CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

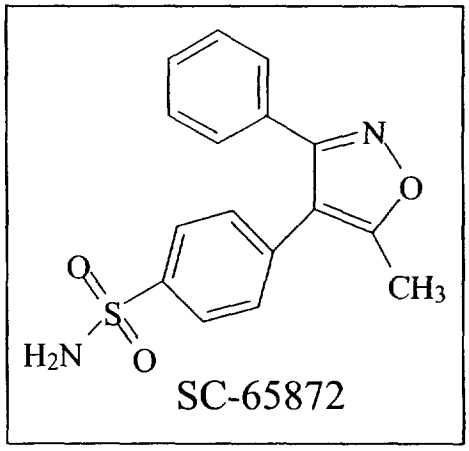
21-341

PHARMACOLOGY REVIEW

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS (HFD-550)

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA	**21-341**
DRUG:	Bextra; Valdecoxib; SC-65872
SPONSOR:	Pharmacia G.D. Searle LLC 4901 Searle Parkway Skokie, IL 60077
SUBMISSION DATE:	January 15, 2001
TYPE OF SUBMISSION:	Original [505 (b)(1)]
DATE COMPLETED:	October 11, 2001
REVIEWER:	W. C. Josie Yang, DVM, Ph.D.
CDER STAMP DATE:	January 16, 2001
DATE RECEIVED IN HFD-550:	January 17, 2001
DATE ASSIGNED TO REVIEWER:	January 19, 2001
USER FEE DUE DATE:	November 16, 2001
DRUG CATEGORY:	NSAID, Cyclooxygenase 2 (COX-2) Inhibitor
FORMULA:	4-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide; $C_{16}H_{14}N_2O_3S$; MW=314.36



SC-65872

INGREDIENTS	QUANTITIES (MG)			Function
	10 mg	20 mg	40 mg	
Valdecoxib	10.0	20.0	40.0	Active Ingredient
Lactose Monohydrate, NF				
Microcrystalline Cellulose, NF				
Pregelatinized Starch, NF				
Croscarmellose Sodium, NF				
Magnesium Stearate, NF				
Purified Water, USP				

CAS Nº: 181695-72-7

INDICATION: Prevention and Treatment of Acute Pain in Adults; Treatment of Primary Dysmenorrhea; Relief of Signs and Symptoms of Osteoarthritis and Adult Rheumatoid Arthritis

DOSAGE FORM: 5 mg, 10 mg, 20 mg and 40 mg film coated tablets.

RELATED DRUG/INDs/NDAs/DMFs:

KEY WORDS: SC-65872; Valdecoxib, COX-2; NSAID

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

The pharmacological actions and pharmacodynamics of valdecoxib were investigated in various *in vitro* and *in vivo* studies. The non-clinical safety of valdecoxib was evaluated in the following species:

- mice - acute single dose, 2- and 13-week repeated dose toxicity and two year carcinogenicity studies
- rat - acute single dose, 2-, 4-, 13- and 26-week repeated dose toxicity, reproductive (Segment I, Segment II, and combined Segment II/III) and 2-year carcinogenicity studies;
- rabbit - embryo/fetal development toxicity studies
- dog - acute single dose and 2-, 4-, and 52-week repeated dose plus special renal function toxicity studies;
- monkey - 2-, 4-, and 52-week week repeated dose toxicity studies.

The mutagenic and clastogenic potentials of valdecoxib and its active metabolite, SC-66905, were also evaluated.

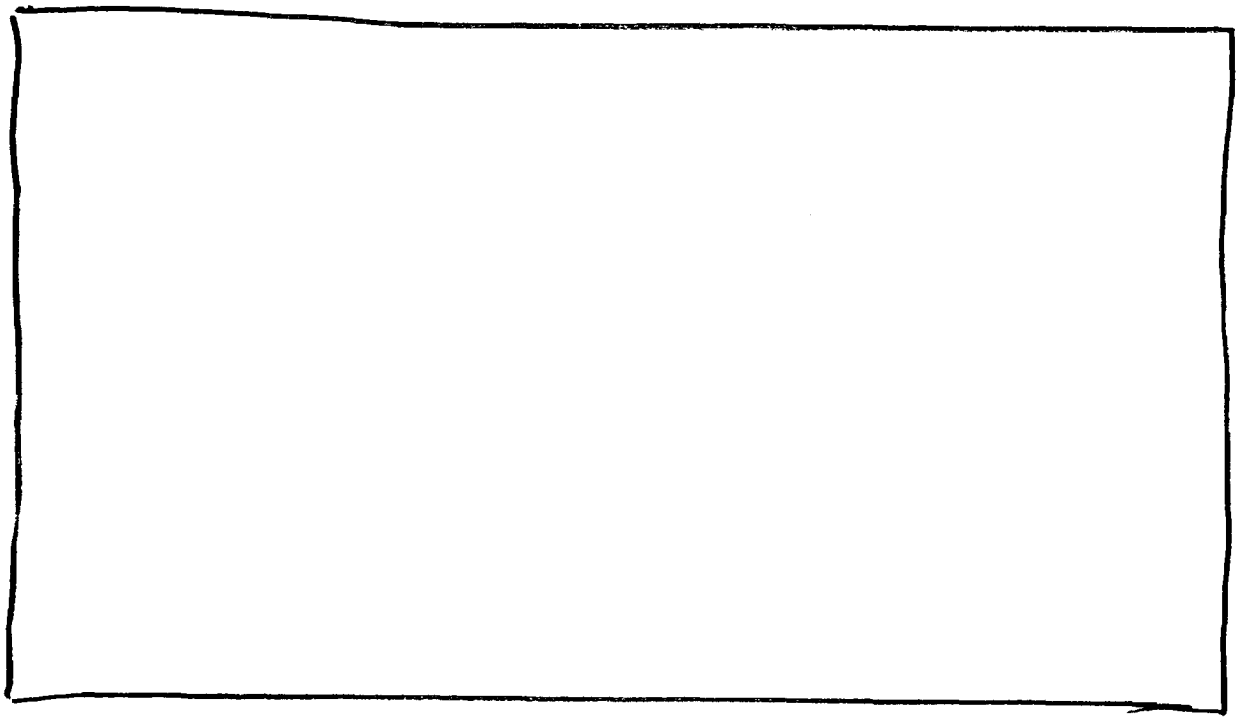
Approval of valdecoxib is recommended with the changes on the labeling as stated below.

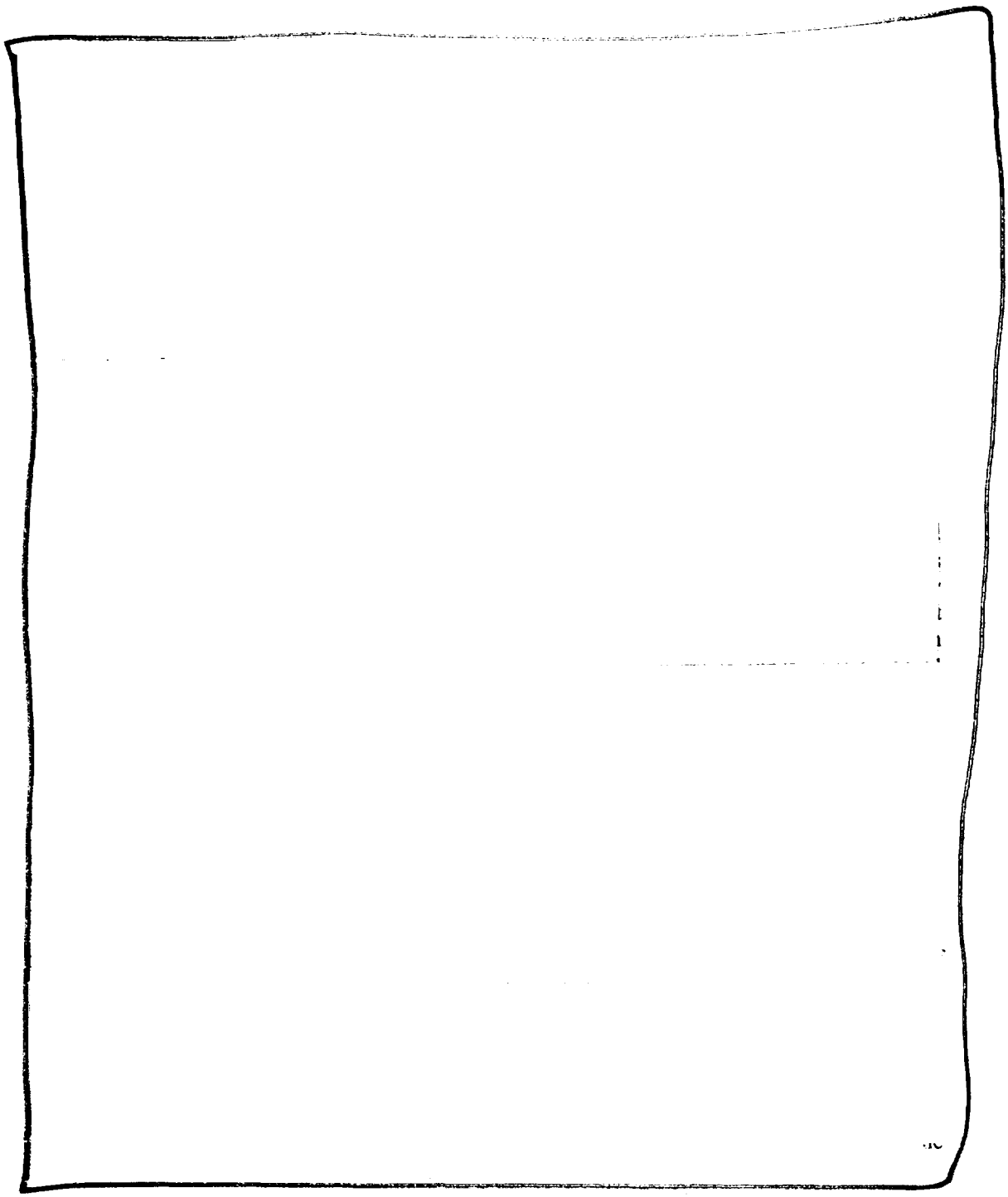
B. Recommendation for Nonclinical Studies

N/A

C. Recommendations on Labeling

The following changes on the labeling are recommended.
Carcinogenesis, mutagenesis, impairment of fertility:





II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings

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 to 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 exacerbated by placing dogs on 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 the 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. Although these observations occurred in the dog and monkey but not in the mouse or rat, test-article caused toxicity through the mechanism of in situ inhibition of phagocytic cell functions could not be ruled out.

Transient antinatriuretic effects (decreases in urinary sodium excretion) of 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 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 AUC0-24 for valdecoxib and SC-66905, respectively) 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 at 20 mg QD as measured by the $AUC_{0\text{-}24}$). 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 sternebrae 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 malformation 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 sternebrae should be reflected on the labeling.

B. Pharmacologic Activity

Valdecoxib (SC-65872) and SC-66905, an active metabolite, preferentially inhibited human recombinant COX-2 mediated PGE_2 production *in vitro*.

Valdecoxib (SC-65872) was demonstrated to have anti-inflammatory, analgesic, and anti-pyretic properties in various animal models.

C. Nonclinical Safety Issues Relevant to Clinical Use

Based on the toxicity observed in the animal studies as stated above, close monitoring of adverse events of microbial infections and renal complications in addition to GI injury in humans is highly recommended.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

NDA 21-341
HFD-550/Division File
/JYang
/ROsterberg
/KJohnson
/CDeBellas

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1. PHARMACOLOGY

1.1. OVERVIEW

The actions of currently available marketed NSAIDs to inhibit the production of prostaglandins (PGs) by cyclooxygenases (COX) can be divided into three groups:

- modification of the enzymes by acetylation of a serine residue at the active site, such as aspirin thus resulting in an irreversible inhibition of COX activity;
- induction of time-dependent irreversible inhibition of enzymes, such as indomethacin or flurbiprofen; and
- induction of reversible competitive inhibition, such as ibuprofen and mefenamate.

The common side effects shared by NSAIDs are as followings:

- GI ulceration and intolerance,
- inhibition of platelet aggregation via blockade of thromboxane (TBX) synthesis,
- inhibition of uterine motility resulting in prolongation of gestation,
- inhibition of PG-mediated renal function, and
- hypersensitivity reactions.

Two distinct COX enzymes, COX-1 and COX-2, were identified recently. COX-1, a constitutively expressed form, displays in blood, vessels, gut and kidney that produce PGs which are required for normal physiological functions. COX-2, an inducible isoenzyme, is encoded by a different gene from COX-1 and only exists in high concentrations under the inflammatory condition induced by cytokines or inflammatory mediators or following mitogenic stimulation. COX-1 mRNA could be detected in all tissues with highest expressed levels found in platelets, vascular endothelial cells, liver, stomach, spleen, kidney collecting tubules and colon. In contrast, COX-2 mRNA levels were extremely low in all normal tissues except rat brain. Both enzymes have approximately 60% homology and are able to convert arachidonic acid to PGH_2 with similar affinity. The amino acid residues thought to be essential for this enzymatic conversion are conserved in both structures.

It has been postulated that NSAID-induced GI toxicity is caused by the inhibition of PGs which were mainly regulated by COX-1 in the GI tract and required for normal physiological function. Most currently available NSAIDs inhibit the COX-1 and COX-2 nonselectively or have preferential selectivity for COX-1 except two recently approved NSAIDs, celecoxib and rofecoxib. The action of mechanism of action of celecoxib and rofecoxib is believed due the inhibition of prostaglandin synthesis mainly through the inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, both celecoxib and rofecoxib do not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Valdecoxib (SC-65872 - $C_{16}H_{14}N_2O_3S$), 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.

