CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

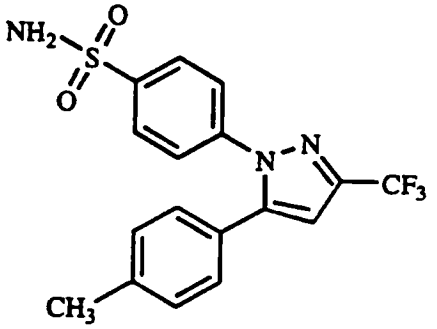
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-998
PRODUCT: Celebrex™ (celecoxib) Capsules, 100 mg & 200 mg
SPONSOR: Searle
4901 Searle Parkway
Skokie, IL 60077
TYPE OF SUBMISSION: Original, 1P

SUBMISSION DATES: 6/29/98, 8/24/98, 9/3/98, 10/1/98, 10/8/98, 10/16/98, 10/21/98, 10/30/98, 11/11/98, 11/19/98, 11/23/98, 12/10/98
REVIEWER: Sue-Chih Lee, Ph.D.

1. Synopsis

Celecoxib (SC-58635), a diarylsubstituted pyrazole compound, is a member of a novel class of agents that selectively inhibits cyclooxygenase-2 (COX-2). COX-2 is on the most part an inducible form which is responsible for inflammation of tissues while COX-1 is constitutive and is normally expressed in tissues throughout the body. Many currently available NSAIDs are considered non-selective COX inhibitors. The sponsor claims that celecoxib inhibits COX-2 approximately 300-fold more effectively than COX-1 in in vitro studies. Celecoxib is intended for use as an oral anti-inflammatory and analgesic agent for the acute or chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), and management of pain.



In support of this application, the sponsor has submitted a total of 30 pharmacokinetic studies. Out of these, 2 studies (one single dose and one multiple dose studies) were conducted in Japanese healthy subjects and were not reviewed in full length because they did not add new information to this application. It was noted that results from additional studies were used to support the labeling and were included in the summary section but the individual reports were not provided in Section 6. This reviewer has since reviewed the PK information of these studies. The following is a brief summary of the pharmacokinetic study results.

Pharmacokinetic characteristics of celecoxib

Absorption: Following a single dose under fasted conditions, peak plasma celecoxib concentrations (Cmax: ~600-900 ng/mL for a 200 mg dose) occur approximately 3 hours postdose. Relative to an oral suspension, Celebrex capsules have a relative bioavailability of 99%. Because of the low aqueous solubility of celecoxib, absolute bioavailability studies have

not been conducted. Multiple dose pharmacokinetics of celecoxib can generally be predicted from the single dose pharmacokinetics.

Effects of food and antacid: When Celebrex capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in Cmax of 39% (200 mg capsules) to 62% (100 mg capsules) and total absorption (AUC) of from 10% to 20% (for both strengths). Coadministration of Celebrex with an aluminium and magnesium containing antacid resulted in a reduction in plasma celecoxib concentrations (Cmax: ↓ 37%; AUC: ↓ 10%).

Dose proportionality: Both AUC and Cmax are not dose proportional. The dose adjusted parameter values are reduced with an increase in dose due to the poor solubility of the drug. However, the AUC is "roughly" dose proportional between the 100 mg and 200 mg doses. The deviation from dose proportionality is reduced under fed conditions.

Distribution: Celecoxib is highly plasma protein bound (~97%) and the binding is linear within clinical dose range. In vitro studies indicate it binds to both human plasma albumin and, to a lesser extent, α_1-acid glycoprotein. The apparent volume of distribution at steady state (Vss/F) is approximately 400 L.

Metabolism: Celecoxib metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors in in vitro models.

Excretion: Celecoxib is eliminated predominantly by metabolism with little (~3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 57% of the dose was excreted in the feces and 27% excreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite with low amounts of the glucuronide also appearing in the urine. The low solubility of the drug appears to prolong the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. Under fasted conditions, the terminal half-life is approximately 11 hours. The apparent plasma clearance (CL/F) is about 500 mL/min.

Special populations

Effects of age: At steady state, elderly subjects (over 65 years old) had a 40% higher Cmax (1363 vs. 973 ng/mL) and a 48% higher AUC (8675 vs. 5871 ng.hr/mL) compared to the young subjects. Elderly females had higher celecoxib Cmax and AUC than elderly males but these increases are thought to be due to lower body weight in elderly females. There are no studies conducted in pediatric subpopulation.

Effects of gender: A meta analysis revealed that female subjects had a (13%) lower Cmax than male subjects after a single dose of celecoxib. On the other hand, there was no significant difference in Cmax between genders after multiple dosing. Terminal half-life was found to be

longer in females than in males (single dose studies: 13.9 hrs vs 11.4 hrs; multiple dose studies: 9.5 hrs vs. 7.8 hrs.). However, the analysis did not show any significant differences in celecoxib AUC between genders.

Effect of body weight: A meta analysis showed that single-dose Cmax was lower in subjects with higher body weights (regression coefficient: about –5 ng/mL per kg).

Effect of race: A meta analysis of pharmacokinetic studies revealed a (30-40%) higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this difference is unknown.

Hepatic insufficiency: A pharmacokinetic study showed that steady state celecoxib AUC increased (~30%) in volunteers with mild hepatic impairment (Child-Pugh Class I) and more than doubled (270%) in volunteers with moderate hepatic impairment (Child-Pugh Class II) when compared to the matching control group. Patients with severe hepatic impairment have not been studied.

Renal insufficiency: In a cross-study comparison, celecoxib AUC was approximately 40% lower in patients with chronic moderate renal insufficiency (GFR 25-60 mL/min) than that seen in subjects with normal renal function. No significant relationship was found between GFR and celecoxib clearance. Further, patients with severe renal insufficiency have not been studied.

Drug interactions

In vitro studies: In vitro studies indicate that celecoxib is not an inhibitor of cytochrome P450 2C9, 2C19 or 3A4. Although not a substrate, in vitro studies indicate that celecoxib is a moderately potent inhibitor of cytochrome P450 2D6. (The Ki value for inhibition of bufuralol 1'-hydroxylation was ~4.2 μM, which is 9-fold weaker than quinidine.) In Study 015 (elderly vs. young), 5 out of 22 elderly subjects had a Cmax value equal to or greater than the Ki value (~1.6 μg/mL) even after the 2 poor metabolizers in this study were excluded. Therefore, there is a potential for an in vivo drug interaction with CYP2D6 substrate.

