CLINICAL PHARMACOLOGY
BPCA SUMMARY REVIEW

NDA: 20-998/SE5-021	Submission Date(s): 6-20-2006
Brand Name	Celebrex
Generic Name	Celecoxib Capsules
Reviewer	Srikanth C. Nallani, Ph.D.
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.
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OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Rheumatology Products
Sponsor	Pfizer, New York, NY
Relevant IND(s)	48,395
Submission Type; Code	Original; P
Formulation; Strength(s)	Capsule; 50 and 100 mg
Indication	Juvenile Rheumatoid Arthritis
Proposed Dosage Regimen	≥10 – ≤25 kg body weight – 50 mg capsule > 25 kg body weight – 100 mg capsule

1 Executive Summary

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, information contained in supplement SE5-021 to NDA 20-998 is acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Summary of CPB Findings

Celecoxib was approved for marketing for the treatment of rheumatoid arthritis in adults in 1998. Agency issued a Pediatric Written Request (PWR) on January 25, 2002 and subsequently amended it on December 12, 2005 to extend the time frame for submission of information outlined in the PWR. Pfizer submitted current supplement SE5-021 on June 20, 2006 to fulfill the requirements of PWR.

The submission consists of three new Clinical/Clinical Pharmacology studies:

- A single clinical efficacy study # 319-1127/N49-01-02-195 (also simply referred to as Study # 195) "a randomized, double-blind, multicenter, active-controlled

parallel-group study to evaluate the efficacy and safety of celecoxib suspension compared to naproxen suspension in patients with JRA".

- A relative bioavailability study of celecoxib commercial capsule and suspension formulation used in study 195 in healthy volunteers (study # 1162).
- A relative bioavailability study of celecoxib administered as capsule contents sprinkled on applesauce and intact capsules in healthy adult volunteers (Study #1202).

In addition, a dose-proportionality and food effect bioavailability study # 088 submitted in the original NDA in 1998 was resubmitted to support the 50 mg capsules.

Although pediatric patients in this clinical study (#195) were administered celecoxib suspension (100 mg/5 mL), 50 mg and 100 mg capsule formulations are being proposed for marketing due to problems in developing a commercially viable pharmaceutically elegant product. While celecoxib 100 mg capsule formulation was investigated in a variety of clinical studies and is currently marketed, clinical experience with celecoxib 50 mg capsule formulation in adults comes from studies #088 (n= 24) and Study #001 (n=4, exploratory single dose study) from original submission. Pediatric subjects have not been administered the capsule formulation at the proposed 50 mg or 100 mg strengths.

Dosing regimen employed in the clinical trial and the proposed dosing regimen:

Dosing Scheme Employed in the JRA Trial					
Treatment Group	9-12 kg	13-25 kg	26-37 kg	38-50 kg	>50 kg
Suspension	25 mg BID	50 mg BID	75 mg BID	100 mg BID	150 mg BID
Suspension	50 mg BID	100 mg BID	150 mg BID	200 mg BID	300 mg BID
Proposed Dosing Scheme					
Weight Category	≥10 and ≤25 kg		>25 kg		
Capsule	50 mg BID		100 mg BID		

Exposure-Response of celecoxib in JRA patients:

The pharmacometrics review conducted by Dr. Venkatesh Atul Bhattaram (see appended pharmacometrics review for a detailed review) focused on study N49-01-02-195 to address the following questions "Is the dose/dosing regimen and the proposed formulation switch (suspension to capsule) by the sponsor reasonable?". This question was raised at the pre-sNDA meeting following the bioavailability differences (see below) noted in the clinical trial formulation and the proposed to-be-marketed capsule formulation.

- Results from the relative bioavailability study # 1162, conducted after the clinical trial # 195, indicate that the celecoxib C_{max} and AUC from the proposed to-be-marketed commercial capsule was 50% and 15% higher compared to oral suspension formulation employed in the clinical efficacy study.

