CLINICAL PHARMACOLOGY 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.
Pharmacometrics Team Leader	Joga Gobburu, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
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

Table of Contents

1 Executive Summary 2
- **1.1 Recommendation 2**
- **1.2 Phase IV Commitments 2**
- **1.3 Summary of CPB Findings 2**

2 QBR 12
- **2.1 General Attributes 12**
- **2.2 General Clinical Pharmacology 13**
- **2.3 Intrinsic Factors 33**
- **2.4 Extrinsic Factors 37**
- **2.5 General Biopharmaceutics 37**
- **2.6 Analytical 40**

3 Labeling 41

4 Appendix 43
- **4.1 Proposed labeling 43**
- **4.2 Pharmacometrics Review of Study #195 ..... 73**
- **4.3 Synopsis of Study # 1162 ..... 110**
- **4.4 Synopsis of Study # 1202 ..... 113**
- **4.5 Synopsis of Study # 088 ..... 115**
- **4.6 OCP filing memo 118**

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 Phase IV Commitments

None

1.3 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.

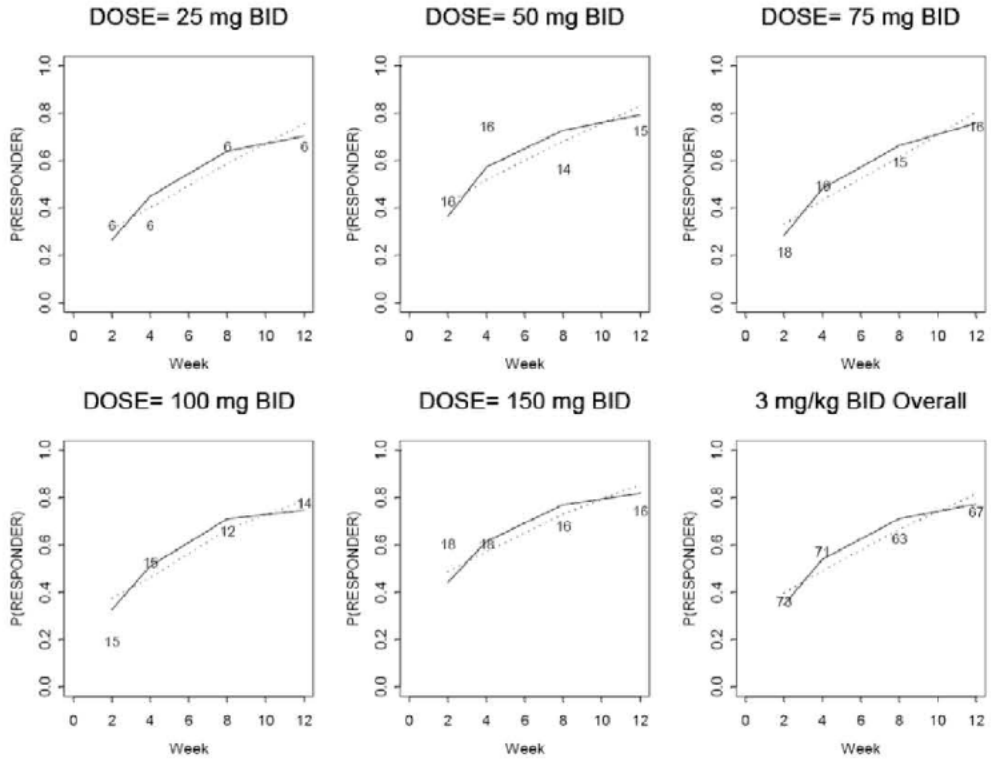
- Results of a relative bioavailability study (#1202) of celecoxib administered as capsule contents sprinkled on applesauce in healthy adult volunteers indicated similar C_{max} and AUC.

Exposure-Response (Efficacy):

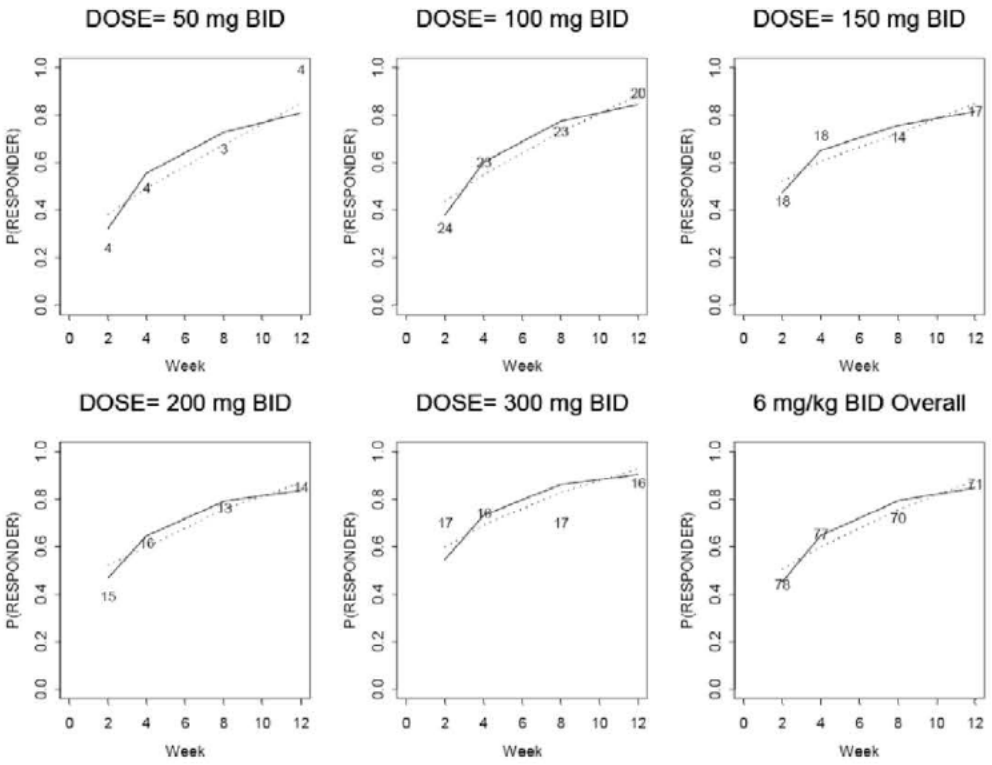
Exposure-response analysis was submitted by the sponsor as supportive evidence for the proposed dosing regimen. JRA-30 DOI data (binary outcome, responders=1 or non-responders=0) from 152 JRA subjects were used for the E/R analysis: 73 JRA subjects with 274 observations over Weeks 2, 4, 8 and 12 in the 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



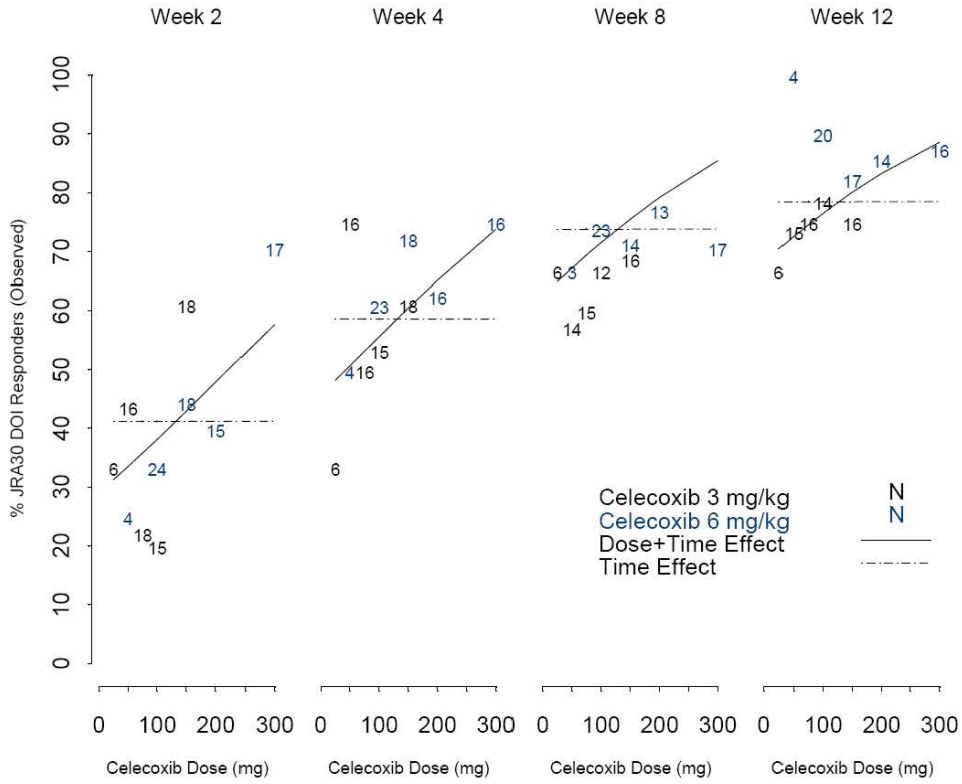
Observed and Predicted Probability of Responders for Celecoxib 6 mg/kg BID



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.

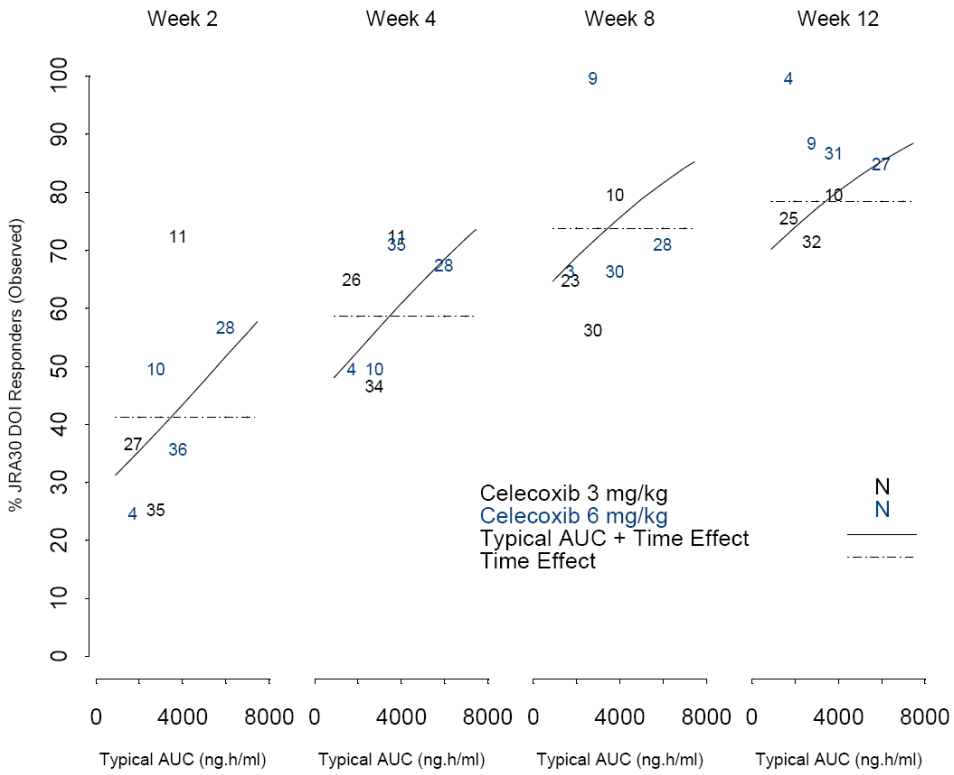
The dose and exposure-related increases in response rate are presented in the two figures below, where dose- and AUC(0-12)- response plots are plotted separately for each week (2, 4, 8, and 12).

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 Model.

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.

2 QBR

2.1 General Attributes

In 1998, celecoxib was approved for the treatment of rheumatoid arthritis in adults. Agency issued a Pediatric Written Request on January 25, 2002 and amended it once to extend the time frame for submission of study reports (12/19/2005). Accordingly, Pfizer submitted the Pediatric Study Reports for Pediatric Exclusivity Determination on 20th of June 2006.

Celecoxib is an anti-inflammatory agent that acts by inhibiting the inducible form of the enzyme cyclooxygenase (COX-2).

Celecoxib is poorly soluble in water. While an oral suspension (100 mg/5mL) was studied in clinical trials, capsule formulation (50 mg and 100 mg strengths) for oral administration is proposed for marketing.

Other approved products for JRA include,

- Rofecoxib (Vioxx): Approved on August 18th 2004 but withdrawn on September 20th 2005 by Merck, due to concerns of cardiovascular safety concerns.
- Meloxicam (Mobic): Approved on August 18th 2005
- etanercept (Enbrel) is the only TNF-α antagonist

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A single clinical efficacy study # 319-1127/N49-01-02-195 (referred to as Study # 195 in all future references) "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".

Study Design

Study N49-01-02-195 was a 12-week, randomized, double-blind, active-controlled safety and efficacy study evaluating 2 doses of a celecoxib suspension compared with a marketed suspension. Secondary objectives were to compare the PK profile of a celecoxib suspension in children with JRA to an adult cohort with RA, and to obtain PK information to guide the dosing of celecoxib in pediatric population.

Dose/Dosing Regimen

JRA patients received celecoxib suspension in the double-blind phase of the study at a targeted dosage of 3 or 6 mg/kg BID, or naproxen suspension at a targeted dosage of 7.5 mg/kg BID. The dosing used for naproxen (approximately 7.5 mg/kg BID) was based upon recommendations from the pediatric rheumatology community for a therapeutic range of 10 to 20 mg/kg/day and is consistent with the labeled dose of naproxen for treatment of JRA. The dosing of celecoxib (approximately 3 and 6 mg/kg BID) in JRA patients was extrapolated from the recommended adult dose of celecoxib for RA. The actual doses (in mg) administered to these patients followed an allometric pattern. For example, clearance (unadjusted for body weight) in a 10-kg subject was assumed to be approximately 25% of that in a 70-kg adult. Hence, a 10-kg subject received either 25 or 50 mg BID in Study 195 for the low and high dose groups, which are 25% of the approved adult RA doses of 100 and 200 mg BID, respectively.

Fixed dosages were administered according to weight category (determined by patient weight at Baseline) as shown in table below, producing a range of delivered dosages in mg/kg for each target dosage and weight category. Adult RA patients received celecoxib suspension 200 mg BID for 2 weeks.

	Dosage Administered / Delivered Dosage Range (Highest to Lowest Weight)		
Patient Weight	Celecoxib 3 mg/kg BID Target	Celecoxib 6 mg/kg BID Target	Naproxen 7.5 mg/kg BID Target
9-12 kg	25 mg BID	50 mg BID	62.5 mg BID
	2.1-2.8 mg/kg BID	4.2-5.6 mg/kg BID	5.2-6.9 mg/kg BID
13-25 kg	50 mg BID	100 mg BID	125 mg BID
	2.0-3.8 mg/kg BID	4.0-7.7 mg/kg BID	5.0-9.6 mg/kg BID
26-37 kg	75 mg BID	150 mg BID	187.5 mg BID
	2.0-2.9 mg/kg BID	4.1-5.8 mg/kg BID	5.1-7.2 mg/kg BID
38-50 kg	100 mg BID	200 mg BID	250 mg BID
	2.0-2.6 mg/kg BID	4.0-5.3 mg/kg BID	5.0-6.6 mg/kg BID
>50-100 kg[a]	150 mg BID	300 mg BID	500 mg BID
	1.5-2.9 mg/kg BID	3.0-5.9 mg/kg BID	5.0-9.8 mg/kg BID

BID = Twice daily.

[a] Upper limit of 100 kg shown only to illustrate potential lowest delivered dosage; no upper weight limit for patients was specified in the study protocol.

Source: Study 195 CSR,[19] Tables 5 and 6

What is primary efficacy endpoint and what is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy measure in the study was the percentage of patients who met the JRA-30 DOI (Definition of Improvement), also known as ACR (American College of Rheumatology) Pediatric 30, at Week 12. A subject was considered a responder by the JRA-30 DOI criteria if there was a ≥30% improvement in ≥3 of the 6 JRA-30 core set components and a >30% worsening in at most 1 JRA-30 core set component; these components included the following: Physician's Global Assessment of Disease Activity, Parent's Global Assessment of Overall Well-being, Parent's Assessment of Physical Function (Childhood Health Assessment Questionnaire [CHAQ] Disability Index), number of joints with active arthritis, number of joints with limitation of motion, and laboratory marker of inflammation (C-reactive protein).

Non-inferiority hypothesis testing was 1-sided at the 2.5% level of significance, or equivalently, non-inferiority of a celecoxib dose was claimed if the lower limit of the 95% 2-sided CI for the difference in the proportion of JRA-30 DOI responders (πC-πN, where πC is the percentage of responders in the celecoxib treatment group and πN is the percentage of responders in the naproxen treatment group) was above –25%. This noninferiority criterion was determined by agreement with the Agency and specified in the PWR.

Data

A total of 242 pediatric JRA subjects (77 in the celecoxib 3 mg/kg b.i.d group, 82 in the celecoxib 6 mg/kg b.i.d group and 83 in the naproxen 7.5 mg/kg b.i.d group) were enrolled in the JRA trial and randomized. All 242 subjects received at least 1 dose of study medication and the majority completed the trial (87% in the celecoxib 3 mg/kg b.i.d treatment group, 86.6% in the celecoxib 6 mg/kg b.i.d treatment group and 89.2% in the naproxen 7.5 mg/kg b.i.d treatment group). A total of 43 adult subjects with RA were assigned to celecoxib 200 mg b.i.d.

Table: The demographic features of the subjects included in the data analysis

Summary of Demographics, Concomitant Medication and Formulation (Subjects With PK data)

	JRA 3 mg/kg BID (N = 73)		JRA 6 mg/kg BID (N = 79)		Adult RA 200 mg BID (N = 36)	
Age (yr): Mean (SD)	10.47	(4.19)	10.37	(4.24)	52.09	(16.56)
Median (Range)	11.3	(2.0-16.3)	11.1	(2.3-16.9)	52.55	(18.9-83.2)
Distribution by Age Category N (%)						
2 to ≤5 years	13	(17.8)	15	(19.0)		
>5 to ≤11 years	22	(30.1)	25	(31.6)		
>11 to <17 years	38	(52.1)	39	(49.4)		
≥18 years					36	(100)
Weight [c] (kg): Mean (SD)	35.74	(15.39)	37.15	(18.1)	81.97	(15.31)
Median (Range)	35.9	(12.2-68.0)	37.3	(10.6-92.7)	81.70	(53.3-112.8)
Distribution by Weight Category N (%)						
< 13 kg	3	(4.1)	2	(2.5)		
≥13 to ≤25 kg	18	(24.7)	26	(32.9)		
>25 to ≤38 kg	20	(27.4)	21	(26.6)		
>38 to ≤50 kg	15	(20.5)	13	(16.5)		
>50 kg	17	(23.3)	17	(21.5)	36	(100)
Gender N (%)						
Female	56	(76.7)	52	(65.8)	22	(61.1)
Male	17	(23.3)	27	(34.2)	14	(38.9)
Race N (%)						
White	39	(53.4)	44	(55.7)	36	(100)
Black	7	(9.6)	7	(8.9)		
Asian	1	(1.4)	3	(3.8)		
Not listed	26	(35.6)	25	(31.6)		
Methotrexate Therapy: N (%)						
Yes	35	(47.9)	31	(39.2)	18	(50)
No	38	(52.1)	48	(60.8)	18	(50)
Fed: Nobs (%)						
Yes	94	(35.3)	117	(41.9)	41	(16.3)
No	172	(64.7)	162	(58.1)	211	(83.7)
Formulation Lot: Nobs (%)						
Lot 1 (SP16928, 100 mg/5 mL strength)			101	(36.2)	252	(100)
Lot 2 (K0300839, 100 mg/5 mL strength)			178	(63.8)		
Lot 3 (SP16927, 50 mg/5 mL strength)	266	(100)				

SD = Standard deviation.
Nobs = Number of observations (concentrations)
N = Number of subjects.
Fed = See Section 5.5.

