High fat meal vs. fast:
Compared to the fast conditions, administration of 200 mg celecoxib with high fat (75 g) meal resulted in a slower rate of absorption (Tmax: increased from 2.4 to 3.4 hrs) and a greater extent of absorption (AUC_{0-48}: ↑22%; AUC_{∞}: ↑11%; Cmax: ↑39%).

Medium fat vs. fast: Following administration of 200 mg celecoxib with "medium fat" (8 g) meal, Tmax increased to 3.7 hrs, but both the AUC and Cmax increased to a less degree (AUC_{0-48}: ↑12%; AUC_{∞}: ↑1%; Cmax: ↑31%).

Antacid: Coadministration of antacid to fasted subjects reduced both the rate and extent of absorption of celecoxib (AUC_{0-48}: ↓6%; AUC_{∞}: ↓10%; Cmax: ↓37%) although Tmax was largely unaffected.

Table 1: Arithmetic Mean (±SD) Parameter Values

Fast/Fed/Antacid	AUC_{0-48} ng.hr/mL	AUC_{∞} ng.hr/mL	Cmax ng/mL	Tmax hr	T1/2 hr
Fast	5884 ± 2293	6564 ± 2383	806 ± 411	2.4 ± 0.8	14.1 ±11.4
High-Fat Meal	7141 ± 2787	7318 ± 2818	1042 ± 355	3.4 ± 1.3	6.3 ± 2.8
Medium-Fat Meal	6607 ± 2719	6894 ± 2832	952 ± 244	3.7 ± 0.8	6.2 ± 2.5
Fast/Antacid	5729 ± 2628	6116 ± 2712	507 ± 259	2.5 ± 1.1	10.6 ± 3.1

Table 2: Ratio of parameter values and the corresponding 90% confidence intervals

Comparison	AUC_{0-48} ng.hr/mL	AUC_{∞} ng.hr/mL	Cmax ng/mL
High fat meal vs. Fast	122.3%	110.7%	139.2
Medium fat meal vs. Fast	111.6%	100.8	131.3
Fast + Antacid vs. Fast	94.5%	89.7%	62.7%

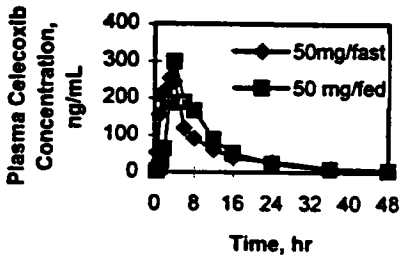
Conclusions:

- Administration of celecoxib 200 mg with high (75 g) and medium (8 g) fat content meals in the morning resulted in a slower rate of absorption (Tmax at 4 hours) with an increase in Cmax (~30% for medium fat meal; ~40% for high fat meal) and AUC (10-20% for high fat meal) relative to administration in the fasting state.
- Administration of celecoxib 200 mg with antacid, given under a fasting state, resulted in a similar Tmax (~ 2.5 hours) with a decrease in Cmax (37%) and AUC (~ 10%) relative to dosing under the fasting state.

b. 100 mg Commercial Capsules (Study 088)

This study examined the food effect on the bioavailability of 50 and 100 mg capsules after a single dose administration in 24 healthy subjects. Since the sponsor does not intend to market the 50 mg capsules, the focus will be on the 100 mg capsules. The detailed study design is shown on page 76.

Under fast conditions, Cmax was reached within 2-3 hours after dosing. Food delayed but increased the extent of absorption. As shown in the table below, mean Tmax increased to 4-5 hours and mean AUC_{∞} increased approximately 10% for both strengths when the dosage forms were taken immediately following a high-fat breakfast.



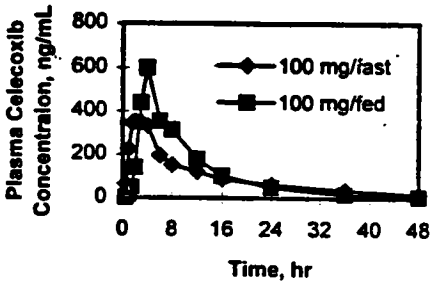


Table 1: Arithmetic Mean ±SD (%CV) Parameter Values

Parameter	50 mg/Fast	50 mg/fed	100 mg/fast	100 mg/fed
AUC_{0-48} (ng.hr/mL)	2426 ± 2183 (90.0)	2601 ± 1873 (72.0)	4463 ± 3387 (75.9)	5215 ± 3313(63.5)
AUC_{∞} (ng.hr/mL)	2694 ± 2592 (96.2)	2759 ± 2281 (82.7)	5127 ± 4020 (78.4)	5419 ± 3890(71.8)
Cmax (ng/mL)	321 ± 178 (55.5)	354 ± 130 (36.6)	455 ± 275 (60.5)	747 ± 382 (51.1)
Tmax (hr)	2.9 ± 1.6 (53.9)	4.5 ± 1.4 (30.3)	2.6 ± 1.2 (47.0)	5.0 ± 2.4 (47.9)
T1/2 (hr)	11.0 ± 6.7 (60.7)	6.5 ± 3.9 (60.2)	16.0 ± 10.2 (63.5)	6.9 ± 3.0 (44.5)

The ratios of least square means (high fat/fast) and the corresponding 95% CI for both AUC and Cmax are given in the table below. When taken with a high fat meal, the Cmax and AUC of the 100 mg capsules increased 62% and 10-20%, respectively.

Ratio of Least Square Means and 95% Confidence Interval

Parameter	Ratio of Least Square Means (95% CI)	
	50 mg Capsules	100 mg Capsules
AUC_{0-48}(fed)/ AUC_{0-48}(fast)	1.12	1.20
AUC_{∞}(fed)/ AUC_{∞}(fast)	1.07	1.07
Cmax (fed)/Cmax (fast)	1.15	1.62

Dose proportionality: Under fed conditions, both the AUC and Cmax were dose proportional for the 50 mg and 100 mg doses. Under fast conditions, the ratios of dose-adjusted parameter means (100 mg capsule/50 mg capsule) were 0.71, 0.92 and 0.95 for Cmax, AUC_{0-48} and AUC_{∞}, respectively.

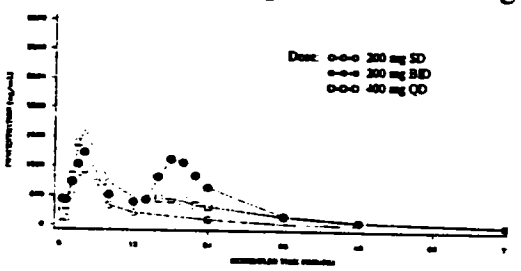
Comments:

1. The sponsor did not explain why a shorter T1/2 was observed under fed condition as compared to fast conditions. Since the drug has low aqueous solubility, the T1/2 observed under fast conditions might be complicated by the dissolution/absorption process.
2. Large variabilities for Cmax and AUC were observed for both the 50 mg and 100 mg strengths.

DOSAGE REGIMEN: 200 mg BID vs. 400 mg QD (Study 043)

For better patient compliance, a treatment regimen of once-daily dosing is considered more desirable than twice-daily dosing. The primary objective of this study was to examine the feasibility of QD dosing. Twenty-four healthy subjects were given a single 200 mg dose followed 3 days later by a multiple dose phase in which subjects received 200 mg BID or 400 mg QD for 7 days and then were crossed-over to receive the alternate treatment. The detailed design is given on page 97.

Plasma data: The figure below shows the plasma concentration-time profiles for the single dose and multiple dose phases. For the 200 mg BID regimen, the morning trough levels were higher than the afternoon (12 hr after morning dose).



