

Study Design	Two phase, three period, single dose, crossover
Study Population	N=11 healthy Caucasian subjects, 2 in pilot phase and 9 in randomized phase. 8M, Ages 20-50, weight 66.6-82.5 kg
Treatment Group	A: Valdecoxib tablets B: [¹⁴ C] _____ C: nonradiolabeled
Dosage and Administration	A: 20 mg (2x10 mg tablets) valdecoxib single dose, lot RCT 10678 with 240 mL water. Consumed 180 mL water 1, 2 and 3 hours postdose, overnight fast Other arms with [¹⁴ C] _____ and nonradiolabeled _____ (20 mg) is mentioned in this review only for comparison to PO data
Sampling: Blood	For Valdecoxib, SC-66905 and SC 67817: At predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours postdose.
Urine	For [¹⁴ C] _____ treatment only: measurements at -12-0 hrs predose, 0-1, 2-3, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 hrs postdose.
Feces	For [¹⁴ C] _____ treatment only Up to 216 hours post dose
Analysis	

Observations:

Results of only the valdecoxib tablet arm will be discussed here. The mean (SD) plasma pharmacokinetic parameters of valdecoxib and SC-66905 (M1) are shown in the following table:

Valdecoxib 20 mg PO (n=9) PK Parameters	Valdecoxib	SC-66905
AUC _{0-inf} (hr*ng/mL)	3195.3±690.0	306.1±53.3
C _{max} (ng/mL)	283.8±61.9	20.9±8.1
T _{max} (hr)	3.1±0.5	4.4±1.7
T _{1/2} (hr)	7.7±2.4	7.5±2.0

The _____ radiolabeled arm showed results very similar to the previous study (radiolabeled valdecoxib). No new information is added with this study except that the pharmacokinetic parameters after a 20 mg oral dose of valdecoxib.

Bioequivalence with respect to AUC and C_{max} was not established between the _____ formulations and the oral tablet formulation of valdecoxib. The valdecoxib and

SC-66905 AUC was 22-32% higher with the valdecoxib as compared to the radiolabeled and oral solution formulation. The C_{max} was lower (10%) with the oral valdecoxib formulation. The 90% CIs are represented in the following Table.

Table Plasma Exposures of Valdecoxib and SC-66905 after Single 20 mg Doses of Valdecoxib Tablets Relative to IV [¹⁴C]

Plasma PK Parameter by Analyte	Treatment Mean (% CV) (a)		Valdecoxib PO		
	Valdecoxib 20 mg PO (N=9)	20 mg IV (N=9)	Ratio	90% Confidence Interval for Ratio	p Value
Analyte = Valdecoxib					
AUC(0-lgc) (hr ng/mL)	3116 (19)	2594 (28)	1.22	(1.12, 1.34)	0.001
AUC(0-inf) (hr ng/mL)	3195 (22)	2609 (29)	1.24	(1.14, 1.36)	<0.001
C _{max} (ng/mL)	284 (22)	312 (13)	0.90	(0.75, 1.07)	0.299
T _{max} (hr)	3.11 (18)	1.33 (70)	NAV	NAV	NAV
T _{1/2} (hr)	7.69 (32)	7.41 (31)	NAV	NAV	NAV
Analyte = SC-66905					
AUC(0-lgc) (hr ng/mL)	293 (19)	226 (28)	1.32	(1.16, 1.49)	0.001
AUC(0-inf) (hr ng/mL)	306 (17)	253 (25)	1.23	(1.13, 1.34)	<0.001
C _{max} (ng/mL)	20.9 (39)	20.2 (42)	1.05	(0.92, 1.19)	0.521
T _{max} (hr)	4.39 (38)	2.28 (35)	NAV	NAV	NAV
T _{1/2} (hr)	7.49 (26)	9.00 (46)	NAV	NAV	NAV

from LS means used in the statistical analysis. Nine subjects from randomized phase of study were included in the statistical analysis (2 pilot subjects excluded). NAV = not available or analysis not performed.

- The LS mean value for valdecoxib AUC_{0-inf} after the oral tablet dosing was statistically significantly higher (24%, p<0.001) compared to [redacted]
- Oral absorption from valdecoxib tablets was markedly slower than conversion of prodrug to valdecoxib after IV administration of [redacted] [mean T_{max} = 3.11 hr (oral) vs. 1.33 hr (IV)], resulting in 10% lower average C_{max} after oral valdecoxib compared to [redacted]
- For SC-66905 (M1), peak concentration (C_{max}) and total (AUC) plasma exposure after tablet dosing were higher than those after [redacted]. Average SC-66905 T_{max} after oral valdecoxib (4.39 hr) occurred almost two-fold later compared to [redacted] (2.28 hr).
- It should be noted that equal milligram doses of valdecoxib and [redacted] do not contain equimolar amounts of valdecoxib due to molecular weight differences between the two compounds [MW = 314 (valdecoxib) vs. [redacted]]. Assuming 100% conversion of [redacted] to valdecoxib, a 20 mg dose of [redacted] would be converted to about 17 mg of valdecoxib, which may account for the observed differences in valdecoxib AUC values between the two treatments.

Conclusions:

At equal milligram doses of valdecoxib and [redacted] there was approximately a 24% difference in exposure (higher with valdecoxib), but at equimolar doses the exposure may be similar as 20 mg dose of [redacted] would get converted to 17 mg of valdecoxib.

Study E91-96-02-001: A double blind, placebo-controlled, single rising dose tolerability, safety and pharmacokinetic study of oral valdecoxib in healthy male subjects

This study comprised of a dose-escalation phase (1-400 mg) to determine the maximum tolerated dose (MTD) and a confirmation phase to verify the MTD. The rising-dose phase consisted of 9 groups of 4 subjects, and the confirmation phase had a single group of 8 subjects who received the MTD of 400 mg. The study design is given in the following Table.

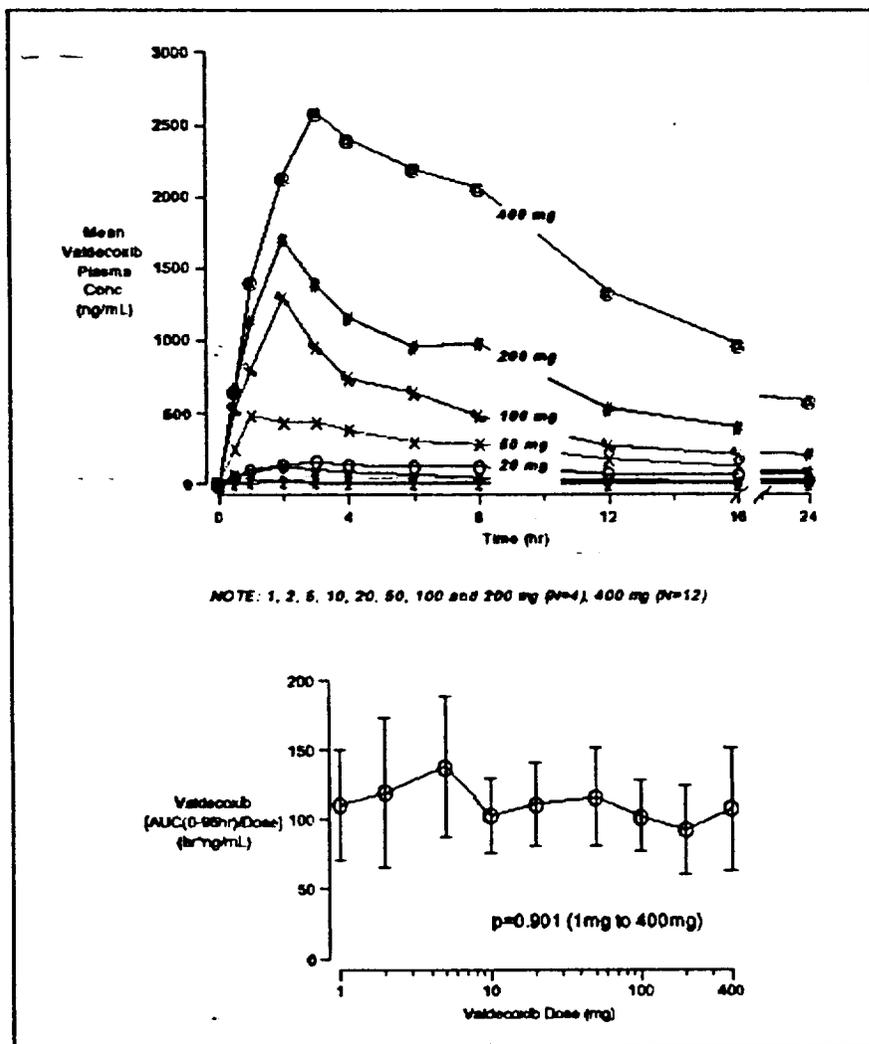
Study Design	Single-center, double-blind, placebo-controlled, randomized, sequential-panel
Study Population	N=68 healthy Caucasian subjects, 24 on placebo and 4 each on all doses except 400 mg, 12 subjects on 400 mg 68M, Ages 18-50, weight 60-85 kg
Treatment Group	I-IX: Valdecoxib capsules, different doses, 4 on valdecoxib and 2 subjects on placebo in each group X: fed arm
Dosage and Administration	I-IX: 1, 2, 5, 10, 20, 50, 100, 200 and 400 mg valdecoxib single dose, with 250 mL water under fasting conditions. X: 20 mg fed (high fat-50 gms of fat) (N=4)
Sampling: Blood	For Valdecoxib, SC-66905: At predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72 and 96 hours postdose.
Urine	For Valdecoxib, SC-66905: 10-0 hours predose and 0-24 hours postdose.
Analysis	

Observations:

The proportionality in mean plasma concentrations of escalating doses of valdecoxib in shown in the following Figures.

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Figure: Proportionality in mean plasma concentrations of valdecoxib and dose adjusted (to 1 mg dose) valdecoxib AUC 0-96hr after single doses of valdecoxib capsules between 1 and 400 mg



The pharmacokinetic parameters for valdecoxib and SC-66905 (M1) is shown in the following Table:

Table: Dose Proportionality in Valdecoxib AUC0-96hr after Single Oral Doses of Valdecoxib Capsules Between 1 mg and 400 mg.