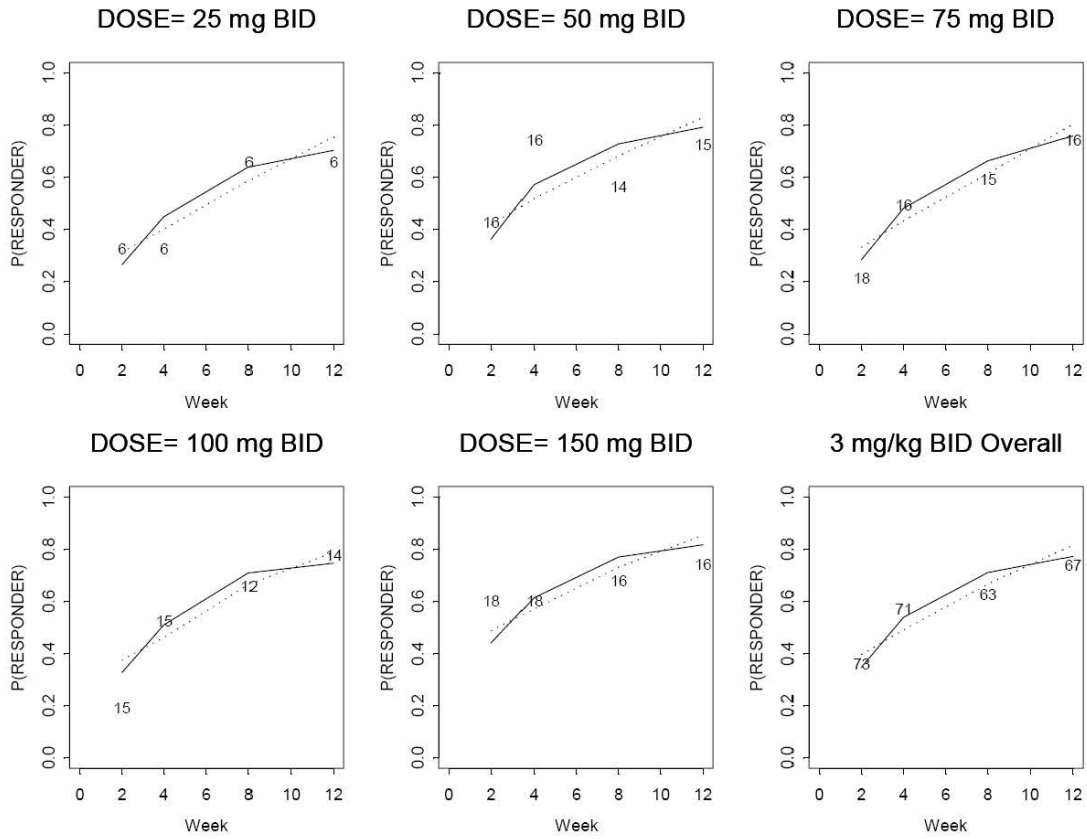
Exposure-Response (Efficacy):

Exposure-response analysis was submitted by the sponsor as supportive evidence for the proposed dosing regimen. Dr. Venkatesh Atul Bhattaram reviewed the population PK and exposure-responses analyses (see attached pharmacometrics review). 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

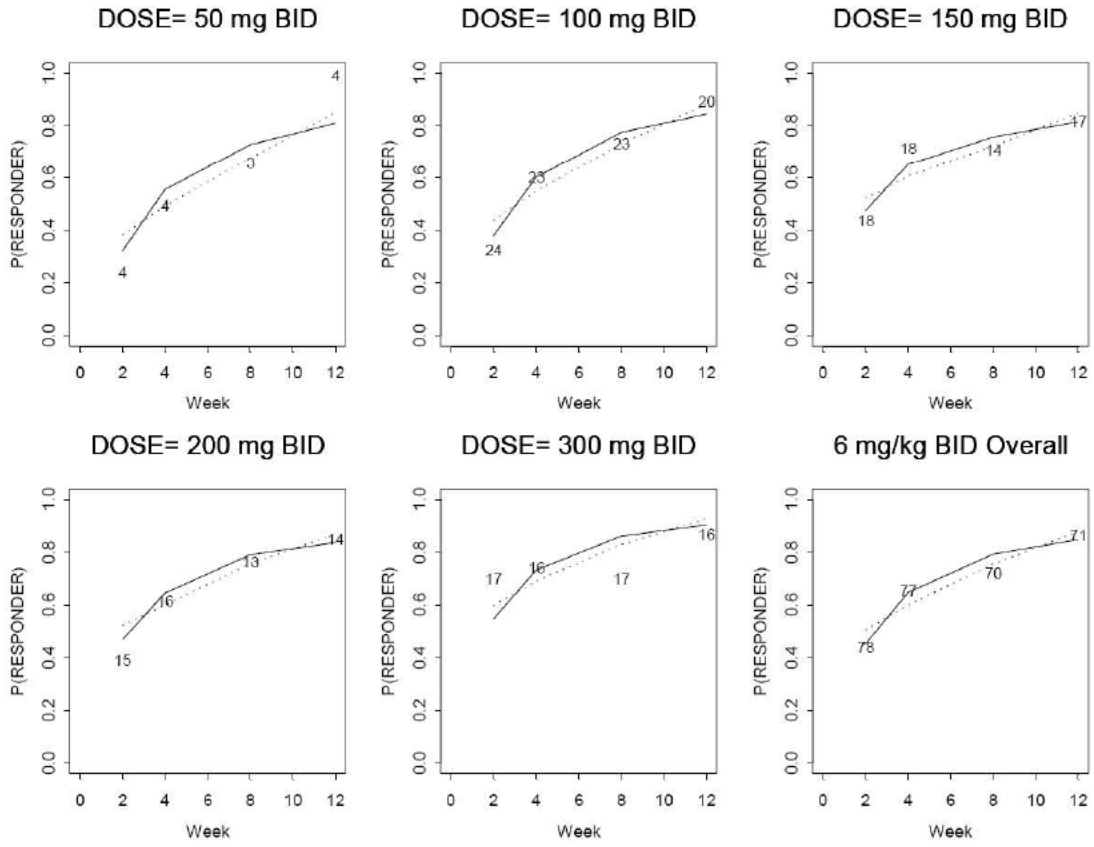
mg/kg BID groups, respectively. The plots indicate that adequate fits were obtained with both models.

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



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 $AUC_{(0-12)}$ effect); dotted line represents model prediction from Model 3 (linear time effect plus linear typical $AUC_{(0-12)}$ effect); shown are the mean of the model-predicted probability of responders at each time point and dose.

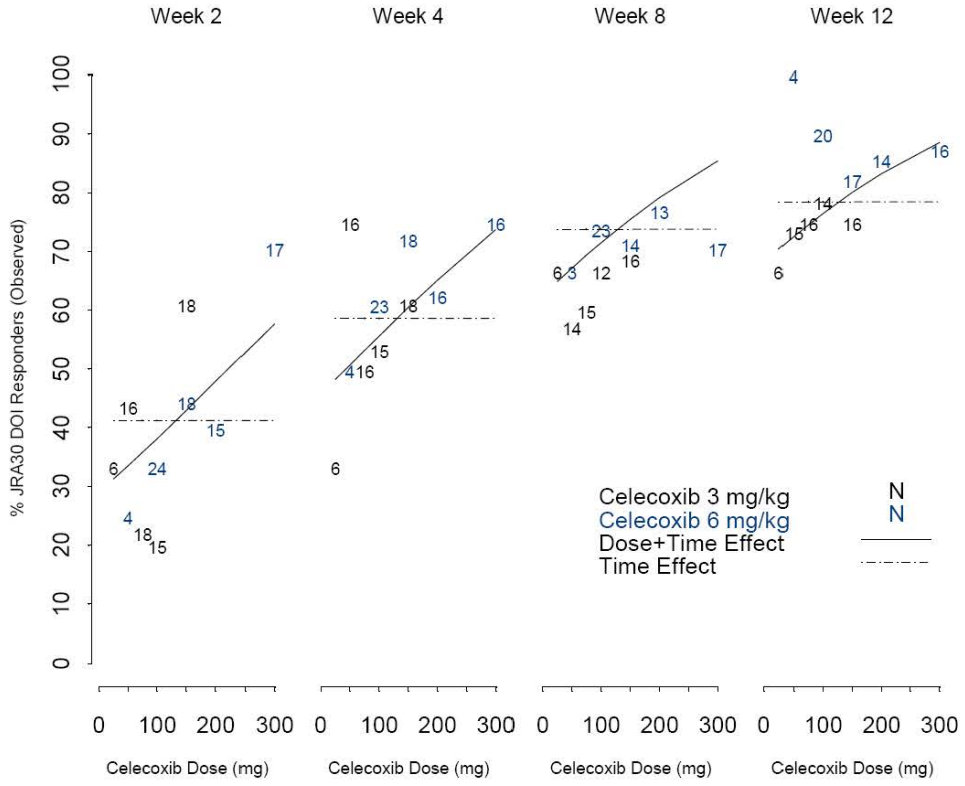
Observed and Predicted Probability of Responders for Celecoxib 6 mg/kg BID



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 $AUC_{(0-12)}$ effect); dotted line represents model prediction from Model 3 (linear time effect plus linear typical $AUC_{(0-12)}$ effect); shown are the mean of the model-predicted probability of responders at each time point and dose.

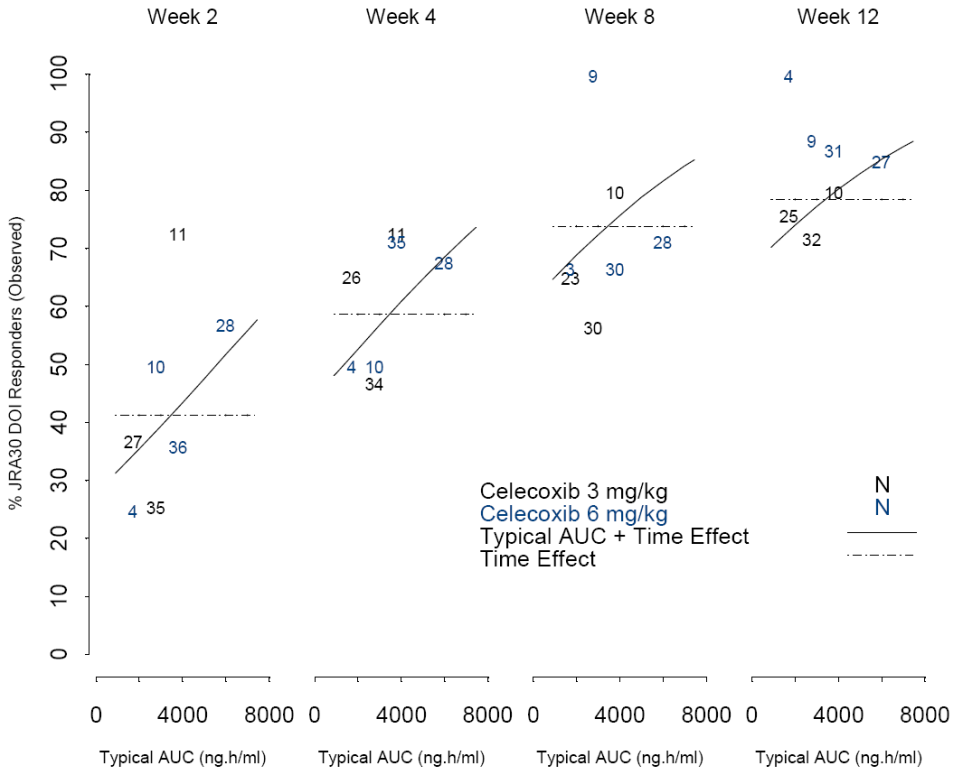
The dose and exposure-related increases in response rate are presented in the two figures below, where dose- and AUC(0-12)- response plots are plotted separately for each week (2, 4, 8, and 12).

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.

Safety:

In general, non-steroidal anti-inflamatory drugs (NSAIDs) including the COX-2 inhibiting drugs are known for causing GI disorders (upper abdominal pain, GI bleeding). All COX-2 inhibiting drugs carry a black box warning for the risk of myocardial infarction in adults.

Overall, the greatest incidence of adverse events occurred in the GI and infections and infestations SOCs. The most commonly occurring (>5% subjects) adverse events in the

celecoxib 3 mg/kg BID treatment group were headache NOS (13%); abdominal pain upper and pyrexia (each 7.8%); nausea and cough (each 6.5%); nasopharyngitis and diarrhoea NOS (each 5.2%). The most commonly occurring adverse events in the celecoxib 6 mg/kg BID treatment group were headache NOS (9.8%); pyrexia (8.5%); arthralgia, abdominal pain NOS, and cough (each 7.3%); abdominal pain upper, vomiting NOS, and nasopharyngitis (each 6.1%). Additional pharmacometric analyses were not conducted with regard to side-effects.

A list of all treatment emergent adverse events by system organ class are listed in the table below. In depth review of safety aspects of the NDA submission can be found in the Medical Officer review.

Incidence of Adverse Events Occurring in ≥5.0% of Subjects in Any Treatment Group[a,b] in Decreasing Frequency Within a System Organ Class

System Organ Class/ Adverse Event Preferred Term	Celecoxib 3 mg/kg BID (N = 77)		Celecoxib 6 mg/kg BID (N = 82)		Naproxen 7.5 mg/kg BID (N = 83)	
Any Event, N (%)	**49**	**(63.6)**	**57**	**(69.5)**	**60**	**(72.3)**
Eye Disorders	**4**	**(5.2)**	**4**	**(4.9)**	**4**	**(4.8)**
Gastrointestinal Disorders	**20**	**(26.0)**	**20**	**(24.4)**	**30**	**(36.1)**
Abdominal Pain NOS	3	(3.9)	6	(7.3)	6	(7.2)
Abdominal Pain Upper	6	(7.8)	5	(6.1)	8	(9.6)
Vomiting NOS	2	(2.6)	5	(6.1)	9	(10.8)
Diarrhoea NOS	4	(5.2)	3	(3.7)	7	(8.4)
Nausea	5	(6.5)	3	(3.7)	9	(10.8)
General Disorders and Administration Site Conditions	**10**	**(13.0)**	**9**	**(11.0)**	**15**	**(18.1)**
Pyrexia	6	(7.8)	7	(8.5)	9	(10.8)
Infections and Infestations	**19**	**(24.7)**	**16**	**(19.5)**	**22**	**(26.5)**
Nasopharyngitis	4	(5.2)	5	(6.1)	4	(4.8)
Injury and Poisoning	**3**	**(3.9)**	**5**	**(6.1)**	**4**	**(4.8)**
Investigations	**2**	**(2.6)**	**9**	**(11.0)**	**6**	**(7.2)**
Musculoskeletal, Connective Tissue, and Bone Disorders	**6**	**(7.8)***	**8**	**(9.8)**	**14**	**(16.9)**
Arthralgia	2	(2.6)	6	(7.3)	3	(3.6)
Nervous System Disorders	**13**	**(16.9)**	**9**	**(11.0)**	**17**	**(20.5)**
Headache NOS	10	(13.0)	8	(9.8)	13	(15.7)
Dizziness (exc Vertigo)	1	(1.3)	1	(1.2)	6	(7.2)
Respiratory, Thoracic, and Mediastinal Disorders	**6**	**(7.8)**	**12**	**(14.6)**	**12**	**(14.5)**
Cough	5	(6.5)	6	(7.3)	7	(8.4)
Skin & Subcutaneous Tissue Disorders	**8**	**(10.4)**	**6**	**(7.3)***	**15**	**(18.1)**

Note: Celecoxib 3 mg/kg BID = 50 mg/5 mL; Celecoxib 6 mg/kg BID = 100 mg/5 mL; Naproxen 7.5 mg/kg BID = 125 mg/5 mL.

Abbreviations: NOS = Not otherwise specified

[a] Includes only TESS adverse events that were reported up to 28 days after the last dose of study medication.

[b] If a subject had more than 1 adverse event within a system organ class, that subject is counted once in the overall incidence for that system organ class.

* p-Value ≤0.10 in system organ class from pairwise comparison with naproxen using Fisher's exact test.

- ***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 [$AUC_{(0\text{-}12)}$], 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)
$AUC_{(0\text{-}12)}$ (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 $AUC_{(0\text{-}12)}$

[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.

