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**APPLICATION NUMBER: NDA 20998/S007**

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**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

**FOR CELEBREX (CELECOXIB)**

**Applicant: Searle**

**December, 1999**

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW  
FOR CELEBREX (CELECOXIB)**

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## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-156

Submission Date: June 25, 1999  
July 28, 1999  
October 6, 1999

Drug Name: Celebrex (Celecoxib) 200 mg capsules  
Formulation & Strength: 200 mg capsules

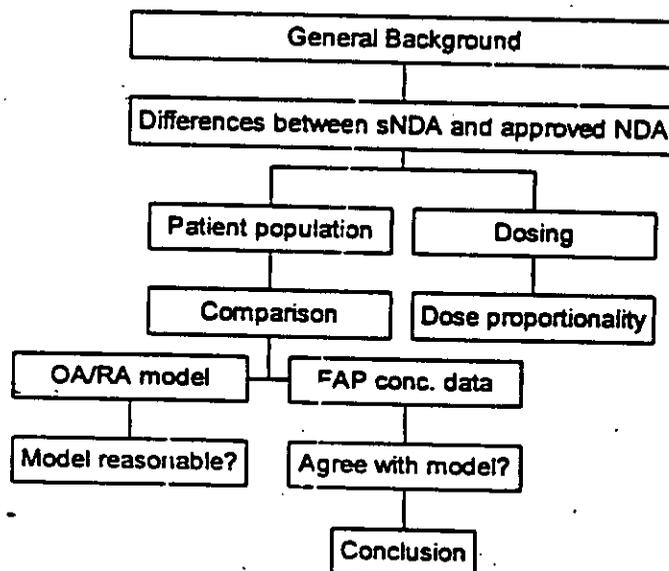
Applicant: Searle  
4901 Searle Parkway  
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Reviewer: Z. John Duan, Ph.D.  
Pharmacometrician: Jogarao Gobburu, Ph.D.  
Type of Submission: Supplemental New Drug Application

This is a review of the Clinical Pharmacology and Biopharmaceutics (CPB) studies submitted in the sNDA 21-156 in support of reduction and regression of colorectal adenomatous polyps by celecoxib. Celecoxib was approved under NDA 20-998 for the relief of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in adults. Thirty pharmacokinetic studies were submitted in the NDA 20-998. In the current sNDA, the applicant submitted two studies to support the new indication.

### I. SYNOPSIS

This review will be completed by using the Question Based Review approach, which will follow the logic below.



**1. What is the general background information about this sNDA?**

Celecoxib (SC-58635), a diarylsubstituted pyrazole compound, is a specific cyclooxygenase 2 enzyme (COX-2) inhibitor. Overexpression of COX-2, has been shown to be related to the development of colorectal cancer. The proposed indication in this supplemental NDA for celecoxib is for the reduction and regression of colorectal adenomatous polyps (believed to be precursors and surrogate endpoints for the development of colon cancer) which may lead to the development of colon cancer in patients with Familial Adenomatous Polyposis.

Celecoxib was approved under NDA 20-998, as a member of a novel class of agents that selectively inhibits cyclooxygenase-2 (COX-2), for the relief of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in adults. In NDA 20-998, the applicant submitted a total of 30 pharmacokinetic studies. The following is a brief summary based on the Clinical Pharmacology Section of the package insert.

Pharmacokinetic characteristics of celecoxib

**Absorption:** Following a single dose under fasted conditions, peak plasma celecoxib concentrations ( $C_{max}$ : ~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  $C_{max}$  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 aluminum and magnesium containing antacid resulted in a reduction in plasma celecoxib concentrations ( $C_{max}$ : decrease 37%; AUC: decrease 10%).

**Dose proportionality:** Although both AUC and  $C_{max}$  are not dose proportional (the dose adjusted parameter values are reduced with an increase in dose due to the poor solubility of the drug), the AUC is "roughly" dose proportional between 100 mg and 400 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,  $\alpha_1$ -acid glycoprotein. The apparent volume of distribution at steady state ( $V_{ss}/F$ ) 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 30 L/hr.

