscle		(N=108)			(N=120)			(N=118)			(N=113)			
	1) #B - Lipoma	0	0.31	0.00	0	0.38	0.00	1	0.17	6.00	0	0.14	0.00	.31
	2) #M - Rhabdomyosarcoma	1	0.31	3.27	0	0.30	0.00	0	0.22	0.00	0	0.17	0.00	1.00
Skin		(N=107)			(N=118)			(N=119)			(N=111)			
	1) #B - Basal Cell Adenoma	3	1.54	1.95	1	1.71	0.59	0	1.03	0.00	1	0.73	1.36	.85
	2) #B - Fibroma	2	5.01	0.40	8	4.90	1.63	3	3.58	0.84	3	2.50	1.20	.21
	3) #M - Fibrosarcoma	2	2.33	0.86	3	2.41	1.24	3	1.93	1.56	0	1.32	0.00	.66
	4) #M - Hemangiosarcoma(d)	1	0.62	1.62	1	0.68	1.46	0	0.40	0.00	0	0.29	0.00	.90
	5) #B - Keratoacanthoma	1	1.26	0.79	0	1.26	0.00	2	0.82	2.17	1	0.56	1.79	.20
	6) #B - Lipoma	0	0.33	0.00	1	0.32	3.11	0	0.24	0.00	0	0.11	0.00	.67
	7) #M - Schwannoma	0	0.27	0.00	0	0.30	0.00	1	0.24	4.11	0	0.19	0.00	.43
	8) #B - Sebaceous Cell Adenoma	1	0.97	1.03	1	0.96	1.03	1	0.86	1.52	0	0.40	0.00	.69
	9) #M - Sebaceous Cell Carcinoma	1	0.82	1.82	1	0.66	1.54	0	0.44	0.00	0	0.29	0.00	.81
	10) #M - Squamous Cell Carcinoma	1	0.32	3.09	0	0.30	0.00	0	0.24	0.00	0	0.13	0.00	1.00
	11) #B - Squamous Papilloma	2	0.64	3.12	0	0.62	0.00	0	0.46	0.00	0	0.28	0.00	1.00
	12) Combine #2 and #3	4	7.40	0.84	11	7.23	1.52	6	5.50	1.09	3	3.87	0.78	.34

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Trend through the high dose; values unadjusted for multiplicity unless footnoted otherwise

(c) Includes multiple adenomas

(d) Includes multiple hemangiosarcomas

		MALES												
TISUE	MORPHOLOGIC CHANGE	CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE			TREND P-VALUE ^(b)
		OBS'D	EXP'D	RATIO ^(a)	OBS'D	EXP'D	RATIO ^(a)	OBS'D	EXP'D	RATIO ^(a)	OBS'D	EXP'D	RATIO ^(a)	
Skin (cont'd)		(N=107)			(N=118)			(N=119)			(N=111)			
	13) Combine #5 and #11	3	1.91	1.57	0	1.89	0.00	2	1.36	1.43	1	0.51	1.23	.52
	14) Combine #5, #10, and #11	4	2.22	1.80	0	2.20	0.00	2	1.64	1.22	1	0.94	1.06	.66
	15) Combine #8 and #9	2	1.58	1.26	2	1.62	1.23	1	1.10	0.91	0	0.89	0.00	.85
Small intestine		(N=108)			(N=120)			(N=119)			(N=113)			
	1) #M - Carcinoma	0	0.35	0.00	1	0.35	2.89	0	0.19	0.00	0	0.12	0.00	.65
Spleen		(N=108)			(N=120)			(N=119)			(N=113)			
	1) #M - Hemangiosarcoma	0	0.31	0.00	1	0.36	2.83	0	0.17	0.00	0	0.14	0.00	.69
	2) #M - Sarcoma, NOS	1	0.66	1.51	1	0.73	1.37	0	0.34	0.00	0	0.27	0.00	.89
Testis(es)		(N=108)			(N=120)			(N=119)			(N=113)			
	1) #B - Interstitial Cell Tumor (c)	8	8.24	0.97	6	8.33	0.72	7	6.18	1.14	6	4.27	1.40	.19
	2) #B - Mesothelioma	0	0.34	0.00	1	0.36	2.82	0	0.19	0.00	0	0.12	0.00	.68
Thymus		(N=100)			(N=114)			(N=117)			(N=104)			
	1) #B - Thymoma	0	0.31	0.00	1	0.38	2.67	0	0.18	0.00	0	0.14	0.00	.69
	2) #M - Thymoma	1	0.31	3.20	0	0.38	0.00	0	0.18	0.00	0	0.14	0.00	1.00
	3) Combine #1 and #2	1	0.63	1.60	1	0.75	1.33	0	0.36	0.00	0	0.28	0.00	.91
Thyroid(s)		(N=108)			(N=120)			(N=119)			(N=113)			
	1) #B - C Cell Adenoma (d)	3	3.62	0.79	6	3.92	1.53	2	3.03	0.66	2	2.24	0.89	.57
	2) #M - C Cell Carcinoma	1	0.36	2.88	0	0.38	0.00	0	0.17	0.00	0	0.13	0.00	1.00
	3) #B - Follicular Cell Adenoma	3	1.74	1.72	0	1.90	0.00	1	1.77	0.58	3	1.59	1.89	.39
	4) Combine #1 and #2	4	4.14	0.97	6	4.24	1.42	2	3.25	0.62	2	2.37	0.84	.69
Tongue		(N=107)			(N=118)			(N=119)			(N=113)			
	1) #B - Fibroma	0	0.31	0.00	1	0.38	2.63	0	0.17	0.00	0	0.14	0.00	.69