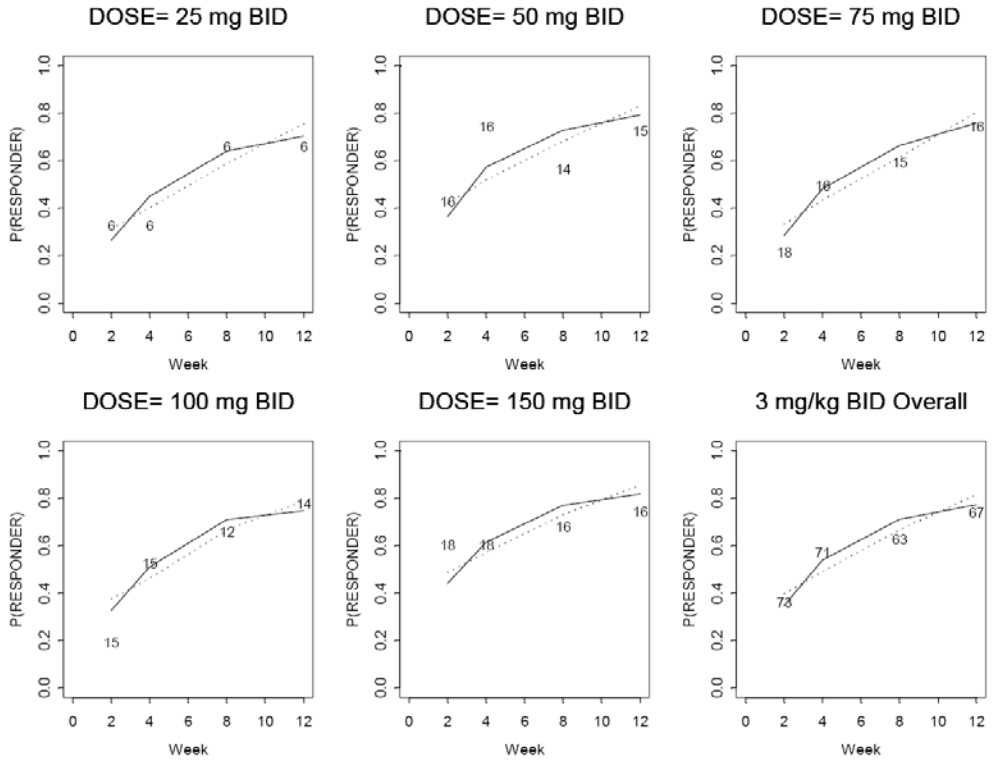
- Results of a relative bioavailability study (#1202) of celecoxib administered as capsule contents sprinkled on applesauce in healthy adult volunteers indicated similar C_{max} and AUC.

Exposure-Response (Efficacy):