### Special populations

**Effects of age:** At steady state, elderly subjects (over 65 years old) had a 40% higher  $C_{max}$  (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  $C_{max}$  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  $C_{max}$  than male subjects after a single dose of celecoxib. On the other hand, there was no significant difference in  $C_{max}$  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 gender.

**Effect of body weight:** A meta analysis showed that single-dose  $C_{max}$  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  $K_i$  value for inhibition of bufuralol 1'-hydroxylation was  $\sim 4.2 \mu\text{M}$ , which is 9-fold weaker than quinidine.) In Study 015 (elderly vs. young), 5 out of 22 elderly subjects had a  $C_{\text{max}}$  value equal to or greater than the  $K_i$  value ( $-1.6 \mu\text{g/mL}$ ) 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  $C_{\text{max}}$  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. However, in post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin.

#### **2. What are the major differences between this sNDA and the approved NDA?**

There are two major differences.

- The new sNDA is for reduction and regression of colorectal adenomatous polyps which may lead to the development of colon cancer in patients with Familial Adenomatous Polyposis, a new population compared to the approved NDA.
- A new dose will be used for the proposed new indication, i.e. 400 mg (2 × 200 mg capsules) twice per day, which is different from 100 to 200 mg twice per day for the approved indication.

**3. Is the dose proportionality proved?**

Although both AUC and  $C_{max}$  are not dose proportional (the dose adjusted parameter values are reduced with an increase in dose due to the poor solubility of the drug), the AUC is "roughly" dose proportional between 100 mg and 400 mg doses. The deviation from dose proportionality is reduced under fed conditions.

**4. By what means, did the applicant try to prove the two populations are similar in drug exposure?**

The applicant conducted a study entitled "A comparison of celecoxib population pharmacokinetics in patients with familial adenomatous polyposis versus patients with osteoarthritis (OA) and rheumatoid arthritis (RA)." The objective of this study was to obtain empirical Bayes estimates of the celecoxib plasma clearance (CL/F) in the familial adenomatous polyposis (FAP) patient population from the population PK model developed in the OA and RA patient population. Based on this model, comparisons of the celecoxib CL/F between these two populations were made. Eighty-seven celecoxib plasma concentrations from 52 FAP patients were included in this analysis.

The study was a double-blind, randomized, placebo-controlled, parallel group study of the safety and efficacy of 100 or 400 mg BID celecoxib versus placebo in FAP patients, (clinical study IQ4-96-02-001). The FAP patients were sampled at trough prior to their morning dose at the 3-month and 6-month (final) visits. A comparison of the PK data in the FAP population to the OA/RA patient population was performed using a population pharmacokinetic model developed to describe the pharmacokinetics of celecoxib in OA and RA patients (clinical report N49-98-07-824).

**5. Does the population PK study confirm the similarity of the drug exposure in different populations?**

The empirical Bayes estimates of celecoxib plasma CL/F in the FAP patients are very similar to the estimates for the OA and RA patients and are consistent with the population mean estimate based on the OA/RA population PK analysis.

**6. Is the population PK model developed for OA/RA population reasonable?**

Although the estimated CL/F obtained from the model had a reasonable agreement

with those from the studies with dense sampling ( $34.7 \pm 2.2$  L/hr vs. 31.4 - 45.1 L/hr), the estimated values of other PK parameters, such as  $t_{1/2}$  and V/F; from the model are different from the values obtained from studies with dense sampling ( $t_{1/2}$ : 2.8 hours vs. 11 hours and V/F:  $141 \pm 35$  L vs. 194 - 557 L). However, for comparing the overall exposure (AUC) between the previous OA/RA and current FAP populations, the model developed is adequate.