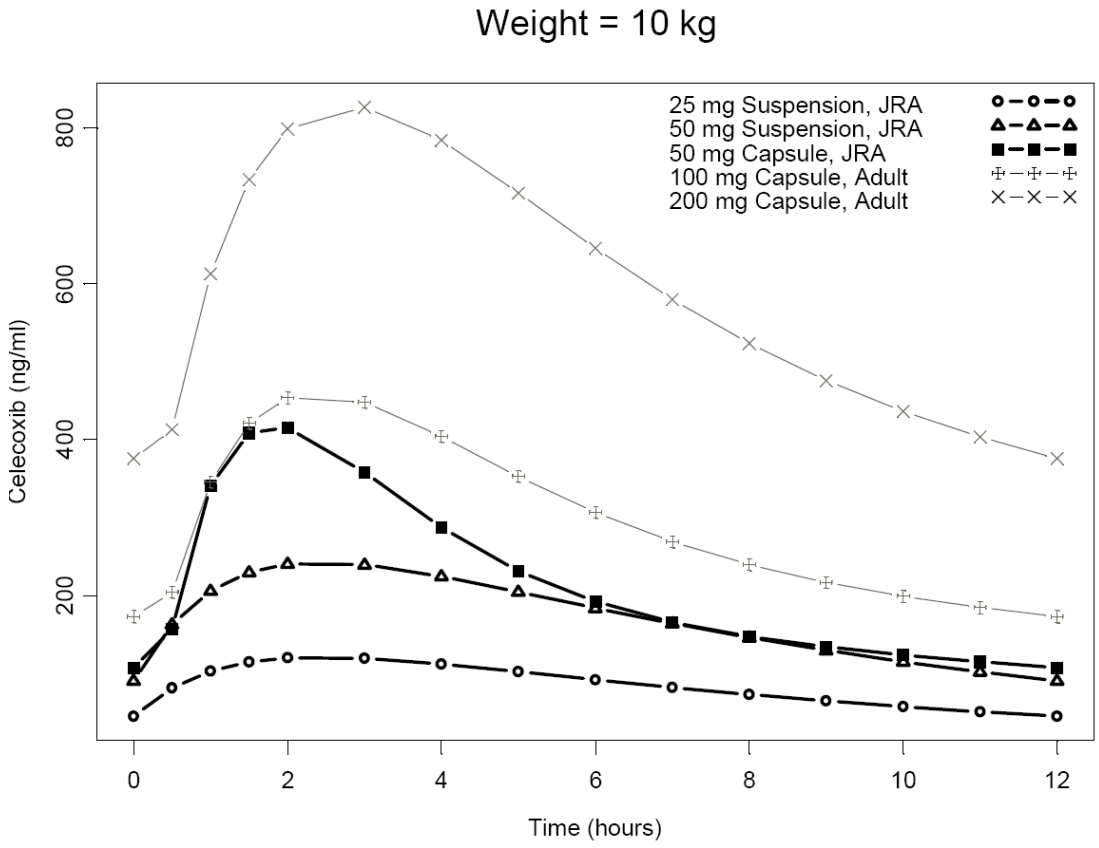
- ***Switch from Clinical trial formulation to the to-be-Marketed Formulation***

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 capsule and suspension is that the dosage forms are not bioequivalent; 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. Relative bioavailability study results indicate that the 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.

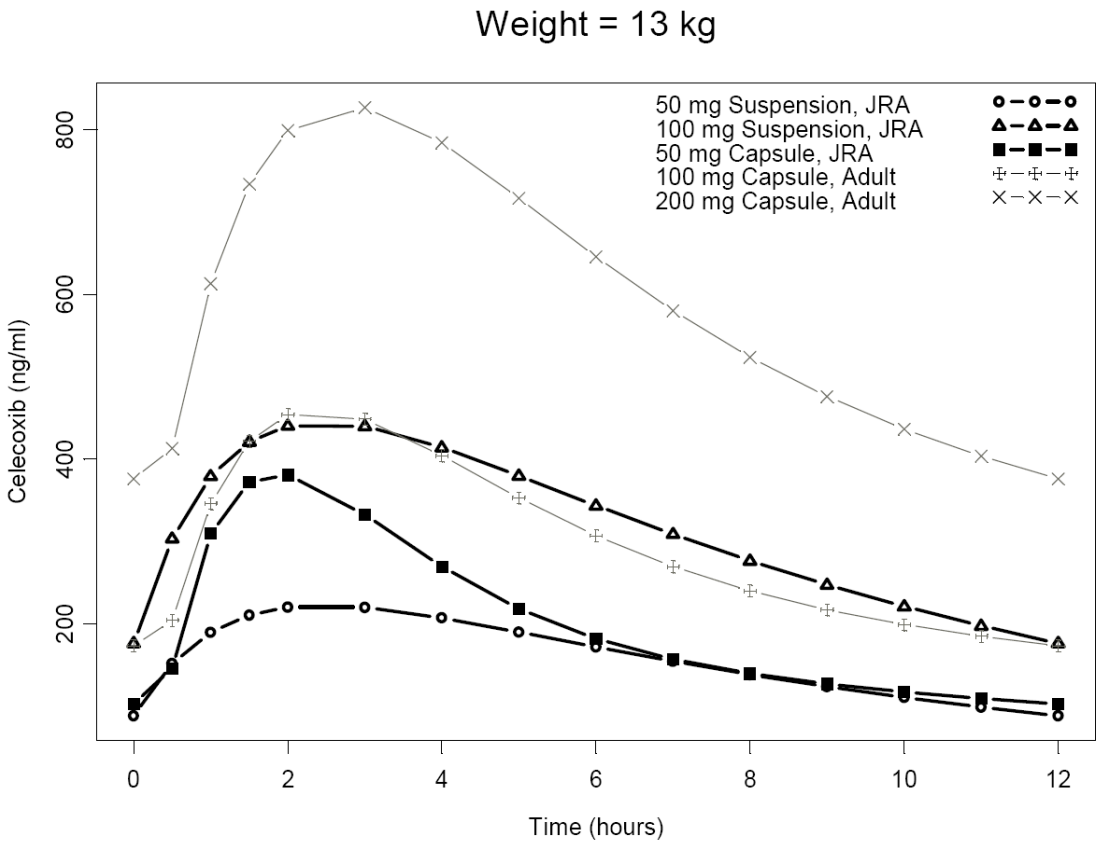
The prediction of pediatric capsule PK profiles was made using historical capsule parameter estimates while borrowing the estimated influence of weight on CL/F and V/F in the JRA trial. The justification for this bridging approach is demonstrated in 12, where the simulated mean suspension profiles (using Parameter Set 3 in table below) 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 Model (Parameter Set 2 in table below).

Predicted Mean Steady-State Concentration Profile for a 10-kg Subject Receiving a 50-mg BID Capsule Dose Relative to Typical JRA Suspension and Adult Capsule Profiles



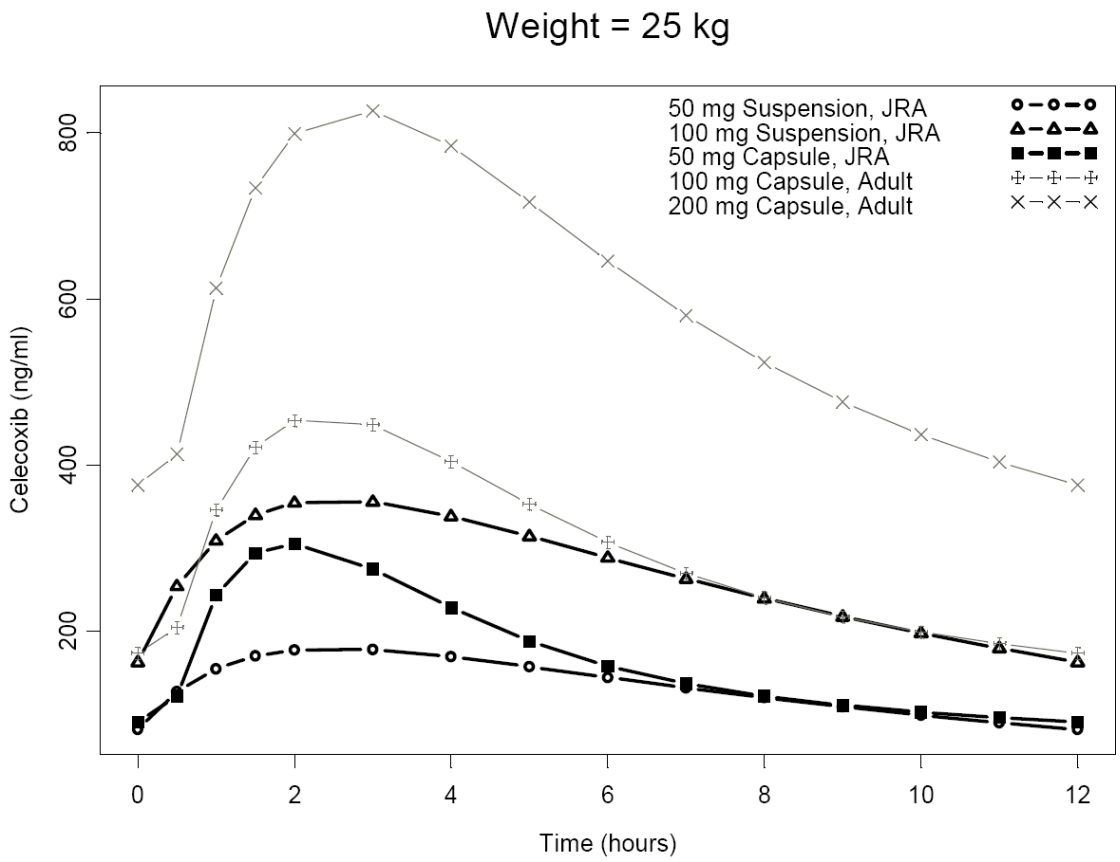
Weight = 10 kg (Figure above): A small number of subjects (N= 5) weighing between 10 and <13 kg received 25- or 50-mg BID suspension doses. It is evident that the predicted suspension concentrations in the JRA trial for a 10-kg subject receiving 25- and 50-mg BID suspension doses are lower than those 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.

Predicted Mean Steady-State Concentration Profile for a 13-kg Subject Receiving a 50-mg BID Capsule Dose Relative to Typical JRA Suspension and Adult Capsule Profiles



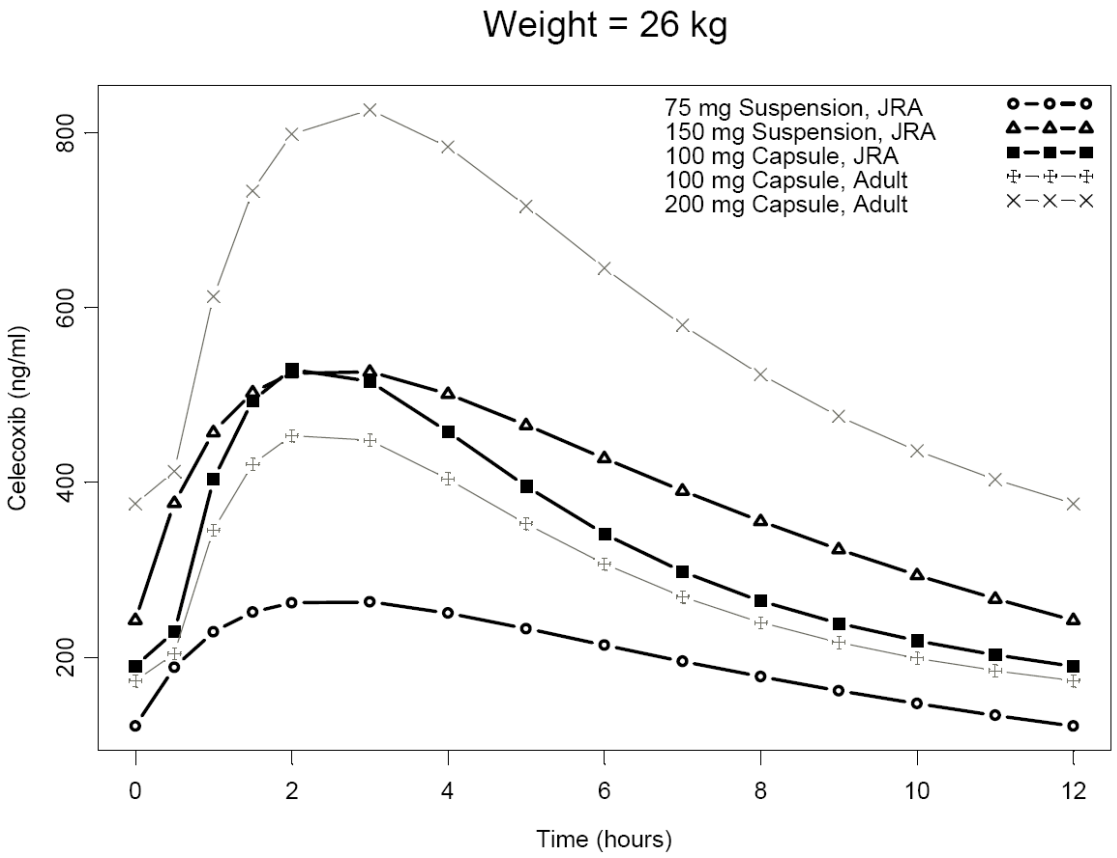
Weight = 13 kg (Figure above): Predicted concentrations for a 50-mg BID capsule dose in a 13-kg subject are within the range of those predicted for 50- and 100-mg BID suspension doses in the JRA trial. Given that the capsule predictions are not very different between a 10-kg and a 13-kg subject, the 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.

Predicted Mean Steady-State Concentration Profile for a 25-kg Subject Receiving a 50-mg BID Capsule Dose Relative to Typical JRA Suspension and Adult Capsule Profiles



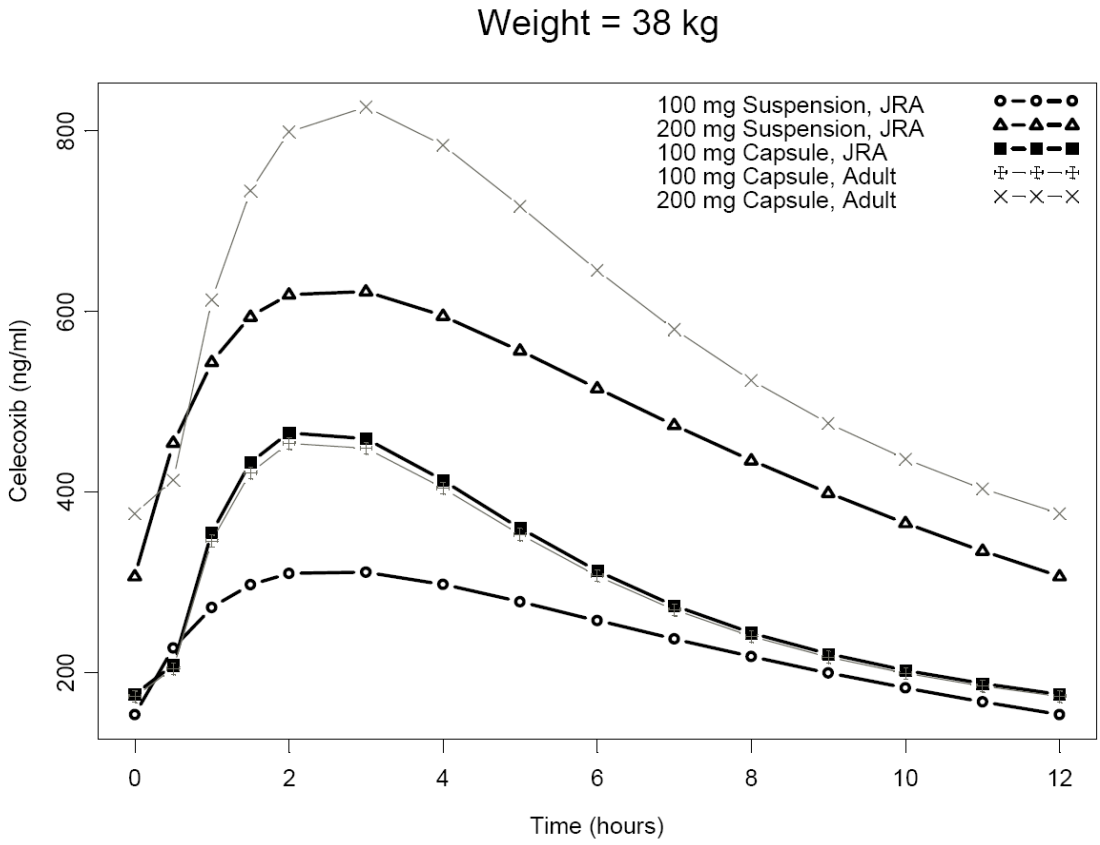
Weight = 25 kg (Figure above): Predicted concentrations for a 50-mg BID capsule dose in a 25-kg subject are within the range of those predicted for 50- and 100-mg BID suspension doses in the JRA trial.

Predicted Mean Steady-State Concentration Profile for a 26-kg Subject Receiving a 100-mg BID Capsule Dose Relative to Typical JRA Suspension an Adult Capsule Profiles



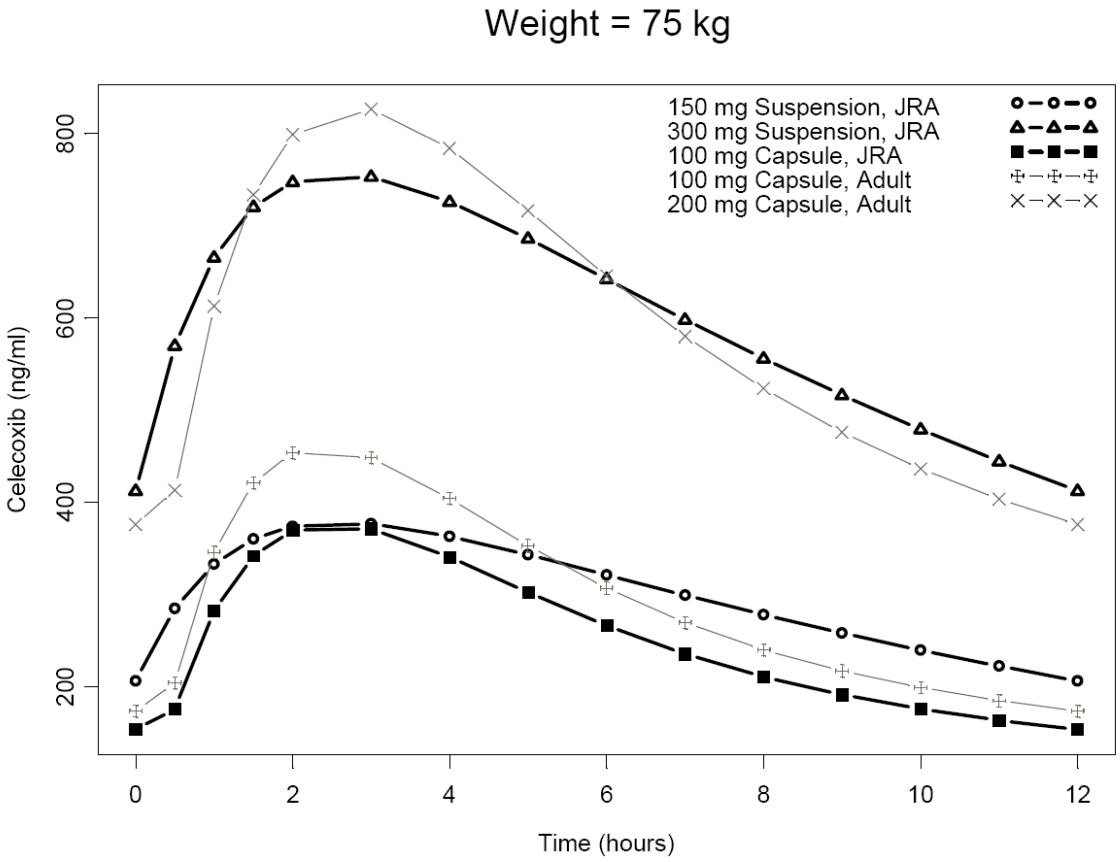
Weight = 26 kg (Figure above): This weight represents the cut off point where a higher dose of the capsule may be administered. As shown in the figure, the predicted concentrations for a 100-mg BID capsule dose in a 26-kg subject are within the range of those predicted for 75- and 150-mg BID suspension 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.