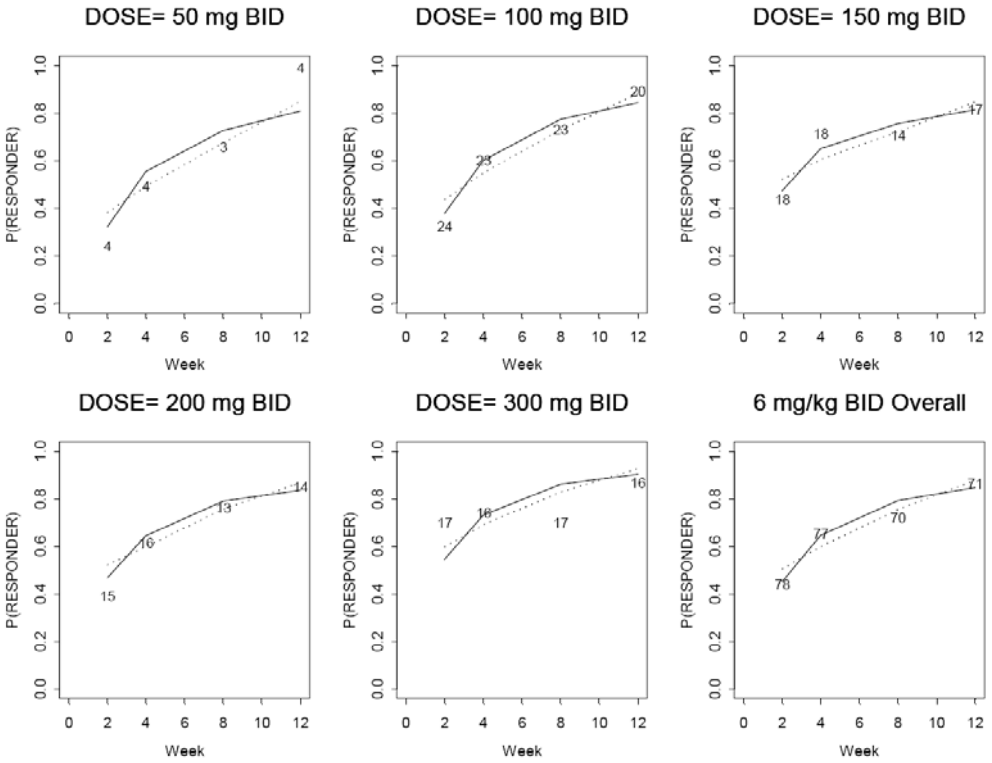
Exposure-response analysis was submitted by the sponsor as supportive evidence for the proposed dosing regimen. JRA-30 DOI data (binary outcome, responders=1 or non-responders=0) from 152 JRA subjects were used for the E/R analysis: 73 JRA subjects with 274 observations over Weeks 2, 4, 8 and 12 in the 3 mg/kg BID group, and 79 JRA subjects with 296 observations over Weeks 2, 4, 8 and 12 in the 6 mg/kg BID group. Observed responder data (not last observation carried forward) were used for E/R analysis.

Observed % responders (JRA-30 DOI) versus time, dose, and AUC (0-12) show a time-dependent increase in % responders. Two figures below show the observed and model-predicted (Models 3 and 7) probability of responders by week for the 3 mg/kg and 6 mg/kg BID groups, respectively. The plots indicate that adequate fits were obtained with both models.

Observed and Predicted Probability of Responders for Celecoxib 3 mg/kg BID



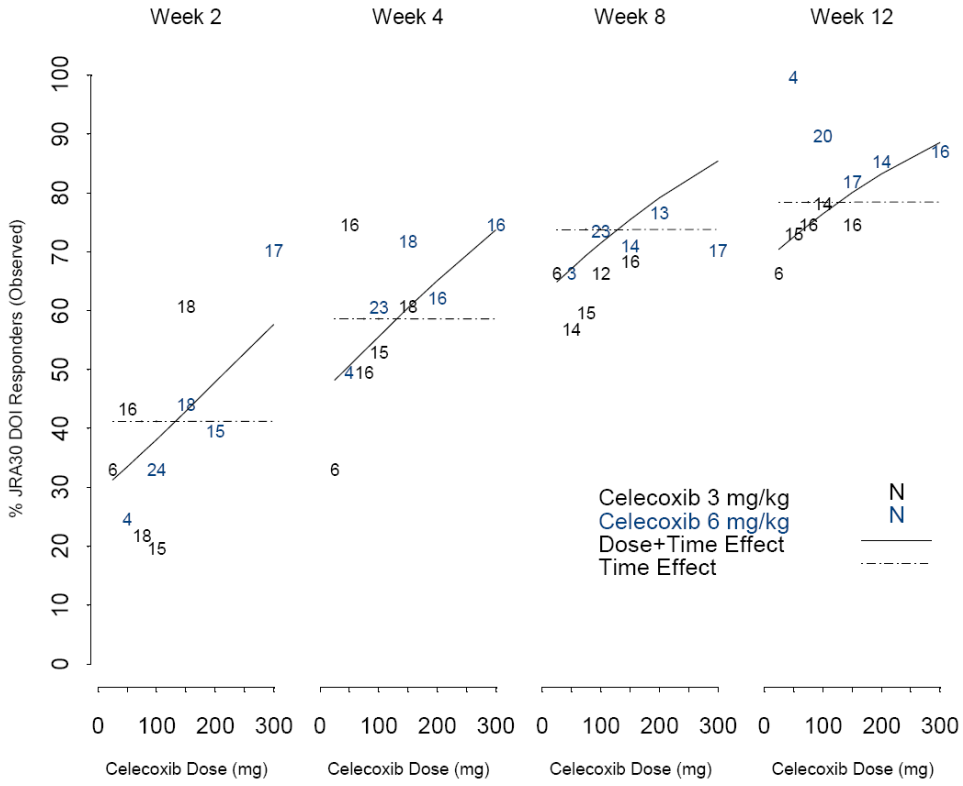
Observed and Predicted Probability of Responders for Celecoxib 6 mg/kg BID