#### **7. What conclusion can we draw?**

The model developed by the applicant to describe the time course of plasma concentrations for OA/RA patient population is adequate to compare overall exposure (AUC) between the previous OA/RA and the current FAP populations. The model assumes linearity which may be a reasonable assumption considering the pharmacokinetics under fed conditions. Further, the plasma concentrations of celecoxib measured in the FAP population and those measured in the OA and RA populations are comparable. Therefore, population (FAP vs. OA/RA) and dosing changes (400 mg vs. 200 mg) do not raise significant concerns from Clinical Pharmacology and Biopharmaceutics perspective in terms of predictable drug exposure between the two populations.

## **II. GENERAL COMMENTS**

The following comments have been discussed with and concurred by Dr. Jogarao Gobburu, the pharmacometrics Scientist of DPEI.

1. Reliability of the proposed pharmacokinetic model: the model developed by the applicant to describe the time course of plasma concentrations is adequate to compare overall exposure (AUC) between the previous OA/RA and current FAP populations. The model assumes linearity which may be a reasonable assumption considering the pharmacokinetics under fed conditions.
2. Although the estimated CL/F values obtained from the model have a good agreement with those from studies with dense sampling, the estimated values of other PK parameters such as  $t_{1/2}$  and V/F from the model are quite different from those obtained from the studies with dense sampling. Therefore, caution needs to be exercised for using this model for other purposes, such as changing dosing schedule and designing future trials.
3. The plasma concentrations of celecoxib measured in the FAP population and those measured in the OA and RA populations are comparable.

## **III. LABELING COMMENTS**

1. The following statements in CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption, Food Effect Section:

Should be changed to:

**CELEBREX should be administered with food for the FAP population.**

2. The following statements:

**"taken with food"**

should be added to the Section of **DOSAGE AND ADMINISTRATION** and the last paragraph of the Section:

will be changed to:

**Familial adenomatous polyposis (FAP):** Standard medical care for FAP patients should be continued while on CELEBREX. For the reduction and regression of adenomatous colorectal polyps which may lead to the development of colorectal cancer in patients with FAP, the recommended oral dose is 400 mg (2 X 200 mg capsules) taken with food twice per day.

3. The statements, in Clinical Pharmacology Section, that the doses in patients with moderate hepatic impairment should be reduced and the use of CELEBREX in patients with severe hepatic impairment is not recommended should be repeated or referenced in Warning Section, Precaution Section, and **DOSAGE AND ADMINISTRATION** Section.
4. The statements, in Warning Section, that treatment with CELEBREX is not recommended in patients with advanced kidney disease should be repeated or referenced in Precaution Section and **DOSAGE AND ADMINISTRATION** Section.

#### **IV. RECOMMENDATION**

The comparison between FAP population and OA/RA population is considered to be adequate, and the plasma celecoxib concentrations measured between the two populations are comparable. Therefore, population and dosing changes do not raise significant concerns and the sNDA is approvable from Clinical Pharmacology and Biopharmaceutics perspective.

Please forward the General Comments and Labeling Comments to the applicant.

IS/  
Atiqur Rahman, Ph.D. 12/15/99  
Date

Team Leader  
Division of Pharmaceutical Evaluation I

IS/  
John Duan, Ph.D. 12/14/99  
Date

Reviewer  
Division of Pharmaceutical Evaluation I

CPB Briefing date: 11/29/1999

CC: NDA 21156 original  
HFD-150 Division File  
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## APPENDIX II. INDIVIDUAL STUDY SYNOPSIS

### *1. Report No. NQ4-99-07-812*

**Study title:** A comparison of celecoxib population pharmacokinetics in patients with familial adenomatous polyposis versus patients with osteoarthritis and rheumatoid arthritis.

**Investigator:**

**Study period:** Information not available.

**Study formulation:** 100 mg and 200 mg capsules

#### **Objectives:**

The objective of this analysis was to obtain empirical Bayes estimates of the celecoxib plasma clearance (CL/F) in the familial adenomatous polyposis (FAP) patients based on the population PK model developed in the OA and RA patient population. Based on this model, comparisons of the celecoxib CL/F between these two populations were made.