The mean pharamcokinetic parameter values are tabulated below. For the 200 mg BID treatment group, the PM dose yielded a 16% higher mean AUC than the AM dose. The accumulation ratio based on the AUC values was estimated to be 2.3 for the 200 mg AM dose and 2.0 for the 400 mg dose. The 400 mg QD regimen resulted in a 15% lower mean AUC_{0-24} and a 28% higher mean Cmax when compared to the 200 mg BID regimen (90% CI: 79.4-91.5% for AUC; 116.4-141% for Cmax). The sponsor considers the difference in bioavailability between the two regimens not clinically significant and that once a day dosing is possible.

Mean±SD (%CV) Pharamcokinetic Parameter Values

AUC (ng.mL/hr)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	Accumulation Ratio
Single Dose 200 mg				
0-12 hrs: 5654 ± 1789 0-24 hrs: 7597 ± 2470 •0-48 hrs: 8761 ± 3062 (35%)	1052 ± 324 (31%)	4.0 ± 1.2	8.8 ± 2.4	-
200 mg BID				
0-12 hrs • AM dose: 8281 ± 3230 (39%) • PM dose: 9601 ± 3264 (34%) 0-24 hrs: 17882 ± 6259	1254 ± 414 (33%) 1256 ± 427 (34%) 1255 ± 406 (30%)	3.8 ± 0.5	7.3 ± 2.2	158%
400 mg QD				
•0-24 hr: 15615 ± 6090 (39%)	1760 ± 634 (36%)	4.6 ± 1.2	10.2 ± 2.8	-

Urine data: Very small amount of the drug was excreted unchanged in the urine (≤0.02% of dose). Data for the metabolites were not provided.

Conclusions:

- At steady state, the 400 mg QD dosing resulted in a 15% lower mean AUC_{0-24} and a 28% higher mean Cmax when compared to the 200 mg BID regimen.

- After 200 mg BID dosing, the PM dose had higher AUC and trough levels than the AM dose. It is unclear whether this was due to interoccasional variability, circadian variation or simply food effect (different calorie content between evening and morning meals).

Comments:

1. The Tmax for the 200 mg BID regimen as listed by the sponsor is in error.
2. In the labeling, the sponsor is not explicitly proposing the use of a 400 mg dose but indicates that this dose has been studied.

Effect of Dosing Time: AM Dosing vs. PM Dosing (Study 069)

This study was designed primarily to compare the 400 mg QD AM dosing to 400 mg QD PM dosing in healthy subjects. Twenty-four subjects were given a single 400 mg dose on Day 1 followed 3 days later by a multiple dose phase in which subjects received 400 mg QD at 8AM or 7PM with low fat meal for 10 days and then were crossed-over to receive 400 mg QD at the alternate dosing time. The study design is given on page 92.

Plasma data:

Figure a: 0-72 hrs

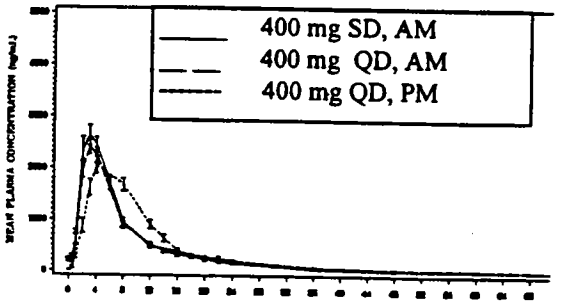
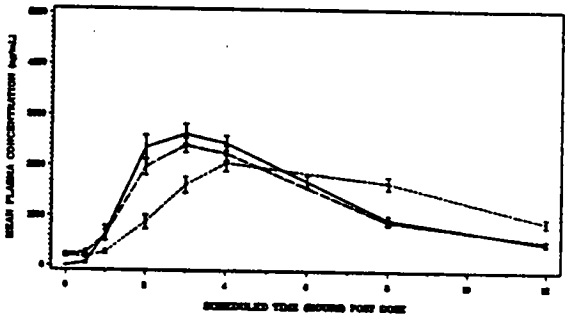


Figure b: 0-12 hrs



AM vs. PM Dosing: Compared to AM dosing, mean plasma concentrations following PM dosing tended to be lower during 0-5 hour postdose (with a longer Tmax), greater during 5-14 hours postdose and then were similar between 16-72 hours postdose. The mean ratios (PM/AM) were 1.09 (90% CI: 102.8-115.7%) for $AUC_{0\text{-}24hr}$ and 0.84 (90% CI: 75.6-94.2%) for Cmax. Cmin was lower for the PM dosing with a PM/AM ratio of ~0.75.

Table: Mean ± SD Parameter Values

Dosage Regimen	$AUC_{0\text{-}24hr}$ ng.hr/mL	Cmax ng/mL	Tmax hr	T1/2 hr
400 mg SD, AM	20208 ± 6621 22160 ± 7463*	2893 ± 930	3.1 ± 1.2	7.7 ± 2.4
400 mg QD, AM	18955 ± 6001	2565 ± 738	3.2 ± 0.6	10.1 ± 8.7
400 mg QD, PM	21034 ± 7703	2214 ± 758	4.5 ± 1.9	7.3 ± 2.8

* AUC_{∞}

The mean trough levels at the presumed steady state fluctuated appreciably on various days, suggesting high variabilities in the bioavailability of the drug.

Study Day	Mean Trough Levels, ng/mL	
	400 mg QD AM	400 mg QD, PM
Days 10-13	220-340	206-303
Days 26-29	200-337	157-263

Multiple vs. Single Dosing: Based on the observed AUC and Cmax values, no accumulation was found after 400 mg QD dosing when compared to a single dose administration.

Urine Data: Very small amount of the drug (~0.01% of the dose) was excreted unchanged in the urine. Approximately 40% of the dose was renally excreted as the metabolite SC-62807, the majority of which was excreted within the first 12 hours (See Figure). When compared to the PM dosing, the amount of SC-62807 excreted in the first 4 hours was substantially greater following AM dosing which is consistent with the observations of the plasma celecoxib concentrations.

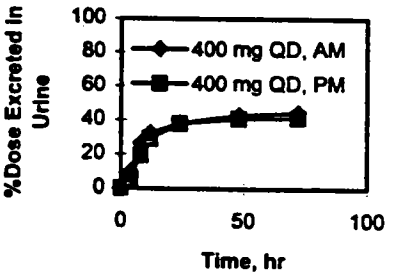


Table: Amount of SC-58635 and SC-62807 Excreted in Urine

Dosage Regimen	Study Day	Amount Excreted*, (μg)	
		SC-58635	SC-62807
400 mg SD, AM	Day 1	40.65 ± 26.55	145857 ± 36941
400 mg QD, AM	Day 13	42.3 ± 14.8	168684 ± 28817
	Day 29	50.7 ± 21.9	178095 ± 37116
400 mg QD, PM	Day 13	33.0 ± 17.7	166746 ± 44395
	Day 29	42.5 ± 15.6	162223 ± 32546

*0-48 hrs for Day 1 and 0-72 hrs for all other study days

Conclusion:

- With 400 mg QD regimen, PM dosing and AM dosing had comparable AUC values (PM/AM: 1.09) but PM dosing gave a longer Tmax and lower Cmax (PM/AM: 0.84) and Cmin (PM/AM: ~0.75).
- Approximately 40% of the dose was renally excreted as SC-62807 (M2) and only ~0.01% of the dose was excreted unchanged in the urine.

Comments:

1. In this study, PM dosing gave a lower Cmin while Study 043 suggested otherwise. Both studies showed a 10-15% higher AUC following PM dosing.
2. There are discrepancies in the urinary excretion data for SC-62807 (pages 58-59 of Volume 1.90 and page 1.72 of Volume 1.82) but both show the total urinary excretion of this metabolite was about 40% of dose.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Effect of Age: Healthy Young vs. Elderly Subjects (Study 015)

This study evaluated the pharmacokinetics of celecoxib in 24 healthy young (<50 years) and 24 healthy elderly (≥65 years) subjects. Each subject received a single oral dose of celecoxib

200 mg on Day 1, followed by celecoxib 200 mg BID dosing that began on Day 3 and ended after single morning dose on Day 10. (Additional 4 elderly and 4 young volunteers received single and BID doses of placebo.) Plasma and urine samples for celecoxib assay were collected at predetermined intervals for 48 hours after single dose and for 96 hours after last BID dose, respectively. The detailed study design is given in Appendix 1 (p. 102).