1.2. PHARMACODYNAMIC EFFECTS RELATING TO PROPOSED INDICATIONS

Study Type	Species/Indicator	Treatment/Route	Dose	Findings
ANTI-INFLAMMATORY/ANALGESIC ACTIVITIES				
Effects on Adjuvant-Induced Arthritis	♂ Lewis Rats 10/group	po bid for 10 days (6-8 hr apart)	Valdecoxib: 0-3 mg/kg/day; Parecoxib: 0-0.3 mg/kg/day; SC-66905: 0-10 mg/kg/day	Dose-related inhibition of adjuvant- induced arthritis with ED_{50} values: Valdecoxib - 0.036 mg/kg/day; Parecoxib - 0.078 mg/kg/day; SC-66905 - 1.68 mg/kg/day.
Effects on Carrageenan-Induced Inflammatory (Hargreaves Model) Hyperalgesia, Edema, and PGE_2 Production	♂ SD Rats 5-10/group	po single dose	Valdecoxib: 0, 30 mg/kg	↓ hyperalgesia by 81% at 3 hr post-dose; ↓PGE_2 by 81% in paw exudate at 2 hr post-dose.
	♂ SD Rats 5/group			↓ hyperalgesia, paw edema, PGE_2 in paw exudate, and PGE_2 in CSF by 62%, 63%, 74%, and 86%, respectively.
	♂ SD Rats 5/group	po single dose	Valdecoxib: 0, 30 mg/kg Naloxone: 0.5 mg/kg sc	Valdecoxib blocked carrageenan-induced hyperalgesic pain; subcutaneous administration of Naloxone at 0.5 mg/kg did not alter the analgesic action of Valdecoxib.
	♂ SD Rats 5-8/group	po single dose	Valdecoxib: 0, 1, 3, 10, 30, 50, and 100 mg/kg	Dose-dependent ↓ of hyperalgesia and paw edema with ED_{50}'s (mg/kg): Hyperalgesia / Edema Valdecoxib 13.7 / 5.9 SC-66905 1.5 / 1.06
	♂ SD Rats 5/group	po single dose	valdecoxib: 0, 5, 30 mg/kg	↓ hyperalgesia and paw edema at 30 mg/kg. Hyperalgesia / Edema Single Dose ↓91% / ↓67%
		bid for 8-day	Valdecoxib: 2.5, 15 mg/kg bid	Repeated Dose ↓100% / ↓69%
	♂ Lewis Rats 4-13/group	po single dose	valdecoxib: 0, 0.03, 0.3, 10 mg/kg	↓ PGE_2 in CSF to undetectable levels at 1 and 3 hr postdose with 10 mg/kg; ↓ PGE_2 levels in paw exudate by 43% and 57% 4 hr after dosing with 0.03 and 0.3 mg/kg, respectively.
		bid for 7-day	0.5 mg/kg	↓ PGE_2 levels in CSF to normal levels at 24 hr post 1st dose.
	♂ SD Rats 2-4/group	intrathecal single dose	valdecoxib: 0, 30, 100, 300 μg	≥100 μg: ↓ hyperalgesia, paw edema, and PGE_2 in paw exudate and CSF
	♂ SD Rats 5/group	iv or po single dose	valdecoxib: 0, 50, 200 μg	↔
Effects on Hyperalgesia and Allodynia in Post-Surgical Pain Model	♂ SD Rats 6/group	po single dose	valdecoxib: 0, 3, 10, 30, and 100 mg/kg	Dose-dependent reduction of tactile allodynia and thermal hyperalgesia.
		iv single dose		
ANTI-PYRETIC ACTIVITY				
Effect on LPS-Induced Fever in Dogs	♀ Beagle Dogs 4/group	po single dose	Valdecoxib: 0, 0.5, 5 mg/kg	Blocked LPS-induced fever at 5 mg/kg.

1.2.1. REFERENCES

1.2.1.1.1. Valdecoxib, SC-66905 and Parecoxib: Effect on Adjuvant-Induced Arthritis in Rats; Date: 01-Feb-2000, Document No. BRD96D1796a. (Vol. 1.13)

1.2.1.1.2. Valdecoxib Inhibits Hyperalgesia and Allodynia in Rat Model of Post-Operative Pain; Date: 16-Feb-2000, Document No. BRD99D1997. (Vol. 1.13)

1.2.1.1.3. Effect of Valdecoxib on Edema, Hyperalgesia and Prostaglandin Production in the Rat Carrageenan Model; Date: 28-Jan-2000, Document No. BRD99D1991. (Vol. 1.13)

1.2.1.1.4. Effect of Valdecoxib (SC-65872) on PGE_2 Levels in Cerebrospinal Fluid and Paw Exudates/Synovial Fluid in Rat Adjuvant Arthritis; Date: 26-Jan-2000, Document No. BRD98D1917. (Vol. 1.13)

1.2.1.1.5. Distribution of Valdecoxib (SC-65872): Into the Central Nervous System in the Rat; Date: 20-Jan-2000, Document No. BRD98D1930. (Vol. 1.13)

1.2.1.1.6. Valdecoxib (SC-65872): Inhibitory Activity on Fever, Cyclooxygenase-1 and Cyclooxygenase-2 in Dogs; Date: 13-Jan-2000, Document No. BRD98D1901. (Vol. 1.13)

1.2.1.1.7. Effect of Naloxone on the Analgesic Activity of Valdecoxib (SC-65872); Date: 25-Jan-2000, Document No. BRD98D1911. (Vol. 1.13)

1.2.1.1.8. Effect of Intrathecal Administration of Valdecoxib (SC-65872) on Hyperalgesia, Edema and PGE_2 Production in Hargreaves Model; Date: 01-Feb-2000, Document No. BRD98D1916. (Vol. 1.13)

1.2.1.1.9. Valdecoxib Rapidly Reverses Inflammatory Hyperalgesia and Prostaglandin E_2 Production; Date: 01-Feb-2000, Document No. BRD98D1928. (Vol. 1.13)

1.2.1.1.10. Evaluation of Valdecoxib and SC-66905, COX-2 Inhibitors, as an Anti-Inflammatory and Analgesic Agent; Date: 20-Apr-2000,Document No. BRD98D1929a. (Vol. 1.13)

1.2.1.1.11. Evaluation of Single Vs. Chronic Administration of Valdecoxib (SC-65872) on Hyperalgesia and Edema; Date: 26-Jan-2000, Document No. BRD99D1931. (Vol. 1.13)

1.3. GENERAL AND MECHANISM RELATED PHARMACODYNAMICS

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Study Type	Species/Indicator	Treatment/Route	Dose/Conc.	Findings
Inhibition of COX-1 in Rat Whole Blood	SD Rats	*in vitro*	valdecoxib: 50 μM	Valdecoxib: partially ↓ arachidonic acid-induced TXB2; SC-66905: ↔.
	♂ SD Rats 3/group	po bid for 3 days	valdecoxib: 0, 15 mg/kg	Partial inhibition of A23187- induced TXB2 production *ex vivo*.
In vitro Selectivity for COX-2 Inhibition	hCOX-1/hCOX-2 transfected insect cells	*in vitro*	valdecoxib: 0.001 - 100 μM	IC_{50} for hCOX-2 = 0.005 μM; IC_{50} for hCOX-1 = 140 μM.
			SC-66905: 0.001 - 100 μM	IC_{50} for hCOX-2 = 0.18 μM; IC_{50} for hCOX-1 = 1120 μM.
Inhibition of COX	Human COX-2 Sheep Seminal Vesicle COX-1	*in vitro*	valdecoxib: 0.001- 100 μM SC-66905: 0.001 - 100 μM	Time-dependent inhibition of hCOX-2: Valdecoxib: k_i (24 μM), k_{inact} (0.32 sec^{-1}) SC-66905: k_i (63.8 μM), k_{inact} (0.056 sec^{-1}) Reversible IC_{50} and competitive inhibition: Valdecoxib: Reversible IC_{50} hCOX-2 187 μM, sCOX-1 92 μM; Comp Inh sCOX-1 k_i 34.4 μM SC-66905: Reversible IC_{50} hCOX-2 200 μM, sCOX-1 385 μM; Comp Inh sCOX-1 k_i 136.0 μM
Reversibility of binding to COX-1/COX-2	hCOX-1/hCOX-2 transfected insect cells	*in vitro*	valdecoxib: 25 μM	50% valdecoxib remained bound to COX-2 while only 10% remained bound to COX-1 after dialysis.
Effect on Prostaglandin Production in Carrageenan-Induced Air Pouch	♂ Lewis Rats 5-6/group	po single dose	Valdecoxib: 0.01 - 2 mg/kg SC-66905: 0.3 -5 mg/kg	Completely ↓ prostaglandin production with ED_{50} values of: Valdecoxib: ED_{50} (mg/kg) 0.05 ± 0.02 SC-66905: ED_{50} (mg/kg) 0.81 ± 0.13
Inhibition of COX-1 in Rat Stomach Mucosa	♂ Lewis Rats 6-8/group	po single dose	Valdecoxib: 0.01 - 10 mg/kg	Partially ↓ prostaglandin production with an ED_{50} of >10 mg/kg
Inhibition of LPS-Induced PGE_2 production by COX-2	♂ Lewis Rats 5-6/group	iv single dose	Valdecoxib: 0.003 - 10 mg/kg	Completely ↓ COX-2 activity at ≥1 mg/kg with ED_{50} of 0.03 mg/kg
	♀ Beagle Dogs 2/group	po single dose	Valdecoxib: 0, 5 mg/kg	Effectively ↓ LPS-induced COX activity by 83% and 91% at 1 and 5 hr post dosing, respective.
Inhibition of COX-1 in Whole Blood	♂ Lewis Rats 4-6/group	iv single dose	Valdecoxib: 0.003 - 10 mg/kg	Partially ↓ COX-1 by 23% at 10 mg/kg.
	♀ Beagle Dogs 7/group	po single dose	Valdecoxib: 0, 5 mg/kg	↔ (no effect)
Inhibition of Urinary PGE_2	♂ Lewis Rats 6/group	po single dose	Valdecoxib: 30 mg/kg	Partially ↓ COX-1 by 44% and 18% with Valdecoxib and SC-66905, respectively.
Effect of COX inhibitors on Mouse Air Pouch PGE_2 and Serum TXB_2	♀ SKH-1 Mice 6-9/group	po single dose	0.1 - 100 mg/kg	ED_{50} (mg/kg) values: Valdecoxib: Air Pouch PGE_2 6, Serum TXB_2 >100 SC-66791: 3, >100 SC-70245: 2, 101 SC-75416: 2, 5 SC-74719: 24, 8 SC-69340: >100, >100 Dexamethasone: 0.4, >50 SC-58560: 2, 0.2 Indomethacin: 0.2, 0.1 Naproxen: 6, 8 Diclofenac: 0.2, 9

Study Type	Species/Indicator	Treatment/Route	Dose/Conc.	Findings
Inhibition of COX COX-2	hCOX-1/hCOX-2 transfected insect cells	*in vitro*	0.01 nM-1000 μM	ID_{50} (μM) values: hCOX-1 / hCOX-2 Valdecoxib 140 / 0.005 SC-66791 114 / 0.004 Rofecoxib >1000 / 0.239 SC-75416 61 / 0.078 SC-74719 38 / 82 SC-69340 >100 / 68 Dexamethasone 0.1 / 1.1 SC-58560 0.005 / 48 Indomethacin 0.1 / 1.1 Naproxen 32 / 235 Diclofenac 0.03 / 0.01
Distribution of valdecoxib in CNS	♂ SD Rats 5/group	po single dose	100 mg/kg	Rapid distribution to CNS tissue and plasma, within 30 minutes after administration.
Binding of COX-1 and COX-2	Murine COX-2 Sheep COX-1	*in vitro*	[^{3}H]Valdecoxib: 0.35-150 nM	COX-1: minimal binding; COX-2: Saturation K_d = 3.2 nM; Assoc. rate = 4.5 x $10^6 min^{-1}M^{-1}$; Dissoc. Rate = 7.1 x $10^{-3} min^{-1}$

1.3.1. REFERENCES

1.3.1.1.1. Evaluation of Valdecoxib, Parecoxib and SC-66905 Using Human Recombinant COX-1 and COX-2 Enzymes; Date: 21-Apr-2000, Document No. BRD96D1793b. (Vol. 1.14)

1.3.1.1.2. X-Ray Crystal Structure and Mechanism of In Vitro Selectivity of Valdecoxib; Date: 11-Jan-2000, Document No. BRD99D1998. (Vol. 1.14)

1.3.1.1.3. Characterization of [3H]-Valdecoxib Binding to Cyclooxygenase-2; Date: 25-Feb-2000, Document No. BRD00D2037. (Vol. 1.14)

1.3.1.1.4. Valdecoxib: Inhibition of Cyclooxygenase 1 and 2 Activities in Rodent and Human Whole Blood; Date: 17-Jan-2000, Document No. BRD96D1791a. (Vol. 1.14)

1.3.1.1.5. Celecoxib Binding and Enzyme Assays; Date: 21-Jan-2000, Document No. BRD99D1967a. (Vol. 1.14)

1.3.1.1.6. Study of Parecoxib and SC-66905 in Various Binding and Enzyme Assays; Date: 08-Mar-2000, Document No. BRD00D2035. (Vol. 1.14)

1.3.1.1.7. Evaluation of Selective COX Inhibitors and Conventional NSAIDS Using Human Recombinant COX-1 and COX-2 Enzymes; Date: 11-Feb-2000, Document No. BRD00D2034. (Vol. 1.14)

1.3.1.1.8. Effect of COX Inhibitors on Mouse Airpouch PGE2 and Mouse Serum TXB2; Date: 23-Mar-1999, Document No. BRD99D2007a. (Vol. 1.13)

1.3.1.1.9. Valdecoxib: Selective COX-2 Inhibition In-Vivo; Date: 20-Jan-2000, Document No. BRD96D1794a. (Vol. 1.13)

1.4. SAFETY PHARMACOLOGY

Reports of studies with SC-65872 (valdecoxib) related to safety pharmacology were summarized in the following table.

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

1.4.1. REFERENCES

1.4.1.1.1. Valdecoxib: Gastrointestinal Damaging Activity in Rodents; Date: 18-Jan-2000, Document No. BRD96D1789a. (Vol. 1.15)

1.4.1.1.2. Effect of SC-65872, a Cyclooxygenase-2 Inhibitor, on Renal Blood Flow in Sodium Deficient Male Munich Wistar Rats; Date: 15-Apr-1996, Document No. BRD96D1799. (Vol. 1.15)

1.4.1.1.3. Four Day Neurobehavioral Study of Orally Administered SC-65872 in the Rat (EX 4460); Date: 22-May-1996, Document No. P30E4460. (Vol. 1.15)

1.4.1.1.4. Five Day Oral Gavage Study With SC-65872 to Evaluate Potential Effects on Selected Urine Parameters in the Rat (EX 4457); Date: 20-Aug-1996, Document No. P30E4457. (Vol. 1.15)

1.4.1.1.5. Cardiopulmonary Assay of SC-65872 in Guinea Pigs (EX 4464); Date: 09-Jul-1996, Document No. P30E4464. (Vol. 1.15)

1.4.1.1.6. The Effects of SC-65872 and Ketorolac on Renal Blood Flow and Renal Function in Salt Depleted Dogs; Date: 14-Oct-1996, Document No. BRD96D1819. (Vol. 1.16)

1.4.1.1.7. Acute Hemodynamic Effects of the Intravenous Administration of SC-65872 in Anesthetized Beagle Dogs; Date: 24-May-1996, Document No. P30E4459. (Vol. 1.16)

1.4.1.1.8. Evaluation of Hemodynamics and Electrocardiograms in Conscious Dogs After Oral Administration of SC-65872 (EX4966); Date: 20-Sep-2000, Document No. P30E4966. (Vol. 1.16)

2. TOXICOLOGY

2.1. ACUTE TOXICITY STUDIES

2.1.1.1. Acute Oral Toxicity Study of SC-65872 in the Rat, SA4931; Date: 04-Oct-2000, Document No. P30S4931. (Vol. 1.27)

Study Nº: SA4931
Report Nº: P30S4931/M3099339 (TK)
Study Aim: To evaluate potential acute toxicity of SC-65872 following a single oral dose to rats.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: ♂ - 0, 400, 800, and 1600 mg/20 ml/kg po
♀ - 0, 200, 400, and 800 mg/kg po single dose
Animals: CD IGS rats [redacted]-9 weeks of age, weighing 163.9-321.5g, 12/sex/group.
Study Location: G.D. Searle, 4901 Searle Parkway, Skokie, IL 60077 [redacted]
GLP/QAU Compliance: Yes
Study Date: 8/10-24/1999
Study Design: Groups of 12/sex rats were given a single oral dose of SC-65872 or vehicle as shown in the following table. Animals were sacrificed on Day 3 or Day 15.