#### **Subjects:**

A total of 111 celecoxib plasma concentrations from 60 FAP patients were obtained. Eighty-seven celecoxib plasma concentrations from 52 FAP patients were included in this analysis. The remaining 24 data records containing missing dose times or concentrations were excluded in the analysis.

#### **Study Design:**

The FAP study was a double-blind, randomized, placebo-controlled, parallel group study of the safety and efficacy of 100 or 400 mg BID celecoxib versus placebo in FAP patients, clinical study IQ4-96-02-001. Blood samples for celecoxib determination were obtained at trough at the 3 and 6 month visits. Due to the limitations with a trough sampling design, a population pharmacokinetic model was not developed for the FAP patient population. However, a comparison of the PK data in the FAP population to the OA/RA patient population was performed using a population pharmacokinetic model developed to describe the pharmacokinetics of celecoxib in OA and RA patients, clinical report N49-98-07-824.

The FAP patients were sampled at trough prior to their morning dose at the 3-month and 6-month (final) visits. The patients were queried as to the date and time of their last dose and the elapsed time between the previous dose and blood sample was determined. The majority (-75%) of the sample times was between 8 and 20 hours post-dose. Four data records had concentration values below the assay sensitivity and were

set to the assay sensitivity limit of 10 ng/ml. Two patients (ID=50380106 and ID=51200028) with values below the assay sensitivity had extreme outlying elapsed times (i.e., >130 hours). These two observations were not included in the time profile plots in order to maintain good resolution for the remaining observations whose elapsed times were less than 32 hours.