Pharmacokinetic results: Mean celecoxib plasma concentrations after multiple dosing (Day 10) in elderly subjects were 1.5- to 3-fold those in young subjects. One elderly subject (no. 221, 73 year-old Caucasian female) had celecoxib plasma concentrations after both single dose and BID dosing that were substantially higher than any other subject in this study or any other study (Cmax: 2660 ng/mL on Day 1, and 10200 ng/mL on Day 10). The results summarized below include subject no. 221 except those for $AUC_{(0-\infty)}$ and terminal T1/2, which could not be estimated in this subject. At steady state, mean apparent clearance was 40% smaller and mean AUC_{0-12} and Cmax values were approximately 70% greater in the elderly than those in the young group. Mean T_{max} was comparable in both groups (2.41 hr vs. 2.72 hr) and the mean terminal T1/2 was slightly longer in the elderly group (12.4 vs. 11.3 hr).

As observed in previous studies, less than 0.1% of the dose was excreted unchanged in the urine. The amount of metabolite SC-62807 excreted renally was 18.6% of dose in the elderly group and 14.0% in the young group. (Reviewer's note: Previous studies showed urinary excretion of metabolite SC-62807 was about 20% of dose in healthy young volunteers.)

Celecoxib Pharmacokinetic Parameter	Treatment Group Mean (CV)[a]		Ratio:[b] Elderly / Young	95% Confidence Interval for Ratio[(b)]
	Elderly (N=24)	Young (N=24)		
After Single Oral Dose of Celecoxib 200 mg (Day 1)				
$AUC_{(0-48)}$ (hr·ng/ml)	10385 (70%)	6270 (30%)	151.9%	(121.1%, 190.6%)*
$AUC_{(0-\infty)}$ (hr·ng/ml)	10143 (46%)[(c)]	6694 (30%)[(c)]	146.2%	(118.6%, 180.2%)*
C_{max} (ng/ml)	1019 (54%)	598.3 (54%)	176.3%	(131.2%, 236.8%)*
T_{max} (hr)	1.95 (39%)	3.42 (45%)	-	-
Terminal T1/2 (hr)	12.8 (34%)[(c)]	11.7 (39%)[(c)]	-	-
CL/F (L/hr/70 kg)	22.3 (30%)[(c)]	31.7 (34%)[(c)]	-	-
Vd/F (L/70 kg)	390 (30%)[(c)]	533 (51%)[(c)]	-	-
SC-62807 XU(0-48) (% of dose)	18.3 (45%)	15.6 (44%)	-	-
After Multiple BID Doses of Celecoxib 200 mg (Day 10)				
$AUC_{(0-12)}$ (hr·ng/ml)	11852 (113%)	5871 (35%)	172.0%	131.1 - 225.6 %*
$AUC_{(0-\infty)}$ (hr·ng/ml)	19446 (80%)[(c)]	9697 (38%)	185.2%	(144.3%, 237.6%)*
C_{max} (ng/ml)	1808 (104%)	973.2 (46%)	167.4%	(126.0%, 222.4%)*
$C_{min(0)}$ (ng/ml)	884.0 (154%)	391.4 (45%)	-	-
T_{max} (hr)	2.41 (43%)	2.72 (36%)	-	-
Terminal T1/2 (hr)	12.4 (21%)[(c)]	11.3 (33%)	-	-
CL/F (L/hr/70 kg)	23.7 (41%)	38.4 (46%)	-	-
Vd/F (L/70 kg)	448 (48%)[(c)]	630 (56%)	-	-
SC-58635 $XU_{(0-12)}$ (% of dose)	0.008 (205%)	0.006 (73%)	-	-
SC-62807 $XU_{(0-12)}$ (% of dose)	18.6 (38%)	14.0 (45%)	-	-

[a]Arithmetic mean [b]Ratio based on geometric means [c]N=23 [d]XU: Amount excreted in urine

- *Elderly females vs. young females:* There were statistically significant differences in steady-state celecoxib $AUC_{(0-12)}$, C_{max} and CL/F between elderly females and young females. In the elderly females, even after excluding subject 221, mean $AUC_{(0-12)}$ and C_{max} were approximately twice as high and CL/F was only half of the values observed in young females.
- *Elderly males vs. young males:* Mean Cmax and AUC were approximately 25-30% greater in elderly males than in young males.

Multiple-dose Celecoxib PK Parameter	Treatment Group Mean (CV)[a]		Ratio[b]:	95% CI for Ratio
	Elderly Male (N=12)	Young Male (N=11)	Elderly Male / Young Male	
AUC(0-12) (hr·ng/ml)	8238 (32%)	6440 (33%)	130.5%	(98.6%, 172.8%)
C_{max} (ng/ml)	1254 (24%)	1089 (48%)	124.2%	(91.2%, 169.1%)
CL/F (L/hr)[d]	26.0 (24%)	35.1 (40%)	74.0%	(47.4%, 100.6%)
	Elderly Female (N=12)	Young Female (N=13)	Elderly Female/ Young Female	
AUC(0-12) (hr·ng/ml)	15466 (119%) 10309 (44%)[c]	5389 (35%)	223.3% 188.7%[c]	(142.0%, 351.2%) (136.9%, 260.1%)[c]
C_{max} (ng/ml)	2362 (109%) 1649 (44%)[c]	875.3 (41%)	221.8% 189.3%[c]	(139.4%, 353.0%) (132.2%, 271.1%)[c]
CL/F (L/hr)[d]	20.6 (46%) 22.3 (36%)[c]	42.0 (38%)	49.2% 53.1%[c]	(23.2%, 75.1%) (27.1%, 79.0%)[c]

[a]Arithmetic mean; [b]Ratio based on geometric means; [c]Subject #221 excluded.

Pharmacodynamic results: These data were reviewed by Dr. Maria Villalba, Medical Officer of HFD-550. The sponsor claimed the following:

- There were no statistically significant differences between elderly and young subjects in the mean changes of platelet aggregation induced by arachidonic acid or collagen. The mean change was greater for elderly females (-12.00±26.92) than for all elderly subjects (-5.58±20.73) though not statistically significant.
- There were statistically significant changes from pretreatment in platelet counts between elderly and young subjects at 8 hours postdose on Day 1 and at 8 hours postdose on Day 9, but these differences were not considered to be clinically significant because the magnitude of changes was greater for subjects receiving placebo.

Reviewer's comments:

1. Two subjects (elderly females; #221 & 222) in this study had unusually high plasma celecoxib concentrations. Subject #221 had the highest level among all studies. A genotype screening of v1 mutation indicated that these two subjects had the wild type 2C9 (i.e., not poor metabolizers). However, three v2 mutations were not screened.
2. Even when both Subjects #221 and 222 were excluded in the analysis, the mean (±SD) Cmax for elderly group was 1363±433 ng/mL, which was 40% higher than the young group. The mean value for AUC_{0-12} without these two subjects could not be calculated because individual data for AUC_{0-12} were not provided.

Gender Effect on Celecoxib Pharmacokinetics

Study 015: Based on the above study, the mean parameter values for males and females in the elderly and young groups are tabulated below.