Group	Dose (mg/kg)		Dose Vol. (ml/kg)	Nº of Animals	Nº of Animal Sacrificed	
	♂	♀			Day 3	Day 15
1	0	0	20 ml/kg	12/sex/group	6/sex/group	6/sex/group
2	400	200				
3	800	400				
4	1600	800				

The following observations were conducted.

- Mortality and Clinical Signs - 1x/day.
- Body Weights - Pre-R, Days 1, 2, 4, 8, and 14.
- Food Consumption - Pre-R and 1x/week.
- Hematology and Serum Chemistry - Days 3 and 15 (prior to sacrifice). The following parameters were analyzed.

HEMATOLOGY		
RBC	Mean Corpuscular Hemoglobin (MCH)	WBC/Differential
Hemoglobin (Hb)	Mean Corpuscular Hemoglobin Concentration (MCHC)	Blood Cell Morphology
Hematocrit (Ht)	Mean Platelet Volume	Large Unstained Cells (Activated Lymphocyte,
Mean Corpuscular Volume (MCV)	Platelet Count	Monocyte, and/or Immature Bone Marrow Cells)

SERUM CHEMISTRY					
Glucose	Sorbitol Dehydrogenase (SDH)		Alanine Aminotransferase (ALT)	Aspartate Aminotransferase (AST)	
Urea Nitrogen	Globulin	Albumin	Triglycerides	Alkaline Phosphatase (ALP)	Sodium
Creatinine	Albumin/Globulin Ratio		Total Bile Acids	Potassium	Chloride
Total Protein	Cholesterol		Total Bilirubin	Calcium	Inorganic Phosphorus

- Necropsy - Days 3 and 15 (6/sex/group). The following tissues were collected and preserved in 10% buffered formalin. Bone marrow smears were not prepared. Histopathological examination of grossly observed lesions was performed.

Adrenal Gland (Both)		Small Intestine (Duodenum, Jejunum, Ileum)		Spleen
Bone, Sternum (Including Marrow)		Kidneys (Both)	Lungs (Both)	Stomach
Brain	Heart	Liver	Ovaries (Both)	Thymus
Large Intestine (Cecum, Colon, Rectum)		Spinal Cord (Lumbar)	Testes (Both)	Lesions

- PK/TK - Blood was collected from 6 rats/sex/group at 2 hr post dosing. Blood samples from Group 1 (Control) were not analyzed. Plasma samples were shipped to [redacted] for the determination of SC-65872 and SC-66905 levels.

Results:

- Clinical Signs and Mortality - Two ♀ @ 800 mg/kg were found dead (Days 3 or 4) due to treatment-caused GI toxicity (small intestinal perforation and associated peritonitis) with clinical signs of cold to touch, rough coat, reduced feces, nose discharge and mouth crust prior to death.
- Body Weights and Food Consumption - No remarkable changes were noted. A transient dose-dependent decrease in body weight gain between Days 1 and 2 was noted in the SC-65872 treated groups (♂: ↓15.4%, ↓32.6%, and ↓44% of control values, respectively; ♀: ↓33.8%, ↓60%, and ↓64% of control values, respectively).
- Clinical Pathology - Increases in neutrophils (↑2-3x of control) and monocytes (↑~1.5x of control) were noted in some Groups 2-4 ♀. On Day 3, a dose-related increase in cholesterol levels was noted in both ♂ (1.3x, 1.7x, and 2.0x of control values, respectively) and ♀ (1.6x, 1.8x, and 2.3x of control values, respectively) of all SC-65872-treated groups. An increase in total bile acids was noted in Groups 3 and 4 ♂ on Day 3 (1.5x and 2.2x of control, respectively). These changes were not observed on Day 15.
- PK - SC-65872 was orally absorbed and systemically available at 2 hr post-dose as shown in the following table. The plasma concentrations of SC-65872 and the active metabolite, SC-66905, increased with dose. It appeared that higher plasma concentrations of SC-65872 and lower plasma concentrations of SC-66905 were detected in ♀ when compared to ♂ at equivalent doses.

Dose (mg/kg)		Time	SC-65872 (μg/ml)		SC-66905 (μg/ml)	
♂	♀	(hr)	♂	♀	♂	♀
400	200	2	26.2±0.724	35.2±0.777	8.52±0.628	2.54±0.0799
800	400	2	33.3±2.67	45.9±4.16	11.1±0.777	3.07±0.207
1600	800	2	34.8±2.65	57.5±2.98	11.9±0.744	3.79±0.162

- Gross and Histo-pathology - Drug-induced toxicological changes were limited to the GI. Gross lesions of GI ulceration/perforation with microscopic characteristics of duodenal mucosal erosion/ulceration and chronic active of intestinal serosal surfaces were identified in 2♀ @ 400 mg/kg (Day 3 sacrifice) and 3♀ @ 800 mg/kg (2 on Day 3 and 1 on Day 15 sacrifice) at scheduled terminal sacrifice. GI pathological changes were also observed in 2♀ that were found dead during Days 3 or 4.

Therefore, the NOAEL (no-observable-adverse-effect-level) for SC-65872 was 200 mg/kg in ♀ and undefined (>1600 mg/kg) in ♂.

2.1.1.2. Acute Intravenous Toxicity Study of SC-65872 in the Rat, SA4933; Date: 17-Oct-2000, Document No. P30S4933. (Vol. 1.112)

Study Nº: SA4933
Report Nº: P30S4933/M3099341 (PK)
Study Aim: To evaluate potential acute toxicity in rats following a single iv dose of SC-65872.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0 and 3.5 mg/17.2 ml/ kg/30 min iv
Dosing Frequency: single dose
Animals: ♂ & ♀ CD (IGS) rats, weighing 182-267 g, 8-9 weeks of age, 10/sex/group
Study Location: G.D. Searle & Co., 4901 Searle Parkway, Skokie, IL 60077.
GLP/QAU Compliance: Yes
Study Date: Dosing Initiation - 7/12-13/1999
Day 3 Sacrifice - 7/15/1999
Day 15 Sacrifice - 7/26/1999
Study Design: Two groups (n=10/sex) of rats were given a iv infusion dose of SC-65872 or vehicle as shown in the following table. Animals were sacrificed on Day 3 or Day 15.

Group	Infusion Dose (mg/kg/30 min)	Dose Concentration	Nº of Animals	Nº of Animal Sacrificed	
				Day 3	Day 15
1	0	0	10/sex/group	5/sex/group	5/sex/group
2	3.5	0.2 mg/ml			

The following observations were conducted.

- Mortality and Clinical Signs - Day 1: 10 and 30 min and 2 hr after dosing; Days 2-15: 1x/day.
- Body Weights - Pre-R, Days 1, 3, 8, and 15.
- Food Consumption - Pre-R and 1x/week.
- Hematology and Serum Chemistry - Days 3 and 15 (prior to sacrifice). The following parameters were analyzed.

HEMATOLOGY			
RBC	Mean Corpuscular Hemoglobin (MCH)		WBC/Differential
Hemoglobin (Hb)	Mean Corpuscular Hemoglobin Concentration (MCHC)		Blood Cell Morphology
Hematocrit (Ht)	Mean Platelet Volume	Large Unstained Cells (Activated Lymphocyte,	
Mean Corpuscular Volume (MCV)	Platelet Count	Monocyte, and/or Immature Bone Marrow Cells)	

SERUM CHEMISTRY					
Glucose	Sorbitol Dehydrogenase (SDH)		Alanine Aminotransferase (ALT)		Aspartate Aminotransferase (AST)
Urea Nitrogen	Globulin	Albumin	Triglycerides	Alkaline Phosphatase (ALP)	Sodium
Creatinine	Albumin/Globulin Ratio		Total Bile Acids	Potassium	Chloride
Total Protein	Cholesterol		Total Bilirubin	Calcium	Inorganic Phosphorus

- Necropsy - Days 3 and 15 (5/sex/group). The following tissues were collected and preserved in 10% buffered formalin. Organ weights were not recorded. Bone marrow smears were not prepared. Histopathological examination was not performed.

Large Intestine (Cecum, Colon, Rectum)			Small Intestine (Duodenum, Jejunum, Ileum)			Spleen
Brain	Heart	Stomach	Liver	Kidneys (Both)	Thymus	Injection Site

- PK/TK - Blood was collected within 5 min (targeted for 3 min) post infusion on Day 1. Plasma samples were shipped to [redacted] for the determination of SC-65872 and SC-66905 levels.

Results:

- Clinical Signs and Mortality - One control died 10 min post dose as a results of anesthesia complication with signs of reduced activity, motor incordination, reduced body tone and gasping prior to death. Salivation was noted in 4 Group 2 animals and ventral staining was seen in 1 Group 2 rat.
- Body Weights and Food Consumption - No significant differences in food consumption, mean body weights and body weight gains between groups were recorded.
- Clinical Pathology - There were no significant changes in hematology and serum chemistry parameters.
- PK - Mean (±SE) plasma SC-65872 and the active metabolite, SC-66905, concentration at 3 min post iv 30 min infusion were was shown in the following table. The plasma concentrations of SC-65872 and the active metabolite, SC-66905, increased with dose. It appeared that higher plasma concentrations of SC-66905 was detected in ♂ when compared to ♀. Similar observation was noted in the previous study when rats were given a single oral dose of SC-65872.

Dose (mg/kg)	SC-65872 (μg/ml)		SC-66905 (μg/ml)	
	♂	♀	♂	♀
3.5	3.36 ±0.241	3.78 ± 0.194	0.268 ± 0.0368	0.101 ± 0.009

- Gross- and Histo-Pathology - No treatment-related gross lesions were identified.

Therefore, MTD was not achieved as no treatment-induced changes in any of the monitored parameters.

2.1.1.3. Acute Oral Capsule Toxicity Study of SC-65872 in the Dog, SA4932; Date: 07-Sep-2000, Document No. P30S4932. (Vol. 1.28)

Study Nº: SA4932
Report Nº: P30S4942/M3099340 (TK)
Study Aim: To evaluate potential acute toxicity of SC-65872 following a single oral dose to dogs.
Compound: [redacted]
Vehicle Control: [redacted]

Dose & Route: 0, 60, 240, and 480 mg/kg
Animals: ♂ and ♀ beagle dogs [redacted] 8-9 months of age, weighing 5.6-8.9 kg, 2/sex/group.
Study Location: G.D. Searle, 4901 Searle Parkway, Skokie, IL 60077 [redacted]

GLP/QAU Compliance: Yes
Study Date: Dosing Initiation - 8/30/1999
Day 15 Sacrifice - 9/13/1999
Study Design: Groups of 1-2/sex dogs were given a single oral dose of SC-65872 or vehicle. Animals were sacrificed on Day 15.

Group	Dose (mg/kg)	Nº of Animals
1	0	2/sex
2	60	2/sex
3	240	2/sex
4	480	2/sex

The following observations were conducted.

- Mortality and Clinical Signs - Day 1: 1-2, 3-4, and 7-8 hr after dosing; Days 2-15: 1x/day.
- Body Weights - Pre-R (2x), Days 2, 8, and 14.
- Food Consumption - Pre-R and Days 3-4 and 10-11.
- Hematology and Serum Chemistry - Days 3 and 15. The following parameters were analyzed.

HEMATOLOGY			
RBC	Mean Corpuscular Hemoglobin (MCH)		WBC/Differential
Hemoglobin (Hb)	Mean Corpuscular Hemoglobin Concentration (MCHC)		Blood Cell Morphology
Hematocrit (Ht)	Mean Platelet Volume	Large Unstained Cells (Activated Lymphocyte,	
Mean Corpuscular Volume (MCV)	Platelet Count	Monocyte, and/or Immature Bone Marrow Cells)	

SERUM CHEMISTRY				
Glucose	Albumin	Triglycerides	Alanine Aminotransferase (ALT)	Calcium
Urea	Globulin (Calculated)	Total Bile Acids	Alkaline Phosphatase (ALP)	Sodium
Creatinine	A/G Ratio (Calculated)	Total Bilirubin	Aspartate Aminotransferase (ASP)	Chloride
Total Protein	Cholesterol	Potassium	Inorganic Phosphorus	

- Necropsy - Day 15. The following tissues were collected and preserved in 10% buffered formalin (except for the testes which were fixed in Bouin's). Organ weights were not recorded. Due to no lesions were considered as treatment-related, histological examination was not performed.

Adrenal Gland (Both)	Heart	Small Intestine (Duodenum, Jejunum, Ileum)		Spleen
Bone, Sternum (Including Marrow)		Kidneys (Both)	Lungs (Both)	Stomach
Brain	Injection Site	Liver	Ovaries (Both)	Thymus
Large Intestine (Cecum, Colon, Rectum)		Spinal Cord (Lumbar)	Testes (Both)	Lesions

- PK/TK - Blood was collected on Day 1 from each animal at 2 hr post dosing. Blood samples from Group 1 (Control) were not analyzed. Plasma samples were shipped to [redacted] for the determination of SC-65872 and SC-66905 levels using a validated [redacted]

Results:

- Clinical Signs and Mortality - No death occurred. No remarkable clinical observations were noted.
- Body Weights and Food Consumption - No significant differences in food consumption, mean body weights and body weight gains between groups were recorded.
- Clinical Pathology - There were no significant changes in hematology and serum chemistry parameters.

- PK - SC-65872 was orally absorbed and systemically available at 2 hr post-dose as shown in the following table. The plasma concentrations of SC-65872 and the active metabolite, SC-66905, increased with dose. It appeared that higher plasma concentrations of SC-65872 and SC-66905 were detected in ♀ when compared to ♂.