**Results:**

*Assay performance:*

Method used: ✓

Range: ✓                      ng/mL

Linearity: linear within the range

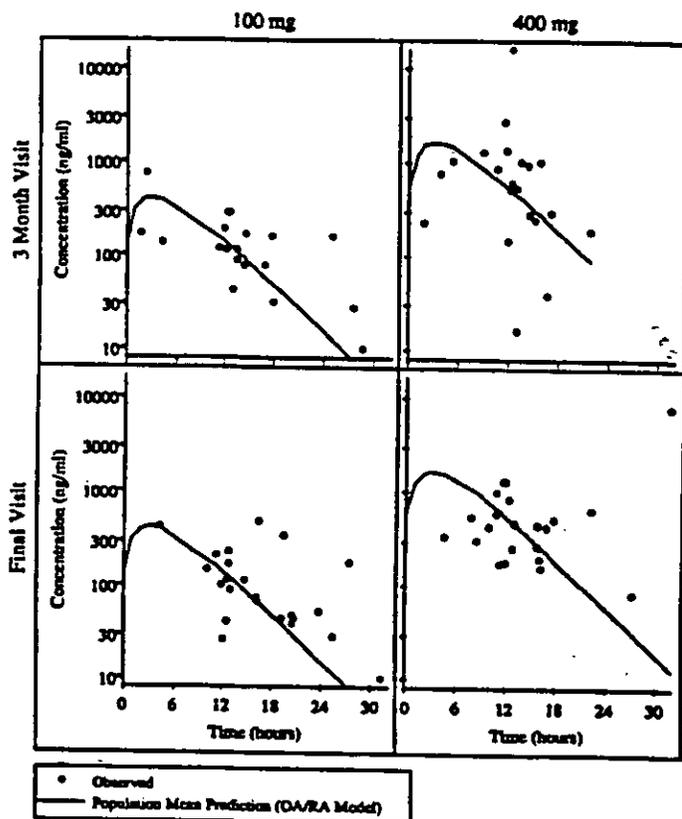
Specificity: chromatograms acceptable

Precision (%CV): 1.8 – 18.4%

Recovery: 94.5-104%

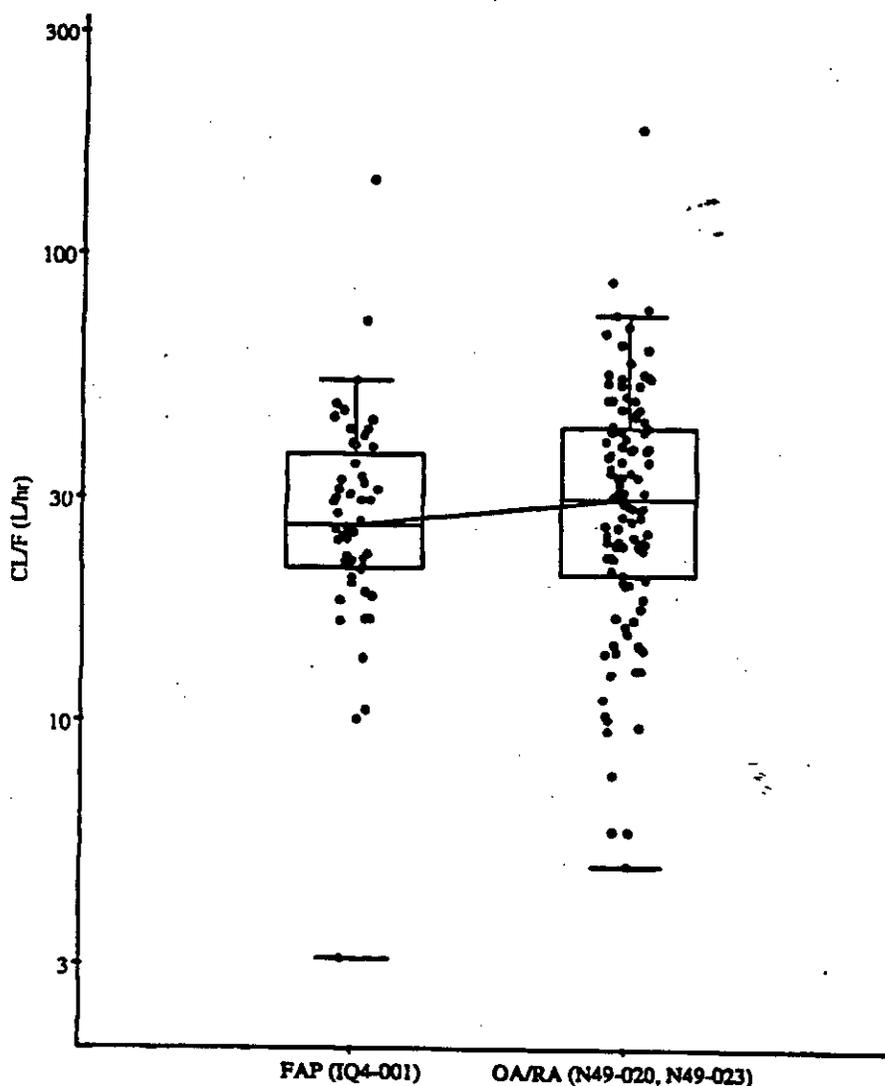
*Population pharmacokinetics*

The celecoxib plasma concentrations in FAP patients at the 3-month and 6-month (final) visits following 100 or 400 mg BID celecoxib are plotted versus time in the following Figure.



For comparison, population mean predictions of the celecoxib plasma concentrations using the base model parameter estimates given in the OA/RA population model are also shown in the above Figure.

Box-plots of the empirical Bayes predictions of celecoxib CL/F for both the FAP and OA/RA patient populations based on the final population PK model are shown in the following Figure.



Summary statistics for the individual celecoxib CL/F for both the FAP and OA/RA patient populations are given in the following Table.

**Table. Summary Statistics of Individual Celecoxib Plasma CL/F Estimates**

Summary Statistic	FAP (L/hr)	OA/RA (L/hr)
N	52	110
Mean ± SEM	31.0 ± 2.8	34.1 ± 2.1
Standard Deviation	20.2	22.3
Median	26.4	29.9
Range (Min - Max)	3.10 - 145	4.94 - 187

The empirical Bayes estimates of celecoxib plasma CL/F in the FAP patients are very similar to the estimates for the OA and RA patients and are consistent with the population mean estimate based on the OA/RA population PK analysis.