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Trend through the high dose; values unadjusted for multiplicity unless footnoted otherwise

(c) includes multiple interstitial cell tumors

(d) includes multiple adenomas

TISSUE	MORPHOLOGIC CHANGE	CONTROLS			LOW DOSE			MED DOSE			HIGH DOSE			TREND
		OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	P-VALUE(b)
Combinations Across All Tissues		(N=108)			(N=120)			(N=119)			(N=113)			
	1) #B - All Fibromas	2	6.37	0.37	9	5.32	1.69	3	3.80	0.79	3	2.52	1.19	.20
	2) All Fibromas and Fibrosarcomas (c)	4	7.87	0.51	12	7.84	1.53	6	5.54	1.08	3	3.78	0.80	.29
	3) #B - All Hemangiomas	1	1.13	0.88	2	1.21	1.66	1	0.95	1.06	0	0.71	0.00	.79
	4) #M - All Hemangiosarcomas	1	1.54	0.65	3	1.78	1.69	1	0.85	1.05	0	0.74	0.00	.72
	5) Combine #3 and #4	2	2.75	0.73	5	2.84	1.76	2	2.03	0.99	0	1.38	0.00	.75
	6) #B - All Lipomas (d)	0	0.83	0.00	2	1.14	1.75	1	0.60	2.00	0	0.43	0.00	.47
	7) #M - All Schwannomas	2	1.21	1.65	1	1.28	0.79	1	0.86	1.16	0	0.67	0.00	.88
	8) (#B(e) and #M) - All Schwannomas	2	1.51	1.32	2	1.57	1.27	1	1.09	0.92	0	0.82	0.00	.88

APPEARS THIS WAY
ON ORIGINAL

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Trend through the high dose; values unadjusted for multiplicity unless footnoted otherwise

(c) Fibrosarcomas appeared in only one tissue (skin) and hence were not combined across tissues

(d) No liposarcomas to combine (among themselves or with lipomas)

(e) Benign schwannomas appeared in only one tissue (heart) and hence were not combined across tissues