Single Dose PK Parameter by Analyte	Cmax (ng/mL)	Tmax (hr)	Treatment Group Mean (% CV)				
			AUC(0-96hr) (hr ng/mL)	AUC(0-lqc) (hr ng/mL)	AUC(0-inf) (hr ng/mL)	T1/2 (hr)	AUC(0-96hr)/Dose (hr ng/mL)
Analyte = Valdecoxib							
1 mg (N=4)	11.8 (23)	1.75 (29)	110 (36)	107 (34)	114 (37)	5.75 (44)	-110.3 (36)
2 mg (N=4)	25.0 (17)	1.38 (55)	238 (45)	236 (45)	240 (44)	5.73 (28)	119.2 (45)
5 mg (N=4)	65.8 (30)	2.25 (56)	691 (37)	681 (36)	691 (36)	6.17 (36)	138.2 (37)
10 mg (N=4)	127 (24)	2.00 (0)	1029 (26)	1015 (26)	1029 (26)	5.80 (25)	102.9 (26)
20 mg (N=4)	170 (16)	2.25 (43)	2224 (27)	2146 (24)	2253 (30)	6.92 (22)	111.2 (27)
50 mg (N=4)	634 (61)	3.50 (89)	5793 (30)	5780 (30)	5791 (30)	7.30 (15)	115.9 (30)
100 mg (N=4)	1295 (28)	2.00 (0)	10223 (25)	10114 (26)	10207 (25)	5.23 (21)	102.2 (25)
200 mg (N=4)	1704 (40)	3.01 (66)	18514 (34)	18159 (33)	18545 (35)	7.64 (33)	92.6 (34)
400 mg (N=12)	3109 (34)	3.75 (46)	43014 (41)	42567 (41)	43076 (41)	8.69 (25)	107.5 (41)
P-value: (a) 1 to 400 mg	NAV	NAV	NAV	NAV	NAV	NAV	0.901
Analyte = SC-66905							
1 mg (N=4)	0.97 (25) (b)	4.00 (43) (b)	4.63 (80)	3.86 (80)	10.0 (d)	9.21 (c)	4.6 (80)
2 mg (N=4)	2.35 (18)	3.50 (16)	15.8 (42)	13.8 (49)	NAV	NAV	7.9 (42)
5 mg (N=4)	8.40 (61)	4.75 (32)	65.8 (35)	63.2 (38)	76.6 (31)	8.61 (45)	13.2 (35)
10 mg (N=4)	14.2 (44)	3.00 (27)	129 (29)	124 (32)	133 (27)	5.43 (23)	12.9 (29)
20 mg (N=4)	18.5 (13)	5.50 (52)	281 (18)	272 (19)	281 (19)	6.12 (26)	14.0 (18)
50 mg (N=4)	55.9 (39)	4.00 (74)	753 (28)	740 (29)	752 (28)	6.81 (15)	15.1 (28)
100 mg (N=4)	176 (37)	2.50 (40)	1608 (25)	1587 (26)	1620 (25)	5.02 (30)	16.1 (25)
200 mg (N=4)	186 (41)	3.26 (58)	2491 (31)	2463 (31)	2509 (29)	6.74 (34)	12.5 (31)
400 mg (N=12)	324 (44)	4.08 (58)	4244 (31)	4108 (31)	4267 (30)	7.99 (30)	10.6 (31)
P-value: (a) 1 to 400 mg	NAV	NAV	NAV	NAV	NAV	NAV	0.002
5 to 400 mg	NAV	NAV	NAV	NAV	NAV	NAV	0.188

(a) P<0.05 (one-way ANOVA), suggested a lack of dose proportionality among mean dose-adjusted AUC(0-96hr) values.

(b) N=3.

(c) N=1.

NAV = not available or analysis not performed.

- Dose proportionality was observed for valdecoxib at doses 1-400 mg, however for SC-66905, dose proportionality was not observed at doses lower than 5 mg.
- In the pilot fed arm with 4 subjects on 20 mg valdecoxib, the Tmax prolonged to 6 hours as opposed to 2 hours in the fasted arm. The overall exposure did not change.

The sponsor has also measured the serum thromboxane B2 concentrations before and after valdecoxib dosing at 100, 200 and 400 mg doses, as shown in the following Table:

Table: Mean (± SD) Serum Thromboxane B2 Concentrations (ng/mL) Under Fasting Conditions Before and After Valdecoxib Dosing

Time	Valdecoxib Dose			
	Placebo (n=24)	100 mg (n=4)	200 mg (n=4)	400 mg (n=12)
Pre-Dose (-30 min)	223.5±112.0	127.2±48.4	198.3±50.2	236.3±119.0
2 hours Post-Dose	197.9±103.5	159.2±85.5	148.5±35.0	235.3±155.7
Change from Baseline (Pre-Dose)	-25.6±46.8	32.0±62.6	-49.8±48.5	-1.02±59.5

This table shows that serum TxB₂ levels (a COX-1 mediated phenomenon) were unaffected at the 100, 200, or 400 mg valdecoxib doses, suggesting that at these high doses, valdecoxib does not inhibit COX-1.

Conclusions:

From this study in healthy volunteers it is concluded that:

- Following single dose administration, valdecoxib, exhibits linear pharmacokinetics over the range of 1 to 400 mg, the AUC₀₋₉₆ and AUC₀₋₁₉₂ increase linearly with doses over the range of 1-400 mg.
- The AUC₀₋₉₆ and AUC₀₋₁₉₂ of its metabolite, SC-66905 (M1), also increase linearly with increasing doses of valdecoxib from 5 to 400 mg.
- Valdecoxib is a selective inhibitor of COX-2 in subjects as demonstrated by an absence of inhibition of serum TxB₂ (a COX-1 mediated phenomenon).

Study N91-00-02-077: Open label, randomized, single-dose, four way crossover study to assess dose proportionality of 10, 20, 40 and 80 mg valdecoxib in healthy adult subjects

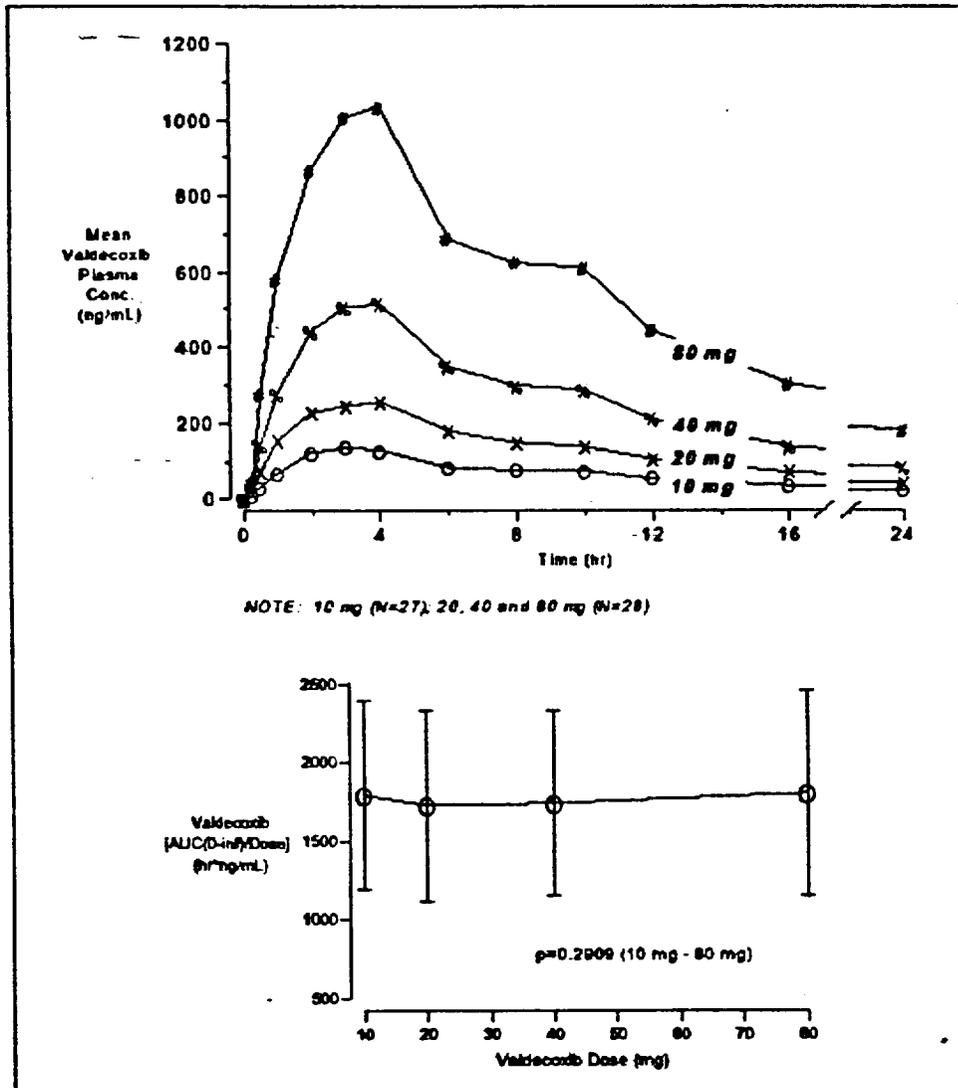
The study design of this dose proportionality study is given in the following Table:

Study Design	Open-label, single dose, randomized, 4-way crossover
Study Population	N=28 healthy subjects, 23 Caucasian, 5 Hispanic 21M and 7F, Ages 19-55, weight 60-85 kg
Treatment Group	I-IV: Valdecoxib tablets, different doses
Dosage and Administration	I-IV: 10, 20, 40 and 80 mg valdecoxib single dose with 250 mL water under fasting conditions. Meals served 4 hours postdose. Randomized on Day 1, 8, 15 and 22 with a 7 day washout between treatments
Sampling: Blood	For Valdecoxib, SC-66905: At predose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours postdose Days 1, 8, 15 and 22.
Urine	For Valdecoxib, SC-66905: 10-0 hours predose and intervals in 0-72 hours postdose on Days 1, 8, 15 and 22.
Analysis	

Observations:

The proportionality in mean plasma concentrations of valdecoxib is shown in the following Figure.

Figure: Proportionality in Mean Plasma Concentrations and Dose-Adjusted (to 10 mg Dose) Valdecoxib AUC_{0-inf} after Single Doses of Valdecoxib Commercial Tablets Between 10 mg and 80 mg.



- The plasma concentration time profile demonstrated dose proportionality and linear pharmacokinetics following single doses of commercial tablets between 10 mg and 80 mg.

The pharmacokinetic parameters for the doses of 10-80 mg valdecoxib is shown in the following Table, demonstrating dose-proportionality. Prior to dose proportionality analysis, pharmacokinetic parameters were dose-normalized to the 10 mg dose.

Table: Dose Proportionality of Single Oral Doses of Valdecoxib Commercial Tablets Between 10 mg and 80 mg.

Single Dose PK Parameter by Analyte	Treatment Mean (% CV)				p Value (a) for Dose Proportionality (10 mg to 80 mg)
	Valdecoxib 1x10 mg (N=27)	Valdecoxib 1x20 mg (N=28)	Valdecoxib 1x40 mg (N=28)	Valdecoxib 2x40 mg (N=28)	
Analyte = Valdecoxib					
AUC(0-l _q c) (hr ng/mL)	1762 (33)	3405 (34)	6886 (33)	14289 (36)	0.2154
AUC(0-inf) (hr ng/mL)	1787 (33)	3450 (35)	6957 (34)	14416 (36)	0.2909
C _{max} (ng/mL)	146 (28)	284 (28)	568 (29)	1091 (40)	0.1648
T _{max} (hr)	3.41 (53)	3.22 (32)	3.08 (35)	3.50 (25)	NAV
T _{1/2} (hr)	8.31 (30)	8.53 (33)	8.84 (29)	9.18 (25)	NAV
CL/F (L/hr)	6.24 (34)	6.50 (34)	6.37 (31)	6.20 (33)	NAV
XU(0-72hr) (μg)	377 (25) (b)	690 (43) (c)	1321 (38) (d)	2380 (35) (c)	NAV
Analyte = SC-66905					
AUC(0-l _q c) (hr ng/mL)	142 (41)	287 (33)	580 (34)	1221 (34)	0.0129
AUC(0-inf) (hr ng/mL)	158 (38) (d)	299 (31)	597 (33)	1240 (34)	0.9022
C _{max} (ng/mL)	10.0 (33)	19.0 (32)	37.5 (36)	79.4 (44)	0.9196
T _{max} (hr)	4.78 (90)	3.93 (47)	3.61 (32)	4.36 (54)	NAV
T _{1/2} (hr)	9.08 (31) (d)	8.45 (35)	8.92 (28)	9.24 (26)	NAV
XU(0-72hr) (μg)	36.0 (33) (d)	65.9 (31) (c)	133 (30) (d)	268 (41) (c)	NAV

(a) p<0.05 (test for linear trend within the ANOVA), suggested a lack of dose proportionality among mean dose-adjusted values.

(b) N=25.

(c) N=27.

(d) N=26.

NAV = not available or analysis not performed.

- The results of the ANOVA indicate that valdecoxib AUC_{0-l_qc}, AUC₀₋₈ and C_{max} values demonstrated dose proportionality from 10 mg through 80 mg (p≥0.1648).
- For SC-66905 (M1), AUC₀₋₈ and C_{max} values also demonstrated dose proportionality (p≥0.9022), but AUC_{0-l_qc} did not (p=0.0129). This is presumably due to the higher dose-normalized AUC_{0-l_qc} value noted for the valdecoxib 80 mg group.