Dose (mg/kg)	Time (hr)	SC-65872 (μg/ml)		SC-66905 (μg/ml)	
		♂	♀	♂	♀
60	2	2.35	4.92	2.07	3.11
240	2	8.44	13.3	3.66	5.92
480	2	11.3	25.2	8.63	12.7

- Gross- and Histo-Pathology - No treatment-related gross lesions were identified.

Therefore, the NOAEL for SC-65872 was >480 mg/kg and MTD was not achieved.

2.2. REPEATED DOSE TOXICITY STUDIES

2.2.1. MOUSE STUDIES

2.2.1.1. Two-Week Range-Finding Dietary Admix Toxicity Study of SC-65872 in the Mouse (EX4473); Date: 11-Jun-1996, Document No. P30E4473. (Vol. 1.29)

Study Nº: EX4473/EHL96028
Report Nº: P30E4473/M3096121
Study Aims: To evaluate the potential of dietary admix for administration of SC-65872 to mice for 2 weeks and to provide information for the selection of dosages for a 13-week study in the mouse
Compound: [redacted]
Dose and Route: [redacted]
Animal: CD-1 mice, ~5 weeks of age, weighing 20.5-31.1 g, 10/sex/group for toxicology study and 21/sex/group for PK study.
Study Site: [redacted]
Study Date: 3/7/1996 - 3/22/1996 (Day 16)
GLP/QAC Compliance: No
Study Design: The animal groupings and dose assignments are shown in the following table.

Toxicology Groups					PK Study Groups		
Group	Intended Dose (mg/kg/day)	Actual Dose (mg/kg/day)		Nº mice/sex	Group	Dose (mg/kg/day)	Nº mice/sex
		♂	♀				
N	0	0	0	10			
1	30	25-29	24-29	10	5	30	21
2	100	95-105	97-117	10	6	100	21
3	300	260-297	259-354	10	7	300	21
4	1000	736-1118	840-1129	10	8	1000	21

The following observations were conducted:

- Mortality and Clinical Signs - 2x/day.
- Body Weights, and Food Consumption - pretreatment and 2x/week.
- Clinical Pathology - Days 15 (♂) & 16 (♀).
- Necropsy and Histopathology - Days 15 (♂) & 16 (♀). At the scheduled necropsies, the following tissues (when present) or representative samples were collected from each Toxicology animal and

preserved in 10% formalin and organs marked with an asterisk were weighed. Paired organs were weighed together.

brain	*cecum	*colon	heart	small intestine (duodenum, jejunum, ileum)	
*liver	lungs	*stomach	testes (both)	and thymus	*kidneys (both)

- PK - Days 4 and 13/14. Blood samples were collected at 0, 5, 11, 15, 20, and 24 hr post dose.

Results:

- Mortality and Clinical Signs - One Group 6 female died on Day 10. Necropsy was not performed on this animal. No remarkable clinical signs were noted.
- Body Weights, and Food Consumption - Lower mean accumulative weight gains were noted for both males (↓31%) and females (↓59%) in the high dose group (1000 mg/kg/day). High dose males had significant lower (↓23%) food consumption during days 1-5.
- Clinical Pathology - Mild decreases (↓15-16%) in red blood cell counts, hemoglobin concentrations, and hematocrit were identified in females given 1000 mg/kg/day and a high dose male. The changes in this male, along with higher absolute neutrophil count, were secondary to enteric blood loss and inflammation associated with test article-related colonic ulceration. The cause of the hematological changes in ♀ was not identified, although enteric blood loss associated with test article-related intestinal injury that was not evident macro- and microscopically. Due to insufficient samples from all females, the levels of sorbitol dehydrogenase (SDH), total bilirubin, cholesterol, glucose, total bile acid, and triglycerides were not determined. SC-65872 associated changes in the clinical chemistry parameters, primarily seen in mice at 1000 mg/kg, are listed in the following table.

Parameters	Dose (mg/kg/day)			
	300		1000	
	♂	♀	♂	♀
ALT	↑47%	↑54%	↑128%	↑24%
SDH	-	-	↑53%	ND
Cholesterol	-	-	↑58%	ND
Triglycerides	-	-	↑96%	ND
Potassium	-	-	↓25%	↓19%

- Organ Weights - Significantly higher absolute (19-79%) and relative liver weights (↑21-89%) were seen animals at ≥300 mg/kg/ml.
- Necropsy and Histopathology - SC-65872 associated intestinal injury characterized by mucosal necrosis or ulceration in the colon was identified in 2/10 ♂ @ 1000 mg/kg/day. These findings are consistent with GI toxicity associated with administration of traditional NSAIDs. Centrilobular hepatocellular hypertrophy (moderate→marked in ♂ and mild→moderate in ♀) was observed in animal given ≥300 mg/kg/day. Increased mitoses in centrilobular areas were also noted in livers of males and females @ 1000 mg/kg/day. Increased extramedullary hematopoiesis was identified in sections of the enlarged spleens collected from ♂ @ 300 and 1000 mg/kg/day.
- PK - SC-65872 was systemically available following dietary admix administration to mice. Sex-difference in drug metabolism was apparent with males attaining approximately 2 to 3-fold higher plasma concentrations compared with females given equivalent dosages. Plasma concentrations of SC-65872 and its active metabolite, SC-66905, increased approximately proportionally with dosage. Plasma concentrations of SC-66905 in males were comparable to females. The mean C_{max} and AUC values for SC-65872 and its active metabolite SC-66905 on Days 13/14 are shown in the following table.

Dose mg/kg/day	SC-65872				SC-66905			
	C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)	
	♂	♀	♂	♀	♂	♀	♂	♀
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

Therefore, the NOAEL for SC-65872 was 100 mg/kg/day for ♂ and 300 mg/kg/day for ♀ based on pathological findings of GI mucosal necrosis/ulceration in ♂ @ 1000 mg/kg and moderate to marked centrilobular hepatocellular hypertrophy in ♂ @ ≥300 mg/kg and ♀ @ 1000 mg/kg/day.

2.2.1.2. Thirteen Week Range-Finding Dietary Admix Toxicity Study of SC-65872 in Mice (EX4514); Date: 05-Jun-1997, Document No. P30E4514. (Vol. 1.30-32)

Study Nº: EX4514/EHL 96084
Report Nº: P30E4514, M3097018 (Companion PK report)
Study Aims: To evaluate the toxic effects of SC-65872 administered as a dietary admix and to provide information for the selection of dosages for a carcinogenicity study in the mouse.
Compound: [redacted]
Dose and Route: 0, 30, 100, 300, and 600 mg/kg/day for ♂, and 0, 60, 200, 600, and 1000 mg/kg/day for ♀, po via dietary admix.
Animal: CD-1 mice, ~8 weeks of age, weighing 23.8-37.5 g, 20/sex/group for toxicology study and 60/sex/group for PK study.
Study Site: [redacted]
Study Date: 6/1/1996 - 9/13/1996 (Day 95)
GLP/QAC Compliance: No
Study Design: Male and female CD-1 mice were randomly assigned to one of 9 dosage groups as shown in the following table. Dosages used in this study were selected based on data from a 2-Week Range-Finding Study (Searle Study EX4473; EHL Study 96028). Due to high mortality observed in animals at the highest dosages (♂: 600 mg/kg/day; ♀: 1000 mg/kg/day), the remaining animals in this dose group were sacrificed on Day 32.

Toxicology Study Groups						Pharmacokinetic Study Groups			
Group	Intended Dose (mg/kg/day)		Calculated Dose (mg/kg/day)		Nº mice/Sex	Group	Intended Dosage (mg/kg/day)		Nº mice/Sex
	♂	♀	♂	♀			♂	♀	
N	0	0	0	0	20/sex				
1	30	60	26.08-30.08	50.99-62.92	20/sex	5	30	60	60/sex
2	100	200	87.86-102.95	174.34-215.11	20/sex	6	100	200	60/sex
3	300	600	256.42-316.03	513.24-632.14	20/sex	7	300	600	60/sex
4	600	1000	516.73-608.76	770.38-978.52	20/sex	8	600	1000	60/sex

The following observations were conducted:

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - Days 0 and 9, and 1x/week thereafter.
- Body Weights, and Food Consumption - 2x pretreatment and 1x/week.
- Clinical Pathology - Days 32 (group 4 only) and 91-95 (Groups N, 1-3).
- Necropsy and Histopathology - Day 32 for Group 4 and Days 91-95 for Groups N and 1-3. At the scheduled necropsies, the following tissues (when present) or representative samples were

collected from each Toxicology animal and preserved in 10% formalin and organs marked with an asterisk were weighed. Paired organs were weighed together.

Gross Lesions	Aorta	Bone, Sternum (Including Marrow)			* Brain
*Adrenal Glands (Both) (Weighed Post Fixation)		Bone, Femur (Including Articular Surface)			Esophagus
Bone Marrow Smear (Except Animals Found Dead)		*Epididymides		Eyes (Both) With Harderian Gland	
Rectum	*Cecum	*Colon		Intestine, Small (Duodenum, Jejunum, Ileum)	
*Liver with Gall Bladder (Drained)	*Lungs (Both)		Lymph Node, Submaxillary		Lymph Node, Mesenteric
Mammary Gland (Females Only, Attached to Skin)		Pancreas		*Pituitary Gland (Weighed Post-Fixation)	
Salivary Gland, Submaxillary	Sciatic Nerve	Skeletal Muscle	Seminal Vesicle	skin (caudal, abdominal region)	
Spinal Cord (Lumbar)	*Spleen	*Stomach	*Testes (Both)		*thymus
*Thyroid Glands (Both), (Weighed Post-Fixation)		Trachea	Urinary Bladder		*Uterus
Vagina (With Cervix).	Tongue	*Ovaries (Both)	*Kidneys (Both)		*heart

- PK - Days 7/8 and 28/29 (Groups 5-8) and Days 87/88 (*prostate Groups 5-7). Blood samples were collected at 0, 5, 11, 15, 20, and 24 hr post dose.

Results:

- Mortality and Clinical Signs - High mortality as shown in the following table was noted for the high dose group. Piloerection, decreased defecation, distended abdomen, and intra-abdominal swelling were major signs were seen in animals that died or were sacrificed moribund. Treatment induced GI toxicity (ulceration/erosion or perforation and associated peritonitis) was the cause of death or moribund sacrifice.

Group	Unscheduled Deaths by Day 32		Total Unscheduled Deaths	
	♂	♀	♂	♀
N	0	0	0	1
1	0	0	0	0
2	0	1	3	4
3	1	7	8	13
4	8	10	8	10

- Body Weights, and Food Consumption - Group 4 males had significant lower body weight (↓6-10%) and weight gains (↓49-84%) during Weeks 2-4 with decreased food consumption during Weeks 1-3. Groups 4 females had significant reduction in food consumption during the whole study and lower body weight gains. There were no SC-65872 -related changes in mean body weights, body weight gains, or food consumption for animals in Groups 1, 2 & 3.
- Hematology - Elevated PMN (polymorphonuclear neutrophil) (↑63-65%), slightly decreased RBC (↓7-9%), Hb (hemaglobulin) (6-9%) and Ht (hematocrit) (↓7-8%), and significantly increased platelet count were noted in Groups 2 & 3 male. These changes were secondary to the SC-65872 induced GI toxicity.
- Clinical Chemistry - Slight increases in ALT (↑73%) were noted for ♂ @ 300 mg/kg/day males and ♀ @ 200 and 600 mg/kg/day. Elevated SDH (↑62%) was seen in Group 3 ♂ & ♀. Group 2 and 3 mice (♂ & ♀) had slightly decreased total bilirubin (↓34-58%) and albumin (↓5-11%). A significant decrease in potassium (↓28%) was observed in ♀ @ 600 mg/kg/day females.
- Organ Weights - Dose-dependent decreases in absolute and relative ovary weights were noted in ♀ @ ≥60 mg/kg/day. The follicular development was essentially normal in these animals. It has been shown that COX-2 is induced in the pre-ovulatory follicles (from granulosa cells) and is involved in the control of follicular rupture during the ovulation process. Therefore, COX-2 inhibition by exaggerated doses of SC-65872 might have resulted in decreased corpora lutea formation. Inhibition of ovulation is also associated with other NSAIDs. Dose-related increases in liver weights (absolute weights and/or organ-to-terminal body weight ratios) were identified in ♂ @ 100 and 300 mg/kg/day and ♀ @ 60, 200, and 600 mg/kg/day. Test article-related increases in

adrenal weights were observed in Group 2 & 3 mice (♂ & ♀). Increased thyroid weights was also identified in ♂ @ 100 and 300 mg/kg/day.

- Gross Pathology - Treatment-related gross pathological changes were limited to the GI tract. Lesions were characterized as ulceration/necrosis and/or perforation in GI tract (most commonly in the colon) with abdominal adhesions. The incidence of SC-65872 caused GI changes is shown in the following table. Enlarged spleens were noted in control and SC-65872 treated groups.

Group	Unscheduled Deaths		Scheduled Terminal Sacrifice	
	♂	♀	♂	♀
N	0	0	0	0
1	0	0	0	0
2	3	4	0	1
3	7	12	0	0
4	7	9	1	0

- Histopathology - Microscopic examinations were not conducted on Groups 3 & 4 animals. Microscopic changes were seen mainly in GI tract, liver and ovaries. Lesions seen in the GI tract were mucosal degeneration/necrosis or erosion/ulceration in the stomach (pylorus), ileum, and colon with or without peritonitis. GI pathological changes associated with SC-65872 treatment is consistent with toxicity seen with administration of NSAIDs. The changes seen in the ovary were characterized by a decrease in leuteal tissue (↓ in size and Nº of copra lutea). Slight to mild and multifocal to diffuse hepatocellular hypertrophy was observed in the livers of Group 2 mice. The following table shows the incidence of microscopic pathological changes in the GI tract, liver and ovary of scheduled sacrificed animals. Histophathological changes observed in Group 2 mice that died during the study included ileal and/or colonic necrosis/ulceration. Subcutaneous inflammation and necrosis (abscessation) was seen in the control ♀ that died during the study.

Microscopic Changes	Group N		Group 1		Group 2	
	♂	♀	♂	♀	♂	♀
GI - necrosis, erosion/ulceration (Total)	0	0	0	0	6/20	9/20
Stomach (pylorus)					1/20	2/20
Ileum					3/20	3/20
Colon					3/20	3/20
Liver - slight→mild, multifocal→diffuse hepatocellular hypertrophy (centrilobular)	0	0	0	0	13/20	8/20
Ovary - ↓ size and Nº of corpora lutea	-	1/20	-	2/20	-	11/20

- PK - Plasma concentrations of SC-65872 increased with dose. Gender difference in the metabolism were noted as higher AUC and C_{max} values were seen in ♀ when similar dose were given (600 mg/kg/day). The mean AUC and C_{max} values for SC-65872 and its active metabolite, SC-66905, on Days 7, 28, and 87 are presented in the following table.