PK Parameter	Treatment Group Mean (CV)[a]		Ratio[b]	95% CI for Ratio
	Young Female (N=13)	Young Male (N=11)	Young Female/ Young Male	
AUC(0-12) (hr·ng/ml)	5389 (35%)	6440 (33%)	83.5%	(61.0%, 114.2%)
C_{max} (ng/ml)	875 (41%)	1089 (48%)	81.6%	(55.8%, 119.4%)
CL/F (L/hr)[d]	42.0 (38%)	35.1 (40%)	119.4%	(83.0%, 155.8%)
	Elderly Female (N=12)	Elderly Male (N=12)	Elderly Female/ Elderly Male	
AUC(0-12) (hr·ng/ml)	15466 (119%) 10309 (44%)[c]	8238 (32%)	142.9% 120.7%[c]	(91.6%, 222.9%) (90.4%, 161.3%)[c]
C_{max} (ng/ml)	2362 (109%) 1649 (44%)[c]	1254 (24%)	145.8% 124.4%[c]	(95.5%, 222.4%) (94.1%, 164.5%)[c]
CL/F (L/hr)[d]	20.6 (46%) 22.3 (36%)[c]	26.0 (24%)	79.4% 85.6%[c]	(53.2%, 105.5%) (61.8%, 109.4%)[c]

[a]Arithmetic mean; [b]Ratio based on geometric means; [c]Subject #221 excluded.

- Elderly females vs. elderly males: When subject #221 was excluded from the analysis, mean celecoxib AUC and Cmax in elderly females was 20-25% higher than in elderly males (not statistically significantly different).
- Young females vs. young males: Mean celecoxib AUC and Cmax were approximately 20% lower in young females than in young males (not statistically significantly different).

Reviewer's comment: Elderly females had higher Cmax and AUC than elderly males. The sponsor attributed this to body weight differences between the two groups without a formal analysis. It is noted that in this study the mean body weight in female subjects was about 20% lower than in male subjects.

Meta Analysis (Effects of Race, Gender and Body Weight)

Statistical analyses were performed on pooled data from Phase I studies to assess the effects of age, gender, body weight and race on celecoxib pharmacokinetics (270 subjects in 9 single dose studies; 112 subjects in 4 multiple dose studies) (See Appendix 1, pp. 111-113). The following factors were found to be statistically significant:

- Gender: Young female subjects had a 13% lower Cmax after single dose administration and longer terminal T1/2 (13.9 vs. 11.4 hrs after single dose) than young males.
- Race: Mean AUC was 30-40% higher (single dose and multiple dose analyses) and mean weight-adjusted steady-state CL/F was 11% lower in Blacks as compared to Caucasians.
- Body weight: Single dose Cmax was lower in subjects with higher body weight.

Reviewer's comments:

In the meta analysis of multiple dose pharmacokinetics, 2 studies were fed studies and the other two were fast studies (fast on pharmacokinetic sampling days). This may not be appropriate since there is some food effect.

Reduced Renal Function

1. Healthy Elderly Subjects with Reduced Renal Function (Study 010)

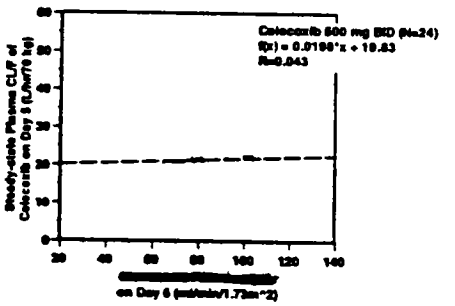
This was a single-blind, randomized, two-period crossover in healthy elderly subjects (GFR: 60-130 ml/min/1.73 m^2) and 24 subjects (8 male, 16 female, 65 to 80 years) completed the study. One of the treatments in this study was celecoxib 200 mg BID for five days, followed by celecoxib 400 mg BID for five days. All doses were given with food and a washout period of seven days separated each period of study. Blood samples were collected up to 12 hours after morning dose on Days 5 and 10 of each period.

The mean pharmacokinetic parameter values are tabulated below. The steady-state pharmacokinetics of celecoxib after 200 mg BID dosing in this study were relatively consistent with previous findings for healthy elderly subjects in a phase I study (Study 015). Increases in mean steady-state AUC(0-12) and C_{max} of celecoxib were approximately proportional to increases in BID doses between the 200 mg and 400 mg doses.

Multiple-dose Pharmacokinetic or Renal Function Parameter	Treatment Mean (CV)	
	Celecoxib 200 mg BID for 5 Days (Day 5) (N=24)	Celecoxib 400 mg BID for 5 Days (Day 10) (N=24)
AUC(0-12) (hr·ng/ml)	10313 (34%)	20027 (34%)
C_{max} (ng/ml)	1588 (37%)	2824 (31%)
$C_{min(0)}$ (ng/ml)	596.6 (41%)	1362 (53%)
T_{max} (hr)	3.29 (37%)	3.75 (30%)
Plasma CL/F (L/hr/70 kg)	21.32 (32%)	21.74 (28%)
GFR (ml/min/1.73 m^2)	79.19 (16%)[a]	78.94 (18%)[b]

[a]GFR on Day 1; [b]GFR on Day 6

Compared to elderly males (N=8), the arithmetic mean steady-state celecoxib AUC(0-12) and C_{max} in elderly females (N=16) were 28% and 29% higher, respectively, after 200 mg BID dosing and 18% and 14% higher, respectively, after 400 mg BID dosing. As shown in the figure, there was no apparent relationship between steady-state plasma of celecoxib on Day 5 and during a 1.5 hour period on Day 6 (average of individual measurements at 3, 3.5, 4 and 4.5 hr postdose).



Reviewer's comment:
The results of this study were consistent with the findings from Study 015 (elderly vs. young subjects under fasted conditions).

2. Patients with Chronic Renal Insufficiency (Study 036)

This was a double-blind, randomized, placebo-controlled, parallel group study conducted to evaluate the effect of celecoxib 200 mg BID or naproxen 500 mg BID on renal function in

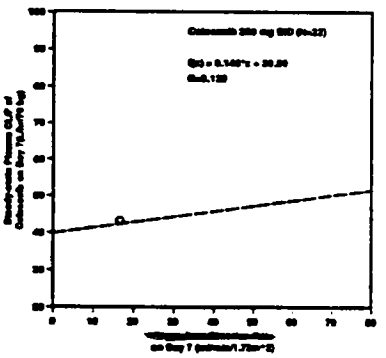
patients with stable, chronic renal insufficiency (mean GFR: 34-48 ml/min/1.73 m^2). Patients with severe renal insufficiency were not evaluated in this study. Twenty-two patients (11 male, 11 female, 43 to 78 years) completed the study. First and last BID doses were given under fasted conditions; all other BID doses were given with food. Blood samples for pharmacokinetic assays were collected for 9 and 72 hours after first and last BID doses, respectively.

Celecoxib pharmacokinetic results are summarized in the table below. Arithmetic mean steady-state plasma CL/F and drug exposure (AUC) of celecoxib were about 47% higher and 43% lower in patients with chronic renal insufficiency when compared with previous findings for subjects with normal renal function in four multiple-dose phase I studies (Appendix 1, p. 113).

Study 036

Single-dose or Steady-state Celecoxib Pharmacokinetic or Renal Function Parameter	Treatment Mean (CV) [Range] Celecoxib 200 mg BID (N=22)
Celecoxib 200 mg Single Dose (Day 1)	
AUC(0-9) (hr·ng/ml)	2457 (50%)
C_{max} (ng/ml)	508.7 (62%)
T_{max} (hr)	4.50 (41%)
Serum Creatinine (mg/dl)	1.35 (32%)
GFR (-1 to 0 hr) (ml/min/1.73 m^2)	36.7 (42%)
GFR (0 to 3 hr) (ml/min/1.73 m^2)	33.3 (38%)
After Celecoxib 200 mg BID for 7 Days (Day 7)	
AUC(0-12) (hr·ng/ml)	5003 (31%)
$C_{max(0-12)}$ (ng/ml)	662.1 (45%)
$C_{min(0)}$ (ng/ml)	356.0 (47%)
$T_{max(0-12)}$ (hr)	4.27 (61%)
CL/F[d] (L/hr/70 kg)	41.5 (44%)
Terminal T1/2 (hr)	13.1 (52%)
GFR[a] (0 to 3 hr) (ml/min/1.73 m^2)	32.0 (42%)

[a]GFR was the average of individual measurements: predose at -1, -0.5 and 0 hr; and postdose at 0, 0.5, 1, 1.5, 2, 2.5 and 3 hr.
[b]N=21 ; [c]N=20



As shown in the figure, there was no apparent relationship between steady-state plasma CL/F of celecoxib on Day 7 and during a three-hour period on Day 7 (average of individual measurements at 0, 0.5, 1, 1.5, 2, 2.5 and 3 hr postdose).