Symbols are observed data and the values (N) represent the total number of subjects (responders + non-responders) in the E-R dataset for each time point and dose; solid line represents model prediction from Model 7 (exponential time effect plus linear typical $AUC_{(0\text{-}12)}$ effect); dotted line represents model prediction from Model 3 (linear time effect plus linear typical $AUC_{(0\text{-}12)}$ effect); shown are the mean of the model-predicted probability of responders at each time point and dose.

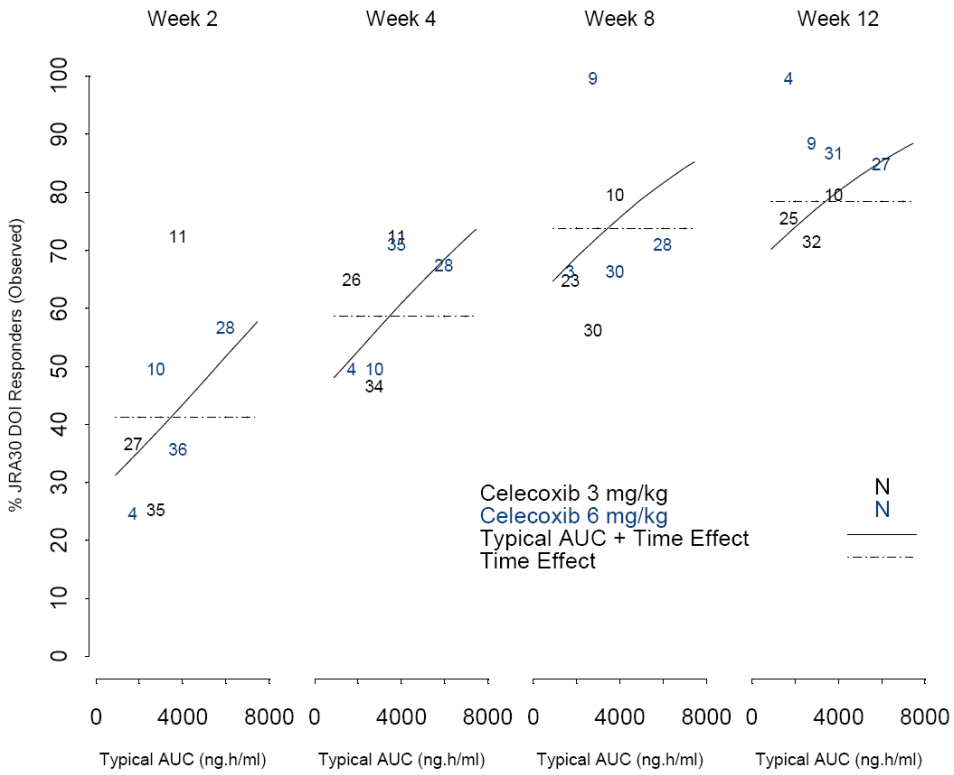
The dose and exposure-related increases in response rate are presented in the two figures below, where dose- and AUC(0-12)- response plots are plotted separately for each week (2, 4, 8, and 12).