In vivo studies:

Glyburide, ketoconazole, phenytoin and tolbutamide: The effect of celecoxib on the pharmacokinetics of these drugs has been studied in vivo and clinically important interactions have not been found.

Fluconazole: Concomitant administration of fluconazole resulted in an increase of 68% in Cmax and 134% in AUC. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole.

Lithium: In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with Celebrex 200 mg BID as compared to subjects receiving lithium alone, which is similar to previous findings with other NSAIDs.

Methotrexate: In an interaction study of rheumatoid arthritis patients taking methotrexate, Celebrex did not have significant effect on the pharmacokinetics of methotrexate.

Warfarin: The effect of celecoxib on the anti-coagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2-5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time.

Bioequivalence of commercial formulations:
The sponsor has shown bioequivalence between the 100 mg and 200 mg commercial capsules. The bioequivalence of the 200 mg commercial capsules to the 200 mg Phase III capsules was demonstrated in a study using a replicate crossover design. However, the 100 mg commercial capsules were not bioequivalent to the 100 mg Phase III capsules (90% CI: 73-90% for Cmax; 89-98% for AUC_∞).

II. Comments

1. Celecoxib has two important features: (a) low aqueous solubility and high permeability, and (b) predominantly eliminated by metabolism via CYP2C9 with approximately 3% of the administered dose excreted unchanged in urine and feces.

2. It is likely that the low aqueous solubility of celecoxib contributed to the high variability in absorption after oral administration.

3. It seems that low solubility of the drug prolonged absorption process making the terminal half-life appear longer than the true elimination half-life of the drug. This is based on the much shorter terminal half-life seen in subjects taking the drug immediately after a meal. The sponsor did not comment on this.

4. Very high plasma celecoxib concentrations (3-9 times of mean values) were observed in 5 out of several hundred (~500-1000) subjects exposed to the 200 mg dose. Two of these subjects were genotyped and were identified as poor metabolizers (i.e., 2C9 deficient). These subjects were on single dose or short term multiple dose use of celecoxib and no serious adverse events occurred during the study. [However, Dr. Maria Villalba, Medical Officer of HFD-550, indicated that some lab tests were performed several days after the last dose and could not have identified all abnormalities occurred during the treatment period.] During marketing of the product, the sponsor is encouraged to evaluate reports of adverse events for signals of concentration related events, and to follow up on these patients and discuss the information collected with the Agency.

5. Although the 100 mg commercial capsules were not bioequivalent to the 100 mg Phase III capsules, this is not considered an approvability issue based on the following reasons:
   a. The clinical division does not consider the lower Cmax (90% CI: 73-90%) has clinical consequences for chronic use in OA and RA patients. In addition, the 100 mg and 200 mg commercial capsules were bioequivalent and the latter were bioequivalent to the Phase III 200 mg capsules.
   b. The sponsor will be required to conduct additional clinical trials to demonstrate the efficacy for pain management. Since commercial capsules will be used in these trials, the failed BE study will cease to be an issue for this indication.

III. Recommendation

The submission has adequately addressed the requirements of the Office of Clinical Pharmacology and Biopharmaceutics. The application is approvable. Comment #4 should be communicated to the sponsor.

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Dennis Bashaw, Pharm.D. 12/16/98

CPB Briefing (Date: 11/24/98)

CC:
NDA 20-998
HFD-550 (Div.File)
HFD-550 (CSO/Lutwak)
HFD-880 (Bashaw)
HFD-880 (Lazor)
HFD-880 (Lee)
HFD-870 (attn: CDR. Barbara Murphy)
HFD-344 (Viswanathan)
AE

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IV. Background

Celecoxib (SC-58635), is a specific COX-2 inhibitor intended for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis and management of pain. Cyclooxygenase (COX) is present in at least two forms in human cells. One form is constitutive (COX-1) and is widely expressed in nearly all tissues throughout the body, including gastric and renal epithelial cells, and platelets. The other form (COX-2) is inducible and is generally expressed in low amounts in normal tissues, but is prominently expressed in inflamed tissues. Many currently available NSAIDs are considered non-selective COX inhibitors. The sponsor claims that celecoxib inhibits COX-2 approximately 300-fold more effectively than COX-1 in in vitro studies. It is thought that COX-2 specific inhibitors will provide efficacy as an antiinflammatory and analgesic agent while minimizes adverse events associated with COX-1 inhibition, e.g., gastrointestinal ulceration and platelet dysfunction.

Celecoxib has an aqueous solubility of about 5 μg/mL at between 5 and 40°C, which is pH independent below pH 9. It is freely soluble in methanol, ethanol, PEG 400 and acetone and very slightly soluble to practically insoluble in oils (< 3 mg/mL in corn oil) and non-polar hydrocarbons. Its pK_a of 11.1 is associated with ionization of the sulfonamide moiety. The apparent octanol/water partition coefficient for celecoxib is above 10^3 at pH 7. Therefore, it is a low solubility, high permeability drug.

V. Formulation

The sponsor intends to market both the 100 mg and 200 mg capsules. As shown in the table below, the formulations for these two strengths are not proportionally similar. (Note: The phase III capsules and commercial capsules have the same formulations but differ in batch size and manufacturing site.)

Ingredient	mg/Capsule	
	100 mg Capsules	200 mg Capsules
SC-58635,	100.0	200.0
Lactose, Monohydrate ✓		
Sodium Lauryl Sulfate ✓		
Povidone, K29-32 ✓		
Croscarmellose Sodium ✓		
Magnesium Stearate ✓		
Purified Water*	-	-

VI. Analytical Methods

Plasma SC-58635 (celecoxib): A assay method was used to analyze the samples. Human plasma (0.3 mL) containing celecoxib and internal standard, SC-59751,

SC-58635 in Urine samples: Human urine containing SC-58635 and its internal standard, SC-59751.

SC-62807 (M2) in Urine samples: Human urine containing SC-62807 is mixed with an internal standard, SC-59046.