Predicted Mean Steady-State Concentration Profile for a 38-kg Subject Receiving a 100-mg BID Capsule Dose Relative to Typical JRA Suspension an Adult Capsule Profiles



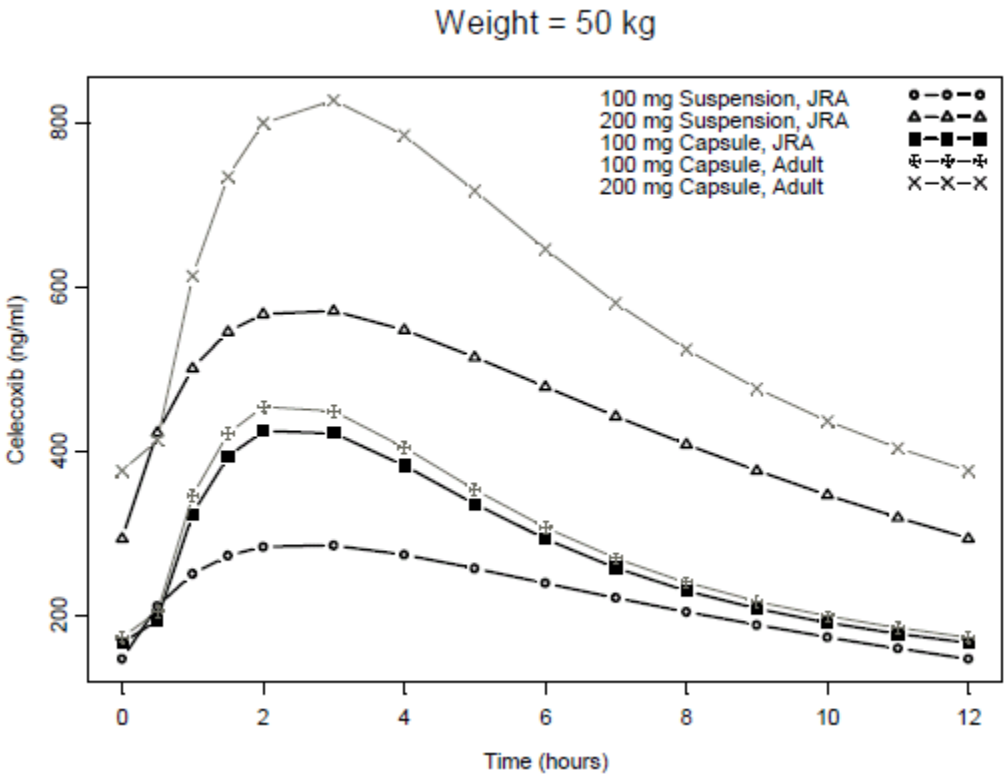
Weight = 38 kg (Figure above): Administration of a 100-mg BID capsule dose to a 38-kg subject (lowest weight to receive 100- and 200-mg BID suspension doses) continues to predict concentrations within the range of those predicted for 100- and 200-mg BID suspension doses in the JRA trial.

Predicted Mean Steady-State Concentration Profile for a 75-kg Subject Receiving a 100-mg BID Capsule Dose Relative to Typical JRA Suspension a Adult Capsule Profiles

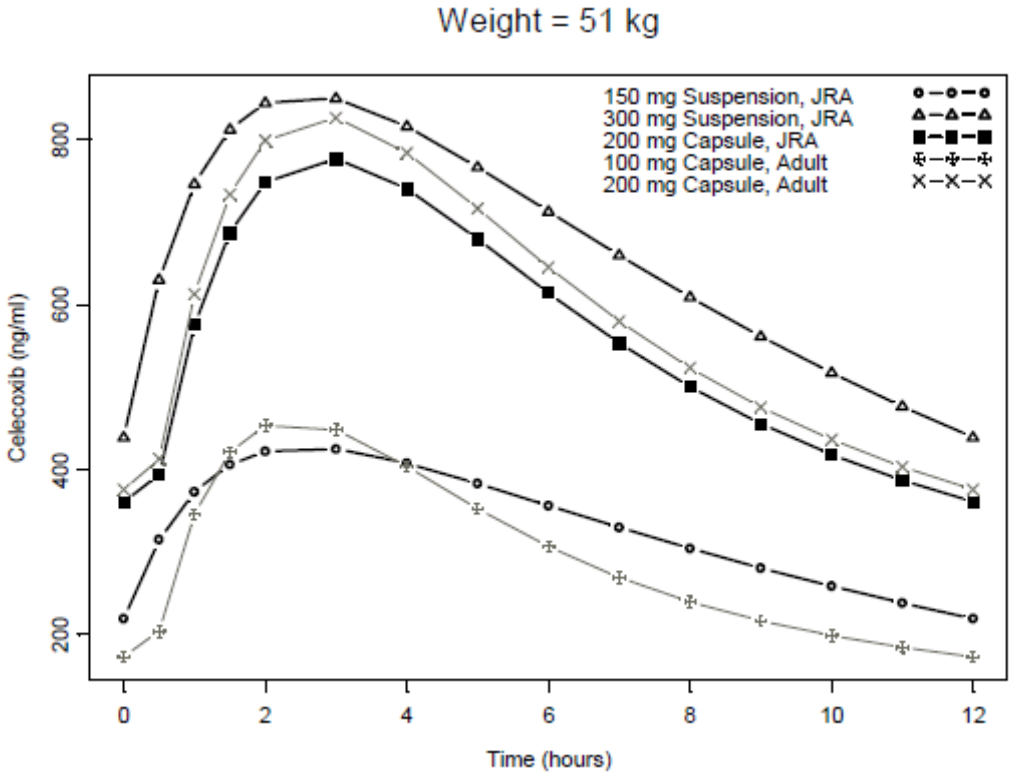


Weight = 75 kg (Figure above): Predicted concentrations for a 100-mg BID capsule dose are slightly lower than those predicted for the 150-mg BID suspension dose in the JRA trial. However, the differences do not appear to be significant enough to increase capsule dose. Hence a 75-kg subject can essentially 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.

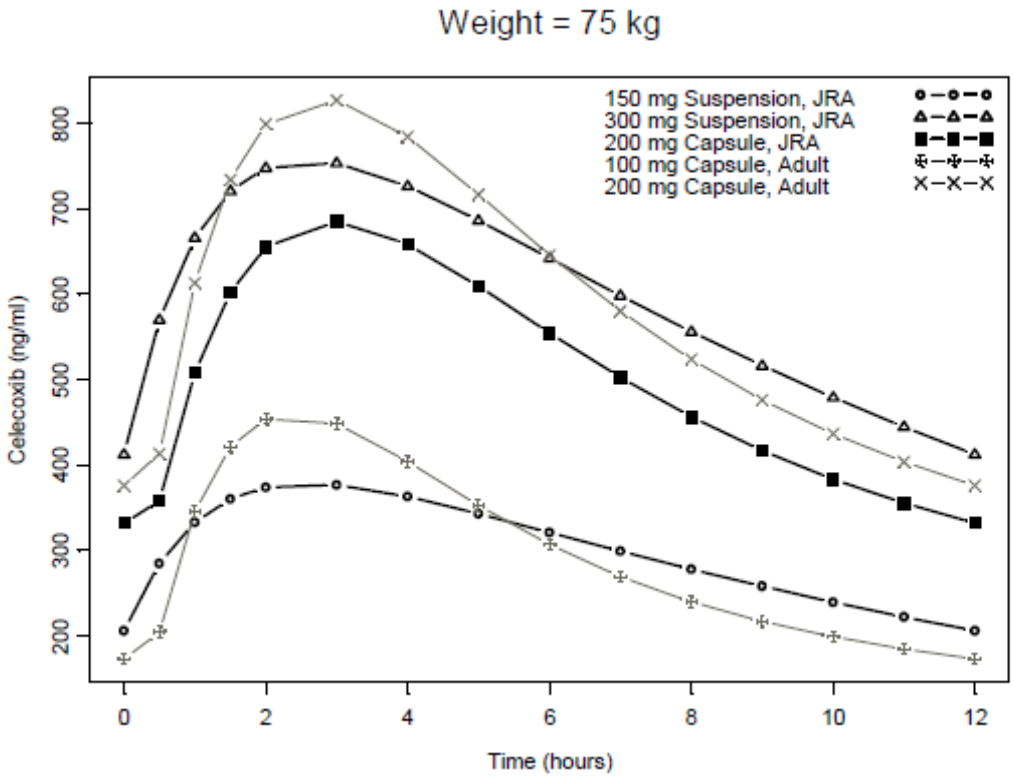
At a pre-sNDA meeting on January 10th 2006, the sponsor was asked to simulate mean concentration-time profile after administration of 200 mg capsules in patients who weigh greater than 50 kg. Sponsor conducted the simulations and provided graphs that show the mean concentration-time profile in patients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

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		

- **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.

2.3 Intrinsic Factors

Age and body weight:

Population PK analysis indicate that body weight influences clearance of celecoxib to a much lesser extent than was assumed by the dosing scheme employed in the JRA trial. Hence, body weight based dose adjustment is recommended for use of celecoxib in treating JRA.

Summary of PK characteristics:

- 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.

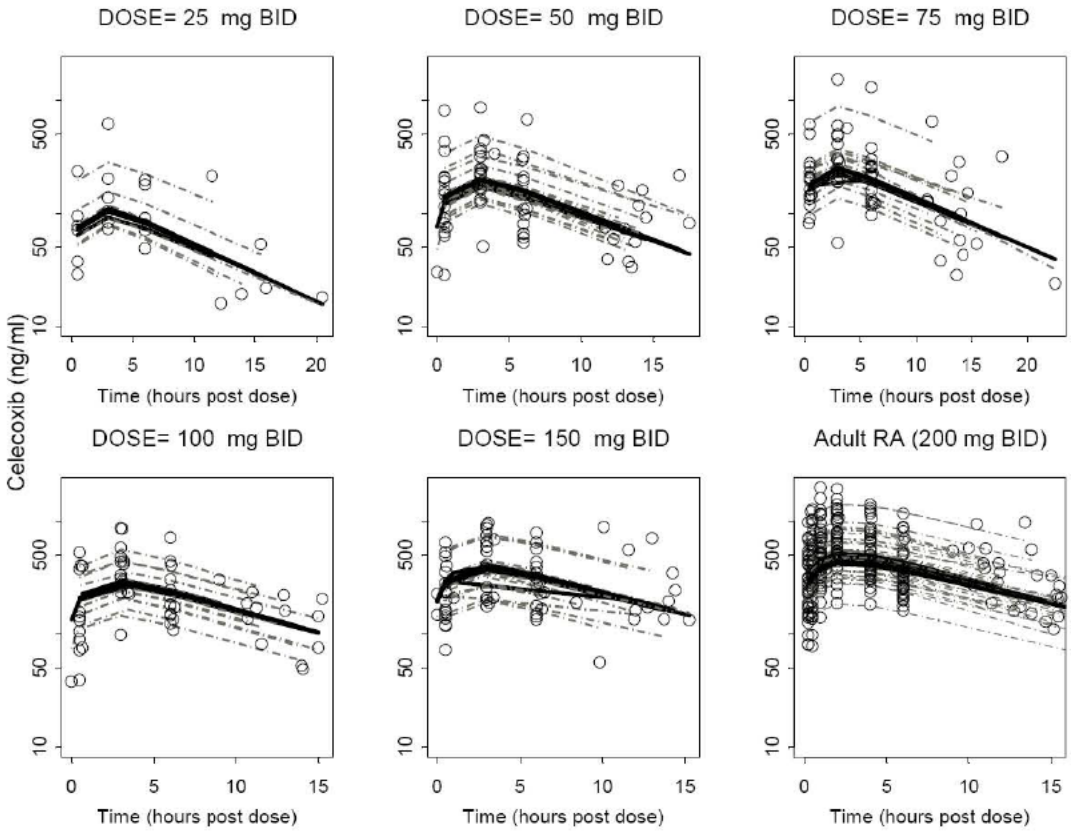
- CL/F values for the 3 and 6 mg/kg groups were pooled within each age category since the median values for the two dose groups were within 10% of each other for the 2 to ≤5 and >5 to ≤11 year categories and within 18% for the >11 to <17 year category.

- 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.

Pharmacokinetics of celecoxib in pediatric subjects: Celecoxib plasma concentration data from 188 JRA and adult RA subjects were used for the population PK analysis: 73 JRA subjects (95% of those randomized) with 266 observations in the 3 mg/kg BID group, 79 JRA subjects (96% of those randomized) with 279 observations in the 6 mg/kg BID group, and 36 adult RA subjects (84% of those enrolled) with 252 observations who received 200 mg BID. The clinic visit times for JRA patients were staggered so as to obtain an adequate distribution of blood sampling times (predose or 12 hours postdose, 0.5, 3, and 6 hours) relative to the time of most recent dose. Adult RA patients had blood samples drawn at the Week 2 visit at predose, 0.25, 0.5, 1, 2, 4, and 6 hours postdose.

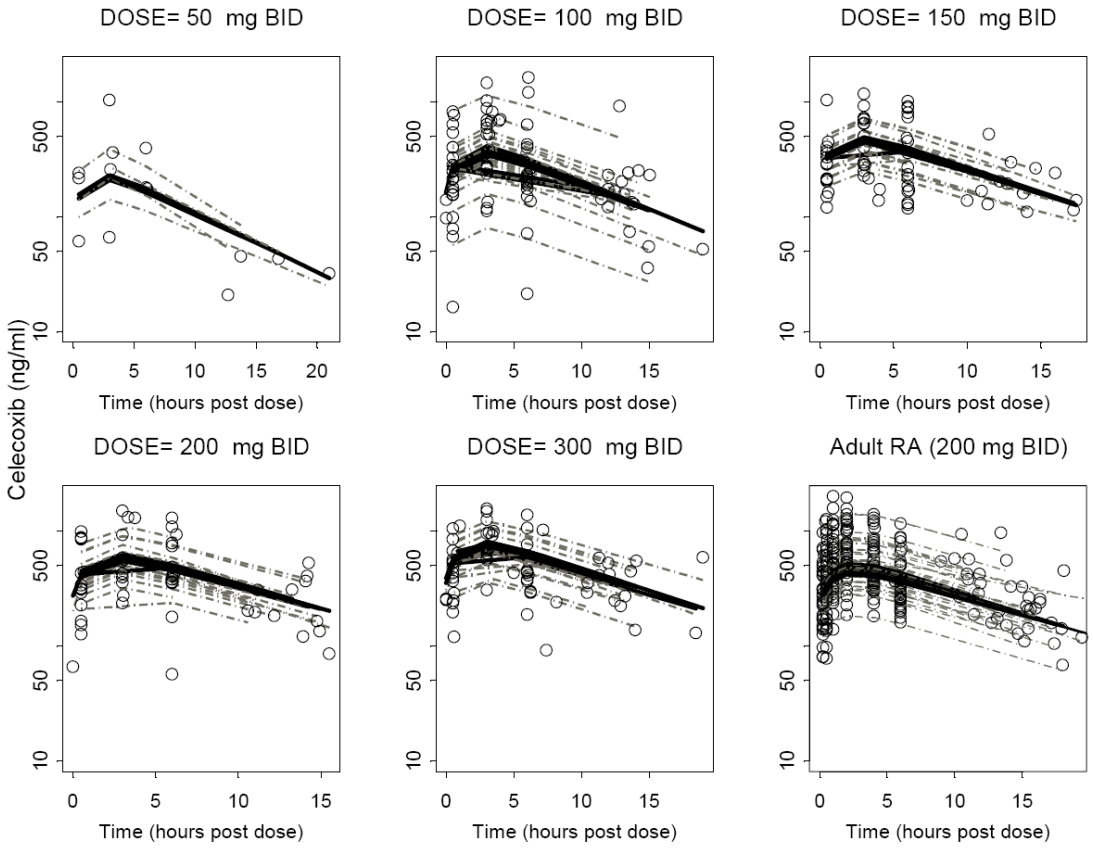
Two figures below show the observed plasma celecoxib concentration-time profiles by dose for the 3 mg/kg and 6 mg/kg groups, respectively, with population (ie, typical individual) and individual Bayes predictions obtained from the 1-compartment model with first-order absorption and body weight as a covariate on CL/F and V/F (Base Model 2). For purposes of reference, the observed and predicted PK profiles in adult RA subjects receiving 200 mg BID suspension are also provided (last plot in figures).

Steady-State Concentration-Time Profiles of Celecoxib in JRA Subjects After 3 mg/kg BID



Open circles are observed data; solid line represents population (i.e. typical individual) predictions; dotted line represents individual (Bayes) predictions.

Steady-State Concentration-Time Profiles of Celecoxib in JRA Subjects After 6 mg/kg BID



Open circles are observed data; solid line represents population (i.e. typical individual) predictions; dotted line represents individual (Bayes) predictions.

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 [$AUC_{(0\text{-}12)}$], 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)
$AUC_{(0\text{-}12)}$ (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 $AUC_{(0\text{-}12)}$

[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.

2.4 Extrinsic Factors

None applicable in this submission

2.5 General Biopharmaceutics

What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The proposed to-be-marketed capsule formulation has a 50% higher C_{max} and 15% higher AUC compared to the oral suspension studied in the pivotal clinical efficacy trial (# 195).

Sponsor conducted

- A relative bioavailability study of celecoxib commercial capsule and suspension formulations in healthy volunteers (study # 1162).

- A relative bioavailability study of celecoxib administered as capsule contents sprinkled on applesauce in healthy adult volunteers (Study #1202).
- A dose-proportionality and food effect bioavailability study # 088 from original NDA (1998).

The following section will address the relative bioavailability of celecoxib suspension, capsule and capsule contents sprinkled over applesauce:

Study # 1162 is an open-Label, randomized, 4-period, 4-treatment, relative bioavailability study of celecoxib commercial capsule and suspension formulations in healthy adult volunteers. The results shown in the table below indicate that the suspension formulation investigated in pivotal efficacy study # 195 has lower bioavailability compared to the to-be-marketed capsule formulation.