Relationship Between Dose and % Responders



Symbols are observed data and the values (N) represent the total number of subjects (responders + non-responders) in the E-R dataset for each time point and dose within each dose group (in black for celecoxib 3 mg/kg; in blue for celecoxib 6 mg/kg); lines represent means of the simulated probability of responders at each dose and week; solid line represents simulation from Model 8 (dose + time effect); dotted line represents simulated probability using Model 5 (time effect only).

Relationship Between Typical $AUC_{(0-12)}$ and % Responders



Symbols (N) are observed data and represent the total number of subjects (responders + non-responders) in the E-R dataset for each time point and $AUC_{(0-12)}$ category within each dose group (in black for celecoxib 3 mg/kg; in blue for celecoxib 6 mg/kg); lines represent means of the simulated probability of responders at each week; solid line represents simulated probability using Model 7 (AUC + Time Effect); dotted line represents simulated probability using Model 5 (Time Effect only).

Taken together, greater percentage of early responders were noted with higher doses or exposures. However, since no placebo group was enrolled in the JRA trial it is difficult to interpret the non-drug based time-trend in JRA-30 DOI responders. The fact that dose and age were highly correlated in the JRA trial further confounds the estimated drug effects on JRA-30 DOI responder status with age.

- ***Dose Calculation for JRA Subjects***

Dosing recommendations for JRA subjects, given the efficacy, safety and PK results of Study N49-01-02-195, were derived by

a) assessing the relative differences in CL/F and AUC(0-12) between JRA and adult RA subjects, and in the percentages of JRA-30 DOI responders at Week 12 (primary efficacy endpoint) between various groups of JRA subjects,

b) evaluating the appropriateness of switching from suspension to the capsule dosage form from an exposure standpoint and

c) simulating the steady-state PK profiles for a set of representative weights for various doses of the capsule to determine appropriate doses for each weight.

The table below summarizes the individual Bayes predictions of celecoxib CL/F and AUC(0-12), and the percentages of JRA-30 DOI responders (last observation carried forward) at Week 12 (primary efficacy endpoint). The results are summarized by different age groups (2 to ≤5 years, >5 to ≤11, >11 to <17 years) for the reason that it is convenient and it allows for a descriptive assessment of exposure-response relationships. Ultimately, dosing recommendations are based on body weight.

Summary of Celecoxib Oral Clearance (CL/F), Steady State Area under the Plasma Concentration-Time Curve [$AUC_{(0-12)}$], and % Responders

Age Group	2 to ≤5 years (N = 28)[a]		>5 to ≤11 years (N = 47)[a]		>11 to <17 years (N = 77)[a]		Adult RA (N = 36)[a]
Weight (kg)							
Median	15.4		28.1		43.8		81.7
Range	(10.6, 37.5)		(15.0, 58.0)		(22.5, 92.7)		(53.3, 112.8)
CL/F (L/h)[b]							
Mean	30.6		33.4		46.0		44.9
%CV	37.0		35.3		42.7		44.4
Range	(15.2, 69.8)		(9.7, 55.1)		(9.3, 137.0)		(14.7, 114.6)
$AUC_{(0-12)}$ (ng•h/mL)							
Nominal Dose (mg/kg)	3	6	3	6	3	6	200 mg
N	13	15	22	25	38	39	36
Mean	1500.3	3200.4	2304.3	5041.5	3243.9	4864.1	5403.6
%CV	47.1	45.3	39.0	48.8	51.0	43.4	49.5
GM Ratio (%)[c]	27.80	59.42	43.81	93.37	59.66	90.31	NA
90%CI (Lower)	21.74	47.04	36.05	77.39	49.95	75.70	NA
90%CI (Upper)	35.55	75.05	53.25	112.64	71.25	107.75	NA
Responders[d]							
N	11	13	15	19	27	34	ND
%	84.6%	86.7%	68.2%	76.0%	71.1%	87.2%	

Abbreviations: NA = Not Applicable; ND = Not Determined; CI = Confidence Interval; %CV = Percent Coefficient of Variation; RA = Rheumatoid Arthritis.