TISSE	MORPHOLOGIC CHANGE	FEMALES										TREND P-VALUE(b)			
		CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE				
		OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	MID DOSE	HIGH DOSE
Adrenal(s)		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #B - Cortex, Adenoma	4	3.83	1.02	4	4.58	0.87	3	2.88	1.04	2	1.81	1.25	.80	.40
	2) #M - Cortex, Carcinoma	3	1.81	1.66	2	2.50	0.80	1	1.40	0.71	0	0.29	0.00	.80	.88
	3) #B - Pheochromocytoma (c)	4	8.38	0.48	13	9.91	1.31(f)	9	8.88	1.53	1	2.82	0.35	.017/.23(e)	.21
	4) #M - Pheochromocytoma (d)	3	1.53	1.96	0	1.91	0.00	1	1.11	0.90	1	0.45	2.20	.82	.67
	5) Combine #1 and #2	7	5.77	1.21	6	7.07	0.85	4	4.22	0.95	2	1.94	1.03	.88	.63
	6) Combine #3 and #4	7	9.94	0.70	13	11.8	1.10	10	8.99	1.43	2	3.28	0.61	.081	.28
Brain		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #M - Astrocytoma	1	0.55	1.80	0	0.75	0.00	1	0.51	1.95	0	0.17	0.00	.85	.71
Cervix		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #B - Leiomyoma	0	0.31	0.00	1	0.37	2.70	0	0.21		0	0.11	0.00	.65	.88
	2) #B - Stromal Polyp	1	0.54	1.86	1	0.90	1.12	0	0.57	0.00	0	0.00	-	.93	.93
Hematopoietic System		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #M - Histocytic Sarcoma	2	1.85	1.08	3	2.40	1.25	1	1.37	0.73	0	0.38	0.00	.60	.72
	2) #M - Lymphoma	2	2.07	0.97	4	2.89	1.38	1	1.70	0.59	0	0.34	0.00	.62	.72
	3) #M - Mononuclear Cell Leukemia	1	0.27	3.72	0	0.45	0.00	0	0.28	0.00	0	0.00	-	1.00	1.00
Kidney(s)		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #B - Lipoma	0	0.31	0.00	0	0.34	0.00	0	0.23	0.00	1	0.12	8.20	-	.12
	2) #M - Liposarcoma	1	0.31	3.24	0	0.38	0.00	0	0.21	0.00	0	0.10	0.00	1.00	1.00
	3) #B - Tubular Adenoma	1	0.71	1.41	1	0.67	1.49	0	0.38	0.00	0	0.24	0.00	.84	.88
	4) #M - Tubular Carcinoma	1	0.68	1.78	1	0.85	1.06	0	0.49	0.00	0	0.00	-	.89	.92
	5) Combine #1 and #2	1	0.73	1.35	0	0.32	0.00	0	0.26	0.00	1	0.68	1.45	1.00	.61
	6) Combine #3 and #4	2	1.27	1.57	2	1.62	1.24	0	0.87	0.00	0	0.24	0.00	.90	.94

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Values unadjusted for multiplicity unless footnoted otherwise

(c) Includes multiple pheochromocytomas

(d) Includes complex pheochromocytomas

(e) Adjusted for multiplicity

(f) P-value = .027 (unadjusted) and .23 (adjusted for multiplicity) for trend through this group

TISSUE	MORPHOLOGIC CHANGE	FEMALES												TREND P-VALUE(b)	
		CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE			THROUGH	
		OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	MID DOSE	HIGH DOSE
Large Intestine			(N=109)		(N=123)		(N=111)		(N=110)						
	1) #B - Granular Cell Tumor (c)	2	0.86	3.55	0	0.77	0.00	0	0.54	0.00	0	0.14	0.00	1.00	1.00
	2) #B - Leiomyoma	0	0.27	0.00	0	0.47	0.00	1	0.28	3.84	0	0.00	--	.28	.28
	3) #M - Leiomyosarcoma	0	0.27	0.00	1	0.45	2.23	0	0.28	0.00	0	0.00	--	.73	.73
	4) Combine #2 and #3	0	0.56	0.00	1	0.95	1.00	1	0.48	2.04	0	0.00	--	.25	.29
Liver			(N=109)		(N=123)		(N=111)		(N=110)						
	1) #B - Hepatocellular Adenoma (d)	2	1.68	1.19	1	1.70	0.59	2	1.01	1.98	0	0.61	0.00	.43	.57
Lymph Node, Mesenteric			(N=109)		(N=122)		(N=111)		(N=110)						
	1) #B - Hemangioma	1	0.84	1.19	1	1.07	0.83	1	0.78	1.29	0	0.32	0.00	.58	.73
Mammary Gland			(N=108)		(N=122)		(N=111)		(N=109)						
	1) #B - Adenoma	1	2.28	0.44	5	2.69	1.83	1	1.44	0.70	0	0.70	0.00	.32	.58
	2) #M - Carcinoma (e)	40	31.4	1.28	36	37.3	0.96	20	20.9	0.96	5	11.5	0.44	.86	.90
	3) #M - Fibroadenoma (f)	48	51.9	0.93	89	55.3	1.25	32	34.3	0.89	12	19.6	0.81	.39	.86
	4) Combine #1 and #2	41	33.4	1.23	40	39.5	1.01	21	21.9	0.98	5	12.2	0.41	.84	.90
Ovary			(N=109)		(N=123)		(N=111)		(N=110)						
	1) #B - Granulosa Cell Tumor (g)	0	0.86	0.00	1	0.76	1.31	1	0.51	1.98	0	0.17	0.00	.27	.43
	2) #B - Luteoma	0	0.27	0.00	1	0.45	2.23	0	0.28	0.00	0	0.00	--	.73	.73
	3) #B - Sertoli Cell Tumor	0	0.27	0.00	0	0.45	0.00	1	0.28	3.83	0	0.00	--	.28	.28
	4) #B - Tubulostromal Adenoma	0	0.27	0.00	1	0.45	2.23	0	0.28	0.00	0	0.00	--	.73	.73
	5) #B - Thecoma	0	0.31	0.00	0	0.38	0.00	0	0.21	0.00	1	0.10	10.3	--	.098
	6) Combine #1, #2, #3, and #5	0	1.55	0.00	2	1.66	1.21	2	1.08	1.88	1	0.72	1.96	.11	.13