Dose mg/kg/day	Sex	SC-65872						SC-66905					
		AUC_{0-24} (μg•hr/ml)			C_{max} (μg/ml)			AUC_{0-24} (μg•hr/ml)			C_{max} (μg/ml)		
		Day 7	Day 28	Day 87	Day 7	Day 28	Day 87	Day 7	Day 28	Day 87	Day 7	Day 28	Day 87
30	♂	3.94	5.55	4.59	0.202	0.351	0.264	1.53	2.69	2.63	0.117	0.167	0.141
60	♀	3.18	1.86	3.03	0.195	0.169	0.162	4.45	4.69	5.70	0.345	0.243	0.280
100	♂	7.68	11.4	9.66	0.519	0.729	0.846	3.63	5.35	5.49	0.321	0.304	0.489
200	♀	7.08	7.9	7.92	0.603	0.532	0.593	11.1	11.2	12.5	0.607	0.666	0.661
300	♂	17.2	24.3	14.3	1.09	1.87	1.26	11.1	12.3	9.69	0.679	0.678	0.751
600	♀	17.9	17.9	ID	1.62	1.99	1.39	24.1	24.1	ID	1.45	1.66	1.22
600	♂	23.9	27.1	NA	1.72	2.29	NA	17.8	17.8	NA	0.940	1.09	NA
1000	♀	21.5	24.8	NA	1.57	1.53	NA	35.1	36.3	NA	2.18	1.78	NA

ID = Insufficient samples, data not calculated; NA = Not available, animals sacrificed at an interim date.

Based upon the presented information, NOAEL for SC-65872 was 30 mg/kg/day for ♂ and could not be determined for ♀ as microscopic changes in GI and liver in ♂ @ ≥100 mg/kg/day and ♀ @ ≥200 mg/kg as well as in ♀ @ ≥60 mg/kg/day.

2.2.1.3. Dietary Admix Toxicity Study of SC-65872 in the Female Mouse (EX4624); Date: 23-Mar-2000, Document No. P30E4624. (Vol. 1.33-34)

Study Nº: EX4624
Report Nº: P30E4624/M3097294 (PK)
Study Aim: To determine effects of SC-65872 on reproductive organs of female mice following 4, 16, 28, 60, or 98 days of treatment and the reversibility of any effects 28 days following the 98 day treatment period.
Compound: [redacted]
Dose & Route: 0, 30, 60, 200 mg/kg po via diet mix
Animals: ♀ CD-1 mice ([redacted]) ~10-11 weeks of age, weighing 28.3-33.0 g, 60/group for toxicology study and 40/group for PK study
Study Location: G.D. Searle, 4901 Searle Parkway, Skokie, IL 60077 [redacted]
GLP/QAU Compliance: No.
Study Date: 3/31-4/1/1997 - 7/7/1997 (terminal sacrifice) or 8/4/1997 (reversal phase sacrifice)
Study Design: Mice were randomly assigned into 7 treatment groups as shown in the following table.

Group	Dose (mg/kg)	Nº of ♀ at Sacrifice						
		Nº of ♀	Day 5 (Week 1)	Day 17 (Week 3)	Day 29 (Week 5)	Day 61 (Week 9)	Day 99 (Week 15)	Reversal Day 29 (Week 19)
Toxicology Animals								
1	0	60	10	10	10	10	10	10
2	30	60	10	10	10	10	10	10
3	60	60	10	10	10	10	10	10
4	200	60	10	10	10	10	10	10
Pharmacokinetic Animals								
5	30	40						
6	60	40						
7	200	40						

The following observations were conducted:

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - Pre-R and 1x/week thereafter.
- Body Weights, and Food Consumption - 2x pretreatment and 1x/week.
- Serum Hormone Determination - Blood samples were collected from 10 animals/sex in Groups 1, 2, 3 and 4 on Days 5, 17, 29, 61, 99, and Reversal Day 29. The following serum hormone levels were determined: luteinizing hormone (Day 99), follicle stimulating hormone (Day 99), estradiol (Day 61), progesterone (Day 61), prolactin (Day 99), cortisol (Day 29), corticosterone (Day 29). Serum samples collected from females sacrificed on Day 5 and 17, or after reversal, were not analyzed.
- PK/TK - Weeks 1 and 4 (Days 3-4 and 25-26, respectively). Blood was collected from 3 animals/group (survival permitting) from Groups 5, 6 and 7 for plasma levels of SC-65872 and SC-66905 determination.
- Necropsy and Histopathology - Days 5 (Week 1), 17 (Week 3), 29 (Week 5), 61 (Week 9), 99 (Week 15) and Day 29 of reversal (study Week 19, reversal Week 4); 10/sex/group in Groups 1-

4. At the scheduled necropsies, the following tissues were collected from each Toxicology animal and preserved in [redacted] fixative and organs marked with an asterisk were weighed. Paired organs were weighed together. The kidney and adrenal gland from Groups 1 & 4 sacrificed on Days 29, 61, 99, and Reversal Day 29 were preserved in half-strength Karnovsky's fixative and processed for electron microscopy. Ovaries, uterus, vagina, and pituitary from the Groups 1 & 4 and ovaries from the Groups 2 & 3 sacrificed on Days 5, 17, 29, 61, 99, and Reversal Day 29 were examined microscopically examined microscopically. In addition, adrenals from the Groups 1 & 4 sacrificed on Days 5 and 17 were processed for microscopic examination.

*adrenal glands (both)	Lesions	*ovaries (both)	*uterus
*kidneys (both) (weighed on Days 29, 99, and Reversal Day 29		*pituitary gland	vagina

Results:

- Calculated Doses - The dosages each animal received were calculated based on the intended test article concentration in the diet, and the body weight and food consumption values. The calculated dosages for each group during Weeks 1-6 are summarized in the following table.

Intended Dose (mg/kg)	Calculated Dose (mg/kg)/% Intended Dose											
	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
30	30.2	101%	31.3	104%	28.4	95%	29.9	100%	30.8	103%	29.9	100%
60	57.2	95%	61.9	103%	62.4	104%	58.4	97%	65.3	109%	57.2	95%
200	189	95%	214.	107%	206	103%	193	97%	199	100%	200	100%

- Mortality and Clinical Signs - Treatment-related deaths was noted in 6♀ @ 200 mg/kg/day as a result of GI toxicity (perforations of ileum, cecum, or colon with or without peritonitis). One (60 mg/kg/day) accidental death was observed on Day 11. There were no treatment-related changes in physical examination.
- Body Weights, and Food Consumption - No remarkable changes in body weights, body weight gains or food consumption.
- Estrous Cycle Evaluation - No effects on estrous cycle length were noted in ♀ @ 200 mg/kg/day.
- Serum Hormone Levels - No treatment-related changes in the levels of LH, FSH, estradiol, progesterone, prolactin, cortisol, corticosterone were noted.
- Necropsy -

  Organ Weights - Transient increases in adrenal weights and adrenal to body weight ratios by 22-38% and 15-35%, respectively in the high-dose group were recorded during Weeks 1, 3, 5, and 9. Reduced ovary weights and ovary to body weight ratios by 16-21% were noted on Weeks 3, 9, 15 and 19. On contrast, increased ovary weights (↑35%) and ovary to body weight ratios (↑30%) were observed in the high-dose group on Week 5. Slightly reduced uterus weights and uterus to body weight ratios were also noted in the high dose group.

  Gross Pathology - GI related gross changes with characteristics of intestinal perforations in ileum, cecum, or colon and associated peritonitis were noted in 6 @ 200 mg/kg that died during the study.

  Histopathology - Histopathological examination were not performed on the animals that died during the study. Treatment-related microscopic changes characterized by the reduction in size and number of corpora lutea were identified in the ovary of several animals @ 200 mg/kg/day. These findings were reversible as comparable luteal tissue in control and high-dose animals sacrificed after a 4-week of recovery. The incidence of luteal changes for each group is summarized in the following table.

Groups	Dose mg/kg	Week 1[a]	Week 3[a]	Week 5[b]	Week 9[a]	Week 15[a]	Week 19	Total No. Affected
1	0	1/10	1/10	0/10	0/10	0/10	0/10	2
2	30	1/10	1/10	0/10	0/10	0/10	0/10	2
3	60	0/10	0/10	0/10	0/10	0/10	0/10	0
4	200	2/10	3/10	5/10	2/9	2/8	0/7	15

[a] Decreased luteal tissue; [b] Increased luteal tissue.

EM - No apparent SC-65872 attributable changes in the adrenal and kidney ultrastructures were noted in 4 Group 4 ♀ sacrificed on Day 29 as stated in the study report.

- PK - Plasma concentrations of SC-65872 increased with dose. The mean AUC and C_{max} values for SC-65872 and its active metabolite, SC-66905, on Days 3 and 25 are presented in the following table.

Dose mg/kg/day	SC-65872				SC-66905			
	AUC_{0-24} (μg•hr/ml)		C_{max} (μg/ml)		AUC_{0-24} (μg•hr/ml)		C_{max} (μg/ml)	
	Day 3	Day 25	Day 3	Day 25	Day 3	Day 25	Day 3	Day 25
30	2.70	2.53	0.199	0.192	3.49	3.57	0.272	0.276
60	5.02	4.45	0.316	0.311	5.71	5.54	0.362	0.413
200	15.9	16.0	1.09	1.45	17.4	16.1	1.15	1.32

Therefore, SC-65872, at a dose of 200 mg/kg/day, caused GI injury, transient increases in adrenal weights and adrenal to body weight ratios, and reversible reduction in size and number of corpora lutea following oral treatment via dietary admix for 98 days with a 4-week reversal phase.

2.2.2. RAT STUDIES

2.2.2.1. Range-Finding Toxicity Study (Escalating Dose Design) With SC-65872 and SC-64933 in the Rat; Date: 20-Feb-1996, Document No. PSA96S-30-EX4405. (Vol. 1.19, p. 1)

Study Nº: EX4405
Report Nº: PSA96S-30-E4405 and MRC95S-30-950226 (Companion PK Study)
Study Aim: To identify the potential target organs or dose limiting toxicity and to evaluate the potential for auto-induction and tolerance following repeated dosing by oral gavage.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 50, 100, 200, 300, or 400 mg/10 ml/kg/dose, bid po (by gavage) for a total of 30 times over 16 days (Phase I Study, dose-escalation with 3-day escalation intervals) or for 5 days (Phase II Study)
Animals: ♂ & ♀ CD rats [redacted] ~7 weeks of age, weighing 170-250 g, 3 or 5/sex/group.
Study Location: G.D. Searle; 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: N/A
Study Date: Phase I study - 7/5/95 - 7/21/95 (Day 17).
Phase II study - 8/3/95 - 8/9/95 (Day 7).
Study Design: The study was conducted in two phases. Animal group and dose assignments were shown in the following table. Phase I was a dose-escalation study with 3-day escalation intervals.

Group	Study Days	Treatment	Dose (mg/kg)	Dose/Day (mg/kg/day)	Nº Animals	Group	Treatment	Dose (mg/kg)	Dose/Day (mg/kg/day)	Nº Animals
Phase I Dose Escalation Schedule						**Phase II Dosing Schedule (5-Day Repeated Does)**				
1	1-16	Vehicle	-	-	5♂ & 5♀	1	Vehicle	-	-	3♂ & 3♀
2	1-4	SC-65872	50	100	5♂ & 5♀	2	SC-65872	300	600	3♂
	4-7	SC-65872	100	200	5♂ & 5♀	2	SC-65872	100	200	3♀
	7-10	SC-65872	200	400*	5♂ & 5♀	3	SC-65872	400	800	3♂
	10-13	SC-65872	300	600	5♂	3	SC-65872	200	400	3♀
	13-16	SC-65872	400	800	5♂					
3	1-16	SC-65872	50	100	5♂ & 5♀					

* Due to toxicity, the ♀ were held at this dosage for the remainder of the study.

The following parameters were evaluated.

- Clinical Observation & Mortality - 1x/day during Pre-R and 2x/day during treatment.
- Food Consumption & Body Weight - Pre-R and 1x/day.
- Clinical Pathology -
  - Hematology - Phase I study: Day 17; Phase II: not performed.
  - Clinical Chemistry - Phase I study: Day 17; Phase II: Day 7.

  The parameters evaluated during these studies are presented in the following table.

HEMATOLOGY	CLINICAL CHEMISTRY	
WBC/Differential	Alanine Aminotransferase (ALT)	Glucose
RBC	Albumin	Inorganic Phosphorus
Hemoglobin (Hb)	Alkaline Phosphatase (ALP)	Potassium
Hematocrit (Ht)	Aspartate Aminotransferase (AST)	Sodium
Mean Corpuscular Volume (MCV)	Calcium	Sorbitol Dehydrogenase (SDH)
Mean Corpuscular Hemoglobin (MCH)	Chloride	Total Bile Acids
Mean Corpuscular Hemoglobin Concentration	Cholesterol	Total Bilirubin
Mean Platelet Volume	Creatinine Urea	Total Protein
Platelets	Globulin	Triglycerides

- Necropsy Gross Pathology and Histopathology -

  Phase I: Day 17. All surviving animals were necropsied and the following listed tissues or representative samples were collected from controls and escalating dose groups only. Samples were preserved in 10% neutral buffered formalin. Tissues designated with an asterisk were weighed at scheduled sacrifice; liver from Group 3 (fixed dose) rats was weighed. Paired organs were weighed together. The parathyroids were weighed with the thyroids and were examined microscopically if they were included in the thyroid sections. Approximately 5 g of liver from all Phase I rats was flash frozen in liquid nitrogen and stored at -70°C for liver enzyme and cytochrome P-450 measurements.

Bone Marrow Smear (Except for Animals Found Dead)		*Lungs (Both)	*Spleen
*Brain	*Kidneys (Both)	Lymph Node, Submaxillary	*Thymus
*Heart	*Liver	Lymph Node, Mesenteric	*Testes
Intestine, Small (Duodenum, Jejunum, Ileum)		Ovaries (Both)	*Thyroid Glands (Both)
Intestine, Large (Cecum, Colon)		Pancreas	Urinary Bladder

  Phase II: Day 7. Only the liver and kidney weighed. Tissues that were identified during macroscopic evaluation as potential target organs were collected.
- PK/TK - Plasma drug levels were determined by [redacted]

  Phase I : Days 4, 7, 10, 13, 16 and 17 at 3 and 24 hr post dosing.

  Phase II: Days 6 and 7 at 3 and 24 hr post dosing.