Conclusions:

- Exposure to valdecoxib and SC-66905 (M1) were generally proportional to dose for oral valdecoxib 10 mg through 80 mg.
- Adverse event (rash, headache and somnolence) rates were similar for all dose groups.

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**MULTIPLE DOSE PHARMACOKINETICS IN HEALTHY SUBJECTS
& MULTIPLE DOSE PROPORTIONALITY STUDIES**

Study E91-96-02-002: Double blind, placebo-controlled, multiple dose, sequential group safety, tolerability and pharmacokinetics study of oral valdecoxib in healthy male subjects

The primary objectives of this study were to determine the safety and tolerability of oral valdecoxib doses of 2, 5, 10, 20, 50, and 100 mg administered twice daily (BID) under fasted conditions, 10 mg administered once daily (QD) under fasted conditions and 10 mg administered QD under fed conditions for 14 days in healthy male subjects. The Study design is given in the following Table:

Study Design	Double-blind, multiple-dose, randomized, placebo-controlled, sequential panel
Study Population	N=84 healthy subjects, 82 Caucasian, 1 Black, 1 Asian 84M, Ages 19-55, weight 60-85 kg
Treatment Group	I-VII: Valdecoxib capsules, different doses, 8 subjects on different doses of valdecoxib, 4 subjects on placebo in 7 groups
Dosage and Administration	I-VII: 2, 5, 10, 20, and 50 mg valdecoxib multiple dose with 250 mL water under fasting conditions for 14 days. Meals served 2 hours postdose. Each group received a single oral dose initially followed by the multiple doses 48 hours after the QD administration ie, Day 1: Single dose Day 3-16: BID Day 17: Single dose 10 mg QD under fasted and fed conditions (30-40 gms fat on Days 1, 10 and 17) ie, Day 1: QD Day 3-17: QD
Sampling: Blood	For Valdecoxib, SC-66905: Day 1: Up to 48 hours after the first dose Day 10: Up to 12 hours after the morning dose Day 17: Up to 48 hours after the morning dose
Urine	For Valdecoxib, SC-66905: Day 0: -10-0 hours predose Day 1 and 17: 0-48 hours
Analysis	

Observations:

- Increases in plasma exposure (AUC and C_{max}) for valdecoxib and SC-66905 (M1) were generally dose-dependent for single and multiple doses of valdecoxib 2 mg to 50 mg.
- Steady-state levels of valdecoxib were obtained within 7 days of BID dosing.

Mean plasma pharmacokinetic parameters for valdecoxib and SC-66905 following BID dosing for 7 and 14 days are summarized in the following Table:

Table: Linear Pharmacokinetics in Plasma AUC after Multiple Oral Doses of Valdecoxib BID for 7 Days.

Steady State Plasma PK Parameter by Analyte	Treatment Group Mean (% CV)				Ratio (95% CI): Linear Kinetics	
	C _{max} (ng/mL)	T _{max} (hr)	AUC(0-12hr) (hr ng/mL)	AUC/Dose (hr ng/mL)	Day 10 vs. Day 1	Day 17 vs. Day 10
Analyte = Valdecoxib						
2 mg BID (N=7)	40.9 (12)	2.00 (0)	291 (14)	145 (14)	1.08 (0.98, 1.20)	1.11 (1.04, 1.19)
5 mg BID (N=8)	109 (36)	1.81 (29)	770 (36)	154 (36)	0.99 (0.84, 1.17)	1.05 (0.97, 1.14)
10 mg BID (N=8)	241 (37)	2.00 (38)	1593 (34)	159 (34)	1.10 (1.00, 1.22)	1.01 (0.94, 1.08)
20 mg BID (N=8)	594 (17)	2.63 (86)	4676 (21)	234 (21)	1.37 (1.13, 1.65)	1.06 (0.95, 1.18)
50 mg BID (N=8)	1626 (20)	2.13 (30)	12039 (24)	241 (24)	1.25 (1.06, 1.46)	0.96 (0.85, 1.09)
p-Values for BID Dose	NAV	NAV	NAV	<0.001 (a)	NAP	NAP
Proportionality	NAV	NAV	NAV	<0.001 (b)	NAP	NAP
Analyte = SC-66905						
2 mg BID (N=7)	2.98 (15)	2.43 (22)	23.8 (15)	11.9 (15)	1.03 (0.87, 1.23)	1.06 (0.97, 1.16)
5 mg BID (N=8)	8.09 (26)	2.50 (30)	66.5 (28)	13.3 (28)	0.99 (0.87, 1.12)	0.94 (0.87, 1.00)
10 mg BID (N=8)	18.1 (45)	2.00 (38)	136 (37)	13.6 (37)	1.05 (0.95, 1.15)	1.00 (0.93, 1.08)
20 mg BID (N=8)	33.1 (23)	2.50 (21)	283 (29)	14.2 (29)	1.02 (0.92, 1.13)	1.00 (0.92, 1.09)
50 mg BID (N=8)	107 (15)	1.88 (35)	849 (14)	17.0 (14)	1.03 (0.94, 1.12)	0.98 (0.89, 1.08)
p-Values for BID Dose	NAV	NAV	NAV	0.108 (a)	NAP	NAP
Proportionality	NAV	NAV	NAV	0.012 (b)	NAP	NAP

NAV = not available or analysis not performed; NAP = not applicable.

- (a) p-Value for group comparison of mean dose-adjusted AUC(0-12hr) values based on ANOVA with treatment as the only source of variation.
 (b) p-Value for linear trend in mean dose-adjusted AUC(0-12hr) values based on ANOVA in footnote (a).

Table: Linear Pharmacokinetics in Plasma AUC after Multiple Oral Doses of Valdecoxib BID for 14 Days.

Steady State Plasma PK Parameter by Analyte	Treatment Group Mean (% CV)					Ratio (95% CI): Day 17 vs. Day 1
	C _{max} (ng/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC(0-12hr) (hr ng/mL)	AUC/Dose (hr ng/mL)	
Analyte = Valdecoxib						
2 mg BID (N=7)	46.0 (21)	1.57 (50)	8.02 (12) (c)	326 (18) (a)	163 (18) (a)	1.19 (1.07, 1.33)
5 mg BID (N=8)	111 (32)	2.01 (27)	7.51 (16)	811 (36)	162 (36)	1.04 (0.89, 1.22)
10 mg BID (N=8)	228 (32)	1.75 (26)	8.05 (20)	1604 (33)	160 (33)	1.12 (1.03, 1.21)
20 mg BID (N=8)	686 (31)	2.25 (21)	9.59 (27)	5039 (27)	252 (27)	1.45 (1.19, 1.75)
50 mg BID (N=8)	1442 (29)	2.38 (22)	10.3 (19)	11802 (28)	236 (28)	1.20 (0.97, 1.48)
p-Values for BID Dose	NAV	NAV	NAV	NAV	0.004	NAP
Proportionality	NAV	NAV	NAV	NAV	0.002	NAP
Analyte = SC-66905						
2 mg BID (N=7)	3.46 (26)	2.29 (21)	7.09 (10) (b)	25.1 (24) (a)	12.5 (24) (a)	1.09 (0.87, 1.37)
5 mg BID (N=8)	7.70 (28)	2.64 (20)	7.46 (16)	63.2 (34)	12.6 (34)	0.92 (0.81, 1.06)
10 mg BID (N=8)	17.1 (37)	2.25 (21)	7.48 (23)	136 (34)	13.5 (34)	1.05 (0.97, 1.14)
20 mg BID (N=8)	33.9 (29)	2.63 (35)	8.82 (25)	286 (31)	14.3 (31)	1.02 (0.93, 1.13)
50 mg BID (N=8)	93.4 (26)	2.63 (57)	11.5 (29)	846 (21)	16.9 (21)	1.01 (0.93, 1.09)
p-Values for BID Dose	NAV	NAV	NAV	NAV	0.227	NAP
Proportionality	NAV	NAV	NAV	NAV	0.038	NAP

(a) N=6.

(b) N=5.

NAV = not available or analysis not performed; NAP = not applicable.

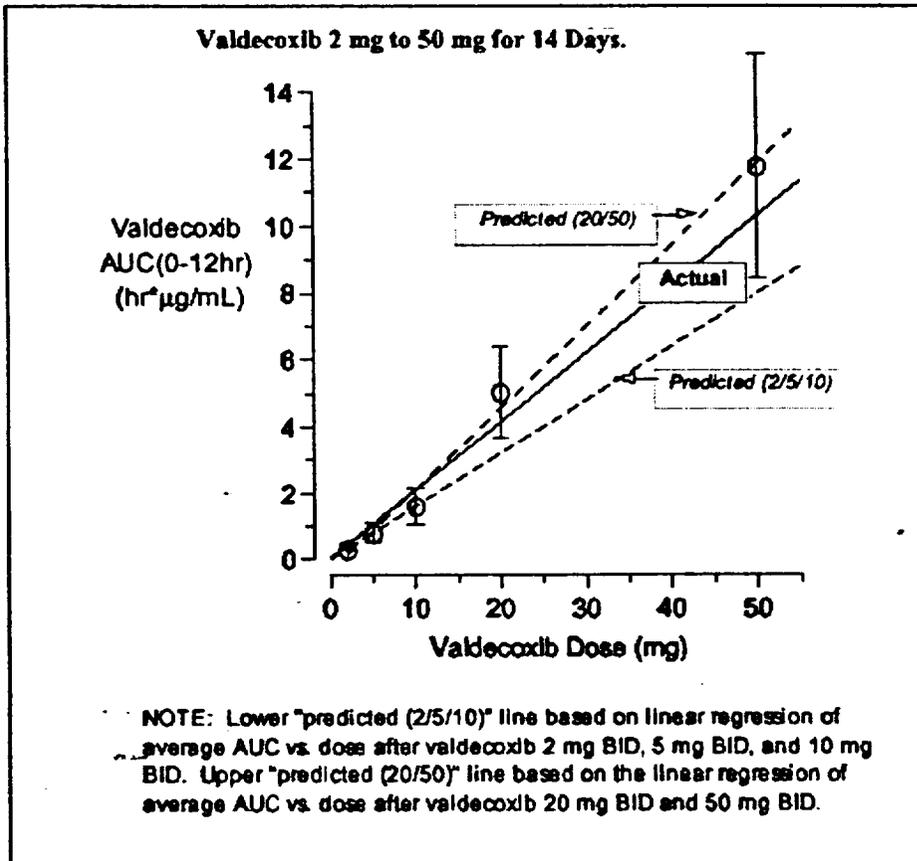
After seven days of dosing:

- Dose adjusted mean AUC_{0-12hr} after valdecoxib BID dosing for seven days showed a dose-dependent increase in steady-state plasma exposure of valdecoxib and SC-66905 (M1), for doses above 10 mg BID ($p \leq 0.012$ for linear trend).
- Based on the 95% confidence intervals for the ratios of steady state $AUC_{0-12hr(SS)}$ on Day 10 relative to Day 1 single dose $AUC_{0-inf(SS)}$ (ratios = 0.99 to 1.37), it was concluded that valdecoxib exhibited approximately linear kinetics for multiple doses between 2 mg BID and 10 mg BID ($AUC_{0-12hr(SS)}/AUC_{0-inf(SS)}$ ratios = 0.99 to 1.10), but showed 25% to 37% higher increases in valdecoxib AUC after 20 mg BID and 50 mg BID dosing.