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Values unadjusted for multiplicity unless footnoted otherwise

(c) Includes tumors in serosa

(d) Includes multiple adenomas

(e) Includes multiple carcinomas

(f) Includes multiple fibroadenomas

(g) Includes multiple granulosa cell tumors

TISSUE	MORPHOLOGIC CHANGE	FEMALES										TREND P-VALUES ^(b)			
		CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE			THROUGH	
		OBS'D	EXP'D	RATIO ^(a)	OBS'D	EXP'D	RATIO ^(a)	OBS'D	EXP'D	RATIO ^(a)	OBS'D	EXP'D	RATIO ^(a)	MID DOSE	HIGH DOSE
Pancreas		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #B - Acinar Cell Adenoma	1	0.34	2.94	0	0.36	0.00	0	0.21	0.00	0	0.10	0.00	1.00	1.00
	2) #B - Islet Cell Adenoma	6	3.44	1.45	3	4.27	0.70	3	2.42	1.24	0	0.86	0.00	.04	.82
Pharynx		(N=108)			(N=123)			(N=111)			(N=108)				
	1) #B - Para Distalis Adenoma (a)	86	67.4	0.96	99	100	0.99	66	60.5	1.09	29	31.7	0.91	.22	.45
	2) #M - Para Distalis Carcinoma	0	0.54	0.00	2	0.81	2.19	0	0.54	0.00	0	0.00	—	.68	.68
	3) Combine #1 and #2	86	68.3	0.97	101	101	1.00	66	61.1	1.08	29	31.9	0.91	.21	.45
Skeletal Muscle		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #M - Sarcoma, NOS	0	0.30	0.00	1	0.34	2.92	0	0.22	0.00	0	0.13	0.00	.85	.70
Skin		(N=107)			(N=121)			(N=111)			(N=108)				
	1) #B - Amelanotic Melanoma	1	0.32	3.15	0	0.38	0.00	0	0.21	0.00	0	0.10	0.00	1.00	1.00
	2) #B - Fibroma	2	0.96	2.08	0	1.12	0.00	1	0.61	1.63	0	0.31	0.00	.80	.85
	3) #M - Fibrosarcoma	0	0.92	0.00	2	1.04	1.92	1	0.55	1.50	0	0.37	0.00	.28	.48
	4) #B - Keratoacanthoma	1	0.27	3.72	0	0.45	0.00	0	0.28	0.00	0	0.00	—	1.00	1.00
	5) #M - Sarcoma, NOS	2	0.61	3.28	0	0.73	0.00	0	0.43	0.00	0	0.23	0.00	1.00	1.00
	6) #M - Squamous	0	0.32	0.00	0	0.36	0.00	1	0.20	4.89	0	0.11	0.00	.23	.32
	7) Combine #2 and #3	2	1.88	1.08	2	2.16	0.93	2	1.28	1.56	0	0.68	0.00	.36	.62
Small Intestine		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #M - Carcinoma	0	0.28	0.00	1	0.47	2.12	0	0.26	0.00	0	0.00	—	.74	.74
	2) #B - Leiomyoma	1	0.34	2.94	0	0.35	0.00	0	0.21	0.00	0	0.10	0.00	1.00	1.00
	3) #M - Leiomyosarcoma	0	0.27	0.00	0	0.46	0.00	1	0.28	3.53	0	0.00	—	.28	.28
	4) Combine #2 and #3	1	0.66	1.80	0	0.76	0.00	1	0.51	1.95	0	0.17	0.00	.60	.71