Results:

- Clinical Observation & Mortality - Three ♀ were sacrificed at moribund in the Phase I study. One death occurred on Day 10 in the fixed dose group during blood collection due to anesthetic

overdose. The other two deaths (one on Day 12 in dose escalation group after receiving 400 mg/kg/day, and one on Day 16 in fixed dose group) were treatment-related by the evidence of perforated jejunal ulcers with secondary peritonitis that were identified in both animals during necropsy. One ♂ @ 600 mg/kg/day was found dead on Day 4 of Phase II study due to treatment caused GI toxicity (a perforated duodenal ulcer and secondary fibrinous peritonitis). These animals had clinical signs of rough coat, reduced activity, reduced fecal output, and ventral staining/wetness prior to death. Decreased feces were also observed in some animals in both Phase I & II studies.

- Food Consumption & Body Weight - Lower food consumption (↓19-35%) was observed in ♀ in dose escalation group throughout Phase I study. Similar observation (↓ food intake by ~21%) was noted in ♀ @ 100 mg/kg/day (fixed dose) during Days 1-4 of Phase I study. Both ♂ & ♀ in the Phase II study had lower (↓25-48%) food consumption. Mean body weights and body weight changes for ♂ rats in the Phase I study were not affected. In contrast, ♀ in the dose escalating group had lower body weights by 6-12% on Days 4-16 of Phase I study. A significant ↓ in body weight gain was noted for ♂ @ 600 mg/kg/day on Day 3, ♂ @ 600 & 800 mg/kg/day on Day 4, and ♀ @ 400 mg/kg/day on Day 2 of Phase II study.
- Liver Enzyme and Cytochrome P-450 Measurements - Fatty acyl Co-A oxidase (FACO) activity in liver homogenates (an indicator of peroxisome proliferation) was not altered. Liver cytochrome P-450 content was increased (1.3-1.6x) in SC-65872 treated ♂ & ♀ in the Phase I study. Western blot analysis of cytochrome P-450 gene family showed a significant induction of cytochrome P-450 2B subfamily in pooled liver samples from rats of the Phase I study. Slight changes in other gene families were seen and a summary table of analysis of results for cytochrome P-450 gene families is shown below.

Group	Cytochrome P-450 Gene Family									
	1A1		2B1, 2B2		2C11		3A1		4A1	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Esc. Dose	↔[a]	0.9[b]	27.5	8.4	0.8	-[c]	1.4	1.9	1.2	1.3
Fixed Dose	0.7	1.6	8.0	5.6	0.8	-	1.1	1.7	0.9	1.1

[a] No change observed.
[b] Values expressed as fold change relative to control.
[c] Not detected.

- Clinical Pathology - Increases in the WBC counts (3.0x) with ↑ in absolute lymphocyte (2.5-2.9x) and neutrophil (3.1-4.7x) counts were noted in ♂ @ escalating dose 100-800 mg/kg/day and fixed dose 100 mg/kg/day of Phase I study. Similarly, ↑ in WBC (1.4-2.2x) and absolute lymphocyte (1.7-2.5x) but not neutrophil counts were observed in the ♀ of Phase I study. Slight but not biological significant ↓ in RBC counts, hematocrit and Hb were identified in the ♀ @ escalating dose (100-400 mg/kg/day) of Phase I study. The following changes that might be to treatment-related were identified in serum chemistry profiles of the Phase I and II studies.

		Chol.	Trigly.	Total Protein	Albumin	Globulin	TBA	Ca^{2+}	Cl^-	TBil	SDH	ALP
PHASE I STUDY (Day 17)												
♂	100→800 mg/kg	↑1.6x	↑1.8x		↓14%	↑1.2x			↓6%		↑1.9x	
♀	100→400 mg/kg	↑2.4x	↑4.7x	↓13%	↓33%	↑1.5x	↑2.6x	↓7%			↑2.0x	
PHASE II STUDY (Day 7)												
♂	600 mg/kg	↑2.1x		↓18%	↓17%	↑1.5x	↑1.7x					
	800 mg/kg	↑4.4x	↑1.9x		↓33%	↑1.5x	↑1.4x					
♀	200 mg/kg	↑1.5x	↑5.6x	↓9%	↓21%		↑3.2x				↑2.0x	
	400 mg/kg	↑1.4x	↑6.8x	↓19%	↓42%		↑5.3x	↓7%		↑1.9x	↑3.2x	↑1.9x

Chol. = Cholesterol; Trigly. = Triglyceride; TBA = Total Bile Acid; SDH = Sorbitol Dehydrogenase; ALP= Alkaline Phosphatase; Tbil = Total Bilirubin.

- Organ Weights - Both ♂ and ♀ of Phase I study had ↑ relative and absolute liver, kidney and spleen weights by ~1.5 x over controls. Increased absolute and relative liver weights (~1.3x) were observed for both ♂ and ♀ of Phase II study.
- Toxicokinetics - Mean plasma concentrations (±SE) of SC-65782 and its active metabolite, SC-66905, in ♂ and ♀ rats during the Phase I and Phase II studies are shown in the following table. Both SC-65872 and SC-66905 plasma concentrations non-proportionally increased with dose. **At similar dose levels, plasma SC-65872 concentrations were 2x higher in the ♀ than in the ♂.**

Day	Time (hr)	Dose (mg/kg/day)		Plasma SC-65872 Levels (μg/ml)		Plasma SC-66905 Levels (μg/ml)	
		♂	♀	♂	♀	♂	♀
PHASE I STUDY							
4	3	100	100	9.23 ± 0.44	26.60 ± 3.8	4.94 ± 0.33	5.36 ± 0.54
7	3	200	200	14.90 ± 1.00	34.70 ± 4.3	7.85 ± 0.24	10.90 ± 2.00
10	3	400	400	21.30 ± 2.30	38.80 ± 5.1	12.00 ± 1.00	17.10 ± 2.00
13	3	600	400	26.70 ± 3.20	32.60 ± 1.9	15.00 ± 3.00	14.40 ± 4.30
16	3	800	400	30.20 ± 5.30	33.80 ± 2.4	18.70 ± 4.60	20.70 ± 6.50
17	24	800	400	3.56 ± 1.72	9.78 ± 2.48	4.72 ± 1.85	10.20 ± 2.40
4	3	100	100	8.75 ± 0.55	24.40 ± 1.50	4.78 ± 0.18	4.93 ± 0.57
7	3	100	100	9.80 ± 0.85	21.00 ± 0.50	4.97 ± 0.21	3.25 ± 0.34
10	3	100	100	9.25 ± 0.85	19.50 ± 0.80	4.34 ± 0.27	3.23 ± 0.11
13	3	100	100	8.47 ± 0.60	17.60 ± 1.10	3.38 ± 0.24	3.12 ± 0.34
16	3	100	100	7.99 ± 1.38	17.70 ± 3.20	2.72 ± 0.23	3.71 ± 1.28
17	24	100	100	0.13 ± 0.10	0.77 ± 0.15	0.19 ± 0.10	0.98 ± 0.24
PHASE II STUDY							
6	3	600	200	28.6 ± 0.60	30.80 ± 3.50	10.30 ± 0.60	6.73 ± 1.54
6	3	800	400	30.9 ± 3.10	57.30 ± 7.30	23.40 ± 4.90	19.20 ± 4.10
7	24	600	200	10.6 ± 4.80	4.60 ± 2.25	6.99 ± 0.70	5.01 ± 2.40
7	24	800	400	25.2 ± 10.9	47.10 ± 5.90	21.80 ± 8.30	26.90 ± 6.60

- Necropsy and Histopathology Findings -

  Phase I Study: Two ♀ sacrificed at moribund had fibrinous peritonitis with extensive adhesions throughout abdominal cavity secondary to multiple perforated ulcers in the small intestine. In the survival animals, a single transmural jejunal ulcer was identified in one ♀ @ 100-400 mg/kg/day group at necropsy. Microscopic examinations of survival animals in escalating dose group showed that lesions, ulcer and/or transmural inflammation, consistent with drug-related were identified in 3/4♀. Slight to mild centrilobular hepatocellular hypertrophy correlated with ↑ liver weights and ↑ cytochrome P-450 contents was noted in 4/4♀ and 5/5♂. Slight to mild subcapsular changes was observed in 2/5♂ and 2/4♀. In the fixed dose group, microscopic examination was limited to the livers. Slight centrilobular hepatocellular hypertrophy was apparent in 4/5♂ and 3/3♀.

  Phase II Study: The gross lesions identified in the ♂ @ 600 mg/kg/day that died on Day 4 were a single perforated ulcer in the proximal duodenum-distal pyloric junction and fibrinous peritonitis. Test-article related gross changes were limited to the intestinal tract. Focal ulcers or with fibrinous peritonitis were found at pyloric-duodenal junction or in the jejunum in ½♂ @ 600 mg/kg/day and 3/3♂ @ 800 mg/kg/day. Small intestinal ulcers or with secondary inflammation of serosa and mesentery (peritonitis) were observed in 3/3♀ @ 400 mg/kg/day but not ♀ @ 200 mg/kg/day. Multiple chronic erosions of the non-glandular gastric mucosa were also seen in 1/3♂ @ 800 mg/kg and 3/3♂ @ 400 mg/kg/day. Histopathological examination of tissues from Phase II study was not done.

2.2.2.2. Two Week Range-Finding Toxicity Study with SC-5872 in the Rat (EX 4511); Date: 10-Dec-1996, Document No. P30E4511. (Vol. 1.36)

Study Nº: EX 4511
Report Nº: P30E4511 & M3096133 (PK)
Study Aim: To evaluate the potential toxic effects, reversibility of these effects and PK of SC-65872 in rats during and after 2-week of repeated oral dosing.
Compound:
Vehicle Control:
Dose & Route: 0, 1, 10 and 50 mg/kg/dose, 5 ml/kg/dose, bid po (by gavage) for 15-18 days (~12 hr apart) for a total of 30 or 36 doses.
Dosing Frequency: bid
Animals: CD rats (♂ & ♀), 8-9 weeks of age, weighing 179.9-300.2 g, 10/sex/group.
Study Location: G.D. Searle; 4901 Searle Parkway, Skokie, IL 60077
GLP/QAU Compliance: N/A
Study Date: initiation of dosing on 5/2/96 and terminal sacrifice on 5/17 - 5/20/96
Study Design: Animal grouping and dosage assignment are presented in the table as follows.

Group Nº	Compound	Dose (mg/kg/dose)	Dose (mg/kg/day)	Nº of Animals/Group
1	Control	-	-	10/sex
2	SC-65872	0.5	1	10/sex
3	SC-65872	5.0	10	10/sex
4	SC-65872	25.0	50	10/sex
5[a]	SC-65872	0.5	1	12/sex
6[a]	SC-65872	5.0	10	12/sex
7[a]	SC-65872	25.0	50	12/sex

[a] Animals in Groups 5 - 7 were used for the PK experiment and were not necropsied.

The following parameters were monitored during the study.

- Mortality and Clinical Signs - 2x/day;
- Physical Examination - 1x on Day -3, and 1x during Weeks 1 & 2;
- Body Weight - Days -3, 1, 8, 14 and 16 or 19.
- Food Consumption - 2x pretreatment and 1x/week during treatment.
- Clinical Pathology - Days 16 or 19.
- Toxicokinetics - Days 1 and 14 at 0.5, 1, 2, 4, 7, and 12 hr post 1st dose, 3/sex for each time point bleeding.
- Necropsy - Days 16 or 19.

Results:

- Mortality and Clinical Signs - No deaths and treatment-related clinical symptoms occurred.
- Body Weight and Food Consumption - Body weights were not affected. Rats @ 50 mg/kg/day had a ↓ in food consumption between Days 8-14.
- Clinical Pathology - Significant ↓ in serum K^+ and Cl^- were observed in Group 4 ♀.
- Toxicokinetics - Mean PK parameters of SC-65872 and SC-66905 are shown in the following table. Females had higher systemic exposure to SC-65872 but not SC-66905.

Day	Dose (mg/kg/day)	C_{max} (μg/ml) ♂	C_{max} (μg/ml) ♀	Exposure Multiple[a] ♂	Exposure Multiple[a] ♀	T_{max} (hr) ♂	T_{max} (hr) ♀	$AUC_{0\text{-}12hr}$ (μg•hr/ml) ♂	$AUC_{0\text{-}12hr}$ (μg•hr/ml) ♀	Exposure Multiple ♂	Exposure Multiple ♀
PK PARAMETERS FOR SC-65872											
1	1	0.095	0.126	2.9	3.9	1.00	2.00	0.466	0.841	2.2	4.0
	10	1.260	1.680	38.9	51.9	2.00	2.00	6.150	10.8	29.1	51.2
	50	5.500	9.950	169.8	307.1	2.00	2.00	29.800	74.7	141.2	354.0
14	1	0.092	0.170	2.8	5.2	1.00	1.00	0.424	0.970	2.0	4.6
	10	1.280	3.050	39.5	94.1	1.00	4.00	5.350	19.4	25.4	91.9
	50	6.140	9.810	189.5	302.8	1.00	1.00	26.500	77.3	125.6	366.4
PK PARAMETERS FOR SC-66905											
1	1	0.024	0.007	-	-	4.00	7.00	0.116	0.027	-	-
	10	0.258	0.192	-	-	4.00	7.00	1.980	1.600	-	-
	50	1.970	0.855	-	-	4.00	2.00	16.50	8.360	-	-
14	1	0.008	0.007	-	-	4.00	4.00	0.020	0.017	-	-
	10	0.238	0.531	-	-	1.00	4.00	1.970	3.140	-	-
	50	1.400	1.640	-	-	1.00	4.00	12.40	15.30	-	-

[a]: Exposure multiple of C_{max} at the ED_{80} for anti-inflammatory activity (0.0324 μg/ml).

[b]: Exposure multiple of the AUC at the ED_{80} for anti-inflammatory activity ($AUC_{0\text{-}24hr}$ = 0422 hr•μg/ml).

- Gross Pathology and Histology - Significant ↑ in absolute and relative liver, kidney, and adrenal weights, significant ↓ in absolute and relative uterus weights and significant ↓ in relative thyroid weights were noted in the ♀ @ 50 mg/kg/day. Gross examinations showed that a chronic focal ulceration in the ileum and linear foci of ulceration/transmural necrosis in the distal jejunum with secondary serosal/peritoneal inflammation were identified in 2 ♀ @ 50 mg/kg/day. GI lesions or pathological changes (ulceration/necrosis) were seen in 3 ♀ @ 50 mg/kg under microscopic examinations. No microscopic abnormalities were found in the kidney. Slight to mild hypertrophy of centrilobular hepatocytes and cells of adrenal zona fasciculata that supported the findings in the organ absolute and relative weights. There were no histopathological changes correlated observations in the kidney, thyroid and uterus weights for the high-dose (50 mg/kg) ♀.

Based upon presented information, the NOAEL for SC-65872 was 10 mg/kg/day (or 5 mg/kg/dose bid) for ♀ and was not established for ♂ under current testing condition.