After 14 days of dosing:

- A similar lack of dose-proportionality in plasma exposures of valdecoxib and SC-66905 was observed after 14 days of valdecoxib BID dosing ($p \leq 0.038$ for linear trend).
- Average ratios of $AUC_{0-12hr(SS)}/AUC_{0-inf(SS)}$ after 14 days of BID dosing (1.04 to 1.45) also showed higher nonlinear (45%) increases in valdecoxib AUC after 20 mg BID dosing. This is also demonstrated in the following Figure:

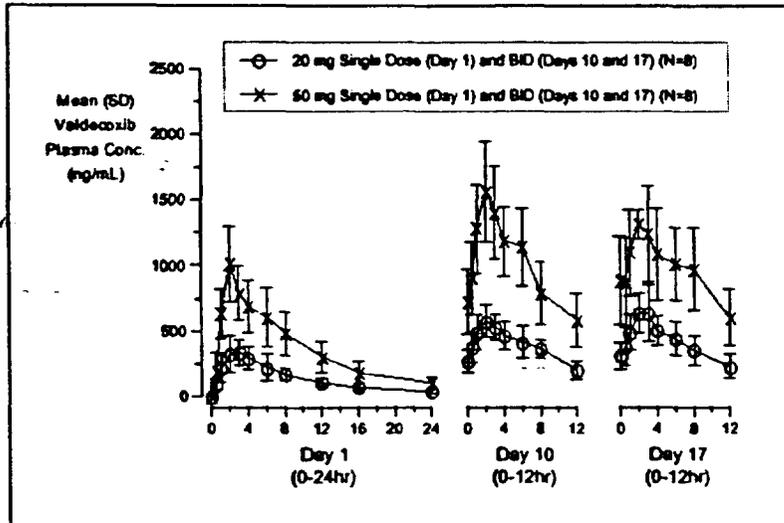
Figure: Relationship Between Dose versus Steady State Valdecoxib AUC_{0-12hr} (Mean \pm SD; N=8) after Multiple BID Dosing of Valdecoxib



- The 20 mg and 50 mg doses have similar dose normalized values and is about 45% higher than that after 2-10 mg doses. There appears to be an increase in bioavailability at multiple BID doses higher than 10 mg.

The mean plasma concentration after repeated dosing is shown in the following figure:

Figure: Plasma Concentrations of Valdecoxib on Day 1 after a Single Dose of Valdecoxib 20 mg or 50 mg, and on Days 10 and 17 after Repeated Doses of Valdecoxib 20 mg BID or 50 mg BID.



- Average ratios of valdecoxib $AUC_{0-12hr(SS)}$ on Day 17 (after 14 days of dosing) relative to those on Day 10 (ratios = 0.96 to 1.11) indicated no statistically significant change in steady state kinetics of valdecoxib between 7 and 14 days of BID dosing for 5 mg, 10 mg, 20 mg and 50 mg dose levels (ratios = 0.96 to 1.06), but not for 2 mg BID dosing (ratio = 1.11). This finding indicated no important changes in steady-state plasma concentrations of valdecoxib after seven days of multiple BID dosing.
- Metabolite: The ratios of mean SC-66905 AUC_{0-12hr} at steady state relative to single dose AUC_{0-inf} suggested that the kinetics of this metabolite did not significantly change after valdecoxib BID dosing between 2 mg to 50 mg (ratios = 0.99 to 1.05).
- The ratios of steady state AUC_{0-12hr} of SC-66905 on Day 17 relative to those on Day 10 (ratios = 0.94 to 1.06) indicated no statistically significant change in average plasma exposure of SC-66905 between seven and 14 days of valdecoxib BID dosing.

The following Table summarizes pharmacokinetic parameters for valdecoxib and SC-66905 after single and multiple once-daily (QD) 10 mg doses of valdecoxib under fed and fasted conditions.

Table: Pharmacokinetics of Valdecoxib after a Single 10 mg Dose (Day 1) and after Multiple (QD) Doses for 7 and 14 Days.

Plasma PK Parameter by Analyte	Treatment Mean (% CV)					
	Day 1 (Single Dose)		Day 10 (After 7 Days of QD Dosing)		Day 17 (After 14 Days of QD Dosing)	
	10 mg SD Fed (N=8)	10 mg SD Fasted (N=8)	10 mg QD Fed (N=8)	10 mg QD Fasted (N=8)	10 mg QD Fed (N=8)	10 mg QD Fasted (N=8)
Analyte = Valdecoxib						
AUC(0-24hr) (hr ng/mL)	1240 (24)	1357 (27)	1385 (23)	1415 (27)	1645 (22)	1479 (20)
AUC(0-lqc) (hr ng/mL)	1381 (27)	1483 (28)	NAV	NAV	NAV	NAV
AUC(0-inf) (hr ng/mL)	1402 (27)	1499 (28)	NAV	NAV	NAV	NAV
C _{max} (ng/mL)	140 (20)	157 (33)	145 (35)	155 (22)	176 (30)	161 (30)
T _{max} (hr)	5.75 (12)	2.50 (30)	5.25 (20)	2.38 (31)	5.38 (22)	2.25 (31)
T _{1/2} (hr)	6.96 (18)	6.97 (12)	NAV	NAV	8.23 (17)	8.11 (16)
Linear PK: (a) Day 10 vs. Day 1	NAP	NAP	1.00 (0.88, 1.14)	0.95 (0.88, 1.02)	NAP	NAP
Linear PK: (b) Day 17 vs. Day 10	NAP	NAP	NAP	NAP	1.19 (1.14, 1.25)	1.06 (0.97, 1.17)
Analyte = SC-66905						
AUC(0-24hr) (hr ng/mL)	99.5 (16)	120 (22)	114 (16)	117 (19)	123 (14)	114 (18)
AUC(0-lqc) (hr ng/mL)	108 (16)	128 (23)	NAV	NAV	NAV	NAV
AUC(0-inf) (hr ng/mL)	115 (15)	135 (21)	NAV	NAV	NAV	NAV
C _{max} (ng/mL)	9.56 (18)	11.2 (31)	9.83 (17)	11.0 (22)	10.3 (12)	9.38 (26)
T _{max} (hr)	5.75 (12)	3.38 (27)	6.00 (0)	3.13 (11)	6.00 (0)	2.88 (22)
T _{1/2} (hr)	6.55 (17)	6.70 (16)	NAV	NAV	7.79 (15)	7.40 (15)
Linear PK: (a) Day 17 vs. Day 10	NAP	NAP	NAP	NAP	1.07 (1.01, 1.14)	0.95 (0.90, 1.01)

(a) Values are the geometric LS mean ratio and 95% confidence interval for the ratio for [AUC(0-24hr)Day 10 / AUC(0-inf)Day 1] or [AUC(0-24hr)Day 17 / AUC(0-24hr)Day 10]. Linear kinetics were demonstrated statistically if the observed 95% confidence interval contained 1.00.

- Administration of valdecoxib with food delayed T_{max} by approximately two to three hours compared to fasted conditions.
- Average AUC and C_{max} of valdecoxib appeared to be comparable between fed and fasted treatment groups, suggesting that the extent of valdecoxib absorption was not affected by food.
- Valdecoxib plasma concentrations after a single 10 mg dose under fasted conditions were predictive of those after 7 or 14 days of QD dosing.
- The 19% increase in valdecoxib AUC_{0-24hr} between 7 and 14 days of QD dosing with food may not be clinically significant, so no dose adjustment would be required during multiple dosing.

Conclusions:

Based on the results of this study in healthy male volunteers it is concluded:

- Single dose pharmacokinetics are generally predictive of multiple dose pharmacokinetics of oral valdecoxib up to 50 mg BID as well as 10 mg QD.
- Steady-state concentrations of valdecoxib and SC-66905 are achieved within 4-7 days with valdecoxib administered up to 50 mg BID as well as 10 mg QD.
- Valdecoxib is readily absorbed, with a mean T_{max} for plasma of approximately 2-4 hours following single and multiple oral doses ranging from for 2 mg to 50 mg.
- Dose Proportionality: Based on the mean dose adjusted AUC_(0-∞) values, dose proportionality for valdecoxib and SC-66905 does not exist within the dose range of 2

mg, 5 mg, 10 mg, 20 mg, and 50 mg valdecoxib BID. But, may exist within the dose range of 2 mg, 5 mg and 10 mg valdecoxib BID.

- **Linearity:** Based on the 95% confidence intervals for the ratios of the mean Day 10 and 17 AUC₍₀₋₁₂₎ to the mean Day 1 AUC_(0-∞) for valdecoxib, it can be concluded that linear kinetics exist for the 2 mg and 5 mg valdecoxib BID dose groups. There may be some deviation from linear kinetics in the 10 mg, 20 mg, and 50 mg valdecoxib BID dose groups, but SC-66905 follows linear kinetics across all dose groups.
- Based in the 95% confidence intervals for the ratios of the mean Day 10 and 17 AUC₍₀₋₂₄₎ to the mean Day 1 AUC_(0-∞) for valdecoxib, it can be concluded that linear kinetics exist for both the 10 mg QD fasted and fed groups, but does not exist for SC-66905.
- There is non-linear accumulation (20%–45% increase in AUC) after 14 days of 20 mg or 50 mg BID dosing.
- At steady state, there was no statistically significant difference in AUC₍₀₋₂₄₎ between the 10 mg valdecoxib QD fasted and 5 mg valdecoxib BID dose groups; C_{max} was statistically significantly greater, and the morning trough concentration was statistically significantly lower, for the 10 mg valdecoxib QD fasted group.

Study N93-97-02-006: A double-blind, randomized, placebo-controlled, multiple-rising dose crossover study to evaluate safety and tolerability of IV parecoxib and compare the PK profile of IV parecoxib to PO valdecoxib in normal healthy subjects

This study has been reviewed by Dr. Sue Chih Lee for _____ and is summarized on page 52 of her review. In this review I will only discuss the pharmacokinetic parameters for the PO valdecoxib arm and its comparison to IV parecoxib. Details of study design have been described in Dr. Lee's review.

The following Table shows the pharmacokinetic parameters of parecoxib and valdecoxib, given at same doses (10 mg or 20 mg) of valdecoxib and parecoxib (as sodium salt). IV parecoxib or oral valdecoxib were administered twice daily (BID) for 7 days in this study

Table: Plasma Exposure of Valdecoxib From Equal Milligram Doses of Oral Valdecoxib and IV Parecoxib (as the Sodium Salt).