Summary of Celecoxib Pharmacokinetic Parameter Values Following Administration of 200-mg and 400-mg Celecoxib Capsule (Reference) and Suspension (Test) Doses, Study A3291162

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	200-mg Suspension (Test)	200-mg Capsule (Reference)		
N	19	19		
Cmax, µg/mL	0.329	0.692	47.6	40.3 to 56.1
AUC(0-3), hr*µg/mL[a]	0.623	0.962	64.7	53.3 to 78.5
AUC(0-tlqc), hr*µg/mL	5.95	7.08	84.0	76.3 to 92.6
AUC(0-∞), hr*µg/mL	6.37	7.51	84.8	76.7 to 93.7
tmax, hr	3.38	3.34	Not Applicable	
t½, hr	11.7	10.5	Not Applicable	
	400-mg Suspension (Test)	400-mg Capsule (Reference)		
N	19	20		
Cmax, µg/mL	0.506	0.880	57.5	48.8 to 67.8
AUC(0-3.5), hr*µg/mL[a]	1.21	1.78	68.0	56.1 to 82.5
AUC(0-tlqc), hr*µg/mL	9.62	11.2	85.6	77.7 to 94.3
AUC(0-∞), hr*µg/mL	10.5	12.1	86.7	78.4 to 95.9
tmax, hr	2.48	3.00	Not Applicable	
t½, hr	12.5	12.2	Not Applicable	

[a] AUC to median tmax of reference treatment

Relative bioavailability of celecoxib capsule contents sprinkled over applesauce:

Study # 1202 was an open-label, randomized, 2-period, 2-treatment, 2-sequence (AB and BA), single-dose relative bioavailability study in 24 healthy adult volunteers comparing single dose PK of 100 mg celecoxib capsule administered intact (Reference) and 100 mg celecoxib capsule contents sprinkled over applesauce (test).

As shown in the table below, results indicate that administration of 100 mg celecoxib as capsule contents sprinkled on applesauce (test) or intact (reference) resulted in mean (90% CI) test/reference ratios of 90.3% (77.90-104.68) for C_{max} and 97.3% (92.44-

102.46) for $AUC_{(0-\infty)}$. The mean time of maximum observed plasma concentration (t_{max}) value for capsule contents on applesauce was within 15 minutes of that for the intact capsule. Celecoxib terminal half-life (t½) values were similar for each treatment, averaging approximately 11 hours.

Summary of Celecoxib Pharmacokinetic Parameter Values Following Single Oral 100-mg Doses as Capsule Contents Sprinkled on Applesauce (Test) and Intact Capsule (Reference) (Study A3191202)

Parameter	Least-Squares Mean Parameter Values		Ratio	90% Confidence Interval
	Capsule Contents on Applesauce (Test)	Intact Capsule (Reference)		
N (n)	24 (22)	24 (23)		
Cmax, µg/mL	0.345	0.382	90.3	77.90 to 104.68
$AUC_{(0-tlqc)}$, µg*hr/mL	3.68	3.80	96.9	92.01 to 102.02
$AUC_{(0-\infty)}$, µg*hr/mL	3.89	3.99	97.3	92.44 to 102.46
tmax, hr	2.92	2.71	Not Applicable	
t½, hr	11.1	11.0	Not Applicable	

N = Number of Subjects; n = Number of Subjects With Results for t½ and $AUC_{(0-\infty)}$.
Parameters are defined in Table 2.
Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean.

Dose-proportionality of celecoxib pharmacokinetics with capsule formulation:

In study #088, submitted in 1998 to support the adult indication, a dose proportional increase in AUC was noted with 50 mg and 100 mg capsule formulations under fasting and fed conditions. However, C_{max} increased dose proportionately only under fasting condition.

	SC-58635 50 mg vs SC-58635 100 mg P-values (a)	
Parameter	Fasting	High Fat Breakfast
AUC(0-48) (ng/mL)*hr	0.226	0.566
AUC(0-lqc) (ng/mL)*hr	0.608	0.296
AUC(0-∞) (ng/mL)*hr	0.896	0.965
Cmax (ng/mL)	<0.001	0.751

(a) Based on dose-adjusted least squares means

High-fat meal administration resulted in a C_{max} increase of 15% and 62% with 50 and 100 mg capsule formulation, respectively; $AUC_{0-\infty}$ increased by 7-12% in the 50 mg dose group and by 7-20% in the 100 mg dose group.

Parameter	SC-58635 50 MG SD High Fat Breakfast/Fasting		SC-58635 100 MG SD High Fat Breakfast/Fasting	
	Ratio (a)	(95% CI)	Ratio (a)	(95% CI)
AUC(0-48) (ng/mL)*hr	1.12	(1.03 - 1.21)	1.20	(1.11 - 1.30)
AUC(0-lqc) (ng/mL)*hr	1.11	(1.02 - 1.21)	1.19	(1.09 - 1.29)
AUC(0-∞) (ng/mL)*hr	1.07	(0.99 - 1.16)	1.07	(0.99 - 1.15)
Cmax (ng/mL)	1.15	(0.92 - 1.43)	1.62	(1.30 - 2.02)

(a) Ratios based on least squares means

Clinical Pharmacology review of original NDA by Dr. Sue-Chih Lee indicates that the AUC is "roughly" dose proportional between 100 mg and 200 mg doses. Any deviation from dose proportionality is reduced under fed conditions.

What are the safety or efficacy issues, if any, for the observed bioavailabity differences between oral suspension and the capsule formulation (to-be-marketed)?

The results from the exposure-response analysis and the clinical efficacy data review indicate that in the trial # 195 both 3 mg/kg and 6 mg/kg doses of celecoxib oral suspension were non-inferior to naproxen (7.5 mg/kg). The sponsor was asked to submit simulations that predict the exposure of celecoxib following 50 mg and 100 mg capsule administration in pediatric subjects of various body weights. The simulations indicate that the predicted plasma concentrations of celecoxib are within the range of those observed in the clinical trial # 195. Hence, the observed differences in the bioavailability of celecoxib with the capsule formulation may not affect the safety or efficacy characteristics compared to those observed with the suspension formulation.

2.6 Analytical

The plasma levels of celecoxib were analyzed employing a validated HPLC/MS/MS method.

3 Labeling

- The sponsor proposed labeling relevant to Clinical Pharmacology aspects of the drug label are acceptable. In addition, for children approaching adult body weight, dosing up to 200 mg BID should be considered.

Clinical Pharmacology pertinent sections of the proposed label are presented below (See complete proposed label in APPENDIX):

CLINICAL PHARMACOLOGY, Pharmacokinetics section:

Absorption, Food Effects:

"In healthy volunteers, the overall systemic exposure (AUC) of celecoxib was equivalent when celecoxib was administered as intact capsule or capsule contents sprinkled on applesauce. There were no significant alterations in C_{max}, T_{max} or $T_{1/2}$ after administration of capsule contents on applesauce."

Special Populations section:

"Pediatric: The steady state pharmacokinetics of celecoxib administered as an investigational oral suspension was evaluated in 152 juvenile rheumatoid arthritis (JRA) patients 2 years to 17 years of age weighing more than 10 kg with pauciarticular or polyarticular course JRA and in patients with systemic onset JRA. Population pharmacokinetic analysis indicated that the oral clearance (unadjusted for body weight) of celecoxib increases less than proportionally to increasing weight, with 10 kg and 25 kg patients predicted to have 40% and 24% lower clearance, respectively, compared with a 70 kg adult RA patient. Twice-daily administration of 50 mg capsules to JRA patients weighing ≥ (b) (4) to ≤25 kg and 100 mg capsules to JRA patients weighing >25 kg should achieve plasma concentrations similar to those observed in a clinical trial that demonstrated the non-inferiority of celecoxib to naproxen 7.5 mg/kg twice daily (see DOSAGE AND ADMINISTRATION)."

INDICATIONS AND USAGE

Celebrex is indicated:

"3) For relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older (see CLINICAL STUDIES)."

PRECAUTIONS

Pediatric Use

"The use of celecoxib in patients 2 years to 17 years of age with pauciarticular or polyarticular course JRA and in patients with systemic onset JRA was studied in a 12- week, double-blind, active controlled, pharmacokinetic, safety and efficacy study, with a 12-week open-label extension. (b) (4) Celecoxib has not been studied in patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features."

DOSAGE AND ADMINISTRATION

"Juvenile Rheumatoid Arthritis:

Pediatric Patients	Dose
≥10 kg to ≤25 kg	50 mg capsule twice daily
>25 kg	100 mg capsule twice daily

Method of Administration

For patients who have difficulty swallowing capsules, the contents of a CELEBREX capsule can be added to applesauce. The entire capsule contents are carefully emptied onto a level teaspoon of cool or room temperature applesauce and ingested immediately with water. The sprinkled capsule contents on applesauce are stable for up to 6 hours under refrigerated conditions (2-8° C/ 35-45° F)."

4 Appendix

4.1 Proposed labeling

(b) (4)

29 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

4.2 Pharmacometrics Review of Study #195

Office of Clinical Pharmacology
Pharmacometrics

NDA	20998
Trade Name	Celebrex
Indication	Juvenile Rheumatoid Arthritis
Primary Reviewer	Srikanth Nallani
Pharmacometrics Reviewer	Venkatesh Atul Bhattaram
Pharmacometrics Team Leader	Joga Gobburu

Table of Contents

Executive Summary 75
Comments to Sponsor 76
Introduction 77
Methods 78
Results 83
PK 83
Exposure-Response 87
Dose Calculation for JRA Subjects 20
Conclusions 33

Executive Summary

Celebrex is an anti-inflammatory agent that acts by inhibiting the inducible form of then enzyme cyclooxygenase (COX-2). Sponsor is seeking approval for use of celecoxib in patients with juvenile rheumatoid arthritis. To demonstrate effectiveness of celecoxib (3 or 6 mg/kg BID) in the juvenile patients, sponsor conducted a non-inferiority trial with naproxen (7.5 mg/kg BID) as active comparator.

Sponsor conducted population pharmacokinetic analysis using data collected in juvenile patients and adults. Body weight and gender were identified as covariates for celecoxib systemic exposure. The pharmacokinetic model was used to propose dosing guidelines using capsules although the data on effectiveness was obtained using a suspension formulation. The criteria for matching exposure of capsules and suspension formulation included the information on plasma concentrations obtained from the clinical trial where both doses were shown to be non-inferior to naproxen. Exploratory exposure-response (ER) analysis was conducted to quantify the effect of dose or AUC (area under the curve) on the primary endpoint (JRA-30 DOI; Definition of Improvement), also known as ACR (American College of Rheumatology) Pediatric 30. ER analysis suggested that a greater percentage of early responders may be achievable with higher doses.

Comments to Sponsor
No comments

APPEARS THIS WAY ON ORIGINAL

Introduction

Juvenile rheumatoid arthritis (JRA) is a chronic inflammatory condition leading to progressive destruction of the joint, causing deformity and eventual joint dysfunction. The estimated annual incidence of JRA is 0.8 to 22/100,000 children, and the estimated prevalence is approximately 8 to 150 per 100,000. JRA is a disease in which the diagnosis is made clinically in a child "less than 16 years of age with arthritis (defined as swelling or limitation of a joint accompanied by heat, pain, or tenderness) for atleast 6 weeks duration with other identifiable causes of arthritis excluded". NSAIDs continue to be used for the treatment of the disease in approximately 80% of the cases of JRA. The only other selective COX-2 inhibitor to have been approved for JRA was withdrawn from all the markets worldwide in 2004.

Celecoxib is an anti-inflammatory agent that acts by inhibiting the inducible form of the enzyme cyclooxygenase (COX-2). Celecoxib is approved for several indications as shown below:

Indication	Dose/Dosing Regimen
Signs and symptoms of • Osteoarthritis • Rheumatoid arthritis	 200 mg daily in q.d or divided (b.i.d) 100 to 200 mg b.i.d
Acute pain and primary dysmenorrhea	400 mg initially followed by an additional 200 mg dose if needed on first day. 200 mg b.i.d as needed on subsequent days
Signs and symptoms of ankylosing spondylitis	200 mg q.d or divided (b.i.d) doses, with dosing upto 400 mg if no effect is observed at lower doses
Reduction of polyps in familial adenomatous polyposis (FAP)	400 mg b.i.d

Sponsor is seeking approval for use of celecoxib in the treatment of patients with JRA. The JRA development program for celecoxib consisted of three studies:

Study	Description
N49-01-02-195	Pivotal PK, Efficacy and safety study (2-17 years)
A3191162	Relative bioavailability of celecoxib suspension and capsule dosage forms in adults
A3191202	Relative bioavailability of celecoxib after ingestion of intact capsule and alternative method (sprinkling contents in apple sauce) in adults

The pharmacometrics review will focus on N49-01-02-195 to address the following questions:

1. Is the dose/dosing regimen proposed by the sponsor reasonable?
2. Are the labeling statements based on pharmacometrics analysis acceptable?

Methods

Study Design

Study N49-01-02-195 was a 12-week, randomized, double-blind, active-controlled safety and efficacy study evaluating 2 doses of a celecoxib suspension compared with a marketed suspension. Secondary objectives were to compare the PK profile of a celecoxib suspension in children with JRA to an adult cohort with RA, and to obtain PK information to guide the dosing of celecoxib in pediatric population.

Dose/Dosing Regimen

JRA patients received celecoxib suspension in the double-blind phase of the study at a targeted dosage of 3 or 6 mg/kg BID, or naproxen suspension at a targeted dosage of 7.5 mg/kg BID. The dosing used for naproxen (approximately 7.5 mg/kg BID) was based upon recommendations from the pediatric rheumatology community for a therapeutic range of 10 to 20 mg/kg/day and is consistent with the labeled dose of naproxen for treatment of JRA. The dosing of celecoxib (approximately 3 and 6 mg/kg BID) in JRA patients was extrapolated from the recommended adult dose of celecoxib for RA. The actual doses (in mg) administered to these patients followed an allometric pattern. For example, clearance (unadjusted for body weight) in a 10-kg subject was assumed to be approximately 25% of that in a 70-kg adult. Hence, a 10-kg subject received either 25 or 50 mg BID in Study 195 for the low and high dose groups, which are 25% of the approved adult RA doses of 100 and 200 mg BID, respectively.

Fixed dosages were administered according to weight category (determined by patient weight at Baseline) as shown in table below, producing a range of delivered dosages in mg/kg for each target dosage and weight category. Adult RA patients received celecoxib suspension 200 mg BID for 2 weeks.

	Dosage Administered / Delivered Dosage Range (Highest to Lowest Weight)		
Patient Weight	Celecoxib 3 mg/kg BID Target	Celecoxib 6 mg/kg BID Target	Naproxen 7.5 mg/kg BID Target
9-12 kg	25 mg BID	50 mg BID	62.5 mg BID
	2.1-2.8 mg/kg BID	4.2-5.6 mg/kg BID	5.2-6.9 mg/kg BID
13-25 kg	50 mg BID	100 mg BID	125 mg BID
	2.0-3.8 mg/kg BID	4.0-7.7 mg/kg BID	5.0-9.6 mg/kg BID
26-37 kg	75 mg BID	150 mg BID	187.5 mg BID
	2.0-2.9 mg/kg BID	4.1-5.8 mg/kg BID	5.1-7.2 mg/kg BID
38-50 kg	100 mg BID	200 mg BID	250 mg BID
	2.0-2.6 mg/kg BID	4.0-5.3 mg/kg BID	5.0-6.6 mg/kg BID
>50-100 kg[a]	150 mg BID	300 mg BID	500 mg BID
	1.5-2.9 mg/kg BID	3.0-5.9 mg/kg BID	5.0-9.8 mg/kg BID

BID = Twice daily.

[a] Upper limit of 100 kg shown only to illustrate potential lowest delivered dosage; no upper weight limit for patients was specified in the study protocol.

Source: Study 195 CSR,[19] Tables 5 and 6

Primary Endpoint

The primary efficacy measure in the study was the percentage of patients who met the JRA-30 DOI (Definition of Improvement), also known as ACR (American College of Rheumatology) Pediatric 30, at Week 12. A subject was considered a responder by the JRA-30 DOI criteria if there was a ≥30% improvement in ≥3 of the 6 JRA-30 core set components and a >30% worsening in at most 1 JRA-30 core set component; these components included the following: Physician's Global Assessment of Disease Activity, Parent's Global Assessment of Overall Well-being, Parent's Assessment of Physical Function (Childhood Health Assessment Questionnaire [CHAQ] Disability Index), number of joints with active arthritis, number of joints with limitation of motion, and laboratory marker of inflammation (C-reactive protein).

Non-inferiority hypothesis testing was 1-sided at the 2.5% level of significance, or equivalently, non-inferiority of a celecoxib dose was claimed if the lower limit of the 95% 2-sided CI for the

difference in the proportion of JRA-30 DOI responders (π_C-π_N, where π_C is the percentage of responders in the celecoxib treatment group and π_N is the percentage of responders in the naproxen treatment group) was above –25%. This noninferiority criterion was determined by agreement with the Agency and specified in the PWR.

Data

A total of 242 pediatric JRA subjects (77 in the celecoxib 3 mg/kg b.i.d group, 82 in the celecoxib 6 mg/kg b.i.d group and 83 in the naproxen 7.5 mg/kg b.i.d group) were enrolled in the JRA trial and randomized. All 242 subjects received at least 1 dose of study medication and the majority completed the trial (87% in the celecoxib 3 mg/kg b.i.d treatment group, 86.6% in the celecoxib 6 mg/kg b.i.d treatment group and 89.2% in the naproxen 7.5 mg/kg b.i.d treatment group). A total of 43 adult subjects with RA were assigned to celecoxib 200 mg b.i.d.

PK: Celecoxib plasma concentration data from 188 JRA and adult RA subjects were used for the population PK analysis: 73 JRA subjects (95% of those randomized) with 266 observations in the 3 mg/kg BID group, 79 JRA subjects (96% of those randomized) with 279 observations in the 6 mg/kg BID group, and 36 adult RA subjects (84% of those enrolled) with 252 observations who received 200 mg BID. The clinic visit times for JRA patients were staggered so as to obtain an adequate distribution of blood sampling times (predose or 12 hours postdose, 0.5, 3, and 6 hours) relative to the time of most recent dose. Adult RA patients had blood samples drawn at the Week 2 visit at predose, 0.25, 0.5, 1, 2, 4, and 6 hours postdose.

Exposure-Response: 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.