2.2.2.3. Two Week Range-Finding Dietary Admix Feasibility Study of SC-65872 in the Rat, EX 4521; Date: 26-Jun-1997, Document No. P30E4521. (Vol. 1.37)

Study Nº: EX 4521
Report Nº: P30E4521 & M3097022 (PK)
Study Aim: To evaluate the feasibility of diet admix for administration of SC-65872 and PK profiles of dietary administration in the rat
Compound: [redacted]
Dose & Route: 0, 10, 30, 100, and 300 mg/kg/day po via dietary admix
Animals: [redacted] CD albino rats, ~7 weeks of age, weighing 145.0-262.4 g, 20/sex/group
Study Location: G.D. Searle & Co., Skokie, IL [redacted]
GLP/QAU Compliance: N/A
Study Date: 7/17/1996 (Day 1) - 7/31/1996 (Day 15)
Study Design: Groups of 20/sex rats were given diet containing SC-65872 at doses of 0, 5 or 30, 100, and 300 mg/kg/day for 2 weeks as presented in the following table.

Group	Intended Dose (mg/kg/day)	Actual Calculated Dose (mg/kg/day)				Nº of Animals (sex/group)
		Days 1-8		Days 8-15		
		♂	♀	♂	♀	
1	0	0	0	0	0	20
2	10	9.5	9.4	10.7	10.5	20
3	30	28.7	28.9	31.9	32.3	20
4	100	91	82	113	108	20
5	300	227	158	-	-	20

The following parameters were monitored during the study.

- Mortality and Clinical Signs - 1x/day;
- Body Weight - 1x/Pre-R on Day -8 and 1x/week on Days 1, 8, and 15.
- PK - Days 6-7 and 14-15. Blood samples were collected from 3/sex of Groups 1-5 at 6:30, 11:30, 17:30 and 21:30 hr on Days 6 and 14 and at 2:30 and 6:30 hr on Days 7 and 15.
- Necropsy - Day 15. All animals found dead or moribund were necropsied. No tissues were collected. Group 5 ♀ and ♂ were sacrificed on Days 7 and 8, respectively.

Results:

- Mortality and Clinical Signs - There were 10 treatment-related deaths as results of GI ulcers/perforations with secondary peritonitis as listed in the following table. The major clinical observations in these animals including reduced activity, cold to touch and ventral staining. Two PK study rats (1♂ @ 10 mg/kg/day, 1♀ @ 30 mg/kg/day) died on Day 14 during blood collection. Due to excessive GI toxicity occurred in Group 5, animals were sacrificed on Days 7 (♀) and 8 (♂).

Animal Nº	Dose (mg/kg)	Day of Death	Death Status	Cause of Death
2518	300	4	Found Dead	Perforated duodenal ulcer (pyloric duodenal junction) with secondary fibrinous peritonitis.
2515	300	5	Found Dead	Perforated pyloric ulcer (stomach) with secondary fibrinous peritonitis.
2517	300	5	Found Dead	Perforated ulcer (pylorus) with secondary fibrinous peritonitis.
2512	300	6	Found Dead	Perforated duodenal ulcer.
2503	300	6	Found Dead	Test-article related GI injury with secondary fibrinous peritonitis.
2407	100	10	Moribund Sacrifice	Severe, diffuse fibrinous peritonitis secondary to test-article related ulceration/transmural necrosis in the proximal duodenum.
2403	100	10	Found Dead	Acute peritonitis (fibrinous) secondary to test-article related jejunal ulceration/transmural necrosis.
2405	100	12	Found Dead	Severe diffuse fibrinous peritonitis due to/associated with a perforated duodenal ulcer.
1407	100	13	Moribund Sacrifice	Perforation in colon-extensive leakage of contents-abdominal cavity-severe peritonitis.
2414	100	13	Found Dead	Perforation-colon with extensive leakage of intestinal contents.

- Body Weights and Food Consumption - Significant reductions in mean body weight changes with reduced food consumption were observed in both ♂ and ♀ @ 100 and 300 mg/kg/day. In addition, ♀ @ 10 and 30 mg/kg/day had ↓ weight gain during Week 1 and ↓ food consumption during Week 2. Mean (±SD) body weight changes and food consumption for each group during treatment are presented in the following table.

Dose Group (mg/kg/day)	Body Weight Change (g)				Food Consumption (g/day)			
	Day 8		Day 15		Days 1-8		Days 8-15	
	♂	♀	♂	♀	♂	♀	♂	♀
0	47.9 ± 7.01	23.3 ± 6.23	38.2 ± 8.25	13.0 ± 7.13	22.4 ± 2.10	17.4 ± 1.72	23.4 ± 2.31	17.8 ± 1.76
10	43.1 ± 10.89	18.5 ± 7.67 (↓21%)	31.2 ± 8.80	10.4 ± 6.49 (↓20%)	21.0 ± 2.85	16.8 ± 1.88	22.1 ± 2.70	16.6 ± 2.54 (↓6.7%)
30	47.2 ± 9.66	20.0 ± 6.79 (↓20.6%)	38.4 ± 9.87	12.5 ± 5.76	22.1 ± 2.53	16.7 ± 1.65	23.3 ± 2.67	16.7 ± 1.97 (↓6.2%)
100	34.5 ± 11.94 (↓28%)	9.6 ± 6.65 (↓59%)	26.6 ± 9.14 (↓30.4%)	4.3 ± 6.80 (↓67%)	19.9 ± 2.25 (↓11%)	14.1 ± 1.26 (↓19%)	21.4 ± 2.13 (↓8.5%)	12.9 ± 2.11 (↓27.5%)
300	6.2 ±10.82 (↓87%)	-11.5 ±5.34 (↓149%)	ND (No Data)	ND	14.8 ± 3.42 (↓34%)	8.7 ± 1.18 (↓50%)	ND	ND

- PK - SC-65821 was absorbed and systemically available following oral administration via diet admix. Apparent higher C_{max} and AUC_{0-24} values for SC-65872 were noted in the females than the males on both Days 6/7 and 14/15. No accumulation of SC-65872 occurred as similar mean C_{max} and AUC_{0-24} values were obtained on both sampling days. The mean PK parameters for SC-65872 and SC-66905, an active metabolite, are presented in the following table.

Dose (mg/kg/day)	N		SC-58672						SC-66905					
			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)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
DAY 6/7														
10	3	3	24	0	0.562	1.51	8.47	26.4	0	0	0.266	0.294	3.82	3.53
30	3	3	0	0	2.24	7.95	27.1	119	0	5	0.961	0.814	12.3	14.5
100	2	3	5	24	8.64	28.8	144	408	5	5	9.57	5.77	105	92.1
300	3	2	20	11	22.8	29.1	329	616	24	20	16	20.3	258	-
DAY 14/15														
10	3	3	0	5	0.783	2.18	10.8	37.3	24	0	0.253	0.276	3.86	3.93
30	3	3	24	0	2.28	8.76	34.6	133	24	5	1	1.09	14.8	17.8
100	3	2	24	5	9.25	32.6	140	501	24	5	6.72	11.5	90.4	163

- Gross Pathology - GI lesions characterized as ulceration/perforation of the pylorus, duodenum or colon with secondary peritonitis (Group 5: 5♀; Group 4: 1♂ & 4♀) were major macroscopic findings.

Based upon presented information, the NOAEL for SC-65872 was 30 mg/kg/day (via dietary admix) for ♂ rats and was no established for ♀ under current testing condition.

2.2.2.4. Two-Week Repeated Dose Oral Gavage Toxicity Study With SC-65872 in Rats, EX4526; Date: 23-Jun-1997, Document No. P30E4526. (Vol. 1.38)

Study Nº: EX4526/CHW6127-308
Report Nº: P30E4526 & M3097105 (PK)
Study Aim: To evaluate the repeatability of the toxicity observed in a previous study (SA4472) tested with same lot of drug (GDS-6111-137), to compare the toxicity of two different lots of test article (E90098, PDR-96S-0607), and to determine the levels of exposure to each lot of test article at same dosages over a 2-week period.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 5, and 25 mg/5 ml/kg bid (10-14 hr apart) by oral gavage.
Animals: ♂ & ♀ (94/sex) Sprague-Dawley (Crl:CD®BR) rats, ~8 weeks of age, weighing 233-279 g for ♂ and 177-233 g for ♀.
Study Location: [redacted]

GLP/QAU Compliance: Yes
Study Date: 7/9/96 (Groups 1, 4-7 and 10-13) and 7/12/96 (Groups 2-3 and 8-9) to 7/24-26
Study Design: Animals were randomized assigned to the dose groups as shown in the following table and given vehicle or SC-65872, 5 or 25 mg/kg bid by oral gavage for 2 weeks.

Toxicology Groups					PK Groups				
Group Nº	SC-65872 Lot Nº	Dose (mg/kg/dose)	Dose (mg/kg/day)	Animals Sex/Group	Group Nº	SC-65872 Lot Nº	Dose (mg/kg/dose)	Dose (mg/kg/day)	Animals Sex/Group
1	Control	0	0	10					
2	GDS-6111-137	5	10	10	8	GDS-6111-137	5	10	4
3	GDS-6111-137	25	50	10	9	GDS-6111-137	25	50	4
4	E90098	5	10	10	10	E90098	5	10	4
5	E90098	25	50	10	11	E90098	25	50	4
6	PDR-96S-0607	5	10	10	12	PDR-96S-0607	5	10	4
7	PDR-96S-0607	25	50	10	13	PDR-96S-0607	25	50	4

The following parameters were monitored during the study.

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - 1x/Pre-R on Day 1 and 1x/week thereafter.
- Body Weight - 1x/Pre-R on Day 1 and 1x/week thereafter.
- PK - Blood samples were collected from 3/sex of Groups 8-13 on Days 1 and 14 at 2 and 12 hr after dosing.
- Terminal Sacrifice - Days 15-16. Necropsy was performed on all animals (unscheduled deaths + terminal sacrificed) in toxicology groups (Groups 1-7). The following tissues from each animal were collected and preserved in 10% neutral formalin: cecum, colon, duodenum, jejunum, ileum, kidneys, stomach, and rectum. No microscopic examination was performed.

Results:

- Mortality and Clinical Signs - Treatment-related clinical observations were pale/thin appearance, distended abdomen, decreased fecal output, hyporeactivity, rough hair coat and anorexia. The following table presents unscheduled deaths and the causes of these deaths during the study.

Group	Nº/Sex	Time of the Death	Findings
7	1 ♀	Day 10	Drug-Related: abdominal adhesion and perforated jejunum
11	1 ♀	Day 11	Drug-Related: abdominal adhesion and perforated ileum/jejunum
13	2 ♀	Days 10 and 14	Drug-Related: abdominal adhesion and perforated ileum/jejunum
7	1 ♀	Day 3	Gavage Error
12	1 ♀	Day 1	Blood Collection Error

- Body Weight - Due to highly variable data obtained from each group, there were no **statistically significant** changes in the mean body weights or body weight gains. However, reduced weight gains were noted in ♂ of Groups 2, 3, 5, and 7 (↓11-24%) and ♀ of Groups 2, 3, and 5 (↓21%). Furthermore, some rats (1/sex in Group 5, 1♀ in Group 6, and 1♂ in Group 7) had lost >10 g of body weight during Weeks 1 or 2.
- PK - Plasma SC-65872 and SC-66905 (an active metabolite of SC-65872) levels after 1st oral dose on Days 1 and 14 are given in the below table. Higher Plasma SC-65872 levels were in the ♀ rats than those in the ♂ on both Days 1 and 14.

Dose (mg/kg)	Time (hr)	N	SC-65872	SC-65872 (μg/ml)		SC-66905 (μg/ml)	
				♂	♀	♂	♀
DAY 1							
5	2	3	Lot A	0.842 ± 0.197	1.62 ± 0.199	0.169 ± 0.0543	0.154 ± 0.00769
	12			0.147 ± 0.0966	0.334 ± 0.0557	0.0939 ± 0.0596	0.0597 ± 0.00243
25	2	3		5.72 ± 0.249	11.1 ± 0.145	2.56 ± 0.513	0.837 ± 0.139
	12			0.527 ± 0.0502	5.26 ± 0.657	0.5 ± 0.0819	0.599 ± 0.0873
5	2	3	Lot B	0.635 ± 0.234	0.689 ± 0.111	0.129 ± 0.0596	0.0508 ± 0.00498
	12			0.0789 ± 0.0434	0.475 ± 0.247	0.058 ± 0.0282	0.0865 ± 0.0351
25	2	3		2.72 ± 1.08	3.95 ± 1.34	0.672 ± 0.449	0.28 ± 0.103
	12			0.638 ± 0.135	3.62 ± 1.14	0.431 ± 0.199	0.406 ± 0.0887
5	2	3	Lot C	0.923 ± 0.0526	1.4 ± 0.375	0.21 ± 0.0196	0.104 ± 0.0386
	12			0.0614 ± 0.00646	0.366 ± 0.0165	0.0458 ± 0.0117	0.062 ± 0.0104
25	2	3		6.24 ± 0.846	7.82 ± 1.25	1.9 ± 0.24	0.788 ± 0.0661
	12			0.924 ± 0.105	5.78 ± 0.95	0.502 ± 0.0401	0.653 ± 0.0884
DAY 14							
5	2	3	Lot A	0.935 ± 0.24	3.11 ± 0.384	0.223 ± 0.0377	0.248 ± 0.0123
	12			0.0655 ± 0.0274	0.792 ± 0.114	0.0561 ± 0.0202	0.134 ± 0.0268
25	2	3		6.35 ± 0.202	16.4 ± 2.78	2.49 ± 0.35	2.89 ± 1.42
	12			0.947 ± 0.317	12.1 ± 4.67	0.614 ± 0.203	2.63 ± 1.01
5	2	3	Lot B	0.867 ± 0.0427	2.68 ± 0.123	0.157 ± 0.0105	0.173 ± 0.0231
	12			0.104 ± 0.0338	1.34 ± 0.337	0.0466 ± 0.0157	0.13 ± 0.0246
25	2	3		3.83 ± 0.626	9.29 ± 0.828	0.743 ± 0.142	1.05 ± 0.196
	12			0.605 ± 0.212	4.12 ± 0.818	0.461 ± 0.177	0.749 ± 0.263
5	2	3	Lot C	1.14 ± 0.0943	2.04 ± 0.14	0.272 ± 0.0127	0.162 ± 0.0215
	12			0.064 ± 0.0249	0.556 ± 0.0554	0.0388 ± 0.00957	0.0784 ± 0.0133
25	2	3		4.45 ± 1.21	6.59	1.39 ± 0.531	1.06
	12	2		0.213 ± 0.0342	3.43	0.14 ± 0.0396	0.819

Lot A = GDS-6111-137 ; Lot B = E90098; Lot C = PDR-96S-0607

- Necropsy - Drug-related gross pathological lesions were observed in Groups 3 (1♂), 5 (1♂ & 2♀), 7 (1♂ & 1♀), and Group 13 (PK animals: 2♀, unscheduled deaths) animals with characteristics of perforated and distended ileum and/or jejunum, adhesions in the abdominal cavity, and dark areas in the mucosa of the glandular stomach or ileum.