**Conclusions:**

1. The celecoxib plasma concentrations in FAP patients are in agreement with the predictions based on the population model developed from the OA and RA patients. The estimates of celecoxib plasma CL/F in the FAP patients are similar to the estimates for the OA and RA patients and are consistent with the population mean estimate based on the OA/RA population PK analysis.
2. The population PK analysis for the OA and RA patients identified racial trends in celecoxib CL/F, however, due to the limited number of Blacks and other noncaucasians in the FAP study, no assessment of the racial effect in the FAP population could be made. The individual estimates of CL/F in the FAP patients demonstrate a trend with body weight that is consistent with the findings observed from the OA/RA population PK analysis.

**Comments:**

1. This study was to obtain empirical Bayes estimates of the celecoxib plasma clearance (CL/F) in the FAP patient population based on the population PK model developed in the OA and RA patient population. Comparisons of the celecoxib CL/F between these two populations are adequate to show the similarity of the overall drug exposures.
2. In-study assay validations for this study are not provided.

**Study title:**

Celecoxib population pharmacokinetic modeling in arthritis patients.

**Investigator & location:**

**Study period:**

Information not available.

**Study formulation:**

100 mg and 200 mg capsules

**Objectives:**

The objective of this analysis is to summarize the pharmacokinetics of celecoxib in the OA and RA patient populations and to investigate the influence of selected covariates (e.g., patient demographics, clinical labs, disease state, etc) on the key pharmacokinetic parameters, apparent volume of distribution (V/F) and apparent clearance (CL/F). A PK data analysis plan was prepared pre-specifying the covariates to be investigated, the handling of missing data and outliers, and the methods used for model development and validation. The covariates specified in the analysis plan include: body weight (kg), height (cm), body surface area (m<sup>2</sup>), gender, age (yrs), race (Caucasian, black or other), time of meal relative to dose (hrs), serum creatinine (mg/dl), estimated creatinine clearance (ml/min), SGOT (u/l), SGPT (u/l), disease state (OA or RA) and compliance rate.

**Subjects:**

The number of patients and observations used in the population PK analysis by study and dose are given in the following Table.

Table. Sample Size by Study and Dose

N	OA STUDY			RA STUDY		Total
	50 mg	100 mg	200 mg	100 mg	200 mg	
Pts.	29	21	28	13	10	110
Obs.	84	62	84	39	30	326

**Study Design:**

A population pharmacokinetic (PK) model was developed to describe the pharmacokinetics of celecoxib in osteoarthritis (OA) and rheumatoid arthritis (RA) patients. Data pooled from two clinical trials in OA and RA patients, clinical study

protocols N49-96-02-020 and N49-96-02-023, respectively, were used to develop the population model. The OA study is a double-blind, randomized, placebo-controlled, parallel group study comparing the safety and efficacy of 50, 100 and 200 mg BID celecoxib versus 500 mg BID naproxen and placebo. The RA study is a double-blind, randomized, placebo-controlled, parallel group study comparing the safety and efficacy of 100, 200 and 400 mg BID celecoxib versus 500 mg BID naproxen and placebo. Only the celecoxib treatment arms of these two studies were used to develop the population PK model.

### **Sampling Design**

A random sampling design was employed to obtain blood samples for assay of celecoxib plasma concentrations. Between 7 and 28 days after receiving their first study medication, patients participating in the population PK substudy at selected investigational sites had three blood samples collected one hour apart. Patients were queried as to the date and time of their most recent dose. The sampling design is considered random since no restrictions were placed on the duration of time between the most recent dose and the time of the first blood draw. However, investigators were instructed to stagger visit times for the PK substudy patients to ensure a wide range of times between time of last dose and the time of the first blood sample.