The demographic features of the subjects included in the data analysis is shown in table below:

	JRA 3 mg/kg BID (N = 73)		JRA 6 mg/kg BID (N = 79)		Adult RA 200 mg BID (N = 36)	
Age (yr): Mean (SD)	10.47	(4.19)	10.37	(4.24)	52.09	(16.56)
Median (Range)	11.3	(2.0-16.3)	11.1	(2.3-16.9)	52.55	(18.9-83.2)
Distribution by Age Category N (%)						
2 to ≤5 years	13	(17.8)	15	(19.0)		
>5 to ≤11 years	22	(30.1)	25	(31.6)		
>11 to <17 years	38	(52.1)	39	(49.4)		
≥18 years					36	(100)
Weight[c] (kg): Mean (SD)	35.74	(15.39)	37.15	(18.1)	81.97	(15.31)
Median (Range)	35.9	(12.2-68.0)	37.3	(10.6-92.7)	81.70	(53.3-112.8)
Distribution by Weight Category N (%)						
< 13 kg	3	(4.1)	2	(2.5)		
≥13 to ≤25 kg	18	(24.7)	26	(32.9)		
>25 to ≤38 kg	20	(27.4)	21	(26.6)		
>38 to ≤50 kg	15	(20.5)	13	(16.5)		
>50 kg	17	(23.3)	17	(21.5)	36	(100)
Gender N (%)						
Female	56	(76.7)	52	(65.8)	22	(61.1)
Male	17	(23.3)	27	(34.2)	14	(38.9)
Race N (%)						
White	39	(53.4)	44	(55.7)	36	(100)
Black	7	(9.6)	7	(8.9)		
Asian	1	(1.4)	3	(3.8)		
Not listed	26	(35.6)	25	(31.6)		
Methotrexate Therapy: N (%)						
Yes	35	(47.9)	31	(39.2)	18	(50)
No	38	(52.1)	48	(60.8)	18	(50)
Fed: Nobs (%)						
Yes	94	(35.3)	117	(41.9)	41	(16.3)
No	172	(64.7)	162	(58.1)	211	(83.7)
Formulation Lot: Nobs (%)						
Lot 1 (SP16928, 100 mg/5 mL strength)			101	(36.2)	252	(100)
Lot 2 (K0300839, 100 mg/5 mL strength)			178	(63.8)		
Lot 3 (SP16927, 50 mg/5 mL strength)	266	(100)				

SD = Standard deviation.
Nobs = Number of observations (concentrations)
N = Number of subjects.
Fed = See Section 5.5.

Model Building

PK

Various compartmental models were used to describe the pharmacokinetics of celecoxib. Model selection was based on goodness of fit plots, changes in objective function. Covariate selection was based on Wald's Approximation Method (WAM)

Exposure-Response

Exposure-response (primary endpoint) analysis was also conducted utilizing all the data collected (i.e., Week 4, Week 8 and Week 12) instead of Week 12 alone. For exposure-response analysis, mixed-effects logistic regression analysis was conducted.

RESPO represents a Bernoulli random variable, where RESPO of 1 reflects a responder and RESPO of 0 reflects a non-responder according to the JRA-30 DOI criterion. The probabilities of the RESPO responses were modeled using mixed effects logistic regression. The Laplacian method, which uses a second order expansion around the empirical Bayes predictions of the interindividual random effects (η's), was implemented in NONMEM and used to approximate the marginal likelihood.

The probability that $RESPO_{ij}$ is 1 is given by the logistic regression function

$$P_{ij} = \frac{\exp^{\lambda_{ij}}}{\left(1+\exp^{\lambda_{ij}}\right)}$$

The first step in developing the Base E-R Model involved testing linear, exponential, quadratic, and saturable time effects within the logit (λ_{ij}) as defined below

$$\lambda_{ij} = \theta_1 + \theta_2 \bullet t_{ij} + \eta_i \qquad \text{(Linear Time Effect)}$$

$$\lambda_{ij} = \theta_1 + \theta_2 \bullet t_{ij} + \theta_3 \bullet t_{ij}^2 + \eta_i \qquad \text{(Quadratic Time Effect)}$$

$$\lambda_{ij} = \theta_2 + (\theta_1 - \theta_2) \bullet \exp(-\theta_3 \cdot t_{ij}) + \eta_i \qquad \text{(Exponential Time Effect)}$$

$$\lambda_{ij} = \theta_1 + \frac{\theta_2 \bullet t_{ij}}{\theta_3 + t_{ij}} + \eta_i \qquad \text{(Saturable Time Effect)}$$

θ_1 is the intercept parameter that reflects the instantaneous logit score of a successful response in the absence of time effect; θ_2 and θ_3 are parameters governing time effect in these models; t_{ij} is the nominal visit time (Weeks 2, 4, 8, and 12) of the j^{th} RESPO derivation of the i^{th} subject relative to baseline; η_i represents the random effect for subject *i*, and its Bayes prediction allows for subject-specific predictions of the probability $p(RESPO_{ij}=1)$. The η_i's are assumed to have zero mean and variance ω^2.

Following the identification of the time effect model, linear functions of dose and AUC effects were incorporated into the logit. An example is shown below for an exponential time effect model and a linear drug effect model

$$\lambda_{ij} = \theta_2 + (\theta_1 - \theta_2) \bullet \exp(-\theta_3 \cdot t_{ij}) + \theta_4 \bullet DRG + \eta_i$$

where θ_4 is the slope of drug effect; DRG denotes celecoxib dose (mg), or the PK-model predicted Bayes AUC(0-12) or typical individual AUC(0-12). Since celecoxib PK is known to reach steady state within 5 days and the efficacy assessments were made over several weeks, AUC(0-

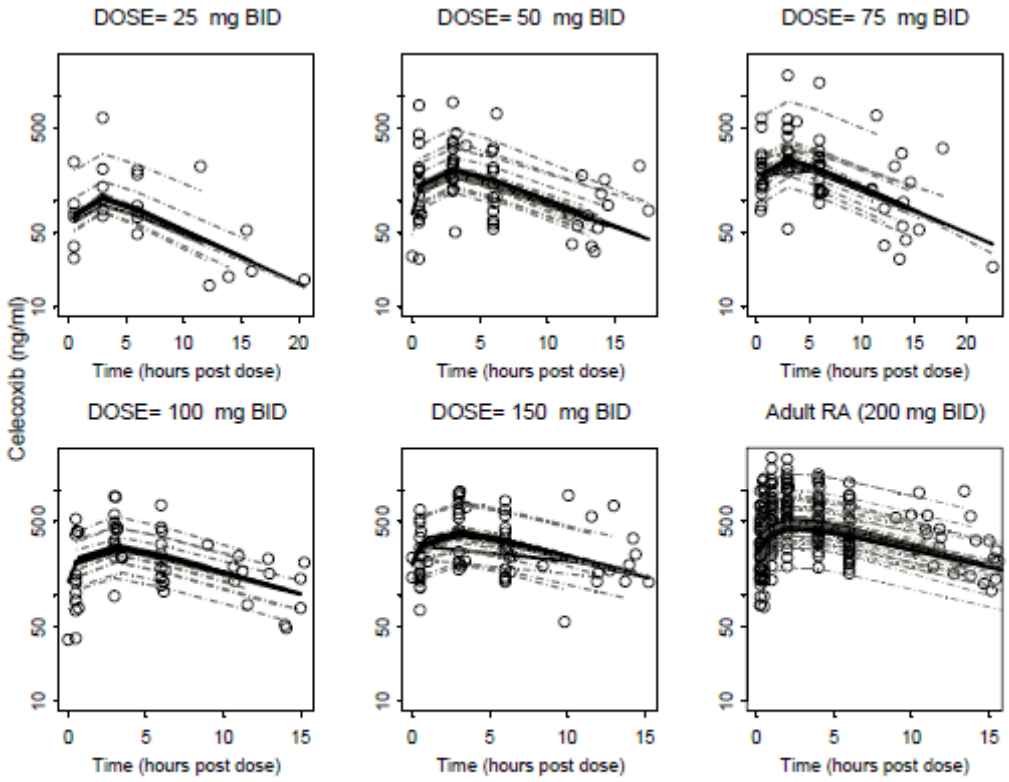
12) for an individual (typical or Bayes) was assumed to be constant at all time points from Weeks 2 through to 12.

For assessment of model adequacy the observed and predicted % responders grouped by time, dose, etc were compared to evaluate goodness of fit. The observed % responders were calculated by dividing the number of responders by total number of responders and non-responders within a grouping. The predicted % responders were calculated by averaging the estimated probabilities under the model. Other goodness of fit criteria included differences in the NONMEM objective function and evaluation of the covariance step (precision of parameter estimates, pairwise correlations of parameters).

Results

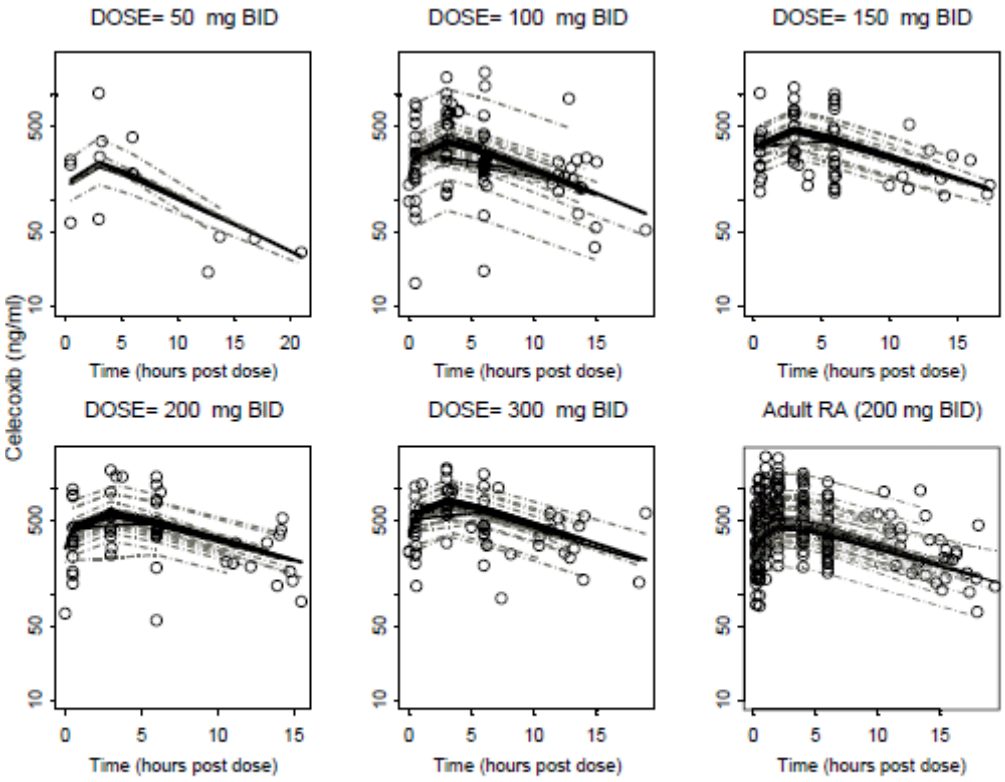
PK

Figure 1 and Figure 2 show the observed plasma celecoxib concentration-time profiles by dose for the 3 mg/kg and 6 mg/kg groups, respectively, with population (ie, typical individual) and individual Bayes predictions obtained from the 1-compartment model with first-order absorption and body weight as a covariate on CL/F and V/F (Base Model 2). For purposes of reference, the observed and predicted PK profiles in adult RA subjects receiving 200 mg BID suspension are also provided (last plot in Figure 1 and Figure 2).



Open circles are observed data; solid line represents population (i.e. typical individual) predictions; dotted line represents individual (Bayes) predictions.

Figure 1. Steady-State Concentration-Time Profiles of Celecoxib in JRA Subjects After 3 mg/kg b.i.d.



Open circles are observed data; solid line represents population (i.e. typical individual) predictions; dotted line represents individual (Bayes) predictions.

Figure 2. Steady-State Concentration-Time Profiles of Celecoxib in JRA Subjects After 6 mg/kg b.i.d

The Final Model covariate sub-model equations were:

$$CL_i = \theta_3 \bullet \left(\frac{Weight_i}{41} \right)^{\theta_7} \bullet (1 + \theta_8 \bullet Sex_i) \bullet e^{\eta(CL)_i}$$

$$V_i = \theta_2 \bullet \left(\frac{Weight_i}{41} \right)^{\theta_6} \bullet e^{\eta(V)_i}$$

$$Frel = 1$$

The summary of the final PK parameters are shown in table below:

Parameter	Model Estimates (SE)			Bootstrap 90% CI
	Base Model	Full Model	Final Model	
MOF	-130.324	-153.56	-138.708	--
ΔMOF	--	23.236	8.384	--
CL/F (L/h)	37.4 (1.43)	38.5 (2.53)	35.2 (1.58)	(32.7, 37.8)
Weight	0.289 (0.064)	0.606 (0.133)	0.265 (0.063)	(0.165, 0.366)
Gender	--	0.149 (0.086)	0.206 (0.074)	(0.086, 0.328)
Age	--	-0.308 (0.095)	--	--
Black Race	--	-0.131 (0.147)	--	--
Other Race	--	-0.001 (0.096)	--	--
Methotrexate	--	0.091 (0.062)	--	--
V/F (L)	405 (32.8)	463 (53)	406 (32.8)	(352.9, 457.3)
Weight	0.487 (0.116)	0.779 (0.228)	0.499 (0.115)	(0.319, 0.692)
Gender	--	-0.1 (0.125)	--	--
Age	--	-0.259 (0.152)	--	--
Black Race	--	-0.196 (0.285)	--	--
Other Race	--	0.057 (0.165)	--	--
Ka (h^{-1})	0.774 (0.078)	0.768 (0.077)	0.778 (0.079)	(0.656, 0.904)
Frel				
Lot	--	0.174 (0.123)	--	--
Food	--	0.125 (0.094)	--	--
Residual Variability (%CV)				
JRA	49.5	49.6	49.5	(45.8, 53.4)
Adult RA	37.9	37.7	37.8	(33.9, 42.0)
Intersubject Variability (%CV)				
CL/F	46.4	44.4	45.9	(39.0, 51.5)
V/F	53.9	52.1	54.5	(41.6, 64.7)
Correlation of etas (CL/F, V/F)	0.87	0.91	0.89	(0.79, 1.0)

The following table shows the summary of estimated interindividual variability in CL/F and V/F. Inclusion of effects of body weight on CL/F and V/F resulted in 5% absolute decrease in interindividual variability.

Model	Description	IIV on CL/F Variance (%CV)	IIV on V/F Variance (%CV)
1	Base Model 1	0.241 (49.1%)	0.369 (60.7%)
2	Base Model 2	0.215 (46.4%)	0.291 (53.9%)
3	Full Model	0.197 (44.4%)	0.271 (52.1%)
4	Final Model	0.211 (45.9%)	0.297 (54.5%)

PK Final Model Predictive Performance (Validation)

Ratios of individual (Bayes) AUC(0-12) to noncompartmental AUC(0-12), and population (typical individual) AUC(0-12) to noncompartmental AUC(0-12) are tabulated by each combination of gender and weight category in Figure 3, 4. The ratios were calculated by dividing the median of the predicted (individual or population) estimate by the median of the noncompartmental values. For the overall evaluation, the median dose normalized AUCs were used. The ratios ranged from 0.81-1.30 for individual / noncompartmental ratios and 0.82-1.45 for population/noncompartmental ratios with no systematic trend toward over or under prediction. Overall, the ratios of dose-normalized AUC(0-12) are no greater than 1.07 (7%), supporting the adequacy of the model fit.

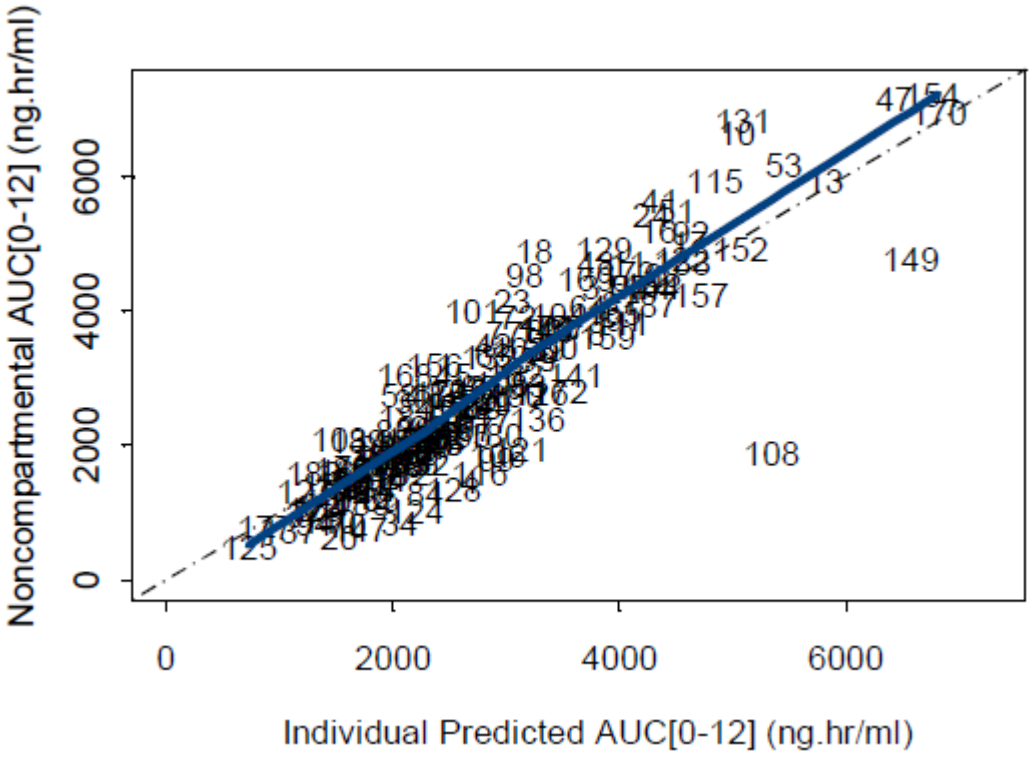


Figure 3. Relationship between noncompartmental AUC0-12 (ng.hr/ml) and individual predicted AUC0-12 (ng.hr/ml).