Reviewer's comment:

The findings suggest lower celecoxib plasma levels in patients with moderate renal insufficiency. This may be caused by reduced tubular reabsorption and/or decreased protein binding. It is noted that unbound fraction was not determined in this study.

Patients with Hepatic Impairment (Study # 016)

This study evaluated the effect of hepatic impairment on the single-dose and steady-state pharmacokinetics of celecoxib. Healthy volunteers with normal hepatic function (n=23) were matched with patients with mild (n=12) or moderate (n=11) hepatic impairment (as determined by the Child-Pugh classification system) by gender, age and weight. MEGX (monoethylglycinexylidide) data comparison for mildly and moderately hepatically impaired subjects support the Child-Pugh system for hepatic impairment classification employed for this study.

Each subject received a single oral dose of celecoxib 100 mg, followed by celecoxib 100 mg BID dosing. Blood and urine samples for pharmacokinetic assay were collected at predetermined intervals for 72 hours after single dose and last BID dose. The detailed study design is given in Appendix 1 (p. 114).

Patients with mild hepatic impairment vs. normal subjects:
Subjects with mild hepatic impairment had higher mean plasma concentrations than normal subjects following single dose administration (Day 1) and at steady state (Day 8). The mean pharmacokinetic parameter values following a single dose and at steady state are tabulated below. A comparison of parameter values between normal and hepatic impairment patients indicated similar trend after a single dose and at steady state.

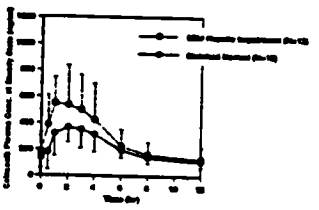


Fig.: Concentration-Time Profile (Day 8)

At steady state, patients with mild hepatic impairment had a 22% lower mean apparent oral clearance (CL/F), a 27% greater AUC(0-12) and a 43% higher Cmax after BID dosing. The difference in CL/F and AUC were not statistically significant but the difference in mean C_{max} was significant. Mean steady-state T_{max} and post steady-state terminal T1/2 of celecoxib were comparable between these patients and normal controls.

Less than 1% of the administered dose was excreted in urine as unchanged celecoxib in patients with mild hepatic impairment and normal control subjects. Steady-state urinary excretion of metabolite, SC-62807 (M2), was statistically significantly higher in mildly-impaired patients than in control subjects (33% vs. 19% of dose, respectively).

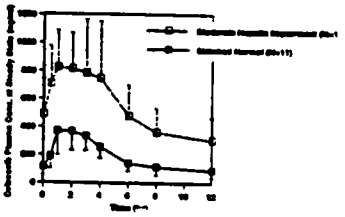
Table: Mild Hepatic Impairment vs. Normal

Celecoxib Pharmacokinetic Parameter	Treatment Group Mean (CV)[a]		Ratio[b] Mild Hepatic/ Normal	95% Confidence Interval for Ratio[(b)]
	Mild Hepatic Impairment (N=12)	Normal Control (N=12)		
After Single Oral Dose of Celecoxib 100 mg (Day 1)				
AUC(0-72) (hr·ng/ml)	3791 (57%)	2999 (36%)	115.7%	(83.9%, 159.7%)
C_{max} (ng/ml)	525.6 (46%)	342.2 (37%)	147.5%	(97.2%, 223.7%)
T_{max} (hr)	2.17 (47%)	2.17 (47%)	-	-

Terminal T1/2 (hr)	11.2 (47%)	10.8 (27%)[d]	-	-
CL/F (L/hr)[d]	34.5 (48%)	37.1 (35%)	86.4%	(62.6%, 119.2%)
Celecoxib XU(0-72)(mg)	0.004 (248%)	0.002 (181%)	84.7%	(1.7%, 4153.6%)
M2 XU(0-72) (mg)	28.5 (39%)	19.5 (55%)	154.2%	(98.0%, 242.6%)
After Multiple Doses of Celecoxib 100 mg BID (Day 8)				
AUC(0-12) (hr·ng/ml)	3518 (53%)	2575 (33%)	127.4%	(90.5%, 179.3%)
C_{max} (ng/ml)	627.9 (47%)	421.8 (32%)	143.4%	(101.9%, 201.7%)*
$C_{min(0)}$ (ng/ml)	181.4 (79%)	134.0 (56%)	117.7%	(69.3%, 199.9%)
T_{max} (hr)	1.92 (47%)	2.08 (43%)	-	-
Terminal T1/2 (hr)	11.0 (32%)	10.4 (26%)[e]	-	-
CL/F (L/hr)	35.1 (43%)	42.1 (27%)	78.5%	(55.8%, 110.5%)
CL/F (L/hr/70 kg)	32.9 (46%)	38.0 (28%)	-	-
SC-58635 XU_{0-12} (mg)[c]	0.004 (173%)	0.005 (151%)	50.5%	(8.5%, 300.5%)
M2 XU_{0-12} (mg)[c]	32.7 (46%)	18.9 (28%)	160.9%	(108.3%, 239.1%)

[a]Arithmetic mean [b]Ratio based on geometric means XU: Amount excreted in urine

Patients with moderate hepatic impairment vs. normal subjects:
Following a single oral dose of SC-58635 100 mg, it was apparent that subjects with moderate hepatic impairment had substantially higher plasma concentrations. The same was observed after multiple dosing (See figure). The mean parameter values are tabulated below.



Compared to matched control subjects, patients with moderate hepatic impairment had a statistically significant (63%) reduction in mean steady-state CL/F of celecoxib, which resulted in significant increases in plasma celecoxib levels (increases of 120% and 170% in mean C_{max} and $AUC_{(0-12)}$, respectively). Mean T_{max} were comparable (2.0 hr in patients vs. 1.9 hr in controls) while post steady-state terminal T1/2 was longer in the patients (13.6 hr vs. 10.7 hr). Mean steady-state 12-hour urinary excretion of unchanged celecoxib and metabolite SC-62807 were 67% and 62% higher, respectively, although not statistically significantly different from normal control subjects. (The power for detecting a 20% difference was not given.) No clinically relevant changes from baseline were found in creatinine clearance, SGOT, SGPT and bilirubin in these patients after celecoxib 100 mg BID dosing for 5 days.