VII. Summary of Bio/PK/PD Characteristics

(Note: For easy reference, the study number cited iction corresponds to the last three digits of protocol numbers given in Appendix 1.)

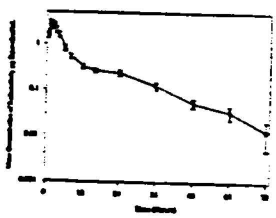
METABOLISM

a. Evaluation of Total Radioactivity in Human Eal Samples (Study 006)

This study was conducted (1) to determine the ADMle of an oral of [^{14}C]celecoxib and (2) to estimate theilability of an oral relative to Each subject received a single 3dose and capsule (containin formulations. The detailed study design is given . This secusses the results from the formulation as related to the first objectiv

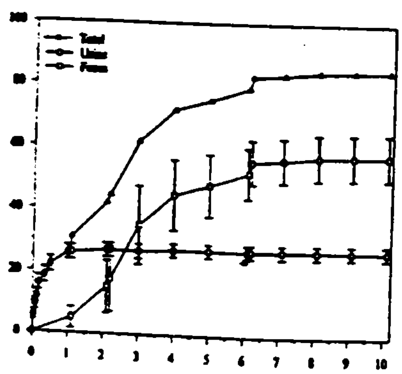
Eight healthy male subjects (2 in pilot phase and 6 inive phase) completed the study. Concentrations of total radioactivity in plasma, red blls, saliva, urine, and fecal samples collected at specified time intervals after dose admini were determined.

Plasma concentration of total Radioactivity: The m plasma concentration of total radioactivity reached aum of 2.75±1.29 μg equivalents/mL at 1.75 hr postdose. Radioactivity in plasma obtained 72 hours after dose administration was not detectable in most subjects. elimination half-life of total radioactivity was approx 17.0±4.0 hrs.



Distribution into red blood cells: Celecoxib concen in plasma and RBC were compared at 1 and 4 hours postdose. The mean concentration activity was slightly lower in red blood cells than in plasma at 1 and 4 hours postdose2.33±0.34 and 1.26±0.22 μg/mL; plasma: 2.43± 0.49 and 1.57±0.17 μg/mL, respectivee mean of individual ratios of RBC/plasma concentrations of total radioactivity we0.3 and 0.80±0.29 at 1 and 4 hours postdose, respectively.

Excretion in urine and feces: Radioactivity was excreted in urine and feces following oral administra of celecoxib. The mean percent of total radioactivity excreted was 27.1±2.2% in the urine samples (0-144 and 57.6±7.3% in fecal samples. As shown in the fi most (95.6%) of the urinary excretion occurred withi first 24 hours postdose while ~78% of the fecal excr occurred within 96 hours postdose.



Saliva: The concentration of radioactivity in saliva was very low at the time periods examined. Most of the saliva samples had no quantifiable concentrations of radioactivity. The amount of radioactivity secreted into the saliva up to 24 hours postdose was negligible.

Total recovery: Recovery from saliva and fecal wipes were very small (~0.14%). The total mean percent of the radioactive dose recovered (84.8±4.9%) were mostly from urine and feces.

Conclusion:

- Celecoxib was not preferentially bound to erythrocytes.
- Secretion of celecoxib into saliva was negligible.
- After oral administration of 300 mg celecoxib, approximately 85% of the dose was recovered from urine and feces (27.1±2.2% of the dose from urine and 57.6±7.3% of the dose from feces).

b. Metabolic Profiles in Biological Samples

Plasma: Plasma samples obtained at 0.5, 3, 4 and 12 hours after oral administration of celecoxib at 300 mg were analyzed The findings were:

- The parent compound was the major species present in plasma. (*Reviewer's note*: In a drug interaction study with fluconazole, the AUC of M2 was found to be comparable to that of the parent compound when celecoxib was administered alone.)
- Three metabolites of celecoxib were found in plasma: SC–60613, SC–62807 and the glucuronide conjugate of SC–62807. Note: These metabolites were shown to be inactive as COX inhibitors in in vitro models.
- SC–60613 is the product of partial oxidation of the methyl moiety of celecoxib to a hydroxyl group and is a minor circulating metabolite as indicated in the table below.
- SC-62807 (M2) is the result of complete oxidation of the methyl moiety of celecoxib to a carboxyl group. Glucuronidation of the carboxyl metabolite forms M1. (See next page for chemical structures.)

Celecoxib and Metabolites in Plasma (in terms of % total radioactivity in plasma samples)

Time ,hr postdose		M1	M2	SC-60613	Celecoxib
0.5	(n=8)	1.10 ± 0.60	12.1 ± 2.6	2.43 ± 0.89	84.4 ±3.6
3	(n=8)	21.0 ± 4.9	21.2 ± 1.9	0.217 ± 0.182	57.6 ± 6.5
4	(n=2)	13.5	21.0	0.00	65.6
12	(n=6)	23.2 ± 4.1	27.0 ± 5.9	0.00 ± 0.0	49.9 ±4.5

Urine: Urine samples collected up to 12 hours postdose were analyzed

- No unchanged drug was detected in the urine.
- The species present in these samples were metabolites M1 and M2. The mean (n=8) cumulative amount of metabolites excreted in the urine within 12 hours postdose was equivalent to 18.8±2.1% of the dose for M2 and 1.48±0.15% of the dose for M1.

Feces: Analysis of fecal samples collected over 8-10 days after dosing gave the following results:

- The radioactivities in fecal samples were associated with metabolite M2 and the parent drug.
- The mean cumulative amount excreted in the feces were equivalent to 54.4 ± 6.8% (M2) and 2.56 ± 1.09% (celecoxib) of the dose, respectively.