2.2.2.5. Four Week Exploratory Oral Gavage Toxicity Study of SC-65872 in Mated and Non-Mated Rats Comparing Female Charles River [redacted] Rats (CRL:CD®(SD)BR(IGS) of Various Ages and Female Charles River Sprague Dawley Rats (CRL:CD®(SD)BR); Date: 23-Oct-2000, Document No. P30E4601. (Vol. 1.39)

Study Nº: EX4601
Report Nº: P30E4601 & M3097186 (PK)
Study Aim: To compare the potential differences in susceptibility of the Crl:CD®(SD)BR female rat and the Crl:CD®(SD)BR(IGS) female rat to the gastrointestinal toxicity of SC-65872.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 3 and 12.5 mg/kg/5 ml po bid (14 hr apart)
Dosing Frequency: Non-mated ♀ were dosed for 21-day. Mated ♀ were dosed for 14 days premating, during mating, and through post-mating Day 7.
Animals: ♀ nulliparous [redacted] rats Crl:CD®(SD)BR(IGS) [redacted] 8-10 weeks of age, weighing 175.0-274.3 g.

♂ ——— Crl:CD®(SD)BR(IGS) rats [redacted] sexually mature proven breeders.

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

GLP/QAU Compliance: No.

Study Date: 2/26/1997 - 3/19-26/1997

Study Design: Animals were randomly assigned to various dosing groups as shown in the following table. On Day 15, ♀ designated for mating were paired with a proven breeder ♂. Paired ♀ were evaluated daily for evidence of mating by the presence of a copulatory plug in the vagina or sperm positive vaginal lavage. If mating was unsuccessful after 7 days, ♀ were paired with a different male until mating was successful or scheduled necropsy (Day 29).

Group	Strain	Dose (mg/kg/dose)	Dose (mg/kg/day)	Non-Mated ♀	N° of Mated ♀
Toxicology Animals					
1	CD IGS	0	0	5	5
2	CD IGS	3	6	10	10
3	CD IGS	12.5	25	10	10
4	CD	0	0	5	5
5	CD	3	6	10	10
6	CD	12.5	25	10	10
Pharmacokinetics Animals					
7	CD IGS	3	6	5	5
8	CD IGS	12.5	25	5	5
9	CD	0	0	3	0
10	CD	3	6	5	5
11	CD	12.5	25	5	5

CD IGS = Crl:CD®(SD)BR(IGS); CD = Crl:CD®(SD)BR

The following parameters were monitored:

- Clinical Signs and Mortality - 2x/day.
- Body Weights - Pre-R, 2x/week during treatment.
- PK/TK - Days 1 and 21 for non-mated ♀ in Groups 7, 8, 10, and 11; Days 1, 14, and Day 7 post-mating for mated ♀ in Groups 7, 8, 10, and 11; Days 1, 14, and 21 for Group 9. Blood samples were collected from Groups 7, 8, 10, and 11 at 2, and 12 hr (prior to 2nd daily dosing) post dose and Group 9 at 2 hr post dose.
- Necropsy - Days 22 (Groups 1-6, non-mated) and 29 (Groups 1-6, mated). Gross examination of small intestine (duodenum, jejunum, and ileum), large intestine (cecum, colon, and rectum), stomach, and kidneys were performed. Tissue collection was done at the discretion of the examining pathologist. Histopathologic examinations were not conducted.
- Determination of mRNA Expression - Left adrenal gland and ½ of left kidney were collected from 5 each in Groups 4 and 6 sacrificed on Day 22 for determination of COX-1, COX-2, and cytochrome P450s (1B1, 3A2, 1A1, 2B1, 1A1, 4A1) SCC (cholesterol side chain cleavage enzyme), 3βH (3β-hydroxysteroid hydroxylase), 11βH (11β-hydroxylase) or 21αH (21α-hydroxylase) mRNA expression.

Results:

- Clinical Signs and Mortality - At similar dose levels, increased mortality was noted in the CD IGS ♀ compared to the CD ♀. The mortality for each group is presented in the following table. Signs of ventral staining, hunched posture, rough coat, reduced number of feces, cold to touch, appears thin, and reduced activity were noted in the animals that died or sacrificed in a moribund condition.

Dose (mg/kg/day)	Total Mortality	Mortality - Non-mated ♀[a]		Mortality - Mated ♀		Total Survival	
		CD IGS	CD	CD IGS	CD	CD IGS	CD
Toxicology Groups							
0	1	1	0	0	0	9/10	10/10
6	4	1	2	1	0	18/20	18/20
25	8	4	0	2	2	14/20	18/20
Pharmacokinetics Groups							
0	0	-	0	-	-	-	3/3
6	4	4	0	0	0	6/10	10/10
25	10	6	1	1	2	3/10	7/10
Toxicology and Pharmacokinetics Groups Combined							
0	1	1	0	0	0	9/10	13/13
6	8	5	2	1	0	24/30	28/30
25	18	10	1	3	4	17/30	25/30

[a] Included females that died before a positive breeding was noted.

- Body Weights - Generally, all animals gained weight during the study. Mean body weight and body weight gains for each group were not analyzed.
- PK/TK - SC-65872 was absorbed and systemically available to CD IGS ♀ and CD ♀. There were no apparent differences in plasma SC-65872 and SC-66905 concentrations between mated and non-mated CD IGS and CD rats. Higher plasma SC-65872 levels were noted in both mated and non-mated CD IGS or CD ♀ after repeated dosing. Mean plasma concentrations of SC-65872 and SC-66905 in mated and non-mated CD IGS or CD ♀ rats are presented in the following table.

Study Day		Plasma Concentration of SC-65872 and SC-66905 (μg/ml) in Mated ♀ Rats							
		Dose[a]	Time	CD IGS Rats			CD Rats		
		(mg/kg/dose)	(hr)	SC-65872	SC-66905	N	SC-65872	SC-66905	N
Pre-Mating	Day 1	3	2	1.35	0.0764	4	1.02	0.0833	4
			12	0.314	0.0368		0.253	0.0405	
		12.5	2	5.80	0.484		4.59	0.407	
			12	2.15	0.202		2.01	0.210	
	Day 14	3	2	1.66	0.106	4	1.43	0.120	4
			12	0.559	0.0622		0.417	0.0706	
		12.5	2	8.54	0.588	2	7.32	0.629	
			12	4.73	0.635		3.18	0.693	
Post-Mating	Day 7	3	2	1.63	0.0794	3	1.25	0.0842	4
			12	0.484	0.0390		0.289	0.0393	
		12.5	2	-	-	0	10.6	0.594	3
			12	-	-		4.93	0.535	
Study Day		Plasma Concentration of SC-65872 and SC-66905 (μg/ml) in Non-Mated ♀ Rats							
		Dose[a]	Time	CD IGS Rats			CD Rats		
		(mg/kg/dose)	(hr)	SC-65872	SC-66905	N	SC-65872	SC-66905	N
Day 1		3	2	1.21	0.0893	4	0.890	0.0818	4
			12	0.203	0.0316		0.187	0.0325	
		12.5	2	5.41	3.97		5.27	0.473	
			12	1.43	0.141		1.44	0.153	
Day 21		3	2	3.09	0.162	3	1.22	0.102	4
			12	1.72	0.120		0.294	0.0541	
		12.5	2	9.83	0.746		9.93	0.797	
			12	3.95	0.642		3.26	0.511	

[a] SC-65872 dose administered twice a day equivalent to 6 or 25 mg/kg/day.

- Necropsy - Treatment-related mortality due to gastrointestinal (GI) injury was observed for all of the SC-65872-treated females that died or were sacrificed moribund during the study. GI injury was characterized by perforation/ulceration of the small intestine (predominantly jejunum) with or without peritonitis. Histologic examinations were not performed.

- Determination of mRNA Expression - No induction of any of the mRNA tested in adrenal glands or kidneys was observed. Data as presented in the following table showed reduced expression levels of cytochrome P450 1B1 and 11βH mRNAs in adrenals of SC-65872 treated animals.

Adrenal Enzyme	Control (0 mg/kg/day)	SC-65872 (25 mg/kg/day)
P450 1B1	0.73 ± 0.08[a]	0.46 ± 0.14
P450 3A2	0.00 ± 0.00	0.00 ± 0.00
P450 SCC	0.81± 0.13	0.67 ± 0.10
P450 3βH	0.83 ± 0.12	0.63 ± 0.17
P450 11βH	1.11 ± 0.34	0.15 ± 0.06
P450 21αH	0.72 ± 0.11	0.63 ± 0.17
COX-1	0.53 ± 0.11	0.60 ± 0.04
COX-2	0.21 ± 0.11	0.34 ± 0.11

[a] mRNA expression data (mean ± SD) are presented as the enzyme cDNA optical density: cyclophilin DNA optical density ratio for each treatment group (n=5).,

Therefore, at comparable exposures, a slight increase in the incidence of SC-65872-related toxicity was observed in CD IGS as compared to CD female rats, suggesting that CD IGS rats were more susceptible to SC-65872 treatment-induced GI injury.

2.2.2.6. Four-Week Oral Gavage Toxicity Study With SC-65872 in Rats, SA4508; Date: 10-Dec-1996, Document No. P30S4508. (Vol. 11.40-43); Evaluation of Total Radioactivity Data in a 4-Week Oral Gavage Toxicity Study With SC-65872 in Rats, SA4508; - Pharmacokinetics, Metabolism and Excretion of [phenyl-^{14}C(U)]SC-65872 in Rat Toxicity Study, SA4508; Date: 12-Nov-1996, Document No. M2096369. (Vol. 1.21); Metabolic Profiling of [phenyl-^{14}C(U)]SC-65872 in the Four Week Rat Toxicity Study, SA4508; Date: 07-Nov-1996, Document No. M3096390. (Vol. 1.21)

Study Nº: SA4508/CHW 6127-302
Report Nº: P30S4508, M3096334 (PK), M3096372 (PK), M2096370 (PK), M2096369 (PK) & M3096390 (PK)
Study Aim: To evaluate the potential toxic effects of SC-65872 in rats following 4-week oral administration.
Compound: [redacted]
Vehicle Control: [redacted]
Dose & Route: 0, 1, 10 and 50 mg/kg/dose, 5 ml/kg/dose, bid po (by gavage) for 15-18 days (~12 hr apart) for a total of 30 or 36 doses.
Dosing Frequency: bid
Animals: Crl:CD®(SD)BR rats (♂ & ♀), 8-9 weeks of age, weighing 181-298 g, 15, 16, 18 or 25/sex/group; additional ♂ & ♀ Crl:CD(SD)BR[redacted] ~8 weeks of age, 202-284 g, 5/sex/group, were used for microsomal P-450 study.
Study Location: [redacted]
GLP/QAU Compliance: N/A
Study Date: Initiation of Dosing - 5/31/96;
Terminal Sacrifice - 6/29-30/96 or 7/16/96
Study Design: The following table presents animal grouping and dosage assignments.

Group Nº	Compound	Dose/Day (mg/kg/Day)		Dose/Dose (mg/kg)		Nº of Animals/Group	
		♂	♀	♂	♀	♂	♀
Toxicology Study Animals							
1	Vehicle	-	-	-	-	25	25
2	SC-65872	5	2.5	2.5	1.25	15	15
3	SC-65872	10	5.0	5.0	2.5	15	15
4	SC-65872	25	12.5	12.5	5.0	15	15
5	SC-65872	50	25.0	25.0	12.5	25	25
PK Study Animals[a]							
6	SC-65872	5	2.5	2.5	1.25	16	16
7	SC-65872	10	5.0	5.0	2.5	16	16
8	SC-65872	25	12.5	12.5	5.0	16	16
9	SC-65872	50	25.0	25.0	12.5	16	16
Radiolabeled Study Animals[b]							
10	SC-65872	2.5	2.5	1.25	1.25	18	18
11	SC-65872	10	10	5.0	5.0	18	18
Microsomal P-450 Study							
1	Vehicle	-	-	-	-	5	5
3	SC-65872	10	5	5.0	2.5	5	5
4	SC-65872	25	10	12.5	5.0	5	5
5	SC-65872	50	25	25.0	12.5	5	5

[a]: Animals were not necropsied.
[b]: Micronzied [pheyl-^{14}C(U)]SC-65872 was given by oral gavage only on the 1st daily dose of Days 1 and 22.

The following parameters were monitored during the study.

- Mortality and Clinical Signs - 2x/day.
- Physical Examination - 1x/week.
- Body Weight - Day 1 and 1x/week during treatment and recovery.
- Food Consumption - 1x/week during treatment.
- Ophthalmic Examination - 1x pretreatment and 1x during week 4.
- Clinical Pathology - Weeks 5 (15/group, Groups 1-5) & 7 (10/group, Groups 1 and 5).
- Toxicokinetics - Days 1 and 25 at 0.5, 1, 1.5, 3, 5, 7, 9, and 12 hr post 1st dose, 3/sex from Groups 6-9 for each time point bleeding. On Days 1 and 22, at 2, 5, 12, 24, 48, 72, 96, 120, 144, and 168 hr post-dose 3/sex/group from Groups 10 & 11 for each time point bleeding. Urine was collected 3/sex animals from Groups 10 & 11 for consecutive 24 hr periods (0-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hr post-dose.
- Liver Microsome Enzyme and P-450 - up to 10 g of liver from 5 additional toxicology animals (Groups 1, and 3-5) during Week 5 were used for post-mitochondrial preparations.
- Necropsy - Unscheduled deaths Weeks 5 (15/group, Groups 1-5) & 7 (10/group, Groups 1 and 5).

Results:

- Mortality and Clinical Signs - One ♀ in Group 5 was sacrificed at moribund on Day 22 with sings of swollen abdomen, pelage discoloration, incoordination and few feces. Severe peritonitis and a perforated jejunum was identified in this animal at postmortem. One PK ♀ in Group 11 was dead shortly after final blood collection. All other animals survived to the respective scheduled sacrifice.
- Body Weight & Food Consumption - Group 5 ♀ had slightly lower body weights relative to controls. Significantly lower body weight gains were noted for Group ♀ during Week 1-2 interval and for Group 5 ♂ during Week 4-5 interval.
- Ophthalmic Examinations - No test article-related changes were noted.
- Clinical Pathology - Lower serum glucose (~10%) and potassium (~20%) for ♀ and higher urine calcium concentration and calcium excretion for both ♂ and ♀ in Group 5 were identified during