Table: Moderate Hepatic Impairment vs. Normal

Celecoxib Pharmacokinetic Parameter	Treatment Group Mean (CV)[a]		Ratio[b] Mod. Hepatic/ Normal	95% Confidence Interval for Ratio
	Moderate Hepatic Impairment (N=11)	Normal Control (N=11)		
After Single Oral Dose of Celecoxib 100 mg (Day 1)				
AUC(0-72) (hr·ng/ml)	6554 (38%)	2663 (31%)	234.2%	(159.1%, 344.9%)*
C_{max} (ng/ml)	458.6 (31%)	325.8 (40%)	146.2%	(97.1%, 220.2%)
T_{max} (hr)	2.77 (82%)	2.91 (42%)	80.6%	(48.8%, 133.2%)
Terminal T1/2 (hr)	14.0 (31%)	11.0 (23%)[d]	129.0%	(97.0%, 171.4%)
CL/F (L/hr)	18.8 (60%)	40.5 (27%)	42.7%	(29.0%, 62.9%)*
SC-58635 $XU_{(0-72)}$ (mg)	0.003 (107%)	0.002 (191%)	129.1%	-
SC-62807 $XU_{(0-72)}$ (mg)	31.1 (40%)	19.9 (48%)	161.8%	(99.3%, 263.4%)

After Multiple Doses of Celecoxib 100 mg BID (Day 8)				
AUC(0-12) (hr·ng/ml)	6458 (41%)	2288 (33%)	269.8%	(194.3%, 374.8%)*
C_{max} (ng/ml)	951.6 (37%)	424.8 (34%)	219.9%	(167.3%, 289.1%)*
$C_{min(0)}$ (ng/ml)	487.4 (53%)	112.6 (50%)	402.9%	(233.8%, 694.2%)*
T_{max} (hr)	2.00 (55%)	1.91 (37%)	-	-
Terminal T1/2 (hr)	13.6 (41%)	10.7 (29%)[d]	122.5%	(93.0%, 161.4%)
CL/F (L/hr)	19.9 (72%)	49.5 (44%)	37.1%	(26.7%, 51.5%)*
CL/F (L/hr/70 kg)	16.2 (77%)	43.4 (43%)	-	-
SC-58635 XU(0-12) (mg)	0.007 (114%)[d]	0.004 (145%)	166.9%	(11.4%, 2451.6%)
SC-62807 XU(0-12) (mg)	31.5 (63%)[d]	16.9 (45%)	162.3%	(90.3%, 291.8%)

[a]Arithmetic mean [b]Ratio based on geometric means XU: Amount excreted in urine

Conclusion:

- Total plasma clearance of SC-58635 after single and multiple dosing was 22% and 63% lower in mildly and moderately hepatically impaired subjects relative to their matched normal subjects; this difference was statistically significant for the moderately hepatically impaired group comparison.
- The AUC and C_{max} values were statistically greater for the moderately hepatically impaired subjects compared to their matched normal subjects.
- Only C_{max} was statistically different for the mildly hepatically impaired subjects compared to their matched normal subjects following multiple dosing.

Reviewer's comment: Patients with severe hepatic impairment were not studied.

DRUG-DRUG INTERACTIONS

Celecoxib is highly plasma protein bound and extensively metabolized after oral administration. Previous experiences indicate that NSAIDs may affect the renal function and alter the pharmacokinetics of drugs that are eliminated mostly by the kidney. Therefore, the drug-drug interaction studies for celecoxib were conducted based on considerations of potential plasma protein binding displacement, inhibition of metabolism and reduction of renal excretion.

In Vitro Studies (Report M3097243)

Celecoxib was examined for its ability to inhibit cytochrome P450 (CYP) isoform-specific catalytic activities associated with CYP2C9, CYP2C19, CYP2D6 and CYP3A4. In vitro interactions were tested by incubating marker substrates with human liver microsomes in the presence of celecoxib or CYP isoform-selective chemical inhibitors, providing initial predictive information on the potential for drug-drug interactions.

The Ki values for both celecoxib and isoform selective inhibitors are tabulated below. The results indicate that :

- Celecoxib is not a potent in vitro inhibitor of CYP2C9, CYP2C19 or CYP3A4, and has low potential to inhibit the metabolism of substrates mediated by these P450 isozymes.
- Celecoxib appears to be a moderately potent in vitro inhibitor of CYP2D6, though approximately 10-fold less potent than the known CYP2D6 inhibitor, quinidine.

CYP Isoform	Marker Activity	Inhibitor	Apparent Ki (μM)
CYP2C9	Tolbutamide 4-Hydroxylation	Celecoxib	44.4
		Sulphaphenazole	0.585
CYP2C19*	S-Mepheytoin 4'-Hydroxylation	Celecoxib	17.8
		Omeprazole	5.64
CYP2D6	Bufuralol 1'-Hydroxylation	Celecoxib	4.19
		Qunidine	0.466
CYP3A4	Testosterone 6β-hydroxylation	Celecoxib	106
		Ketoconazole	0.0483

Note: Pooled (N = 8) human liver microsomes were used in the study except for CYP2C19.

Reviewer's comment:
The sponsor concluded that the apparent Ki (4.19 μM or 1.6 μg/mL) for the inhibition of CYP2D6 by celecoxib is approximately 3-fold higher than clinical plasma concentrations achieved after 200 and 400 mg/day doses (100 and 200 mg b.i.d., respectively) and, therefore, celecoxib at the recommended doses is not expected to substantially inhibit the metabolism of other drugs that are metabolized via the 2D6 isozyme. It should be noted that elderly subjects (the expected OA population) tend to have higher plasma celecoxib levels. In study 015, 2 elderly subjects had very high plasma concentrations (steady state Cmax of 3.2 and 10.2 μg/mL, respectively). Even after excluding these 2 subjects, 4 out of the 22 (18%) elderly in this study had Cmax greater than the Ki value. Therefore, the potential for a drug-drug interaction with CYP2D6 substrate in vivo cannot be neglected.

In Vivo Studies:

Fluconazole (Study 072)

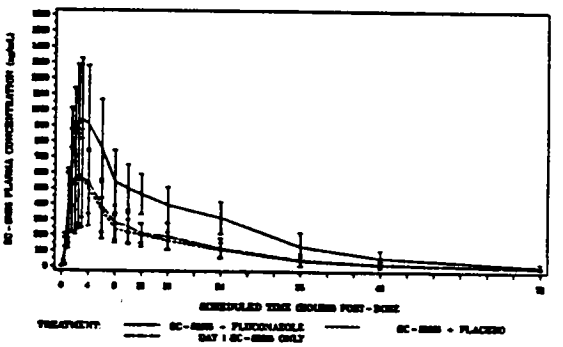
Study 072 was designed to examine the effect of two inhibitors (fluconazole and ketoconazole) on the pharmacokinetics of celecoxib in two parallel groups of healthy volunteers. The fluconazole group will be discussed first.

Fluconazole has been reported to inhibit the metabolism of CYP2C9 substrate and, therefore, may also inhibit the metabolism of celecoxib. The fluconazole group was designed to examine the effect of multiple dosing of fluconazole on the single dose pharmacokinetics of celecoxib and to assess the safety and tolerability of the coadministration. Seventeen healthy subjects in fluconazole group completed the study. On Day 1, subjects received a single dose of celecoxib 200 mg alone. On Days 10 and 19, subjects were administered celecoxib 200 mg as a single dose at the same time as the fluconazole dose. On Days 4-10, subjects were randomized to receive either fluconazole 200 mg QD or placebo. On Days 13-19, subjects were crossed over to receive the

alternate treatment of placebo or fluconazole 200 mg QD. Plasma concentrations of celecoxib and its metabolites (SC-60613 & SC-62807) were determined along with urine excretion of celecoxib and SC-62807 (M2). The detailed study design is given in Appendix 1 (p. 121).

Plasma fluconazole concentrations: On Days 10 and 19, mean plasma fluconazole concentrations reached a maximum of 11.42 (±1.8) ng/mL at 2 hrs postdose and decreased to 3.57 (±0.9) ng/mL at 72 hrs postdose. Mean trough plasma fluconazole concentrations ranged on Days 7-10 and for Days 16-19. A steady state condition could not be confirmed due to a rising trend in trough levels.

Plasma concentrations and urinary excretion of celecoxib: The mean plasma celecoxib concentration-time profiles at baseline (Day 1) and after coadministration with placebo or fluconazole are shown in the figure. Subjects receiving placebo had mean plasma concentrations similar to the baseline values. Coadministration with fluconazole resulted in much higher plasma celecoxib concentrations with an increase of 68% in Cmax and 134% in AUC_{inf} when compared to the placebo treatment. Mean half-life of celecoxib increased from 9.8 to 11.2 hrs. The amount of celecoxib excreted unchanged renally within 72 hrs postdose increased from < 10 μg to 24 μg (see table below). These results suggested that fluconazole inhibit the metabolism of celecoxib.