Mean Percent of Dose Excreted In Urine and Feces

	Glucuronide of SC-62807 (M1)	SC-62807 (M2)	SC-60613	Celecoxib
Urine $_{(0\text{-}12\ hrs)}$	1.48 ± 0.15	18.8 ± 2.1	-	-
Feces	-	54.4 ± 6.8	-	2.56 ± 1.09

Conclusion:

- Urinary radioactivity was associated with M1 and M2. No unchanged drug was detected in the urine.
- Fecal radioactivity was associated with unchanged drug and M2.
- Metabolism of celecoxib was extensive. After oral administration, only approximately 2.56 ± 1.09% of the recovered total radioactivity in urine and feces was unchanged drug.

c. Proposed Metabolic Pathway

d. In Vitro Studies: Determination of P450 Isoforms in the Metabolism of Celecoxib

The in vitro metabolism of ^{14}C-celecoxib was investigated using human liver microsomes and cDNA-expressed human cytochrome P450 enzymes. The major metabolites of celecoxib generated by human liver microsomes, SC-60613 and SC-62807, are the same as the major (unconjugated) metabolites found in vivo. The apparent K_m and V_{max} for celecoxib metabolism by a pool of human liver microsomes were estimated to be 49.3 µM (18.8 µg/mL) and 735 pmole/min/mg, respectively. The following studies were conducted using a protein concentration of 1.0 mg/mL.

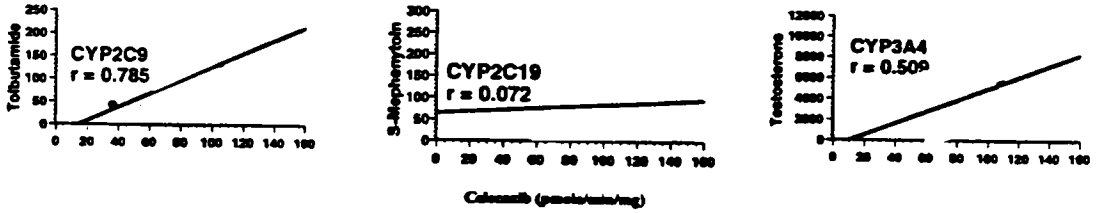
Celecoxib metabolism by cDNA-expressed human P450 enzymes: As shown in the table below, human recombinant CYP2C9, CYP2C19 and CYP3A4 were each found to be capable of metabolizing ^{14}C-celecoxib (at 10 µg/mL or 26 µM) to ^{14}C-SC-60613 in vitro. Metabolism of ^{14}C-celecoxib was not detectable with human recombinant CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2E1 and CYP3A5.

Table: Percent of Celecoxib Converted to SC-60613

1A2	2A6	2B6	2C9	2C19	2D6	2E1	3A4	3A5	PHM[1]
<0.5	<0.5	<0.5	38.7	64.4	<0.5	<0.5	2.1	<0.5	48.2

[1]Pooled human liver microsomes

Correlation of celecoxib metabolism with metabolism of P450 isoform-specific substrates by human liver microsomes: Specific enzymatic activities for ^{14}C-celecoxib metabolism at the celecoxib substrate concentrations of 2.6 and 10 µM (~1.0 and 3.81 µg/mL) were determined for 16 individual human microsome samples and compared to the known (phenotyped) specific enzymatic activities of the same microsomes for a series of cytochrome P450 isoform-specific substrates. The figures below present the correlation between isoform specific substrate metabolism and celecoxib metabolism at 2.6 µM celecoxib substrate concentration. Celecoxib metabolism correlated strongly with CYP2C9 (tolbutamide hydroxylase; $p < 0.001$). The correlation was weaker for CYP3A4 (testosterone 6β-hydroxylase; $p < 0.05$), and there was no correlation for CYP2C19 (S-mephenytoin 4'-hydroxylase). Similar results were obtained at the higher celecoxib substrate concentration (10 µM).



Inhibition of celecoxib metabolism by known cytochrome P450 inhibitors: The experiments with known inhibitors of P450 were performed at a ^{14}C-celecoxib substrate concentration of 10 µg/mL and inhibitor concentrations of 20 µM furafylline, 0.3 - 100 µM sulfaphenazole, 0.3 - 30 µM omeprazole, 20 µM mephenytoin, 20 µM quinidine, 20 µM DDTC, 20 - 100 µM troleandomycin (TAO) or 0.5 - 1.0 µM ketoconazole.

Further evidence for the importance of CYP2C9 in ^{14}C-celecoxib metabolism by human liver microsomes was provided by the finding that sulfaphenazole, a potent and specific CYP2C9 inhibitor, inhibited both ^{14}C-celecoxib and tolbutamide to the same extent (80-90%) in six individual human microsome samples. Other cytochrome P450 isoform selective inhibitors were less effective (omeprazole/CYP2C19; troleandomycin/CYP3A4; ketoconazole/CYP3A4), or ineffective (furafylline/CYP1A; quinidine/CYP2D6; DDTC/CYP2E1) as inhibitors of ^{14}C-celecoxib metabolism by human liver microsomes.

Table: Percent Inhibition of Celecoxib Metabolism by Various Inhibitors

1A	2C9	2C19	2C19	2D6	2E1	3A4	3A4
furafylline	sulfa-phenazole	omeprazole	mepheny-toin	quini-dine	DDTC	TAO	ketoconazole
10.0	80.0	57.3	4.3	0	0	0	-
-	70.4 (10μM)	27.5 (10μM)	-	-	-	14.7 (100 μM)	36.9 (1.0 μM)

*Inhibitor concentration at 20 μM unless otherwise specified.

Conclusion:

- Human recombinant CYP2C9, CYP3A4 and CYP2C19 were each found to be capable of metabolizing celecoxib.
- CYP2C9 is judged to be most important in human metabolism of celecoxib based on correlation analysis using a series of characterized human microsome samples (high correlation found between celecoxib and tolbutamide metabolism) and the strong inhibition of celecoxib metabolism by the specific CYP2C9 inhibitor, sulfaphenazole.

Reviewer's comment:

All the above in vitro metabolism studies were performed at a high celecoxib concentration (10 μg/mL) except for the correlation study which used a celecoxib concentration (1 μg/mL) within the range found at the recommended dose (steady state Cmax: < 2 μg/mL after 200 mg BID).