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Values unadjusted for multiplicity unless footnoted otherwise

(c) Includes multiple adenomas

TISSUE	MORPHOLOGIC CHANGE	FEMALES												TREND P-VALUE(b) THROUGH	
		CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE				
		OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	MID DOSE	HIGH DOSE
Spleen		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #M - Sarcoma, NOS	0	0.33	0.00	1	0.36	2.80	0	0.21	0.00	0	0.11	0.00	.83	.67
Stomach		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #B - Glandular, Squamous Papilloma	0	0.31	0.00	0	0.34	0.00	0	0.23	0.00	1	0.12	8.17	—	.12
	2) #M - Leiomyosarcoma	0	0.33	0.00	1	0.36	2.78	0	0.20	0.00	0	0.11	0.00	.83	.67
	3) #M - Nonglandular, Squamous Cell Carcinoma	0	0.27	0.00	0	0.46	0.00	1	0.28	3.53	0	0.00	—	.28	.28
Thymus		(N=108)			(N=121)			(N=108)			(N=106)				
	1) #B - Thymoma	0	0.31	0.00	1	0.38	2.83	0	0.28	0.00	0	0.11	0.00	.66	.69
Thyroid(s)		(N=108)			(N=123)			(N=111)			(N=110)				
	1) #B - C Cell Adenoma	4	4.55	0.88	4	5.27	0.78	4	3.32	1.21	3	1.86	1.62	.34	.17
	2) #M - C Cell Carcinoma	1	0.66	1.51	1	0.75	1.33	0	0.40	0.00	0	0.19	0.00	.87	.89
	3) #B - Follicular Cell Adenoma	1	0.58	1.77	1	0.83	1.58	0	0.48	0.00	0	0.32	0.00	.89	.82
	4) #M - Follicular Cell Carcinoma	1	0.66	1.53	0	0.75	0.00	1	0.38	2.54	0	0.20	0.00	.57	.65
	5) Combine #1 and #2	5	5.15	0.97	5	6.02	0.83	4	3.74	1.87	3	2.08	1.43	.47	.28
	6) Combine #3 and #4	2	1.18	1.70	1	1.34	0.78	1	0.91	1.10	0	0.57	0.00	.77	.88
Urinary Bladder		(N=108)			(N=123)			(N=111)			(N=108)				
	1) #B - Transitional Epithelium, Papilloma	0	0.27	0.00	1	0.45	2.23	0	0.28	0.00	0	0.00	—	.73	.73

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Values unadjusted for multiplicity unless footnoted otherwise