Valdecoxib Plasma PK Parameter by Dosing Regimen	Treatment Mean (% CV)		Ratio	Valdecoxib PO / Parecoxib IV	
	Parecoxib 10 mg IV (N=8)	Valdecoxib 10 mg PO (N=8)		90% Confidence Interval for Ratio	p-Value from ANOVA
Dosing Regimen = Single Dose					
AUC(0-12c) (hr ng/mL)	1487 (30)	1674 (26)	1.14	(1.061, 1.226)	0.012
AUC(0-inf) (hr ng/mL)	1541 (30)	1717 (26)	1.13	(1.058, 1.203)	0.011
			0.96(a)	(0.899, 1.022)(a)	0.249(a)
C _{max} (ng/mL)	200 (39)	124 (32)	0.64	(0.515, 0.788)	0.006
			0.54(a)	(0.438, 0.670)(a)	0.001(a)
T _{max} (hr)	0.61 (38)	2.29 (51)	NAV	NAV	0.004
Dosing Regimen = Multiple 10 mg BID Doses for 7 Days					
AUC(0-12hr) (hr ng/mL)	1541 (31)	1820 (28)	1.19	(1.029, 1.380)	0.060
			1.01(a)	(0.874, 1.173)(a)	0.872(a)
C _{max} (ng/mL)	275 (29)	253 (37)	0.91	(0.745, 1.111)	0.395
			0.77(a)	(0.633, 0.945)(a)	0.047(a)
C _{min} (ng/mL)	98.9 (51)	126 (44)	1.30	(1.124, 1.508)	0.013
T _{max} (hr)	0.76 (41)	1.66 (31)	NAV	NAV	<0.001

Valdecoxib Plasma PK Parameter by Dosing Regimen	Treatment Mean (% CV)		Valdecoxib PO / Parecoxib IV		
	Parecoxib 20 mg IV (N=8)	Valdecoxib 20 mg PO (N=8)	Ratio	90% Confidence Interval for Ratio	p-Value from ANOVA
Dosing Regimen = Single Dose					
AUC(0-lqc) (hr ng/mL)	3144 (28)	3583 (31)	1.13	(0.935, 1.374)	0.254
AUC(0-inf) (hr ng/mL)	3236 (29)	3665 (32)	1.13	(0.934, 1.358)	0.262
			0.96(a)	(0.794, 1.154)(a)	0.668(c)
Cmax (ng/mL)	495 (35)	295 (28)	0.60	(0.545, 0.667)	<0.001
			0.51(a)	(0.463, 0.567)(a)	<0.001(c)
Tmax (hr)	0.60 (50)	1.92 (19)	NAV	NAV	<0.001
Dosing Regimen = Multiple 20 mg BID Doses for 7 Days					
AUC(0-12hr) (hr ng/mL)	3511 (27)	4364 (35)	1.21	(1.147, 1.286)	<0.001
			1.03(c)	(0.975, 1.093)(a)	0.324(c)
Cmax (ng/mL)	659 (23)	546 (29)	0.81	(0.685, 0.965)	0.057
			0.69(c)	(0.582, 0.820)(a)	0.006(c)
Cmin (ng/mL)	217 (38)	300 (42)	1.35	(1.160, 1.576)	0.009
Tmax (hr)	0.48 (38)	2.16 (39)	NAV	NAV	0.002

(a) Values are ratio, 90% CI and p-value for the difference between geometric LS means of AUC or Cmax adjusted for molecular weight difference between parecoxib and valdecoxib, where valdecoxib AUC and Cmax values were multiplied by 0.85 [MW 314 (valdecoxib) / MW 370 (parecoxib)] prior to the analysis. Study report used a factor of 0.80 [MW 314 (valdecoxib) / MW 392 (parecoxib sodium)] for MW adjustment of valdecoxib AUC and Cmax. NAV = not available or analysis not performed.

- Average total plasma exposure (AUC) of valdecoxib was 13% to 19% higher after 10 mg doses of valdecoxib compared to parecoxib (as the sodium salt). The two treatments met the bioequivalence criteria for valdecoxib AUC_{0-inf} after single 10 mg dose, but not for AUC_{0-12hr} after multiple 10 mg BID doses.
- After 20 mg doses, average total plasma exposure of valdecoxib was 13% to 21% higher from oral valdecoxib compared to IV prodrug and the 90% confidence intervals for valdecoxib AUC exceeded the upper bounds of the standard equivalence limit of (0.80, 125).
- When adjusted for the difference in molecular weights between parecoxib and valdecoxib (see Table), multiple 10 mg BID doses of valdecoxib tablets and IV parecoxib were bioequivalent for total plasma exposure of valdecoxib [AUC_{0-12hr}]. Bioequivalence for valdecoxib plasma exposure [AUC_{0-12hr}] was demonstrated after multiple 20 mg BID doses which indicates that valdecoxib plasma exposure was comparable from oral valdecoxib and IV parecoxib.
- The Cmax of the parecoxib and valdecoxib treatment differed even after molecular weight adjustment. The differences in peak concentration (C_{max}) of valdecoxib between oral valdecoxib and IV parecoxib were attributed to slower drug absorption from oral valdecoxib, which resulted in lower average C_{max} compared to bolus IV dose.

The evaluation of dose proportionality for the 5 mg to 20 mg valdecoxib doses is shown in the following Table:

Table: Dose Proportionality Assessment (Dose Adjusted PK Parameters After Single Dose Administration of Oral Valdecoxib)

Valdecoxib Plasma PK Parameter by Dosing Regimen	Least Square Means			
	Valdecoxib 5 mg (N=8)	Valdecoxib 10 mg (N=8)	Valdecoxib 20 mg (N=8)	p-Value from ANOVA
Analyte= Valdecoxib				
AUC(0-inf) (hr ng/mL)	198	167	175	0.481
Cmax (ng/mL)	16	12	14	0.526
Xu (0-48) (mcg)	50	55	52	0.772
Analyte= SC-66905				
AUC(0-inf) (hr ng/mL)	18	15	19	0.616
Cmax (ng/mL)	1.0	0.8	1.0	0.653
Xu (0-48) (mcg)	4	4.0	4.5	0.281

Table: Dose Proportionality Assessment (Dose Adjusted PK Parameters After Multiple Dose Administration of Oral Valdecoxib)

Valdecoxib Plasma PK Parameter by Dosing Regimen	Least Square Means			
	Valdecoxib 5 mg (N=8)	Valdecoxib 10 mg (N=8)	Valdecoxib 20 mg (N=8)	p-Value from ANOVA
Analyte= Valdecoxib				
AUC(0-inf) (hr ng/mL)	332	341	371	0.571
Cmax (ng/mL)	26	24	26	0.918
Cmin (ng/mL)	10	11	12	0.375
Xu (0-48) (mcg)	75	105.0	115	0.310
Analyte= SC-66905				
AUC(0-inf) (hr ng/mL)	31	33	36	0.337
Cmax (ng/mL)	2	2.0	2.0	0.823
Cmin (ng/mL)	1.2	1.0	1.3	0.292
Xu (0-48) (mcg)	7.6	6.2	8.2	0.417

- The Table shows dose proportionality between the valdecoxib doses 5 mg to 20 mg.
- Single dose pharmacokinetics are also predictive of multiple dose plasma exposure of valdecoxib.

Conclusions:

- At equimolar doses, the plasma concentration of valdecoxib is comparable from oral valdecoxib and IV parecoxib dosing.
- There is dose proportionality at multiple twice daily dosing of 5 mg to 20 mg valdecoxib.

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PHARMACOKINETICS IN PATIENTS

The pharmacokinetics of valdecoxib were evaluated in dose ranging trials in _____ patients with acute pain. The Medical Officer, Dr. Kent Johnson; and the Pharmacometrics scientist, Dr. Jenny Zheng, have reviewed these studies. Summary Tables have been provided in the Question Based Review Section of this review. The pharmacokinetics of valdecoxib was also evaluated in patients with osteoarthritis (OA) of the knee. A population pharmacokinetic model has been developed by the sponsor to evaluate the effect of covariates on the pharmacokinetics of valdecoxib. The Population Analysis has been reviewed in this section.

POPULATION ANALYSIS

Study N91-00-08-053: Population Analysis in Osteoarthritis Patients

The population analysis was done on a Phase III study. The objective of this analysis is to summarize the pharmacokinetics of valdecoxib in the OA patient population and to investigate the influence of selected covariates (e.g., patient demographics, clinical labs, etc) on the key pharmacokinetic parameter, apparent (oral) clearance (CL/F).

Patient Population:	Osteoarthritis patients
Number:	PK samples on 305 patients
Dose:	5, 10 and 20 QD valdecoxib, 500 mg BID naproxen or placebo
Duration:	12 weeks
Study Design:	Double-blind, randomized, placebo-controlled, parallel group study
Blood Samples:	Two samples 1 hour apart each subject on Week 2 , 6 and 12.

The covariates evaluated were:

- body weight (kg)
- body surface area (m²)
- sex, age (yrs)
- race (Caucasian, Black, or Other)
- time of most recent meal relative to dose (hrs)
- serum creatinine concentration (mg/dl)
- calculated creatinine clearance (ml/min)
- SGOT (u/l), and SGPT (u/l).

The patient covariate descriptive statistics is shown in the following Table:

Table: Patient Covariate Descriptive Statistics (N=305)

Covariate	Mean \pm SD	Median	Min - Max
Age (yrs)	60.1 \pm 11.1	61	30 - 86
Weight (kg)	90.6 \pm 20.9	87.2	46.6 - 165
Height (cm)	168 \pm 10	168	142 - 193
Lean Body Weight (kg)	54.9 \pm 9.5	54.4	37.1 - 80.2
Body Surface Area (m ²)	1.99 \pm 0.34	1.96	1.34 - 2.68
Serum Creatinine (mg/dl)	0.785 \pm 0.175	0.8	0.4 - 1.5
Calculated Cre Clearance (ml/min)	74.2 \pm 24.3	71.0	25.2 - 183
SGOT (u/l)	22.6 \pm 6.4	21	10 - 43
SGPT (u/l)	23.0 \pm 9.6	21	6 - 62
Meal Time (hr)			
Week 2 (N=277)	1.41 \pm 3.76	0.25	0 - 24
Week 6 (N=247)	1.56 \pm 3.90	0.25	0 - 30
Covariate	Frequency	Percent	
Sex			
Female	185	60.7	
Male	120	39.3	
Race			
Caucasian	242	79.3	
Black	42	13.8	
Other	21	6.9	
Meal Time			
\leq 1 hr (Week 2)	248	12.4	
>1 hr (Week 2)	35	87.6	
\leq 1 hr (Week 6)	208	16.8	
>1 hr (Week 6)	42	83.2	

A simulation study was conducted during the protocol development stage to support the design of the population PK substudy for the OA trial. The objective of the simulation study was to investigate power as a function of sample size to detect a 40% difference in CL/F in an arbitrary subpopulation representing 5% of the patient population. The proposed sampling design for each patient consisted of two samples taken 1 hour apart at each of two visits during steady-state dosing. Results of the simulation study suggest that 75 patients per dose group (i.e., 225 patients in the valdecoxib arms) achieves greater than 80% power (5% significance level) to detect a 40% difference in CL/F in a 5% subpopulation.

Final Model

A steady-state one-compartment model as implemented in the PREDPP subroutine ADVAN2 in the NONMEM software was used to describe the valdecoxib plasma concentration-time curves. The structural model was parameterized in terms of the apparent absorption rate constant (k_a), the apparent volume of distribution (V/F), and the apparent clearance (CL/F).

The final model included age and sex as covariates in the CL/F submodel and body weight in the V/F submodel. The final submodels for the PK parameters are given by the expressions:

$$k_a = \theta_1 \exp(\eta_i^{k_a})$$

$$V/F = \theta_2 \left(\frac{wt_i}{90 \text{ kg}} \right)^{\theta_3} \exp(\eta_i^{V/F}) \quad (\eta_i^{V/F} = \theta_7 \eta_i^{CL})$$

$$CL/F = \theta_3 (1 + \theta_5)^{\text{sex}_i} \left(\frac{\text{age}_i}{60 \text{ yrs}} \right)^{\theta_4} \exp(\eta_i^{CL} + \kappa_{ij}^{CL})$$

where for patient i , wt_i denotes body weight, sex_i denotes an indicator variable for sex (0 if male, 1 if female), and age_i denotes age. θ_1 denotes the population mean estimate for k_a . θ_2 denotes the population mean estimate for V/F for patients with a body weight of 90 kg (approximate median rounded to nearest 10 kg). θ_3 denotes the population mean estimate for CL/F for 60 year old males. θ_4 denotes the covariate effect for weight on V/F. θ_5 denotes the fractional change in CL/F for females. θ_6 denotes the covariate effect for age on CL/F. θ_7 denotes the ratio of the interpatient standard deviations between V/F and CL/F (i.e., ω_V/ω_{CL}). The η_i 's and κ_{ij} 's denote the interpatient and interoccasion random effects in the PK parameters, respectively.