PROTEIN BINDING

a. Report MRC-94S-0136

- In an in vitro protein binding study using plasma sample from one subject and employing a dextran–coated charcoal method, celecoxib was found to be highly protein bound at ^{14}C-celecoxib concentrations of 0.3 μg/mL (97.3% bound) and 3.0 μg/mL (90.6% bound), respectively.

b. The Binding of SC-58635 to Mouse, Rat, Dog and Human Plasma Proteins

(Report # M3097065)

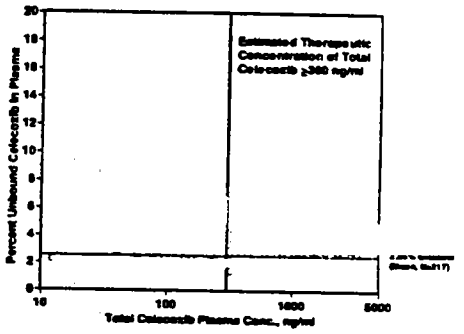
method was employed in this study. ^{14}C-celecoxib concentrations of 0.1, 0.3, 1.0, 3.0 and 10 μg/mL were evaluated. Only the results related to human plasma protein binding is summarized here. (Note: The human plasma was obtained from only one subject.)

- The percentages of binding of ^{14}C-celecoxib to human plasma in vitro at total celecoxib plasma concentrations of 0.1, 0.3, 1.0, 3.0 and 10.0 μg/ml were 98.2%, 97.9%, 96.5%, 96.7% and 96.3%, respectively.
- Celecoxib binds in vitro to both human albumin and α_1-acid glycoprotein.
- The percentages of binding of ^{14}C-celecoxib to human albumin in vitro at celecoxib concentrations of 0.1, 0.3, 1.0, 3.0 and 10 μg/mL were 100, 100, 99.8, 99.9 and 99.8, respectively.
- The percentages of binding of ^{14}C-celecoxib to human α_1-acid glycoprotein in vitro at celecoxib concentrations of 0.1, 0.3, 1.0, 3.0 and 10 μg/mL were 92.4, 91.6, 91.0, 88.4 and 78.6, respectively.

c. Study 032

This study was conducted to evaluate the effects of 600 mg celecoxib BID versus 500 mg naproxen BID on platelet function in normal healthy subjects. Eight volunteers (3 male, 5 female, 20 to 39 years) received a single oral dose of celecoxib 600 mg with food, followed by celecoxib 600 mg BID with food for seven days. Blood samples for total and unbound celecoxib plasma assays were collected for up to 48 hours after single dose and last BID dose, in addition to trough plasma samples on predetermined days.

The dose of celecoxib in this study was higher than the anticipated therapeutic dose for treatment of osteoarthritis or rheumatoid arthritis. Total celecoxib plasma concentrations ranged from 0 to 4000 ng/mL and unbound concentrations ranged from 0 to 22.56 ng/ml. As shown in the figure, the fraction of unbound drug remained rather constant (mean 2.55% unbound). Therefore, within the projected plasma concentration range for the clinical doses, total celecoxib plasma concentrations were considered an adequate measure for determination of celecoxib pharmacokinetics.



Conclusion:
Celecoxib is highly plasma protein bound (~97%). The fraction of unbound drug remained essentially constant (mean 2.55% unbound) at total plasma celecoxib concentrations up to 4000 ng/mL (well above the therapeutic range).

SINGLE DOSE PHARMACOKINETICS

Dose Escalation Study In Healthy Adult Volunteers (Study 001)

The objective of this exploratory study was to determine the safety, tolerability and pharmacokinetics of single, oral escalating doses of celecoxib administered to healthy male subjects. A total of 80 subjects participated and completed the fasting portion of the study. Six of the eight subjects who received the 200 and 400 mg doses under fasting conditions also received a single dose following a high fat breakfast. The detailed study design is given in Appendix 1 (p. 65).

Plasma data: The mean pharmacokinetic parameters for the doses ranging from 5 to 1200 mg are listed below. Under fasting conditions, C_{max} was achieved within 2 hours for all of the doses tested. The sponsor considered that $AUC_{0\text{-}96}$ was dose proportional through the 600 mg dose and less than proportional at the 900-mg and 1200-mg doses. The plasma terminal half-life, $T_{1/2}$, ranged from 7 to 11 hours for the doses of 50-900 mg.

Food delayed peak plasma levels but increased the overall absorption of celecoxib (AUC ↑22% for the 200 mg dose and ↑58% for the 400 mg dose), suggesting a possible food effect.

Table: Mean (±SD) Parameter Values

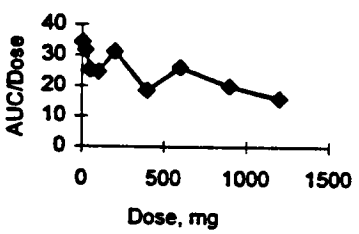
SC-58635 Dose	AUC(0-96) ng*hr/ml	Cmax ng/ml	Tmax hr	T1/2 hr
5 mg (n=4)	171.98 (40.85)	27.98 (9.71)	1.63 (1.11)	4.51 (0.78)
25 mg (n=4)	792.66 (249.30)	133.25 (45.18)	1.25 (0.50)	10.34 3.84)
50 mg (n=4)	1271.48 (307.92)	233.25 (45.07)	2.00 (1.15)	7.69 2.66)
100 mg (n=4)	2465.42 (690.41)	362.00 (155.98)	1.38 (0.75)	8.53 (2.89)
200 mg (n=4)	6271.63 (2846.27)	797.00 (498.78)	1.75 (1.50)	7.57 (5.47)
200 mg*(n=4)	7830.30 (4265.31)	875.50 (749.49)	6.25 (4.03)	9.51 (5.64)
400 mg (n=4)	7417.91 (904.52)	706.75 (104.08)	2.25 (1.50)	7.46 (2.38)
400 mg*(n=2)	11884.16 (3158.40)	1355.00 (7.07)	6.00 (2.83)	4.22 (2.31)
600 mg (n=4)	15725.65 (6689.83)	1771.00 (625.05)	1.50 (1.00)	9.56 (3.72)
900 mg (n=20)	18028.26 (7517.36)	1419.25 (683.38)	1.90 (0.91)	10.92 (5.15)
1200 mg (n=4)	19135.97 (4654.86)	2022.50 (751.99)	2.00 (0.82)	16.39 (17.28)

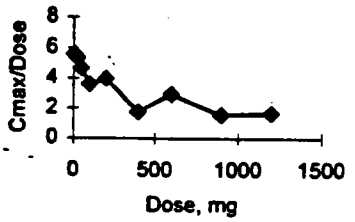
*Fed conditions

Reviewer's comments:

1. This study used a Phase 1 formulation which is different from the to-be-marketed formulation.
2. The sponsor considers that AUC was dose proportional up to 600 mg and less than proportional at 900 mg and above. This information is included in their proposed labeling.