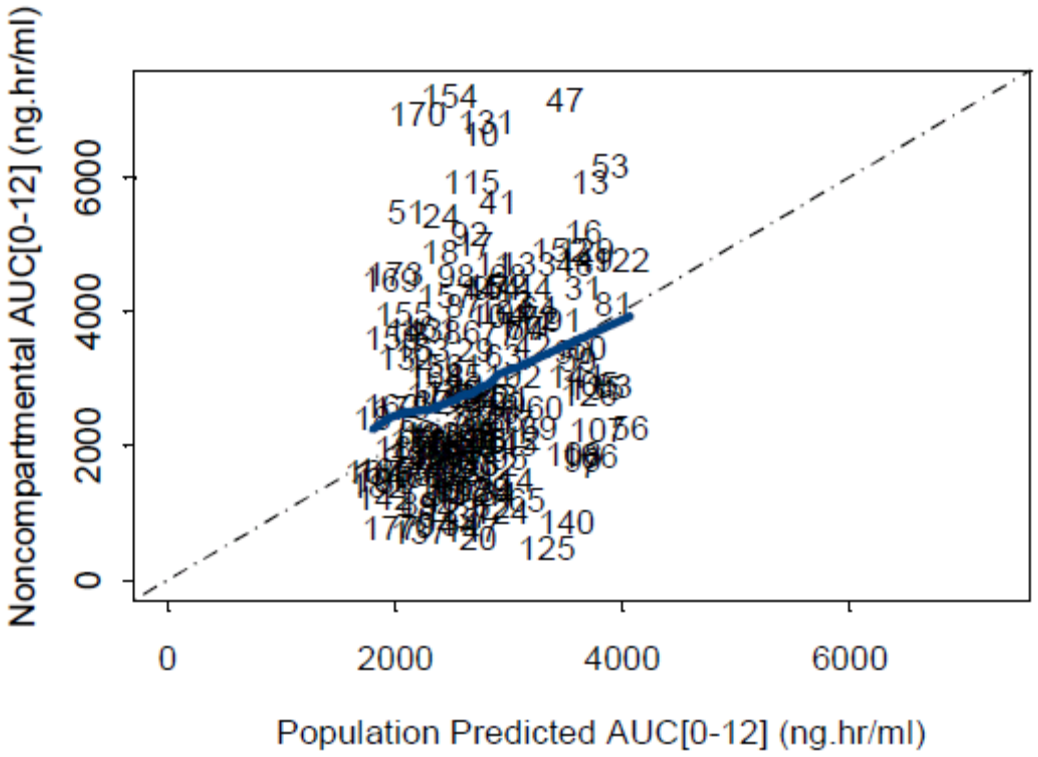


Figure 4. Relationship between noncompartmental AUC0-12 (ng.hr/ml) and population predicted AUC0-12 (ng.hr/ml).

Exposure-Response

Plots of observed % responders (JRA-30 DOI) versus time, dose, and AUC(0-12) revealed a pronounced time-dependent increase in % responders (greater % of responders at later time points relative to dose or AUC(0-12)-related increases in % responder rates). Hence, model building was initially focused on adequately describing the time-dependency in % responders by testing various time-effect (linear, quadratic, exponential and saturable) models. Subsequently, linear models (slope) of dose or AUC(0-12) (typical individual and Bayes predicted) were explored. These E-R analyses were considered exploratory, ie, hypothesis generating and not confirmatory.

Visual inspection of observed versus predicted probabilities of RESPO for the various % responders versus time models indicated that there were no major differences between the linear, exponential, saturable and quadratic models. However, the parameter estimates of the quadratic and saturable models were highly correlated, suggesting over-parameterization. While the linear % responders versus time model was more parsimonious (1 parameter less) and described the data well over Weeks 2 through 12, the exponential model was more consistent with a flattening of the time effect at later time points, as % responders at Week 24 during the open-label phase did not appear to further increase from those at Week 12. Nevertheless, the effects of dose and AUC(0-12) were tested on both % responders versus time (linear and exponential) models to assess the robustness of drug effect under different time effect assumptions. The table below summarizes the results of the addition of a linear drug effect (as a function of Bayes predictions of AUC(0-12), typical individual AUC(0-12), or dose) to the linear and exponential time effect models.

Summary of Base E-R Model Building Steps for % Responders

Model	Description	MOF	ΔMOF	Model Estimates (% RSE)				
				θ_1	θ_2	θ_3	θ_4[a]	ω^2
1	Linear Time Effect	641.974	--	-0.734 (37.7)	0.25 (15.8)	--	--	3.07
2	Bayes $AUC_{(0-12)}$	640.484	1.49	-1.12 (36.6)	0.25 (15.8)	--	0.107 (73.8)	3.03
3	Typical $AUC_{(0-12)}$	637.639	4.335	-1.6 (33.8)	0.25 (15.8)	--	0.251 (53)	2.99
4	Dose	636.151	5.823	-1.51 (29.7)	0.25 (15.8)	--	0.006 (43.9)	2.95
5	Exponential Time Effect	637.662	--	-2.31 (61.9)	2.17 (31.7)	0.255 (67.8)	--	3.22
6	Bayes $AUC_{(0-12)}$	636.252	1.410	-2.68 (53.7)	1.79 (40.7)	0.253 (68.8)	0.106 (75.7)	3.18
7	Typical $AUC_{(0-12)}$	633.408	4.254	-3.17 (47.3)	1.3 (60.5)	0.253 (68.4)	0.253 (53.4)	3.14
8	Dose	631.897	5.765	-3.08 (47.7)	1.39 (52.2)	0.253 (68.4)	0.006 (44.3)	3.09

θ_1 is the intercept parameter that reflects the instantaneous logit score of a successful response in the absence of time and drug effect; θ_2 and θ_3 are parameters governing time effect (Equations 9 and 11 for linear and exponential models, respectively); ω^2 represents the variance of the random effect η_i

%RSE = % Relative Standard Error calculated as |Standard Error/Estimate|*100

MOF = Minimum Objective Function.

ΔMOF = Change in MOF. Reported values for Models 2, 3 and 4 are relative to Model 1; values for Models 6, 7 and 8 are relative to Model 5

[a] = Units of θ_4 are per mg dose (models 4 and 8) and per µg·h/mL Bayes $AUC_{(0-12)}$ (models 2 and 6) and per µg·h/mL typical $AUC_{(0-12)}$ (models 3 and 7)

As shown in table above, the addition of a slope parameter as a function of Bayes AUC(0-12) (Models 2 and 6) did not result in a significant reduction in MOF relative to the models (1 and 5) with no drug effect. However, the addition of a slope parameter as a function of typical AUC(0-12) (Models 3 and 7) resulted in statistically significant ($p<0.05$) reductions in the MOF for 1 degree of freedom relative to Models 1 and 5, respectively, suggesting evidence of an exposure-response relationship. Similarly, the addition of a slope parameter as a function of dose (Models 4 and 8) also resulted in statistically significant ($p<0.05$) reductions in the MOF for 1 degree of freedom relative to Models 1 and 5, respectively, suggesting evidence of a dose-response relationship. It is also noteworthy that the parameter estimates (θ_4) for drug effect are similar (Model 3 versus 7 for AUC(0-12); Model 4 versus 8 for dose) for both time effect models, indicating that the estimated drug effect is robust to the time effect. The predicted η's did not show any systematic bias when plotted against dose or AUC(0-12). Figure 5 and Figure 6 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.

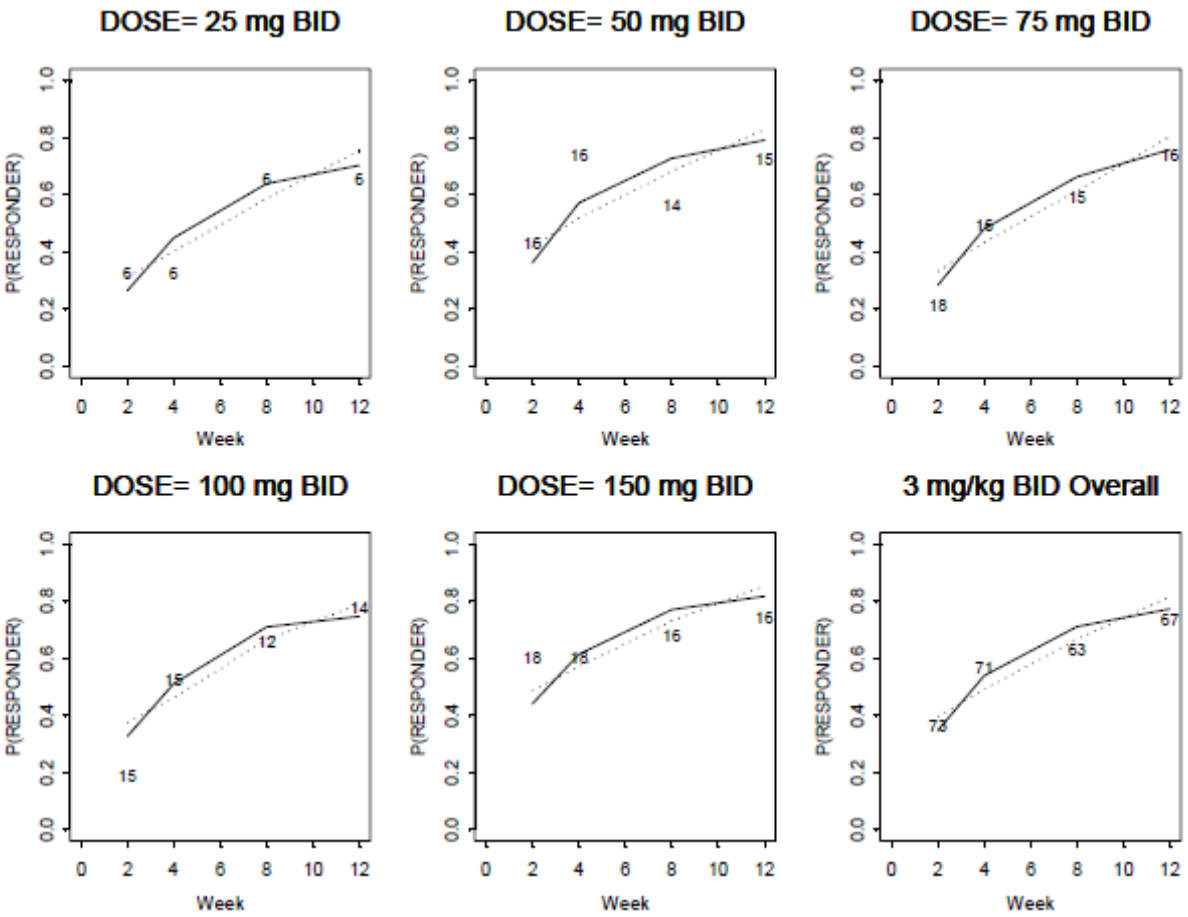


Figure 5. Observed and Predicted Probability of Responders for Celecoxib 3 mg/kg BID
Symbols are observed data and the values (N) represent the total number of subjects (responders + non-responders) in the E-R dataset for each time point and dose; solid line represents model prediction from Model 7 (exponential time effect plus linear typical AUC(0-12) effect); dotted line represents model prediction from Model 3 (linear time effect plus linear typical AUC(0-12) effect); shown are the mean of the model-predicted probability of responders at each time point and dose.

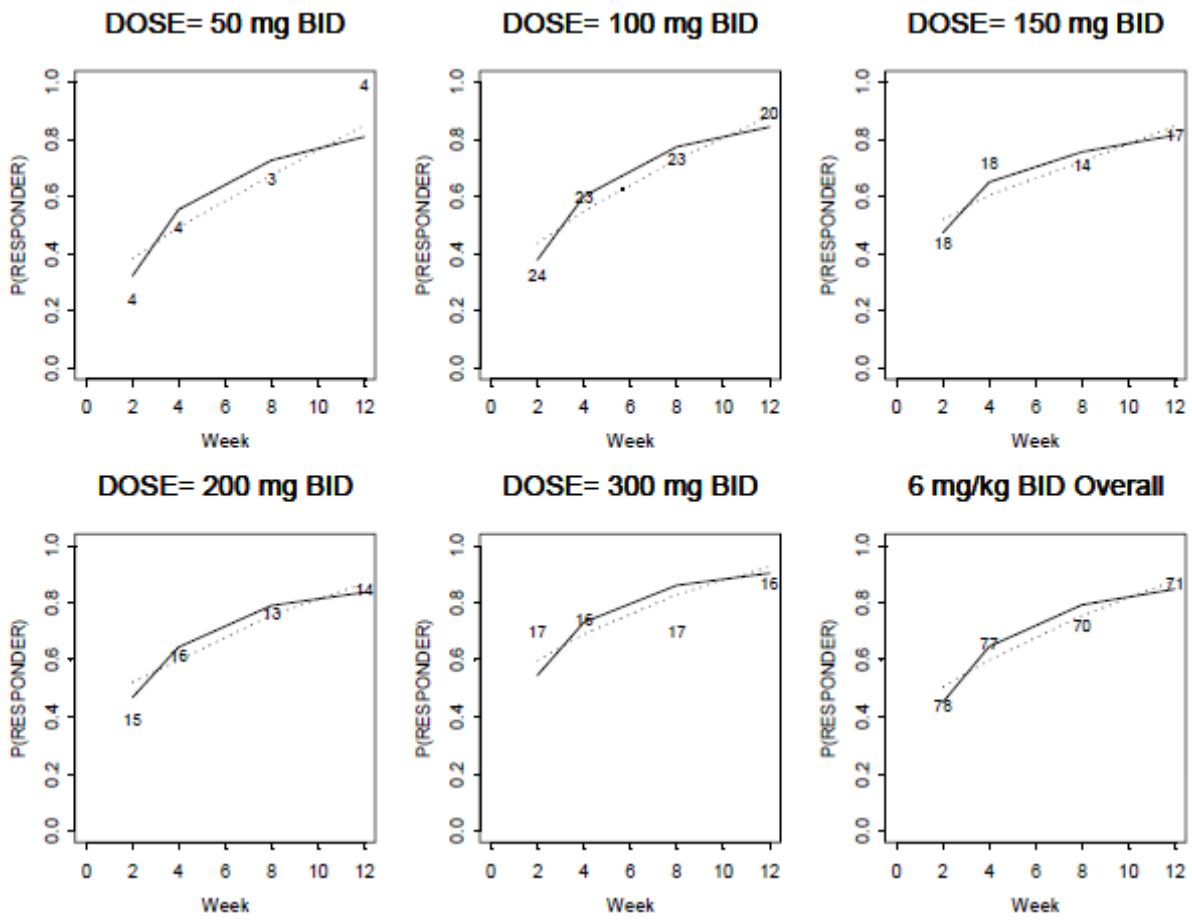


Figure 6. Observed and Predicted Probability of Responders for Celecoxib 6 mg/kg BID
Symbols are observed data and the values (N) represent the total number of subjects (responders + non-responders) in the E-R dataset for each time point and dose; solid line represents model prediction from Model 7 (exponential time effect plus linear typical AUC(0-12) effect); dotted line represents model prediction from Model 3 (linear time effect plus linear typical AUC(0-12) effect); shown are the mean of the model-predicted probability of responders at each time point and dose.

While Figure 5 and Figure 6 provide a visual evaluation of predominantly the time effect on % responders, apparent dose and exposure-related increases in response rate are more discernable in Figure 7 and Figure 8, where dose- and AUC(0-12)- response plots are plotted separately for each week (2, 4, 8, and 12). Though predictions of % responders can be made using the predicted η's from subjects in the JRA trial (as was the case in Figure 6 and Figure 7), simulation was used to obtain a population prediction of % responders for various doses and typical AUC(0-12) values. Simulations were performed using the parameter estimates of the exponential time-effect model with and without the linear effects of dose and AUC(0-12). More specifically, the ηi's for 1000 hypothetical subjects were simulated assuming a normal distribution with mean zero and the estimated variance for each model. The same simulated subjects were then used for each typical AUC(0-12) (894.29, 1000, 2000, 3000, 4000, 5000, 6000, 7000, and 7457.8 ng·h/mL) and for each dose (25, 50, 75, 100, 150, 200 and 300 mg) to provide within-patient AUC(0-12) and dose comparisons, respectively. These values represent the range of model predicted typical AUC(0-12) values with the final PK model and the employed doses in the JRA trial, respectively. The simulated ηi's were then used in the logit models to generate probabilities. These probabilities were averaged to predict the unconditional percentage of responders. The observed % responders for AUC(0-12) were calculated by binning typical AUC(0-12) (calculated from Dose/CL/F for each individual according to his/her weight) into 4 categories; ≤20th percentile, 20-50th, 50-80th, and >80th percentile to facilitate visual inspection; the % responders were then plotted using the median AUC(0-12) value for each category.

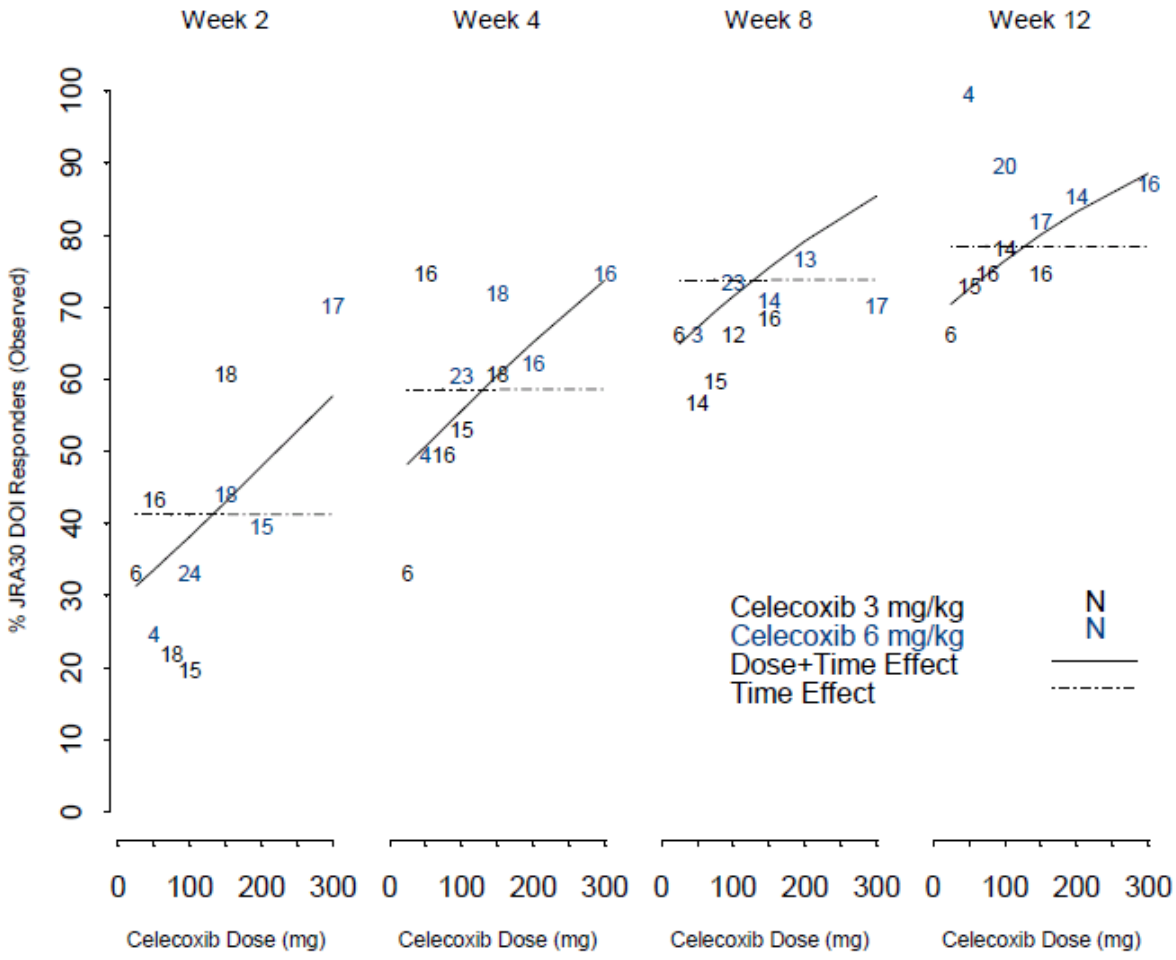


Figure 7. Relationship Between Dose and % Responders

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).