The valdecoxib PK parameter estimates and variance components from the base and final model is shown in the following Table:

Parameter	Base Model		Final Model	
	Estimate ± SE	%CV	Estimate ± SE	%CV
k_a (h ⁻¹)	0.603 ± 0.115	102	0.619 ± 0.119	129
V/F (h) (L)	101 ± 15	75.9 b	111 ± 17	67.1 c
Weight (h)	0.0 a		1.03 ± 0.50	
CL/F (h) (L/hr)	5.07 ± 0.20	25.3	5.86 ± 0.33	20.9
Sex (h)	0.0 a	(84.9) d	-0.250 ± 0.058	(83.0) d
Age (h)	0.0 a		-0.742 ± 0.280	
ρ (%CV)		21.9		21.9

a. For the base model these parameters were fixed to zero (no covariate effects).
b. $\rho_V = \theta_7 \rho_{CL}$. $\theta_7 = 3.00$
c. $\rho_V = \theta_7 \rho_{CL}$. $\theta_7 = 3.21$
d. Intraoccasion (inpatient) CV for CL/F reported in parentheses

Observations:

- Results of the covariate analysis identified sex and age effects on CL/F and body weight effects on V/F.
- The other patient factors including race, BSA, meal time, S_{cre} , CL_{cre} , SGOT, and SGPT either had effects that could be accounted for by age, sex and body weight or did not have statistically significant trends.
- The population mean estimate for CL/F in males at 60 years of age (approximate median age) was 5.86 L/hr, which is similar to that observed in the healthy subjects (6 L/hr).
- The population mean estimate for V/F in patients weighing 90 kg (approximate median weight) was 111 L.
- The covariate effect for sex differences in CL/F indicates that women have a 25% ($\theta_5 = -0.25$) lower CL/F than men.

GENERAL BIOPHARMACEUTICS

Absolute Bioavailability:

Study N91-99-02-070: An open label, randomized, single dose, crossover study to compare the pharmacokinetics and bioavailability of intravenous and oral tablet valdecoxib formulations in healthy adult subjects

The primary objective of this study was to determine the absolute bioavailability of valdecoxib. The study design is given below.

Study Design	Open-label, single-dose, randomized, 2-phase, crossover design
Study Population	N=27 healthy subjects, 20 Caucasian, 1 Hispanic, 1 Asian and 1 Other 19M and 8F, Ages 20-50, weight 60-85 kg
Treatment Group	A = 10 mg valdecoxib IV infused over 30 minutes B = 40 mg (2x20 mg) valdecoxib oral tablets
Dosage and Administration	Single dose on days 1 and 8 in a crossover randomized manner after an overnight fast. Consecutive treatments separated by a washout of 7 days.
Sampling: Blood	For Valdecoxib, SC-66905: Day 1 and 8: Up to 72 hours post dose
Urine	For Valdecoxib, SC-66905: Days 1 and 8: 10-0 hours predose, and 0-4, 4-8, 8-12, 12-24, and 24-48 hours postdose.
Analysis	

Observations:

The pharmacokinetic parameters after the administration of oral and IV valdecoxib formulations is shown in the following Table:

Table: Basic Pharmacokinetic Characteristics of Valdecoxib in Healthy Subjects after Oral and IV Administration of Valdecoxib.

Single Dose PK Parameter ^a by Analyte	Treatment Mean (% CV)		Ratio	Valdecoxib Oral / IV 90% Confidence Interval for Ratio	(a) p-Value (ANOVA)
	Valdecoxib 40 mg PO (2x20 mg) (N=24)	Valdecoxib 10 mg IV Over 30 Min (N=24)			
Analyte = Valdecoxib					
AUC(0-lqc) (hr ng/mL)	5791 (26)	1735 (21)	0.826	(0.790, 0.864)	<0.001
AUC(0-inf) (hr ng/mL)	5819 (26)	1751 (21)	0.823	(0.787, 0.861)	<0.001
Cmax (ng/mL)	530 (29)	260 (21)	0.499	(0.458, 0.544)	<0.001
Tmax (hr)	3.5 (22)	0.6 (22)	NAV	NAV	NAV
CL (L/hr)	7.3 (25) (b)	6.0 (23)	NAV	NAV	NAV

Vss (L)	85.8 (25) (b)	54.5 (20)	NAV	NAV	NAV
MRT (hr)	11.9 (17)	9.4 (22)	NAV	NAV	NAV
Effective Half-Life (hr)	8.3 (17)	6.5 (22)	NAV	NAV	NAV
T1/2 (hr)	8.0 (17)	7.4 (20)	NAV	NAV	NAV
XU(0-lqc) (mg)	1.21 (47)	0.35 (35)	0.824	(0.720, 0.943)	0.022
F (c)	0.829 (12)	NAP	NAV	NAV	NAV
Analyte = SC-66905					
AUC(0-lqc) (hr ng/mL)	481 (29)	114 (27)	1.048	(0.987, 1.114)	0.193
AUC(0-inf) (hr ng/mL)	491 (28)	130 (25)	0.933	(0.883, 0.987)	0.045
Cmax (ng/mL)	36.6 (34)	10.9 (29)	0.824	(0.754, 0.901)	0.001
Tmax (hr)	4.1 (21)	3.0 (37)	NAV	NAV	NAV
MRT (hr)	13.0 (14)	12.3 (20)	NAV	NAV	NAV
Effective Half-Life (hr)	9.0 (14)	8.5 (20)	NAV	NAV	NAV
T1/2 (hr)	7.2 (13)	8.5 (23)	NAV	NAV	NAV
XU(0-lqc) (mg)	0.121 (29)	0.036 (40)	0.875	(0.797, 0.961)	0.023

(a) Ratio (oral/IV), 90% confidence interval and p-value were derived from log-transformed pharmacokinetic parameters. Oral dose PK parameters were dose-adjusted (to 10 mg dose) by dividing by 4.

(b) For oral dose, CL = CL/F, Vss = Vss/F.

(c) Estimate of absolute oral bioavailability (F) = the ratio of oral/IV AUC(0-inf) of valdecoxib, where AUC(0-inf) after oral dose was adjusted to a 10 mg dose.

NAV = not available or analysis not performed; NAP = not applicable.

- The estimate of absolute bioavailability (F) based on oral/IV ratio of valdecoxib AUC (0-∞) was 0.829, indicating that first-pass metabolism of orally-administered valdecoxib was low.
- Following oral administration the effective half-life values for valdecoxib (7.4 hr) and SC-66905 (8.5 hr) were similar to the average T_{1/2} values for valdecoxib (8.0 hr) and SC-66905 (7.2 hr) after IV administration.
- Approximately 4% of the oral and IV dose was excreted in urine as unchanged valdecoxib and SC-66905, indicating extensive hepatic metabolism of both compounds.
- The ratios of the geometric LSM indicated that, following the oral formulation, valdecoxib overall exposure in plasma was 17% lower, and valdecoxib and SC-66905 exposures in urine were 13% to 18% lower, than the corresponding exposure following the IV formulation.
- The incidence of adverse events following administration of oral valdecoxib 40 mg (22%) is lower than that following administration of IV valdecoxib 10 mg (48%).

Conclusions:

The absolute bioavailability of valdecoxib tablets was 83%.

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**BIOEQUIVALENCE OF CLINICAL TRIAL AND
COMMERCIAL FORMULATIONS**

Bioequivalence between Phase I Capsules and Phase II Tablets:

Study N91-97-02-009: An open-label, randomized, four period, two treatment, bioequivalence/comparative bioavailability of valdecoxib capsule vs. immediate release tablet formulations

The primary objectives of this study was to assess the bioequivalence of valdecoxib administered in the form of Immediate Release (IR) tablets 20 mg (2 x 10 mg; test) and capsules 20 mg (2 x 10 mg; reference). The study design is given as follows:

Study Design	Open-label, single-dose, randomized, 4-period, 2-treatment replicate design
Study Population	N=24 healthy subjects, 20 Caucasians, 1 Black and 2 Hispanic, 1 Asian 10M and 14F, Ages 20-55, weight 60-85 kg
Treatment Group	A: 2 x 10 mg valdecoxib capsules (R) B: 2 x 10 mg valdecoxib tablets (T)
Dosage and Administration	Single dose on days 1, 8, 15 and 22 in a randomized manner after an overnight fast. Consecutive treatments separated by a washout of 7 days. Randomized to the following treatment sequences: ABBA or BAAB
Sampling: Blood	For Valdecoxib, SC-66905: Day 1, 8, 15 and 22: Up to 72 hours post dose
Urine	For Valdecoxib, SC-66905: Day 1, 8, 15 and 22: 12 hours predose through 24 hours post dose
Analysis	

Observations:

The bioequivalence assessment for the valdecoxib capsules and tablets are shown in the following Table:

Table: Bioequivalence of Valdecoxib 10 mg Phase I Capsule and Phase II Tablet

Single Dose Plasma PK Parameter by Analyte	Treatment Mean (% CV)		Tablet (N=24) / Capsule (N=24)	
	Valdecoxib 2x10 mg Phase II Tablets (N=24 sub/48 obs)	Valdecoxib 2x10 mg Phase I Capsules (N=24 sub/48 obs)	Ratio	90% Confidence Interval (%) for Ratio
Analyte = Valdecoxib				
AUC _{0-4h} (hr*ng/mL)	3282 (32)	3430 (28)	94.4	(91.2, 97.8)
AUC _{0-∞} (hr*ng/mL)	3322 (32)	3462 (28)	94.7	(91.5, 98.1)
C _{max} (ng/mL)	299 (38)	334 (30)	86.8	(82.0, 92.0)
T _{max} (hr)	3.67 (29)	3.09 (37)	NAV	NAV
T _{1/2} (hr)	9.59 (28)	9.03 (26)	NAV	NAV
Analyte = SC-66905				
AUC _{0-4h} (hr*ng/mL)	267 (37)	278 (33)	94.5	(90.2, 99.1)
AUC _{0-∞} (hr*ng/mL)	280 (36)	290 (33)	95.2	(91.2, 99.5)
C _{max} (ng/mL)	18.9 (49)	21.3 (39)	86.0	(80.8, 91.6)
T _{max} (hr)	4.44 (27)	3.75 (24)	NAV	NAV
T _{1/2} (hr)	9.20 (26)	8.95 (27)	NAV	NAV

NAV = not available or analysis not performed.

Conclusions:

- The two valdecoxib formulations (capsules and tablets) are bioequivalent with respect to valdecoxib and SC-6690 for AUC_s and C_{max}.

Bioequivalence of Phase II and Phase III tablets:

Study N91-99-02-050: An open-label, randomized, four period, two treatment, replicate design study to assess the bioequivalency/comparative bioavailability of valdecoxib Phase II and Phase III tablet formulations

The primary objectives of this study were to assess the bioequivalency of valdecoxib tablet formulations administered in the Phase II and Phase III trials. The secondary objective was to estimate the intra-subject variability of the valdecoxib pharmacokinetic parameters for the Phase II and Phase III tablet formulations.