As shown in the figures below, plots of dose adjusted AUC and Cmax versus dose indicate that there is a downward trend even for doses up to 600 mg for both AUC and Cmax, but the deviation from proportionality is greater for Cmax. The less than proportional increase in AUC is considered to be a result of less absorption due to the low solubility of the drug.





3. The long terminal half-life observed at the 1200 mg dose might be a complication of the absorption process since this is a low solubility drug.
4. The individual PK parameter values are not provided.

MULTIPLE DOSE PHARMACOKINETICS

a. Multiple-Dose Tolerability and PK Study In Healthy Subjects (Study 004)

This study was designed to determine the safety, tolerability and pharmacokinetics of SC-58635 after multiple dose administration in healthy subjects (17-44 yrs). Doses of 40 mg, 200 mg and 400 mg or placebo were administered under fasting conditions as single doses, followed 48 hours later by BID dosing for 7 days. A total of 36 subjects completed the study with 24 subjects on active treatments. The detailed study design is given in Appendix 1 (p. 68).

Plasma data: Steady state plasma levels, as observed through trough plasma concentrations, were achieved within five days of BID dosing. The mean pharmacokinetic parameters following single and multiple dosing are tabulated below.

Mean (±SD) Parameter Values

Dose	AUC[a] ng*hr/ml	Cmax ng/ml	Tmax hr	T1/2 hr	CL/F L/hr/70 kg	V_z/F L/70 kg
Single Dose Phase						
40 mg (n=8)	1217 (±328)	197 (±86)	1.50 (±0.46)	4.18 (±1.95)	34.3 (±9.6)	194 (±81.5)
200 mg (n=7)	5986 (±4032)	646 (±341)	1.64 (±0.69)	8.01 (±2.33)	40.1 (±14.4)	483 (±260)
400 mg (n=8)	13341 (±3010)	1433 (±523)	2.13 (±0.79)	8.87 (±3.57)	31.4 (±6.9)	408 (±208)
Multiple Dose Phase						
40 mg (n=8)	937 (±288)	183 (±52)	1.94 (±0.90)	3.94 (±1.55)	45.1 (±14.4)	239 (±98)

200 mg (n=8)	6726 (±3858)	1115 (±425)	1.75 (±0.71)	7.09 (±2.33)	33.9 (±10.8)	346 (±176)
400 mg (n=8)	11634 (±3745)	1833 (±478)	1.63 (±0.99)	9.57 (±4.16)	38.2 (±13.8)	557 (±407)

(a) $AUC_{0-\infty}$ for single-dose phase and AUC_{0-12} for multiple-dose phase

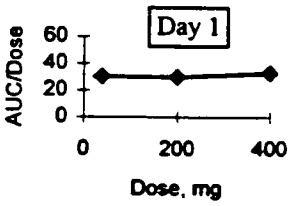
The single dose pharmacokinetics were generally predictive of those during multiple dosing (i.e., linear PK) as demonstrated by mean ratios of steady-state $AUC_{(0-12)}$ to single-dose $AUC_{(0-\infty)}$ of 79.3%, 118.7% and 84.8% for 40 mg BID, 200 mg BID and 400 mg BID doses, respectively. The terminal half-life was between 7 and 10 hours for the 200 mg and 400 mg doses. The accumulation ratios and %fluctuation as calculated from this study are presented below.

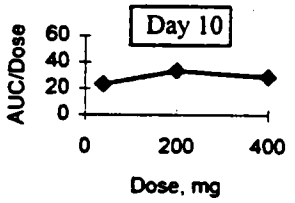
Table: Linearity, % Fluctuation and Accumulation Ratios

Dose	$AUC_{0-12\,(Day\ 10)}$ / $AUC_{inf\,(Day\ 1)}$ (%)	% Fluctuation	Accumulation Ratio[1]	Accumulation Ratio[2]
40 mg	79.3	205.6 (83.4)	1.03	1.88
200 mg	118.7	162.7 (67.1)	1.88	1.77
400 mg	84.8	114.1 (68.9)	1.42	1.19

% Fluctuation = (Cmax-Cmin)/(AUC_{0-12}/12) x 100 (Given as mean ±SD)
Accumulation Ratio[1] = $AUC_{0-12(Day\ 10)}$/ $AUC_{0-12(Day\ 1)}$ (Both mean and 90% CI are given)
Accumulation Ratio[2] = $Cmax_{0-12(Day\ 10)}$/ $Cmax_{0-12(Day\ 1)}$ (Both mean and 90% CI are given)

As shown in the figures below, the AUCs on both Day 1 (single dose) and Day 10 (steady state) appeared dose proportional across the dose groups. The apparent volume of distribution at terminal phase (V_z/F) was 400-500 L.





Reviewer's comment:
Values for CL/F and V_z/F in the individual report (Vol. 1.85, pp. 43, 47) differ from those in the summary (Vol. 1.81, p. 166). The sponsor should clarify.

b. Multiple-Dose Study In Older Subjects (Healthy Volunteers and OA Patients) (Study 003)

This study was conducted to investigate the safety, tolerability and pharmacokinetics in an older population (age: 40-58 yrs). Ten out of 36 subjects were osteoarthritis patients. A single dose of 40, 200, 400 mg or placebo was given to subjects under fasted conditions followed 48 hours later by BID dosing for 14 days. The detailed study design is given on page 69. Note that smoking and caffeine consumption were allowed in this study.

Plasma data: The pharmacokinetic parameters are tabulated below. The peak plasma concentrations were reached within 2-4 hours and half-life ranged from 8 to 15 hours. Steady state plasma levels were achieved within 5 days of BID dosing as observed through the trough plasma concentrations.