[a] Represents number of subjects with evaluable plasma concentration data (i.e. those used for population PK analysis)

[b] Data are arithmetic mean, % coefficient of variation and range of individual (Bayes) CL estimates from the Final Model for the empirical distribution of weight within each category.

[c] Geometric mean (GM) ratio of pediatric to adult $AUC_{(0-12)}$

[d] Primary endpoint. A subject was considered a responder by the JRA-30 Definition of Improvement criterion if there was a ≥30% improvement in ≥3 JRA-30 Core Set variables and a >30% worsening in at most one JRA-30 Core Set variable. The JRA-30 Core Set includes: 1) Physician's Global Assessment of Disease Activity; 2) Parent's Global Assessment of Overall Well Being (CHAQ subsection); 3) Functional Ability (CHAQ Disability Index); 4) Number of Joints with Active Arthritis; 5) Number of Joints with Limited Range of Motion; 6) Laboratory marker of inflammation (C-Reactive Protein). Reported number and % responders (last observation carried forward) are for subjects with evaluable PK data at Week 12.

The following is the summary of the information presented in the table above:

- Mean celecoxib CL/F (L/h) was 32% lower in children 2 to ≤5 years and 26% lower in children >5 to ≤11 years relative to adult RA subjects.
- Mean CL/F estimates in adolescents (>11 to <17 years) were similar (2% higher) to that for adult RA subjects.

- CL/F values for the 3 and 6 mg/kg groups were pooled within each age category since the median values for the two dose groups were within 10% of each other for the 2 to ≤5 and >5 to ≤11 year categories and within 18% for the >11 to <17 year category.

Comparison of CL/F estimates between children 2 to ≤5 years and adolescents (>11 to <17 years) indicate that a 3-fold increase in body weight yielded only a 50% increase in CL/F. Results, based on individual predicted CL/F, are in alignment with the estimated magnitude of influence of weight on CL/F (typical value of CL=35.2*(Weighti/41)^0.265) where CL/F in subjects weighing 10 kg and 30 kg are predicted to be 40% and 20% lower, respectively, than that for a 70-kg subject. These results indicate that weight influences clearance to a much lesser extent than was assumed by the dosing scheme employed in the JRA trial.

- ***Switch from Clinical trial formulation to the to-be-Marketed Formulation***

The sponsor encountered difficulties in developing a commercially viable oral suspension formulation. Hence, the sponsor proposed the use of already approved 100 mg capsule and previously investigated 50 mg capsule for pediatric use. An investigation of relative bioavailability between the commercially available capsules and the oral suspension formulation indicated that the C_{max} and AUC(0-∞) from the suspension are approximately 50% and 15% lower, respectively, relative to the capsule. The sponsor was also suggested to propose the use of capsule contents sprinkled over applesauce in pediatric subjects unable to swallow capsules. Celecoxib C_{max} and AUC was similar when administered to adults as intact 100 mg capsules or 100 mg capsule contents sprinkled over applesauce.

While similar AUC may be expected between the capsule and suspension dosage forms at the same doses, C_{max} would be higher (approximately doubled) for the capsule formulation. Therefore, the rationale for the selection of capsule doses was based on achieving concentrations that do not exceed those observed in the JRA trial using the suspension formulation (safety boundary), while achieving similar overall exposures as those shown to be non-inferior to naproxen (efficacy boundary). Since both the 3 mg/kg BID and 6 mg/kg BID doses of celecoxib were non-inferior to naproxen 7.5 mg/kg BID, concentrations in between those of the two dose groups were targeted.