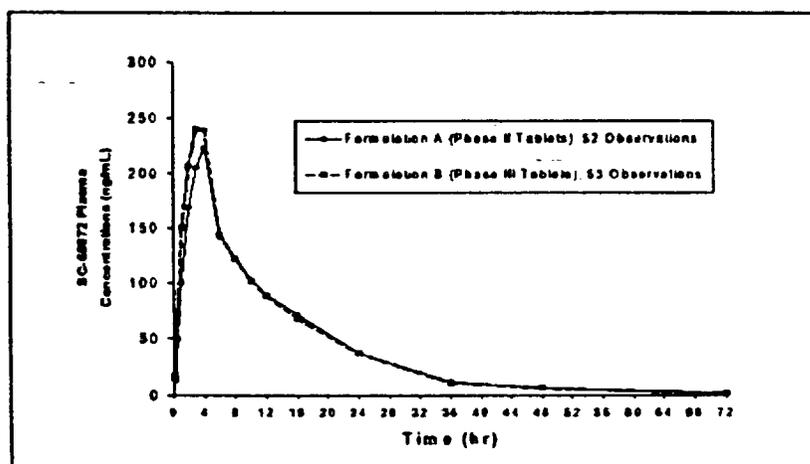
The study design is given as follows:

Study Design	Open-label, single-dose, randomized, 4-period, 2-treatment replicate design
Study Population	N=28 healthy subjects, 23 Caucasians, 2 Blacks and 1 Hispanic, 1 Asian 20M and 4F, Ages 20-55, weight 60-85 kg
Treatment Group	A: 2 x 10 mg valdecoxib Phase II formulation tablet. B: 2 x 10 mg valdecoxib Phase III formulation tablet.
Dosage and Administration	Single dose on days 1, 8, 15 and 22 in a randomized manner after an overnight fast. Consecutive treatments separated by a washout of 7 days. Randomized to the following treatment sequences: ABBA or BAAB

Sampling: Blood	For <u>Valdecoxib, SC-66905</u> : Day 1, 8, 15 and 22: Up to 72 hours post dose
Urine	For <u>Valdecoxib, SC-66905</u> : Day 1, 8, 15 and 22: 12 hours predose through 24 hours post dose
Analysis	

Observations:

The mean plasma concentration time profile for valdecoxib with the Phase II and III formulation is shown in the following Figure:



The mean(SD) pharmacokinetic parameters is shown in the following Table:

Table: Mean (\pm SD) Valdecoxib and SC-66905 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Valdecoxib		SC-66905	
	Phase II Tablets 20 mg SD N = 52	Phase III Tablets 20 mg SD N = 53	Phase II Tablets 20 mg SD N = 52	Phase III Tablets 20 mg SD N = 53
AUC (0-72) (ng/mL*hr)	2878.5 \pm 784.2	3006.3 \pm 779.0	272.3 \pm 84.8	288.3 \pm 92.3
AUC (0-t _{qc}) (ng/mL*hr)	2870.3 \pm 790.4	2996.4 \pm 782.8	262.9 \pm 83.8	278.1 \pm 91.3
AUC (0- ∞) (ng/mL*hr)	2901.5 \pm 810.0	3025.5 \pm 799.1	276.1 \pm 83.9	292.9 \pm 90.8
C _{max} (ng/mL)	236.0 \pm 68.8	262.5 \pm 74.1	17.0 \pm 7.3	18.7 \pm 7.8
T _{max} (hr)	3.52 \pm 0.83	3.13 \pm 0.92	4.71 \pm 2.06	4.26 \pm 1.72
T _{1/2} (hr)	9.06 \pm 2.67	8.96 \pm 2.41	7.79 \pm 1.77	8.01 \pm 2.20
XU (0-t _{qc}) (μ g)	513.30 \pm 260.86	534.05 \pm 253.99	53.60 \pm 18.08	50.66 \pm 24.27

The bioequivalence assessment as shown by the 90% CI is given in the following Table:

Table: Ratios and 90% Confidence Intervals for Valdecoxib and SC-66905
Pharmacokinetic Parameters

Parameter	Least Squares Means		Ratio Phase III/ Phase II	90% Confidence Interval
	Phase III Tablets 20 mg SD N (OBS) = 52	Phase II Tablets 20 mg SD N (OBS) = 52		
Valdecoxib				
AUC (0-72) (ng/mL*hr)	2942.31	2764.07	1.064	(1.025, 1.105)
AUC (0-lqc) (ng/mL*hr)	2930.73	2753.51	1.064	(1.025, 1.105)
AUC (0-∞) (ng/mL*hr)	2957.48	2781.04	1.063	(1.024, 1.105)
Cmax (ng/mL)	257.04	225.86	1.138	(1.063, 1.218)
SC-66905				
AUC (0-72) (ng/mL*hr)	276.59	260.49	1.062	(1.021, 1.104)
AUC (0-lqc) (ng/mL*hr)	266.22	251.08	1.060	(1.017, 1.105)
AUC (0-∞) (ng/mL*hr)	281.87	264.65	1.065	(1.027, 1.104)
Cmax (ng/mL)	17.57	15.81	1.111	(1.047, 1.180)

The inter and intra-subject variability for valdecoxib and SC-66905 pharmacokinetic parameters is shown in the following Table:

Table: Variability (%CV) of Log-transformed Valdecoxib and SC-66905
AUC and Cmax Values Within and Between Subjects

Parameter Variability	Valdecoxib (%CV)		SC-66905 (%CV)	
	Phase II Tablets 20 mg SD	Phase III Tablets 20 mg SD	Phase II Tablets 20 mg SD	Phase III Tablets 20 mg SD
AUC (0-72) (ng/mL*hr)				
Intra-Subject	14.1	9.0	13.9	12.3
Inter-Subject	25.6	28.0	28.4	30.8
AUC (0-lqc) (ng/mL*hr)				
Intra-Subject	14.1	9.0	14.4	13.5
Inter-Subject	26.0	28.3	28.9	31.8
AUC (0-∞) (ng/mL*hr)				
Intra-Subject	14.2	9.0	13.1	11.1
Inter-Subject	26.2	28.5	28.0	29.8
Cmax (ng/mL)				
Intra-Subject	19.9	12.1	20.2	17.7
Inter-Subject	23.8	29.2	33.1	35.3

Conclusions:

- A single dose of 20 mg valdecoxib Phase II tablets was bioequivalent to a single dose of 20 mg valdecoxib Phase III tablets with respect to valdecoxib and SC-66905 AUC and C_{max}.
- For both valdecoxib and SC-66905 AUCs and C_{max}, the intra-subject variability for The Phase III tablets was smaller than that for the Phase II tablets, but the inter-subject variability was slightly larger than that for Formulation Phase III tablets.

Bioequivalence of Phase III and Commercial Tablets:

(A) Bioequivalence of 10 mg Tablets:

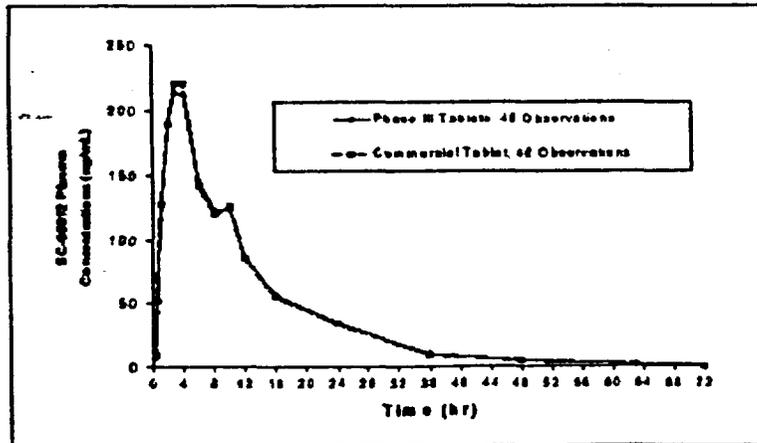
Study N91-99-02-056: A open label, randomized, four period, two treatment, replicate design study to assess the bioequivalency of valdecoxib phase III and commercial tablet formulations

The primary objectives of this study were to assess the bioequivalency of valdecoxib tablet formulations administered in the Phase III trials and Commercial tablet formulations. The secondary objective was to estimate the intra-subject variability of the valdecoxib pharmacokinetic parameters for the Phase III and Commercial tablet formulations. The study design is given as follows:

Study Design	Open-label, single-dose, randomized, 4-period, 2-treatment replicate design
Study Population	N=24 healthy subjects, 12 Caucasians, 9 Blacks and 3 Hispanic 20M and 4F, Ages 24-49, weight 60-85 kg
Treatment Group	A: 2 x 10 mg valdecoxib Phase III formulation tablet. B: 2 x 10 mg valdecoxib Commercial formulation tablet.
Dosage and Administration	Single dose on days 1, 8, 15 and 22 in a randomized manner after an overnight fast. Consecutive treatments separated by a washout of 7 days. Randomized to the following treatment sequences: ABBA or BAAB
Sampling: Blood	For Valdecoxib, SC-66905: Day 1, 8, 15 and 22: Up to 72 hours post dose
Urine	For Valdecoxib, SC-66905: Day 1, 8, 15 and 22: 12 hours predose through 24 hours post dose
Analysis	

Observations:

The mean plasma concentration time profile for valdecoxib with the Phase III and commercial tablets is shown in the following Figure:



The mean (SD) pharmacokinetic parameters for valdecoxib and SC-66905 is shown in the following Table:

Table: Mean (\pm SD) valdecoxib and SC-66905 Pharmacokinetic Parameters

Pharmacokinetic Parameter	Valdecoxib		SC-66905	
	Phase III Tablets	Commercial Tablets	Phase III Tablets	Commercial Tablets
	20 mg SD n = 48	20 mg SD n = 48	20 mg SD n = 48	20 mg SD n = 48
AUC (0-72) (ng/mL*hr)	2771.2 \pm 770.36	2779.9 \pm 710.07	237.8 \pm 59.78	245.8 \pm 65.86
AUC (0-lqc) (ng/mL*hr)	2757.7 \pm 777.66	2763.8 \pm 715.93	227.3 \pm 60.48	233.7 \pm 61.26
AUC (0 \rightarrow) (ng/mL*hr)	2781.1 \pm 788.05	2788.8 \pm 730.48	246.5 \pm 57.41	248.5 \pm 58.02
Cmax (ng/mL)	235.0 \pm 55.56	239.6 \pm 41.56	16.2 \pm 4.53	16.4 \pm 4.08
Tmax (hr)	3.1 \pm 1.37	3.0 \pm 0.84	4.6 \pm 2.25	4.1 \pm 1.84
T1/2 (hr)	8.1 \pm 1.74	8.0 \pm 1.80	8.2 \pm 1.99	7.9 \pm 2.36
XU (0-lqc) (μ g)	409.4 \pm 126.74	424.1 \pm 148.03	56.4 \pm 21.46	59.3 \pm 22.33

The bioequivalence assessment as done by the 90% CIs is shown in the following Table:

Table: Mean Pharmacokinetic Parameters for Commercial Tablets and Phase III Tablets

Parameter	Least Squares Means		Ratio Commercial/Phase III	90% Confidence Interval
	Commercial Tablets 20 mg SD N (OBS) = 48	Phase III Tablets 20 mg SD N (OBS) = 48		
Valdecoxib				
Cmax (ng/mL)	236.0	228.4	1.033	(0.969, 1.102)
AUC (0-72) (hr*ng/mL)	2702.6	2671.8	1.012	(0.967, 1.059)
AUC (0-lqc) (hr*ng/mL)	2685.0	2656.1	1.011	(0.965, 1.059)
AUC (0 \rightarrow) (hr*ng/mL)	2707.9	2678.0	1.011	(0.966, 1.058)
SC-66905				
Cmax (ng/mL)	15.8	15.5	1.023	(0.964, 1.085)
AUC (0-72) (hr*ng/mL)	237.4	230.0	1.032	(0.989, 1.077)
AUC (0-lqc) (hr*ng/mL)	225.6	218.8	1.031	(0.988, 1.075)
AUC (0 \rightarrow) (hr*ng/mL) (a)	240.8	239.6	1.005	(0.970, 1.042)

The inter and intra-subject variability in the pharmacokinetic parameters is shown in the following Table:

Table: Variability (%CV) of Log-Transformed Valdecoxib and SC-66905 AUC and Cmax Values Within Subjects and Between Subjects

Parameter Variability	Valdecoxib (%CV)		SC-66905 (%CV)	
	Phase III Tablets	Commercial Tablets	Phase III Tablets	Commercial Tablets
	20 mg SD	20 mg SD	20 mg SD	20 mg SD
AUC (0-72) (ng/mL*hr)				
Intra-Subject Variability	5.6	9.0	7.8	16.5
Inter-Subject Variability	27.5	21.9	25.1	22.0
AUC (0-lqc) (ng/mL*hr)				
Intra-Subject Variability	5.6	9.0	8.2	12.6
Inter-Subject Variability	27.9	22.2	26.8	25.0
AUC (0 \rightarrow) (ng/mL*hr)				
Intra-Subject Variability	5.6	9.0	9.1	8.3
Inter-Subject Variability	27.9	22.4	22.1	22.8
Cmax (ng/mL)				
Intra-Subject Variability	16.7	13.9	13.8	14.1
Inter-Subject Variability	19.0	11.0	28.4	24.9

Conclusions:

- A single dose of 20 mg (2 x 10 mg) valdecoxib Phase III tablets is bioequivalent to a single dose of 20 mg (2 x 10 mg) valdecoxib commercial tablets with respect to valdecoxib and SC-66905 AUC and C_{max}.
- The intra-subject variability for valdecoxib and SC-66905 AUC was higher (~4%) for the commercial tablets, but the inter-subject for valdecoxib AUC was higher for the Phase III tablets.