>

TISSE	MORPHOLOGIC CHANGE	FEMALES												TREND P-VALUE(b)			
		CONTROLS			LOW DOSE			MID DOSE			HIGH DOSE			THROUGH			
		OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	OBS'D	EXP'D	RATIO(a)	MID DOSE	HIGH DOSE		
Uterus			(N=109)			(N=123)			(N=111)			(N=110)					
	1) #M - Endometrial Carcinoma	1	0.27	3.72	0	0.45	0.00	0	0.28	0.00	0	0.00	-	1.00	1.00		
	2) #B - Endometrial Stromal Polyp (c)	8	7.81	1.01	8	8.16	0.87	4	5.74	0.70	6	3.19	1.88	.74	.21		
	3) #M - Endometrial Stromal Sarcoma	4	1.28	3.12	0	1.45	0.00	0	0.53	0.00	0	0.43	0.00	1.00	1.00		
	4) #B - Granular Cell Tumor	1	0.59	1.45	1	0.80	1.24	0	0.44	0.00	0	0.07	0.00	.84	.89		
	5) #B - Leiomyoma	1	1.13	0.89	2	1.90	1.06	1	0.96	1.02	0	0.00	-	.82	.59		
	6) #M - Schwannoma	1	0.27	3.85	0	0.45	0.00	0	0.27	0.00	0	0.00	-	1.00	1.00		
	7) #B - Squamous Papilloma	1	0.34	2.94	0	0.35	0.00	0	0.21	0.00	0	0.10	0.00	1.00	1.00		
Vagina			(N=108)			(N=123)			(N=111)			(N=110)					
	1) #B - Granular Cell Tumor	1	0.53	1.20	1	1.40	0.72	1	0.77	1.29	0	0.00	-	.55	.63		
	2) #B - Leiomyoma	0	0.66	0.00	1	0.36	2.81	0	0.16	0.00	1	0.61	1.63	.64	.32		
	3) #M - Schwannoma	0	0.28	0.00	0	0.47	0.00	1	0.26	3.88	0	0.00	-	.38	.28		
	4) #B - Stromal Polyp	1	0.27	3.72	0	0.45	0.00	0	0.28	0.00	0	0.00	-	1.00	1.00		
Combinations Across Specific Tissues			(N=109)			(N=123)			(N=111)			(N=110)					
	1) Cervix #1; Uterus #5	1	1.40	0.71	3	2.21	1.36	1	1.24	0.81	0	0.14	0.00	.51	.53		
	2) Cervix #2; Uterus #2 and #3	13	9.70	1.34	9	11.5	0.78	4	7.03	0.57	8	3.75	1.60	.86	.54		
Combinations Across All Tissues			(N=109)			(N=123)			(N=111)			(N=110)					
	1) #B - All Leiomyomas	2	2.82	0.71	4	3.36	1.19	2	1.96	1.02	1	0.88	1.16	.35	.34		
	2) #M - All Leiomyosarcomas	0	0.86	0.00	2	1.28	1.59	1	0.77	1.31	0	0.11	0.00	.32	.39		
	3) Combine #1 and #2	2	3.78	0.53	6	4.64	1.32	3	2.60	1.15	1	1.08	0.92	.19	.25		
	4) #M - All Schwannomas	1	0.90	1.12	0	1.28	0.00	2	0.74	2.71	0	0.09	0.00	.30	.36		

(a) (Observed number of tumors)/(Expected number of tumors)

(b) Values unadjusted for multiplicity unless footnoted otherwise

(c) Includes multiple polype

7.3. HUMAN PHARMACOKINETIC VALUES FOR VALDECOXIB AND SC-66905 AT VARIOUS DOSAGES OF VALDECOXIB IN YOUNG AND ELDERLY SUBJECTS

PK Parameters		Steady-State PK Parameters for Various Dosages					
		10 mg (QD)		20 mg (QD) ^a		40 mg (BID)	
		Young ^b	Elderly ^c	Young	Elderly	Young	Elderly
Valdecocixib	AUC ₀₋₂₄ (hr•µg/ml)	1.479	2.071	2.958	4.142	20.98	29.36
	C _{max} (µg/ml)	0.161	0.225	0.322	0.450	1.328	1.859
SC-66905	AUC ₀₋₂₄ (hr•µg/ml)	0.114	0.160	0.228	0.320	1.41	1.974
	C _{max} (µg/ml)	0.009	0.013	0.018	0.026	0.081	0.114

^a 20 mg values are derived by doubling the PK values at 10 mg/day.

^b "Young" defined as subjects that were ≤66 years of age.

^c Values for elderly were adjusted upward by 40% based on young subject data.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: Nov. 15, 2001

FROM: Kenneth L. Hastings, Dr.P.H.
Acting Associate Director for Pharmacology/Toxicology, ODE V

TO: File

SUBJECT: NDA 21-341
BEXTRA® (Valdecoxib sodium)

I have reviewed the label for BEXTRA and concur with the content of the pharmacology/toxicology sections. This application is approvable based on the pharmacology/toxicology review.

Kenneth L. Hastings, Dr.P.H.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kenneth Hastings
11/15/01 03:36:30 PM
PHARMACOLOGIST