The prediction of pediatric capsule PK profiles was made using historical capsule parameter estimates while borrowing the estimated influence of weight on CL/F and V/F in the JRA trial. The justification for this bridging approach is demonstrated in table below, where the simulated mean suspension profiles for a female result in similar or slightly higher predictions of the observed pediatric and adult suspension data compared to those using the Final Model, thereby supporting the rationale for setting the safety boundary for capsule dose selection to typical concentrations predicted by the Final 3Model.

Mean Steady-State Cmax and AUC(0-12) Estimates from Study 195 and Those Predicted for the Derived Capsule Doses

Weight (kg)	Cmax (ng/mL)			AUC(0-12) (ng•h/mL)		
	Suspension 3 mg/kg BID	Suspension 6 mg/kg BID	Capsule[a]	Suspension 3 mg/kg BID	Suspension 6 mg/kg BID	Capsule[a]
10	120	241	415	1030	2059	2603
13	220	440	380	1921	3842	2428
25	178	356	305	1616	3232	2041
26	263	527	530	2399	4798	4036
38	311	622	466	2893	5786	3650
50	285	570	424	2690	5380	3394

[a] 50 mg BID capsule doses for weight ranging from 10 kg to 25 kg and 100 mg BID capsule doses for weight >25 kg

Weight = 10 kg: A small number of subjects (N= 5) weighing between 10 and <13 kg received 25- or 50-mg BID suspension doses. It is evident that the predicted suspension concentrations in the JRA trial for a 10-kg subject receiving 25- and 50-mg BID suspension doses are lower than those in adults at efficacious RA doses (100- to 200-mg BID capsule doses). Administration of a 50-mg BID capsule dose is predicted to result in slightly higher peak concentrations than those for 25- and 50-mg BID suspension doses. However, since observed concentrations for these subjects in the study were significantly lower (median noncompartmental AUC(0-12) was approximately 20% of that in adult RA subjects at 200 mg BID) than in adults suggests that it may be appropriate to target a higher-than observed exposure for this group of subjects.

Weight = 13 kg: Predicted concentrations for a 50-mg BID capsule dose in a 13-kg subject are within the range of those predicted for 50- and 100-mg BID suspension doses in the JRA trial. Given that the capsule predictions are not very different between a 10-kg and a 13-kg subject, the adequacy of a 50-mg BID capsule dose is driven by the fact that a 13-kg subject was designed to receive a higher dose in the JRA trial compared to a 10-kg subject.

Weight = 25 kg: Predicted concentrations for a 50-mg BID capsule dose in a 25-kg subject are within the range of those predicted for 50- and 100-mg BID suspension doses in the JRA trial.

Weight = 26 kg: This weight represents the cut off point where a higher dose of the capsule may be administered. As shown in the figure, the predicted concentrations for a 100-mg BID capsule dose in a 26-kg subject are within the range of those predicted for 75- and 150-mg BID suspension doses in the JRA trial. Given that the capsule predictions are not different between a 25-kg and a 26-kg subject, the increment to a 100-mg BID capsule dose is primarily driven by the fact that a 26-kg subject received a higher dose in the JRA trial compared with a 25-kg subject.

Weight = 38 kg: Administration of a 100-mg BID capsule dose to a 38-kg subject (lowest weight to receive 100- and 200-mg BID suspension doses) continues to predict concentrations within the range of those predicted for 100- and 200-mg BID suspension doses in the JRA trial.

Weight = 75 kg: Predicted concentrations for a 100-mg BID capsule dose are slightly lower than those predicted for the 150-mg BID suspension dose in the JRA trial. However, the differences do not appear to be significant enough to increase capsule dose. Hence a 75-kg subject can essentially be considered an adult for dosing purposes and can be initially given the lower of the approved adult RA dose of 100 mg BID capsule and increased to a 200-mg BID capsule dose if necessary.