### **Results:**

A steady-state one compartment model was used to fit the pharmacokinetic data with the NONMEM program. The structural model was parameterized in terms of the apparent absorption rate ( $k_a$ ), the apparent volume of distribution ( $V/F$ ), and the apparent clearance ( $CL/F$ ). The covariate analysis identified race and body weight as influential factors on  $CL/F$ . None of the covariates investigated were found to be influential on  $V/F$ . The main steps in the data analysis include: construction of the dataset, missing data assessment, base model (no covariates) development, outlier assessment, model building, final model assessment, and validation of the final model. Since a test dataset from an independent study was not available for external validation of the final model an internal validation of the model was performed using a nonparametric bootstrap resampling technique. Two hundred bootstrap datasets of  $N=110$  patients were constructed based on sampling with replacement of the  $N=110$  patients' observed data vectors. SAS was used to perform the random resampling of the observed patient data listed in Appendix 2.2 to construct the 200 bootstrap datasets. The final model was fit to each of the 200 bootstrap datasets to obtain 200 sets of bootstrap parameter estimates.

The model selection and reduction algorithm results are tabulated below.

**Table. Model Selection and Reduction Algorithm Results**

Model/Covariate Base (ELS)	$\Delta$ ELS (p-value)			Final
	Step 1	Step 2	Step 3	
	-129.739	-161.290	-173.326	-173.326
<b>V/F</b>				
Weight	5.298 (0.0213)	6.765 (0.0093)	3.341 (0.0676)	not incl.
BSA	5.097 (0.0240)	5.603 (0.0160)	4.276 (0.0387)	Not incl.
Age	2.793 (0.0947)	1.896 (0.1685)	3.699 (0.0544)	Not incl.
Race	3.465 (0.1768)	2.766 (0.2508)	1.398 (0.4971)	Not incl.
Disease State	9.609 (0.0020)	5.147 (0.0233)	6.842 (0.0089)	Not incl.
<b>Cl/F</b>				
Weight	9.521 (0.0020)	12.036* (0.0005)	included	12.036 (0.0005)
BSA	11.628 (0.0006)	11.364 (0.0007)	0.0680 (0.7943)	not incl.
Age	6.726 (0.0095)	3.866 (0.0493)	3.920 (0.0477)	Not incl.
Race	31.551* ( $<0.0001$ )	included	included	34.066 ( $<0.0001$ )
Disease State	1.033 (0.3095)	0.039 (0.8434)	0.615 (0.4730)	not incl.

\*Parameter included in the model for the next step.

The pharmacokinetic parameter estimates and variabilities are tabulated below

**Table. Celecoxib PK Parameter Estimates and Variance Components**

Parameter	Base Model		Final Model	
	Estimate $\pm$ SE	%CV	Estimate $\pm$ SE	%CV
$K_a$ ( $\theta_1$ ) (1/hr)	0.368 $\pm$ 0.077	b	0.372 $\pm$ 0.082	b
V/F ( $\theta_2$ ) (L)	146 $\pm$ 38	51.7	141 $\pm$ 35	46.6
Cl/F ( $\theta_3$ ) (L/hr)	28.3 $\pm$ 1.9	64.2	34.7 $\pm$ 2.2	50.3
Blacks ( $\theta_4$ )	1.0a		0.442 $\pm$ 0.070	
Others ( $\theta_5$ )	1.0 a		0.389 $\pm$ 0.109	
Weight ( $\theta_6$ )	0.0 a		0.831 $\pm$ 0.236	
$\sigma$ (%CV)	33.1		33.2	

a. For the base model these parameters were fixed to values corresponding to no covariate effects.  
 b. Insufficient information in the data to estimate an interpatient variance component for  $k_a$ .

The population mean estimate for V/F was 141 L with an interpatient coefficient of variation (CV) of 47%. For CL/F, the population mean estimate for Caucasians at a median weight of 81.4 kg was 34.7 L/hr. The model estimates a 56% reduction in CL/F for Blacks and a similar reduction for other non-Caucasians. However, the results for other non-Caucasians are based on data from only three patients. Increases in CL/F were nearly proportional with body weight. The interpatient CV for CL/F was approximately 50%.