Mean (±SD) Parameter Values

Dose	AUC (a) ng*hr/mL	Cmax ng/mL	Tmax hr	T1/2 hr	CL/F L/hr	Vd/F L
Single Dose						
40 mg	1928 ± 568	277 ± 77	3.4 ± 3.5	7.7 ± 2.9	22.6 ± 7.5	244 ± 107
200 mg	9941 ± 4488	759 ± 374	2.5 ± 1.7	15.2 ± 7.6	25.1 ± 15.2	467 ± 196
400 mg	14064 ± 5428	1103 ± 309	1.9 ± 0.7	14.5 ± 5.7	32.7 ± 13.6	649 ± 269
Multiple Dose						
40 mg	1687 ± 601	326 ± 119	1.7 ± 0.6	7.4 ± 1.7	26.2± 8.4	270 ± 78
200 mg	8155 ± 2427	1187 ± 393	2.1 ± 1.0	12.1 ± 3.7	26.2 ± 6.6	465 ± 205
400 mg	13355 ± 6599	1805 ± 642	3.8 ± 3.6	14.2 ± 4.5	36.4 ± 15.7	796 ± 517

(a) $AUC_{0-\infty}$ for single dose and AUC_{0-12} for multiple dose

The single dose pharmacokinetics observed in the study was generally predictive of that during multiple dosing as evidenced by the ratios of $AUC_{0-12(Day\ 10)}/AUC_{inf(Day\ 1)}$ (0.86) and no unexpected accumulation occurred as indicated by the ratio of $AUC_{0-12(Day\ 10)}/AUC_{0-12(Day\ 1)}$ (~2.0).

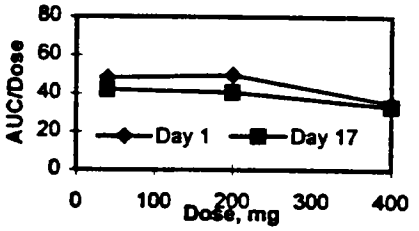
Dose	% Fluctuation	Accumulation Ratio[1]	Accumulation Ratio[2]	$AUC_{0-12(Day\ 10)}$ / $AUC_{inf(Day\ 1)}$
40 mg	181 ± 94	1.26	1.17	0.86
200 mg	83 ± 69	2.03	1.7	0.86
400 mg	82 ± 58	2.25	1.62	0.86

% Fluctuation = $(Cmax-Cmin)/(AUC_{0-12}/12) \times 100$ (Given as mean ±SD)

Accumulation Ratio[1] = $AUC_{0-12(Day\ 10)}/AUC_{0-12(Day\ 1)}$ (Both mean and 90% CI are given.)

Accumulation Ratio[2] = $Cmax_{0-12(Day\ 10)}/Cmax_{0-12(Day\ 1)}$ (Both mean and 90% CI are given.)

Across dose groups, the dose-adjusted AUC decreased somewhat with dose.



Ex-Vivo PGE_2 and TXB_2: Four hours following a single oral dose (Day 1), the thromboxane B2 (TXB_2) induced ex-vivo was significantly lower in the 200 mg and 400 mg dose groups (see table below). Eight days following multiple dosing (Day 10), TXB_2 concentrations were significantly decreased only in the 400 mg dose group. Prostaglandin E_2 (PGE_2) values were statistically significantly lower in all three treatment groups following both single and multiple doses of SC-58635 ($p \leq 0.05$).

Dose	A Day 1*, 0 hr	B Day 1*, 4 hrs	B-A (p-value**)	C Day 10, 4 hrs	C-A (p-value**)
TXB_2 concentration (ng/mL)					
40 mg	23.1 ± 16.1	15.6 ± 17.7	-7.6 ± 11.4 (p = 0.109)	19.7 ± 13.0	-3.4 ± 7.8 (p = 0.461)
200 mg	23.0 ± 10.6	12.0 ± 5.2	-11.0 ± 9.0 (p = 0.016)	16.0 ± 7.5	-6.7 ± 9.8 (p = 0.156)
400 mg	47.7 ± 43.1	25.9 ± 23.8	-21.8 ± 22.5 (p = 0.008)	22.5 ± 17.4	-25.2 ± 32.5 (p = 0.008)
PGE_2 concentration (pg/mL)					
40 mg	67.5 ± 35.3	47.4 ± 23.4	-20.1 ± 25.2 (0.023)	35.0 ± 19.6	-32.5 ± 21.2 (0.008)
200 mg	81.8 ± 40.5	33.5 ± 21.1	-48.3 ± 24.5 (0.008)	24.5 ± 21.1	-62.8 ± 31.9 (0.016)
400 mg	51.8 ±24.1	22.7 ± 13.1	-29.2 ± 13.6 (0.008)	15.7 ± 9.7	-36.1 ± 15.2 (0.008)

*Samples collected on Day 1 for the 40 mg & 200 mg dose groups and on Day 3 for the 400 mg group
**Based on the Wilcoxon signed rank test; n= 8 (40 mg & 400 mg dose groups); n=7 (200 mg dose group)

Reviewer's comments:

1. Reduction in induced PGE_2 on Day 10 was significant for all dose groups when compared to the "baseline value," but the magnitude of the decrease was not related to dose. Since the blood samples for ex-vivo TXB_2 and PGE_2 baseline were collected on different days for the 400 mg group (Day 1 for the 40 mg and 200 mg groups and Day 3 for the 400 mg dose group), this might have compromised the results.
2. The values of CL/F and V/F during the multiple dose phase in the individual report (Vol. 1.87, p. 43) are different from those in the summary (Vol. 1.81, p. 226). The sponsor should clarify.

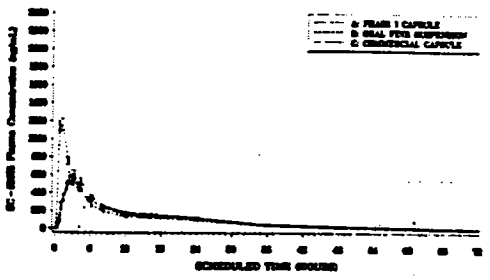
RELATIVE BIOAVAILABILITY

Commercial Capsule 200 mg and Phase I Capsules 100 mg vs. A Suspension (Study 037)

The primary objective of this study was to determine the bioavailability of the Phase I celecoxib capsules (100 mg) and the commercial formulation capsules (200 mg) relative to an oral suspension. Thirty-six healthy subjects received each of the three treatments at a single dose of 200 mg on either Day 1, 8 or 15 according to a randomization schedule. Blood and urine samples were collected up to 72 hours postdose. The detailed study design is given in Appendix 1 (p. 83).