Mean Celecoxib Parameter Values (±SD)

Parameter	Celecoxib (Baseline)	Celecoxib + Fluconazole	Celecoxib + Placebo
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	7991.6 ± 2548.0	16792.9 ± 5058.7**	7282.5 ± 2758.1
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	7731.6 ± 2408.5	16496.9 ± 5155.7 **	7054.9 ± 2799.5
$AUC_{0\text{-}inf}$ (ng.hr/mL)	8133.5 ± 2679.2	17103.8 ± 5424.0**	7397.3 ± 2819.7
C_{max} (ng/mL)	735.3 ± 289.0	1038.7 ± 377.3*	649.0 ± 322.0
T_{max} (hrs)	2.9 ± 1.3	3.4 ± 1.6	2.6 ± 0.8
$T_{½}$ (hrs)	9.8 ± 3.7	11.2 ±3.1	9.6 ± 2.5
$XU_{0\text{-}72\ hr}$ (μg)	4.42 ± 8.62	23.66 ± 21.27	7.51 ± 11.1

*p<0.05; **p<0.001; based on comparison of (celecoxib + fluconazole) vs. (celecoxib + placebo)

Plasma concentrations of metabolite SC-60613: Mean peak plasma concentration of SC-60613 was reached at 2 hours postdose and was below the level of quantitation (<0.100 ng/mL) at 72 hrs postdose. When compared to the celecoxib+placebo treatment, celecoxib+ fluconazole treatment resulted in a decrease of 51.5% in Cmax (from 53.2 to 25.8 ng/mL) and 19.3% in AUC_{inf} (see Table below). Analysis of variance indicated that there was a statistically significant difference between

coadministration with placebo and coadministration with fluconazole for both AUC and Cmax (α=0.05).

Plasma concentrations and urinary excretion of metabolite SC-62807: The mean plasma concentration of SC-62807 reached a maximum at approximately 3 hours postdose and decreased to <10 ng/mL at 72 hrs postdose. When celecoxib was coadministered with fluconazole, mean Cmax decreased appreciably (44%) but there was not much change in mean $AUC_{0\text{-}72}$ or AUC_{inf}. The amount of SC-62807 excreted in the urine from 0-72 hours postdose were comparable between the two treatments, however, it is noted that the excretion rate in the first 24 hours postdose was significantly lower (18%; p=0.030) for celecoxib+fluconazole (1300±517 μg/hr) than for celecoxib+placebo (1579±559 μg/hr).

Parameter	Celecoxib (Baseline)	Celecoxib + Fluconazole	Celecoxib + Placebo
SC-60613			
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	461.5 ± 118.3	261.1 ± 87.0 **	348.8 ± 87.1
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	446.9 ± 117.6	246.4 ± 85.1**	336.9 ± 87.3
$AUC_{0\text{-}inf}$ (ng.hr/mL)	471.5 ± 123.3	293.2 ± 81.0**	363.1 ± 84.7
C_{max} (ng/mL)	78.2 ± 30.4	25.8 ± 9.4 **	53.2 ± 19.2
T_{max} (hrs)	2.4 ± 1.1	2.2 ± 0.7	2.1± 0.8
$T_{½}$ (hrs)	9.4 ± 3.6	15.7 ± 5.7	11.6 ± 5.7
SC-62807			
Parameter	Celecoxib (Day 1)	Celecoxib + Fluconazole	Celecoxib + Placebo
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	5407.2 ± 1406.9	4990.3 ± 1235.1	4887.7 ± 1226.7
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	5378.4 ± 1401.1	4990.3 ± 1235.1	4864.6 ± 1232.1
$AUC_{0\text{-}inf}$ (ng.hr/mL)	5687.5 ± 1168.4	5224.5 ± 1412.3	5085.3 ± 1286.7
C_{max} (ng/mL)	641.9 ± 375.3	287.5 ± 121.8**	504.3 ± 235.6
T_{max} (hrs)	3.1 ± 0.8	3.9 ± 1.3	3.0 ± 0.7
$T_{½}$ (hrs)	11.9 ± 4.2	14.2 ± 5.8	12.1 ± 3.1
$XU_{0\text{-}72\ hr}$ (μg)	47565 ± 12058	45946 ± 14794	46953 ± 13008

**p<0.001

Conclusion:
Coadministration of fluconazole inhibits the metabolism of celecoxib and resulted in an increase of 60.0% in Cmax and 131.2% in AUC_{inf}.

Reviewer's comments:
1. It takes up to 10 days to reach steady state for fluconazole after QD dosing. The 7-day dosing for this study appeared inadequate to reach steady state fluconazole levels.
2. The decrease in Cmax for metabolites SC-60613 and SC-62807 supports the notion that fluconazole inhibits the metabolism of celecoxib.

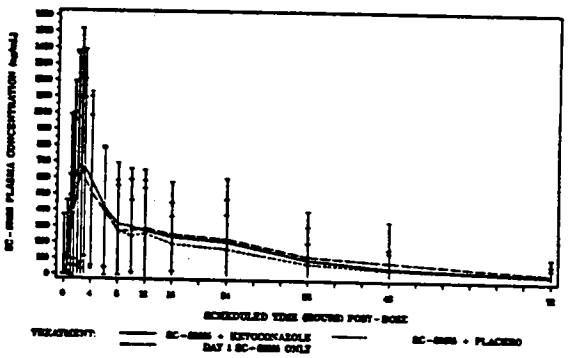
Ketoconazole (Study 072)

Ketoconazole is a potent CYP3A4 inhibitor. As part of Study 072, single dose pharmacokinetics of celecoxib was determined in the presence and absence of steady

state levels of ketoconazole following 200 mg QD administration. The study design is similar to that for fluconazole and can be found in Appendix 1 (p. 121). Eighteen healthy subjects completed the study.

Plasma ketoconazole concentrations: On Days 10 and 19, mean plasma ketoconazole concentrations reached a maximum of 3.36 (±1.29) ng/mL at 2 hrs postdose and decreased to 0.01 ng/mL at 72 hrs postdose, which were consistent with published data. Steady state was reached on celecoxib dosing days (Days 10 and 19).

Plasma celecoxib concentrations:
Following a single dose of celecoxib 200 mg alone, mean peak plasma celecoxib concentration (538.6 ±231.9 ng/mL) was reached at 2.5 hrs postdose. As shown in the figure, coadministration of celecoxib with ketoconazole or placebo gave similar plasma celecoxib concentration-time profiles.



Because one subject (#031) had high plasma levels of celecoxib before the first celecoxib dose, the mean parameter values for celecoxib as tabulated below excluded this subject. Based on least square means of log-transformed parameters, subjects receiving celecoxib with ketoconazole had a 10% higher mean AUC and a 12% lower mean Cmax when compared to subjects receiving celecoxib with placebo. The difference was statistically significant for AUC but not for Cmax. The mean amount of celecoxib excreted unchanged renally remained within the 10-20 μg range following coadministration with ketoconazole.

Mean Celecoxib Parameter Values (±SD)

Parameter (n=17)	Celecoxib (Baseline)	Celecoxib + Ketoconazole	Celecoxib + Placebo
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	7699.1 ± 2184.8	7698.3 ± 2318.5*	7065.6 ± 2517.8
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	7475.9 ± 2180.2	7453.7 ± 2300.3*	6836.5 ± 2480.5
$AUC_{0\text{-}inf}$ (ng.hr/mL)	7914.9 ± 2174.6	7850.5 ± 2294.0*	7211.0 ± 2493.5
C_{max} (ng/mL)	596.5 ± 231.9	567.4 ± 320.3	614.9 ± 214.0
T_{max} (hrs)	2.5 ± 0.9	3.5 ± 1.9	2.8 ± 0.9
$T_{½}$ (hrs)	12.2 ± 2.6	11.2 ±3.3	11.0 ± 3.6
$XU_{0\text{-}72\ hr}$ (μg) (n=6)	19.5 ± 23.3	17.8 ± 22.6	12.5 ± 21.9

*p<0.05; based on a comparison of (celecoxib + ketoconazole) vs. (celecoxib + placebo)

Plasma concentrations of metabolites SC-60613 & SC-62807: Based on least square means of log-transformed parameter values, decreases in C_{max} of metabolites SC-60613 (35%) and SC-62807 (37%) and SC-62807 $AUC_{(0-\infty)}$ (10%) after ketoconazole+celecoxib were statistically significantly different from placebo coadministration. The 11% decrease in SC-60613 $AUC_{(0-\infty)}$ did not demonstrate statistical significance. Excretion of SC-62807 in 72-hour urine after ketoconazole+celecoxib was 17% lower, but not significantly different from placebo.