(B) Bioequivalence of 20 mg and 40 mg Tablets:

Study N91-00-02-078: Open label, randomized, three-way crossover study to assess the bioequivalency of 20 mg and 40 mg valdecoxib tablets in healthy adult subjects:

The primary objective of this study was to compare the bioavailability of single oral doses of three valdecoxib formulations, a 40 mg valdecoxib Commercial tablet, a 20 mg valdecoxib Phase III tablet, and a 20 mg valdecoxib Commercial tablet. The study design is given as follows:

Study Design	Open-label, single-dose, randomized, 3-way crossover design
Study Population	N=30 healthy subjects, 25M and 5F, Ages 20-54, weight 60-85 kg
Treatment Group	A: 1 x 40 mg valdecoxib Commercial formulation tablet. B: 2 x 20 mg valdecoxib Phase III formulation tablets. C: 2 x 20 mg valdecoxib Commercial formulation tablets.
Dosage and Administration	Single dose on days 1, 8 and 15 in a crossover randomized manner after an overnight fast. Consecutive treatments separated by a washout of 7 days.
Sampling: Blood	For Valdecoxib, SC-66905: Day 1, 8 and 15: Up to 72 hours post dose
Urine	None
Analysis	

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Observations:

The plasma concentration time profile for valdecoxib at equal doses after the administration of Phase III tablets and commercial tablets is shown in the following Figure:

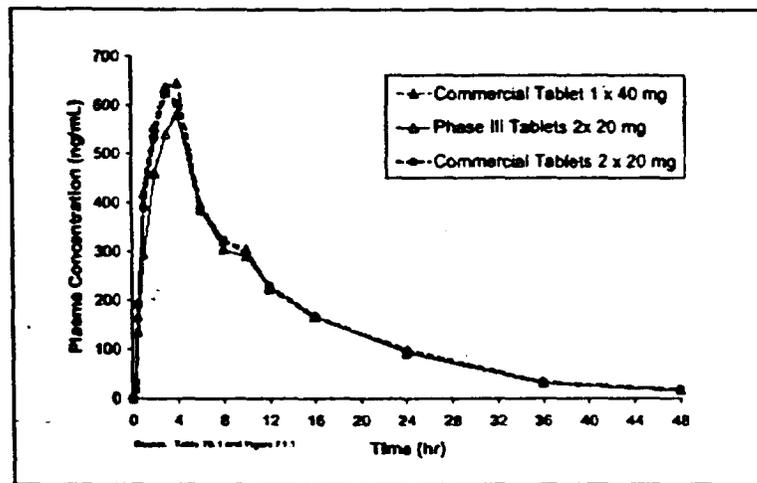


Table: Bioequivalence of Commercial Formulations of Valdecoxib 20 mg and 40 mg Tablets.

Steady State Plasma PK Parameter by Analyte	Treatment Mean (% CV)		2x20 mg (N=30) / 1x40 mg (N=29)		
	Valdecoxib 2x20 mg Commercial Tablets (N=30)	Valdecoxib 1x40 mg Commercial Tablet (N=29)	Ratio	90% Confidence Interval for Ratio	p Value (ANOVA)
Analyte = Valdecoxib					
AUC(0-lqc) (hr ng/mL)	7822 (31)	7969 (37)	0.981	(0.936, 1.028)	0.496
AUC(0-inf) (hr ng/mL)	7872 (31)	8018 (38)	0.982	(0.937, 1.029)	0.510
Cmax (ng/mL)	669 (30)	701 (32)	0.955	(0.885, 1.031)	0.323
Tmax (hr)	3.27 (29)	3.14 (28)	NAV	NAV	0.664
T1/2 (hr)	8.61 (22)	8.52 (22)	NAV	NAV	0.557
Analyte = SC-66905					
AUC(0-lqc) (hr ng/mL)	675 (31)	707 (32)	0.956	(0.907, 1.007)	0.150
AUC(0-inf) (hr ng/mL)	693 (30)	722 (32)	0.961	(0.914, 1.010)	0.186
Cmax (ng/mL)	44.2 (41)	46.5 (36)	0.942	(0.873, 1.016)	0.193
Tmax (hr)	4.37 (37)	3.83 (35)	NAV	NAV	0.173
T1/2 (hr)	8.76 (26)	8.69 (22)	NAV	NAV	0.878

NAV = not available or analysis not performed.

Table: Bioequivalence of Valdecoxib 20 mg Phase III Tablet and 20 mg Commercial Tablet.

Steady State Plasma PK Parameter by Analyte	Treatment Mean (% CV)(a)		Ratio	Commercial / Phase III (b)	
	Valdecoxib 2x20 mg Commercial Tablets (N=30)	Valdecoxib 2x20 mg Phase III Tablets (N=30)		90% Confidence Interval for Ratio	p Value (ANOVA)
Analyte = Valdecoxib					
AUC(0-lqc) (hr ng/mL)	7822 (31)	7333 (25)	1.044	(0.997, 1.094)	0.126
AUC(0-inf) (hr ng/mL)	7872 (31)	7374 (25)	1.045	(0.998, 1.094)	0.119
Cmax (ng/mL)	669 (30)	616 (24)	1.071	(0.993, 1.155)	0.113
Tmax (hr)	3.27 (29)	3.30 (24)	NAV	NAV	0.874
T1/2 (hr)	8.61 (22)	8.49 (22)	NAV	NAV	0.406
Analyte = SC-66905					
AUC(0-lqc) (hr ng/mL)	675 (31)	655 (28)	1.023	(0.971, 1.077)	0.469

AUC(0-inf) (hr ng/mL)	693 (30)	672 (28)	1.025	(0.976, 1.077)	0.406
C _{max} (ng/mL)	44.2 (41)	41.2 (34)	1.060	(0.983, 1.143)	0.199
T _{max} (hr)	4.37 (37)	4.03 (26)	NAV	NAV	0.353
T _{1/2} (hr)	8.76 (26)	8.61 (23)	NAV	NAV	0.448

NAV = not available or analysis not performed.

Conclusions:

- 2x20 mg commercial tablets were bioequivalent to 1x40 mg commercial tablet with respect to valdecoxib and SC-66905 AUCs and C_{max}.
- 2x20 mg Phase III tablets were bioequivalent to the 2x20 mg commercial tablets

Individual Bioequivalence Analysis (IBE):

IBE Analysis was done by Dr. Mei-Ling Chen at the Agency. All the three replicate design studies passed the IBE criteria. The subject-by-formulation (SxF) interaction and the intra-subject variation are shown in the following Table:

Study	N	Ref	Measure	SxF		Within-Subject Standard Deviation			
				Interaction	90% Conf. Int.	Test	Reference	Ratio	90% Conf. Int.
056	24	P3	AUC72	0.106	(0.067 - 0.157)	0.090	0.056	1.603	(1.120 - 2.294)
			AUCI	0.109	(0.070 - 0.161)	0.090	0.056	1.603	(1.120 - 2.294)
			AUCI	0.107	(0.067 - 0.157)	0.090	0.056	1.617	(1.130 - 2.315)
			C _{MAX}	0.101	(0 - 0.194)	0.139	0.167	0.831	(0.581 - 1.190)
050	27	P2	AUC72	0.000	(0 - 0.088)	0.089	0.141	0.630	(0.447 - .887)
			AUCI	0.000	(0 - 0.087)	0.090	0.141	0.635	(0.451 - .895)
			AUCI	0.000	(0 - 0.087)	0.089	0.142	0.629	(0.447 - .886)
			C _{MAX}	0.118	(0 - 0.212)	0.120	0.199	0.601	(0.427 - .847)
009	24	CAP	AUC72	0.000	(0 - 0.056)	0.130	0.084	1.544	(1.079 - 2.209)
			AUCI	0.000	(0 - 0.063)	0.130	0.084	1.547	(1.081 - 2.214)
			AUCI	0.000	(0 - 0.056)	0.130	0.084	1.544	(1.079 - 2.209)
			C _{MAX}	0.000	(0 - 0.151)	0.210	0.116	1.820	(1.272 - 2.604)

There was no significant SxF interaction, however, the 90% CI for SxF interaction showed significance for Study 056. The intra-subject variability was very low. However, the intra-subject variability for the "Test" was 55-60% higher (statistically significant for Study 056 and 009) than that for the "Reference". The clinical impact of this is not known at this time.

OVERALL CONCLUSIONS FROM BIOEQUIVALENCE STUDIES:

- Oral formulations of valdecoxib used in clinical trials program are bioequivalent with respect to both valdecoxib and the metabolite SC-66905.
- Bioequivalence has been established between Phase III formulation and commercial formulation

- Bioequivalence has been established between 2x10 mg commercial tablets and 1x20 mg commercial tablets.
- Bioequivalence has also been established between 2x20 mg commercial tablets and 1x40 mg commercial tablets.

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APPENDIX D

FILING AND REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission			
	Information		Information
NDA Number	21-341	Brand Name	
OCPB Division (I, II, III)	III	Generic Name	Valdecoxib
Medical Division	550	Drug Class	COX-II inhibitor/NSAID
OCPB Reviewer	Tandon	Indication(s)	Acute pain, pain, primary dysmenorrhea, osteoarthritis and rheumatoid arthritis
OCPB Team Leader	Bashaw	Dosage Form	tablets
		Dosing Regimen	10, 20 and 40 mg QD
Date of Submission	01/15/01	Route of Administration	oral
Estimated Due Date of OCPB Review	08/15/01	Sponsor	GD Searle
PDUFA Due Date	01/15/02	Priority Classification	1 S
I. Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1	1	
Isozyme characterization:	X	4	4	
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	3	3	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4	4	
multiple dose:	X	3	3	
Patients-				
single dose:	X	3 (dose ranging)	3 (PK-PD)	
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:	X	2	2	
fasting / non-fasting multiple dose:	X	2	2	
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	X	13	13	
In-vitro:	X	4	4	
Subpopulation studies -				
ethnicity:	X	Pop Analysis		
gender:	X	Pop Analysis		
pediatrics:				
geriatrics:	X	1	1	
renal impairment:	ongoing	1 (N=15)		
hepatic impairment:	X	1	1	
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
PK/PD analysis	X	1 pooled analysis	1	
Population Analyses -				
Data rich:				
Data sparse:	X	1	1	
II. Biopharmaceutics				
Absolute bioavailability:	X	1	1	
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	3 (paracoxib)	3	
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:	X	4	3	
Food-drug interaction studies:	X	2	1	
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class	II			
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		50 + Pop Analysis+ PK/PD	48 + Pop Analysis+ PK/PD	
Fiability and QBR comments				
II.	"X" if yes	Comments		
III. Application filable ?	X			
IV. Comments sent to firm ?	Yes	It has been indicated in Vol 6.15 (changed to Vol 1.139) page 8 that Diskene containing data sets for the PK/PD analysis and NONMEN control files will be provided separately. These are not included in the submission. Please provide the diskette for the PK-PD analysis as well as the population analysis. If already provided, please indicate its location.		
V.				
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	Veneeta Tandon 03/05/01			
Secondary reviewer Signature and Date	Dennis Bashaw			

CC: NDA 21-341, HFD-850(Electronic Entry or Lee), HFD-550(Scmidths), HFD-880(TL, DD, DDD)