As shown in the figure below, there was a greater and more rapid early drug uptake in the oral suspension formulation compared to the Phase I and commercial capsules. However, by approximately 3 hours postdose, mean concentrations in the three formulations were comparable, with mean concentrations in the oral suspension group lowest after 3 hours (mean 72-hour levels were all below the assay sensitivity). It was evident that the oral suspension

formulation had higher C_{max} and shorter T_{max} compared to either the Phase I or commercial capsule formulations. The extent of absorption (AUC_{0-72}) from the two capsule formulations, however, was similar to the oral suspension formulation. The relative bioavailability for the commercial formulation was 99% relative to the suspension.



Urinary excretion of celecoxib was negligible (See tables below). The amount of metabolite M2 (SC-62807) excreted in the urine over 0-72 hours postdose was generally similar for the three formulations (~20-25% of dose).

Table: Mean (%CV) Parameter Values and 90% CI for Ratios

Single-dose Celecoxib Pharmacokinetic Parameter	Treatment Mean (CV)[a]		Ratio: 200 mg Commercial Cap. / Suspension	90% Confidence Interval for Ratio[b]
	Commercial 1*200 mg Capsule (N=36)	Suspension 200 mg (N=36)		
AUC(0-72) (hr·ng/ml)	7648 (32%)	7736 (32%)	99.0%	(94.6%, 103.5%)
AUC(0-∞) (hr·ng/ml)	7830 (31%)	8001 (32%)	-	-
C_{max} (ng/ml)	704.6 (38%)	1229 (37%)	57.8%	(51.1%, 65.4%)
T_{max} (hr)	2.83 (37%)	0.79 (41%)	-	-
Terminal T1/2 (hr)	11.9 (30%)	13.3 (50%)	-	-
CL/F (L/hr)[c]	27.7 (28%)	27.1 (28%)	-	-
SC-58635 XU(0-72) (% of dose)	0.001 (145%)	0.003 (122%)	-	-
SC-62807 XU(0-72) (% of dose)	22.3 (29%)	23.5 (24%)	-	-
Single-dose Celecoxib Pharmacokinetic Parameter	Treatment Mean (CV)[a]		Ratio: Suspension / 100 mg Phase I Cap.	90% Confidence Interval for Ratio[b]
	Suspension 200 mg (N=36)	Phase I 2*100 mg Capsule (N=36)		
AUC(0-72) (hr·ng/ml)	7736 (32%)	7248 (33%)	107.3%	(102.5%, 112.2%)
AUC(0-∞) (hr·ng/ml)	8001 (32%)	7562 (33%)	-	-
C_{max} (ng/ml)	1229 (37%)	619.7 (40%)	197.0%	(174.2%, 222.9%)
T_{max} (hr)	0.79 (41%)	3.00 (33%)	-	-
Terminal T1/2 (hr)	13.3 (50%)	14.0 (38%)	-	-
CL/F (L/hr)[c]	27.1 (28%)	29.0 (31%)	-	-
SC-58635 XU(0-72) (% of dose)	0.003 (122%)	0.001 (222%)	-	-
SC-62807 XU(0-72) (% of dose)	23.5 (24%)	21.3 (31%)	-	-

DOSE PROPORTIONALITY OF COMMERCIAL CAPSULES

To demonstrate dose proportionality between celecoxib 100 mg and 200 mg commercial capsules, the sponsor combined data for 47 subjects who received one celecoxib 200 mg

commercial capsule in bioequivalence study 084 and data for 24 subjects who received one celecoxib 100 mg commercial capsule in food effect study 088. Only data for treatments given under fasted conditions were used (see table below). Individual celecoxib AUC and C_{max} values were doubled for the one 100 mg capsule treatment prior to assessment of dose proportionality by testing the significance of the difference between least square means of the two commercial capsule. From the p-values, the sponsor claimed the two commercial capsules are dose proportional.

Single-dose Celecoxib Pharmacokinetic Parameter	Treatment Mean (CV) or Median (Range)		p-Value for Test of Difference Between Log LS Means[b]
	1*100 mg Commercial (N=24)	1*200 mg Commercial (N=47)	
AUC(0-lqc) (hr·ng/ml)	4416 (77%)	8063 (44%)	0.615
AUC(0-∞) (hr·ng/ml)	5127 (78%)	8829 (48%)	0.296
C_{max} (ng/ml)	455.0 (60%)	801.2 (46%)	0.501
T_{max} (hr)	2.6 (1.5 - 6)	2.5 (1.5 - 8)	NAV
Terminal T1/2 (hr)	16.0 (63%)	12.2 (52%)	0.310
C_{max}/AUC(0-lqc)	0.11 (36%)	0.10 (34%)	NAV

Reviewer's comment:
The validity of this approach is questionable since data from one particular study for each strength was chosen to fit the need. It is noted that there were other studies available but were not selected. For example, Study 019 (food effect study for the 200 mg commercial capsules) gave a mean AUC_∞ of 6564 (±2383) ng.hr/mL following a single dose administration of the 200 mg commercial capsules under fasted conditions. It appears that using this study will fail the dose proportionality in AUC_∞. The sponsor should justify the selection of particular studies for the statistical test. (Additionally, p-values are given in the above table but not the power for detecting a 20% difference. In view of the high variability in parameter values, especially for the 100 mg capsules, this information is essential.) In our view, true dose proportionality between the commercial 100 mg and 200 mg capsules was not established by this analysis.

EFFECT OF FOOD AND ANTACID

a. 200 mg Celecoxib Commercial Capsules (Study 019)

The food effect on the bioavailability of celecoxib 200 mg capsules was assessed in 24 healthy subjects after administration of a single 200-mg dose. Both high-fat and medium-fat meals were examined. In addition, the effect of antacid was also investigated. Detailed study design is given on page 70. The plasma concentration-time profiles (0-12 hrs postdose) are shown in the figure.