Table: Mean (±SD) Parameter Values

Parameter	Celecoxib (Baseline)	Celecoxib + Ketoconazole	Celecoxib + Placebo
SC-60613			
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	457.6 ± 112.1	333.0 ± 87.7*	385.0 ± 103.7
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	436.1 ± 110.1	317.2 ± 87.3	368.6 ± 100.6
$AUC_{0\text{-}inf}$ (ng.hr/mL)	487.6 ± 103.9	363.7 ± 74.5	411.3 ± 105.7
C_{max} (ng/mL)	65.6 ± 18.9	38.5 ± 11.6*	58.5 ± 15.0
T_{max} (hrs)	2.2 ± 0.7	2.9 ± 0.8	2.2 ± 0.8
$T_{½}$ (hrs)	13.6 ± 4.5	14.3 ± 7.1	12.0 ± 4.5
SC-62807			
Parameter	Celecoxib (Day 1)	Celecoxib + Ketoconazole	Celecoxib + Placebo
$AUC_{0\text{-}72\ hr}$ (ng.hr/mL)	6554.7 ± 1737.4	4990.3 ± 1235.1*	4887.7 ± 1226.7
$AUC_{0\text{-}lqc}$ (ng.hr/mL)	6543.1 ± 1725.8	4990.3 ± 1235.1*	4864.6 ± 1232.1
$AUC_{0\text{-}inf}$ (ng.hr/mL)	6764.8 ± 1722.3	5224.5 ± 1412.3*	5085.3 ± 1286.7
C_{max} (ng/mL)	594.1 ± 286.6	287.5 ± 121.8**	504.3 ± 235.6
T_{max} (hrs)	3.2 ± 1.0	3.9 ± 1.3	3.0 ± 0.7
$T_{½}$ (hrs)	14.3 ± 4.3	14.2 ± 5.8	12.1 ± 3.1
$XU_{0\text{-}72\ hr}$ (μg)	56342 ± 13904	45946 ± 14794	46953 ± 13008

*$p < 0.05$ based on a comparison of (celecoxib + ketoconazole) vs. (celecoxib + placebo)

Conclusion:

Based on plasma metabolite data, ketoconazole might inhibit celecoxib metabolism as well. However, the inhibition was considerably less for ketoconazole than for fluconazole. These results confirmed the in vitro finding that CYP2C9 was the primary isozyme involved in celecoxib metabolism.

Reviewer's comments:

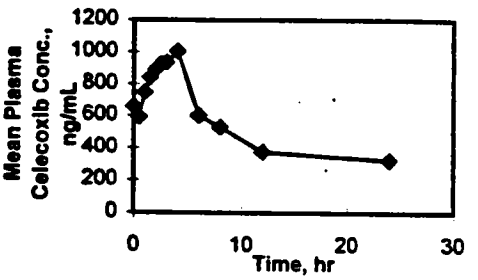
1. Subject had high plasma levels of celecoxib before the first celecoxib dose (Day 1) and, therefore, was excluded from the analysis. The sponsor suspected assay interferences. It is noted that this subject had consistently high plasma celecoxib levels after each of the three doses given on Days 1, 10 and 19 and the Cmax for this subject was about 10-fold that of the mean value. It is also noted that on Days 10 and 19, the pre-dose level for this subject was either near or below the LOQ. Assay interferences did not seem to fully explain the high celecoxib levels in this subject. However, including this subject in the analysis did not change the overall conclusion.
2. Ketoconazole might inhibit celecoxib metabolism as well but the inhibition appeared to be transient in nature (i.e. when ketoconazole plasma concentrations were near the peak).

Methotrexate (Study 017)

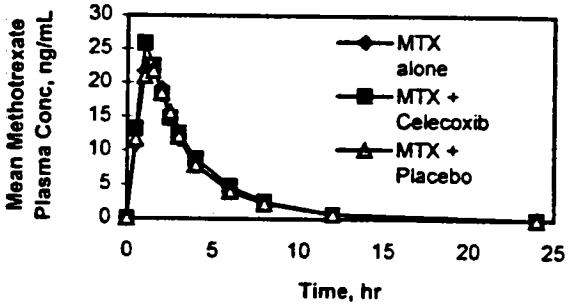
Methotrexate is indicated in the management of severe, active rheumatoid arthritis in patients who have had insufficient response to, or are intolerant of, other treatments including NSAIDs. Urinary excretion is an important route of elimination for this drug. The primary objective of this study was to determine the effect of celecoxib on the plasma pharmacokinetic profile and renal clearance of methotrexate (MTX) in rheumatoid arthritis patients. Fourteen female patients who were on a stable weekly dose

of methotrexate (5-15 mg as a single dose) received a 200-mg dose of celecoxib and placebo twice daily for seven days and then were crossed over to receive the alternate treatment for another 7 days. The detailed study design is given in Appendix 1 (p. 128).

The mean plasma celecoxib concentrations after 200 mg BID administration for 7 days is consistent with previous findings. (Because interference with celecoxib assay was encountered in 7 patients due to concomitant medication, the mean values as shown in the figure were calculated from the remaining 7 subjects.)



Compared to methotrexate administered alone or with placebo, coadministration with celecoxib resulted in a slight increase in the mean plasma methotrexate concentrations (as normalized to a methotrexate dose of 10 mg). The amount of methotrexate excreted unchanged in the urine was also slightly higher when it was coadministered with celecoxib.



Amount of MTX Excreted Unchanged in Urine
Mean±SD (μg)

MTX alone	6782 ± 1874
MTX+Celecoxib	7457 ± 2318
MTX+Placebo	6900 ± 2336

The mean (±SD) methotrexate pharmacokinetic parameter values for the three treatments are tabulated below. The parameter values were similar whether methotrexate was administered alone or with placebo. A comparison of methotrexate+celecoxib vs. methotrexate+placebo indicated that mean Tmax was the same for both treatments and $AUC_{0\text{-}24}$, Cmax and renal clearance were comparable (i.e., the 90% CI of the ratios were within the 80-125% range).

Methotrexate Mean Parameter Values (±SD) (N=14)

Parameter	Day 0 (MTX alone)	MTX + Celecoxib	MTX + Placebo	Ratio** & 90% CI
$AUC_{0\text{-}24}$* (ng.hr/mL)	85.63 ± 18.04	92.41 ± 17.75	85.66 ± 25.18	110.5 100.6-121.3
Cmax * (ng/mL)	24.94 ± 6.61	26.01 ± 7.35	24.45 ± 7.19	106.8 92.5-123.4
Tmax (hr)	1.39 ± 0.45	1.32 ± 0.58	1.32 ± 0.37	-
CL_{renal} (L/hr)	7.98 ± 2.18	7.94 ± 1.61	7.97 ± 1.19	99.6 90.9-108.3

*Dose normalized (to 10 mg methotrexate)

** Ratio of methotrexate parameter values in %; (MTX+celecoxib)/(MTX+placebo)

Conclusion: Celecoxib 200 mg BID dosing did not have a significant effect on the pharmacokinetics of methotrexate.