The final model was fit to each of 200 bootstrap datasets to obtain bootstrap estimates of the population PK parameters (fixed effects) and variance components. For each parameter, the 200 bootstrap estimates were summarized to obtain means, standard errors, and 95% confidence intervals. The bootstrap estimates and confidence intervals are compared to the final model estimates and profile likelihood confidence intervals obtained from the data analysis on the original dataset as shown in the following Table.

Table. Comparison of Final Model and Bootstrap Estimates

Parameter	Final Model Results		Bootstrap Results	
	Estimate ± SE	95% CI	Estimate ± SE	95% CI
$K_a$ ( $\theta_1$ ) (1/hr)	0.372 ± 0.082	0.146 - 0.598	0.343 ± 0.126	0.154 - 0.628
V/F ( $\theta_2$ ) (L)	141 ± 35	47.0 - 224	129 ± 51	39.3 - 227
CL/F ( $\theta_3$ ) (L/hr)	34.7 ± 2.2	30.5 - 39.4	34.4 ± 2.0	30.5 - 38.6
Blacks ( $\theta_4$ )	0.442 ± 0.070	0.353 - 0.577	0.453 ± 0.079	0.323 - 0.618
Others ( $\theta_5$ )	0.389 ± 0.109	0.208 - 0.743	0.424 ± 0.137	0.202 - 0.703
Weight ( $\theta_6$ )	0.831 ± 0.236	0.383 - 1.27	0.848 ± 0.251	0.343 - 1.29
$\omega_v$	46.6 ± 5.0	a	56.5 ± 23.0	23.5 - 111
$\omega_{CL}$	50.3 ± 2.5	a	46.8 ± 5.1	36.7 - 57.0
$\rho_{v,CL}$	0.267	a	0.320 ± 0.522	-0.812 - 1.0

a. Profile likelihood confidence intervals could not be obtained for the variance components since the inclusion of a covariance parameter between V/F and CL/F in the model precludes fixing a single component to several known values needed to construct the likelihood profile.

The bootstrap estimates are within 10% of the final model estimates for the fixed effect PK parameters. For the variance component parameters ( $\omega_v$ ,  $\omega_{CL}$ , and  $\rho_{v,CL}$ ), the bootstrap estimates are within 22% of the final model estimates. The bootstrap and profile likelihood confidence intervals are similar and reflect similar asymmetry relative to the point estimates.

### Conclusion

1. The 326 celecoxib plasma concentrations in 110 OA and RA patients obtained 7 to 28 days after the start of dosing for doses ranging from 50 - 400 mg BID are described by a steady-state one compartment model.
2. Race and body weight differences in apparent clearance were observed.

Differences in clearance due to race result in higher plasma concentrations for blacks and other noncaucasians. However, the results for other noncaucasians are based on data from only three patients and thus, should be interpreted cautiously. Differences in apparent clearance due to body weight result in lower or higher plasma concentrations for heavier and lighter patients, respectively.

3. The implications on dosing for blacks and possibly other noncaucasians as well as for extremely light or heavy patients cannot be fully assessed on the basis of these PK results alone. The clinical implications of these findings will require evaluation of the overall safety and efficacy databases of celecoxib to ascertain possible effects of race and body weight on clinically relevant patient outcomes.

**Comments:**

1. The estimated CL/F obtained from the model had an agreement with other studies with dense sampling ( $34.7 \pm 2.2$  L/hr vs.  $31.4 - 45.1$  L/hr). However, the estimated values of other PK parameters such as  $t_{1/2}$  and V/F from the model are different from the studies with dense sampling ( $t_{1/2}$ : 2.8 hours vs. 11 hours and V/F:  $141 \pm 35$  L vs.  $194 - 557$  L).
2. Therefore, for comparing the overall exposure between FAP and OA/RA populations, this model may be adequate; however, caution should be exercised when using this model for other purposes, such as changing dosing schedule and designing future studies.

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