At the pre-sNDA meeting on January 10th 2006, the sponsor was asked to simulate mean concentration-time profile after administration of 200 mg capsules in patients who weigh greater than 50 kg. Sponsor conducted the simulations and provided graphs that show the mean concentration-time profile in patients who weigh greater than 50 kg.

Weight = 50 kg: Predicted concentrations for a 100-mg BID capsule dose are within those predicted for the 100- and 200-mg BID suspension doses in the JRA trial.

Weight = 51 kg: Predicted concentrations for a 200-mg BID capsule dose are within those predicted for the 150- and 300-mg BID suspension doses in the JRA trial. However, consistent with a conservative approach to dose selection, a 51-kg subject can essentially be considered an adult for dosing purposes and can be given the lower approved adult RA dose of 100 mg BID capsule.

Weight = 75 kg: Predicted concentrations for a 100-mg BID capsule dose are slightly lower than those predicted for the 150-mg BID suspension dose in the JRA trial. However, the differences do not appear to be significant enough to increase capsule dose. Hence a 75-kg subject can essentially be considered an adult for dosing purposes and can be initially given the lower of the approved adult RA dose of 100 mg BID capsule and increased to a 200-mg BID capsule dose if necessary.

- The simulations demonstrate that it is possible to simplify the dosing scheme for JRA subjects such that subjects who weigh between 10 and 25 kg (inclusive) can be administered a 50-mg BID capsule dose, and those who weigh greater than 25 kg can be administered a 100-mg BID capsule dose.

- For the vast majority of JRA subjects, the proposed dosing scheme does not exceed the concentrations observed in the JRA trial using the suspension formulation (safety boundary), while achieving similar overall exposures as those shown to be non-inferior to naproxen (efficacy boundary).

- Subjects weighing between 10 and <13 kg may have higher peak concentrations and similar overall exposures following a 50-mg BID capsule dose relative to those observed in the JRA trial. However, considering that a larger number of slightly heavier children (46 subjects weighing between ≥13 and ≤25 kg versus 5 subjects weighing <13 kg) received higher doses without any safety concerns suggests that a 50-mg BID capsule dose would also be safe and well tolerated in 10 to <13 kg subjects.

- Furthermore, the proposed 50 mg BID capsule dose for subjects weighing between 10 and 25 kg (inclusive) is predicted to yield similar or slightly lower concentrations than those in adult RA subjects receiving 100 mg BID capsule,

suggesting that 100 mg BID capsule doses for these children would not exceed concentrations seen with 200 mg BID doses in adult RA subjects. Given that 200 mg BID capsule doses are commonly used in adult RA subjects and the finding from the current exposure-response analysis that higher doses may yield a greater % of early responders, the proposed dosing scheme may serve to initiate treatment with celecoxib in pediatric subjects with JRA.

Conclusions

- Body weight and gender are predictive covariates of celecoxib systemic exposure. Celecoxib CL/F increases less than proportionally with weight. A 10-kg subject is predicted to have 40% lower clearance compared with a 70-kg adult.
- For the doses administered in the study, celecoxib AUC(0-12) for a 6 mg/kg BID suspension dose was lower in children 2 to ≤5 years, and similar in children >5 to <17 years, relative to that for adult RA subjects receiving a 200-mg BID suspension dose. Nonetheless, exposures are within the range of those observed with approved doses (100- to 200-mg BID capsule) in adult RA subjects.
- Exposure-response analysis suggests that a greater percentage of early responders may be achievable with higher doses.
- Accounting for differences in absorption between suspension and capsule dosage forms, doses of 50 mg BID capsule for JRA subjects weighing between 10 and 25 kg (inclusive) and 100 mg BID capsule for those weighing over 25 kg are predicted to provide similar systemic exposures as those observed in the study and may serve to initiate treatment with celecoxib in pediatric subjects with JRA.
- For children approaching adult body weights, 200 mg BID capsule will achieve systemic exposures as those observed in the study.

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/s/

Suresh Doddapaneni

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