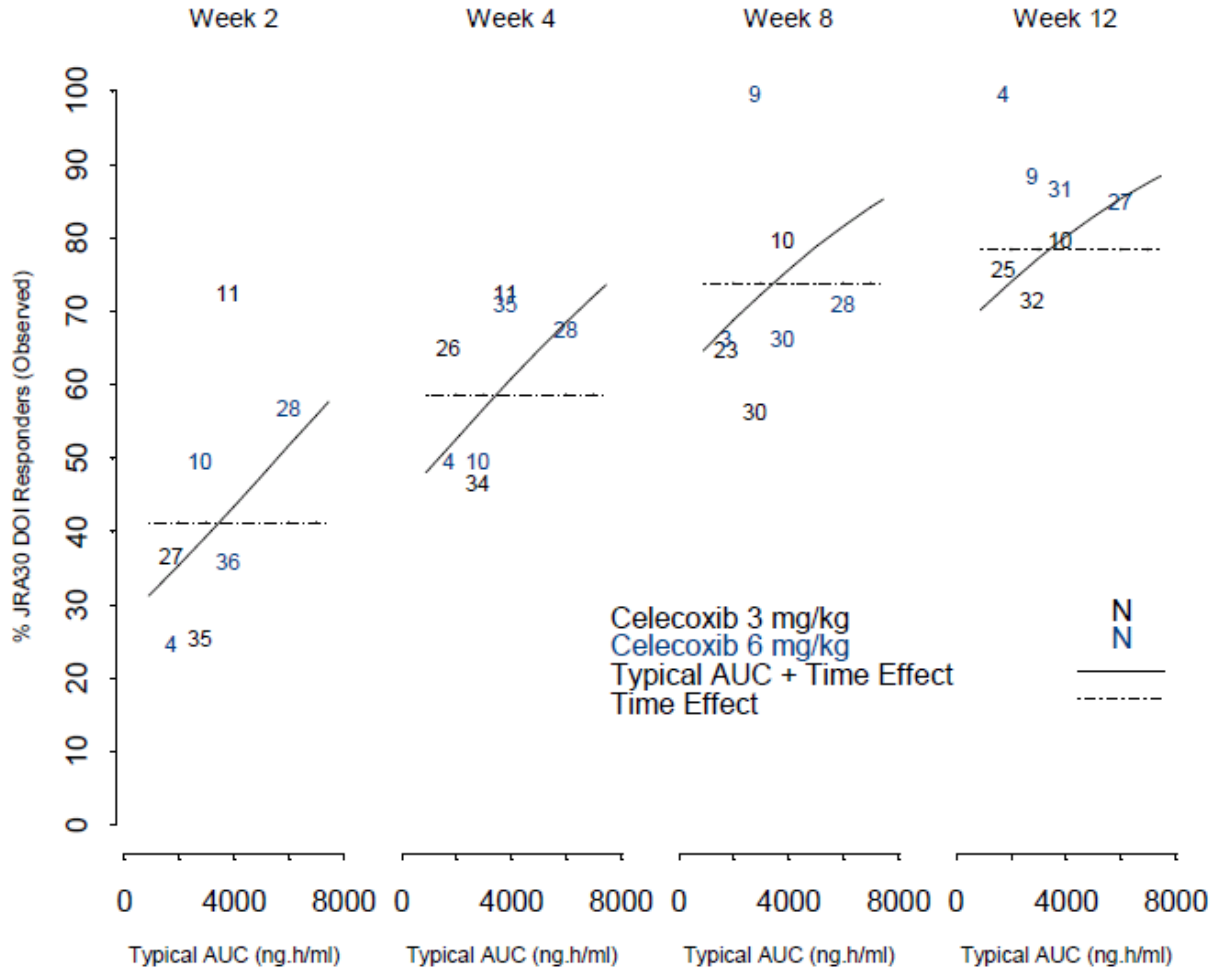


Figure 8. Relationship Between Dose and % Responders

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).

As shown in Figure 7 and Figure 8, the predominant feature in these curves continues to be the pronounced time-dependent increase in % responders while the magnitude of influence of dose or AUC(0-12) is less than that seen with time. However, the incorporation of dose or AUC(0-12) into the model does appear to capture a trend towards greater % responders with higher doses or higher AUCs. For example, doubling the AUC(0-12) from 2000 to 4000 ng·h/mL is predicted to result in an absolute increase of approximately 8 percentage points in JRA-30 DOI responders at Week 2 (35 to 43%), and 6 percentage points at Week 12 (74 to 80%), which correspond to relative increases of 23% at Week 2 and 8% at Week 12, respectively. Similarly, doubling the dose from 100 to 200 mg is predicted to increase % responders by 10 percentage points (38 to

48%) at Week 2 and by 8 percentage points (76 to 83%) at Week 12, corresponding to relative increases of 26% at Week 2 and 9% at Week 12, respectively. Overall, this suggests that a greater % of early responders may be achievable with higher doses or exposures. It is noted that the non-drug based time-trend in JRA-30 DOI responders is difficult to interpret since no placebo group was enrolled in the JRA trial. 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. Due to these limitations, no further model development was undertaken.

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.

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 vs To be Marketed Formulation

An investigation of whether commercially available capsules would be appropriate for children was carried out using prediction of steady-state PK profiles for a set of representative weights at

capsule doses of 50 mg BID or 100 mg BID. The complicating factor in bridging capsule and suspension is that the dosage forms are not bioequivalent; Cmax and AUC(0-∞) from the suspension are approximately 50% and 15% lower, respectively, relative to the capsule (Figure 9).

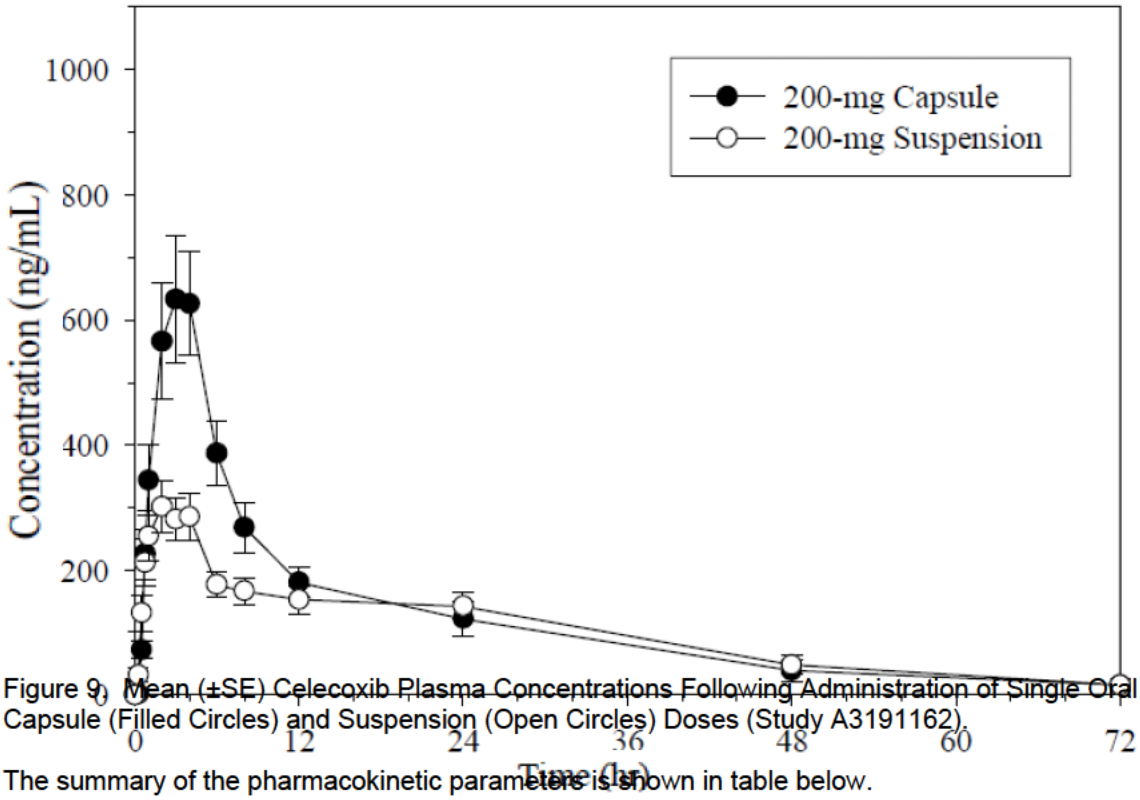


Figure 9. Mean (±SE) Celecoxib Plasma Concentrations Following Administration of Single Oral Capsule (Filled Circles) and Suspension (Open Circles) Doses (Study A3191162).

The summary of the pharmacokinetic parameters is shown in table below.

BEST AVAILABLE COPY

Summary of Celecoxib Pharmacokinetic Parameter Values Following Administration of 200-mg and 400-mg Celecoxib Capsule (Reference) and Suspension (Test) Doses, (Study A3191162)

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	200-mg Suspension (Test)	200-mg Capsule (Reference)		
N	19	19		
Cmax, µg/mL	0.329	0.692	47.6	40.3 to 56.1
AUC(0-3), hr*µg/mL [a]	0.623	0.962	64.7	53.3 to 78.5
AUC(0-tlqc), hr*µg/mL	5.95	7.08	84.0	76.3 to 92.6
AUC(0-∞), hr*µg/mL	6.37	7.51	84.8	76.7 to 93.7
tmax, hr	3.38	3.34	Not Applicable	
t½, hr	11.7	10.5	Not Applicable	
	400-mg Suspension (Test)	400-mg Capsule (Reference)		
N	19	20		
Cmax, µg/mL	0.506	0.880	57.5	48.8 to 67.8
AUC(0-3.5), hr*µg/mL[a]	1.21	1.78	68.0	56.1 to 82.5
AUC(0-tlqc), hr*µg/mL	9.62	11.2	85.6	77.7 to 94.3
AUC(0-∞), hr*µg/mL	10.5	12.1	86.7	78.4 to 95.9
tmax, hr	2.48	3.00	Not Applicable	
t½, hr	12.3	12.2	Not Applicable	

[a] AUC to median tmax of reference treatment

In other words, while similar AUC may be expected between the 2 dosage forms at the same doses, Cmax would be higher (approximately doubled) for the capsule formulation. Therefore, the rationale for the selection of capsule doses is 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 2 dose groups were targeted.

The table below summarizes the parameter estimates previously obtained using the capsule formulation (Parameter Set 1), those derived from the present study (Parameter Set 2), and the assumed estimates used to demonstrate the adequacy of the bridging approach (Parameter Set 3) and to simulate pediatric capsule PK profiles (Parameter Set 4). 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 Figure 12, where the simulated mean suspension profiles (using Parameter Set 3 in table below) 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 Model (Parameter Set 2 in table below).

Table 15. Celecoxib Population Parameter Estimates Used to Bridge Capsule and Suspension Dosage Forms

Parameter	Estimated		For Simulation	
	Historical Capsule (Parameter Set 1)	Final Model (JRA trial) (Parameter Set 2)	Qualification of Bridging Approach (Parameter Set 3)	Prediction of Pediatric Capsule PK (Parameter Set 4)
Formulation	Capsule	Suspension	Suspension	Capsule
Population	Adults in Dental Pain Studies	JRA and Adult RA Subjects	JRA and Adult RA Subjects	JRA Subjects
T_{lag} (h)	0.409	NE	0	0.409
Ka (1/h)	0.554	0.778	0.778	0.554
Dose Effect	-0.483	NE	0	-0.483

APPEARS THIS WAY ON ORIGINAL

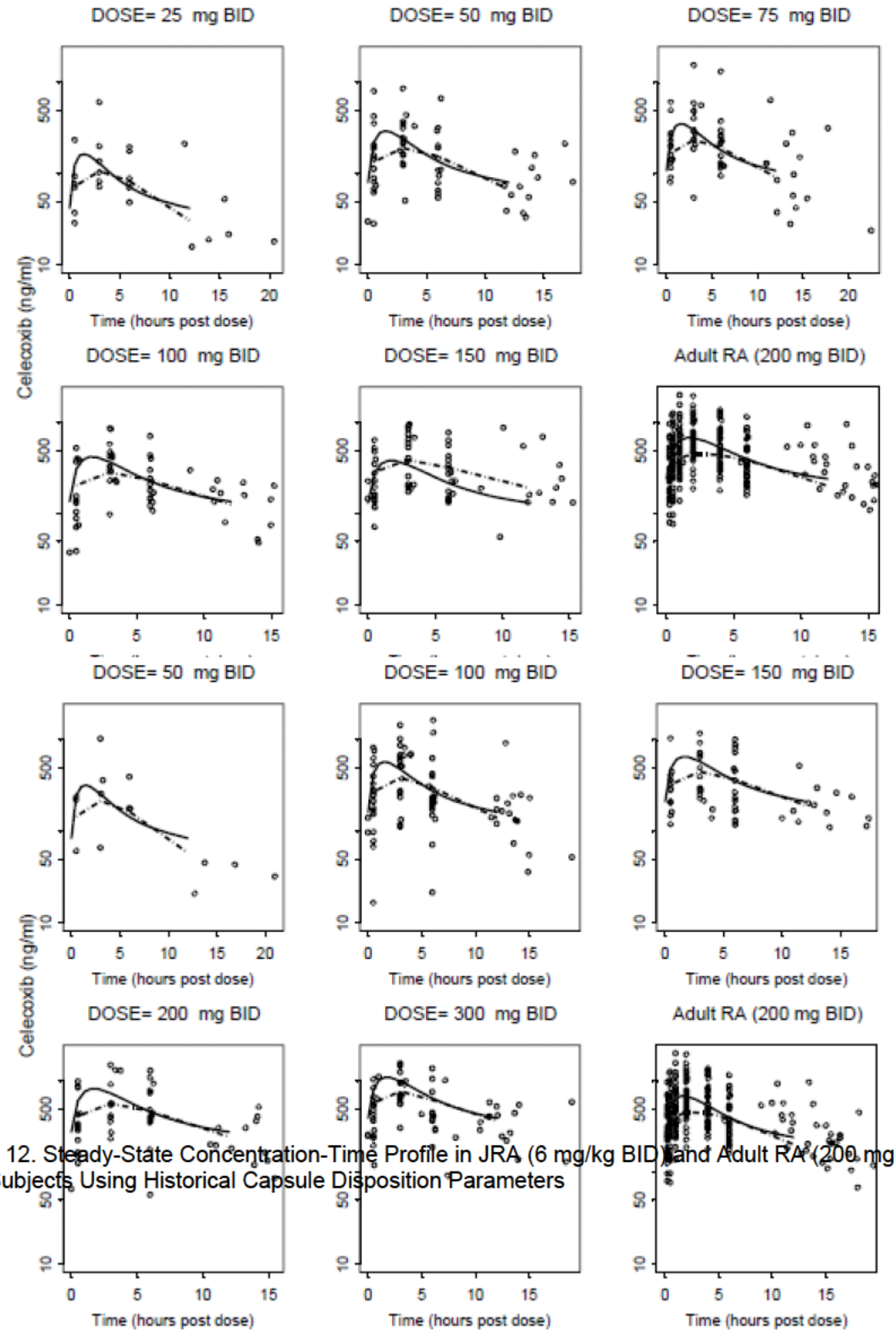
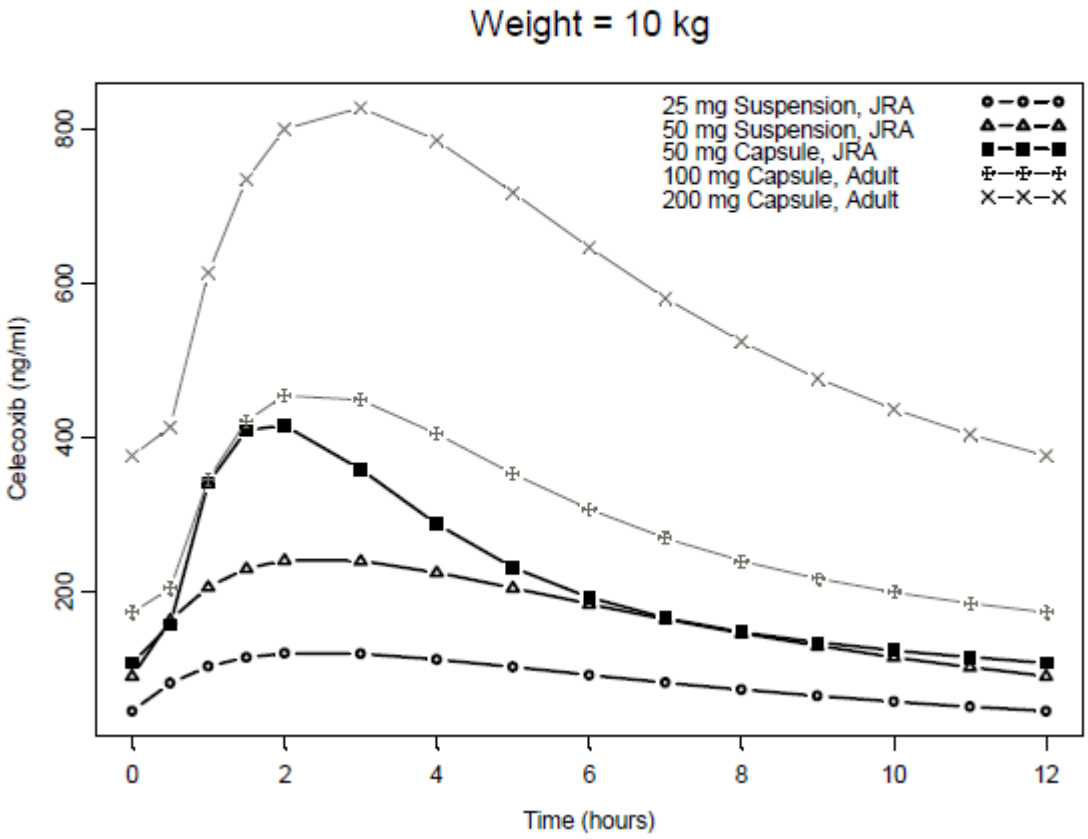


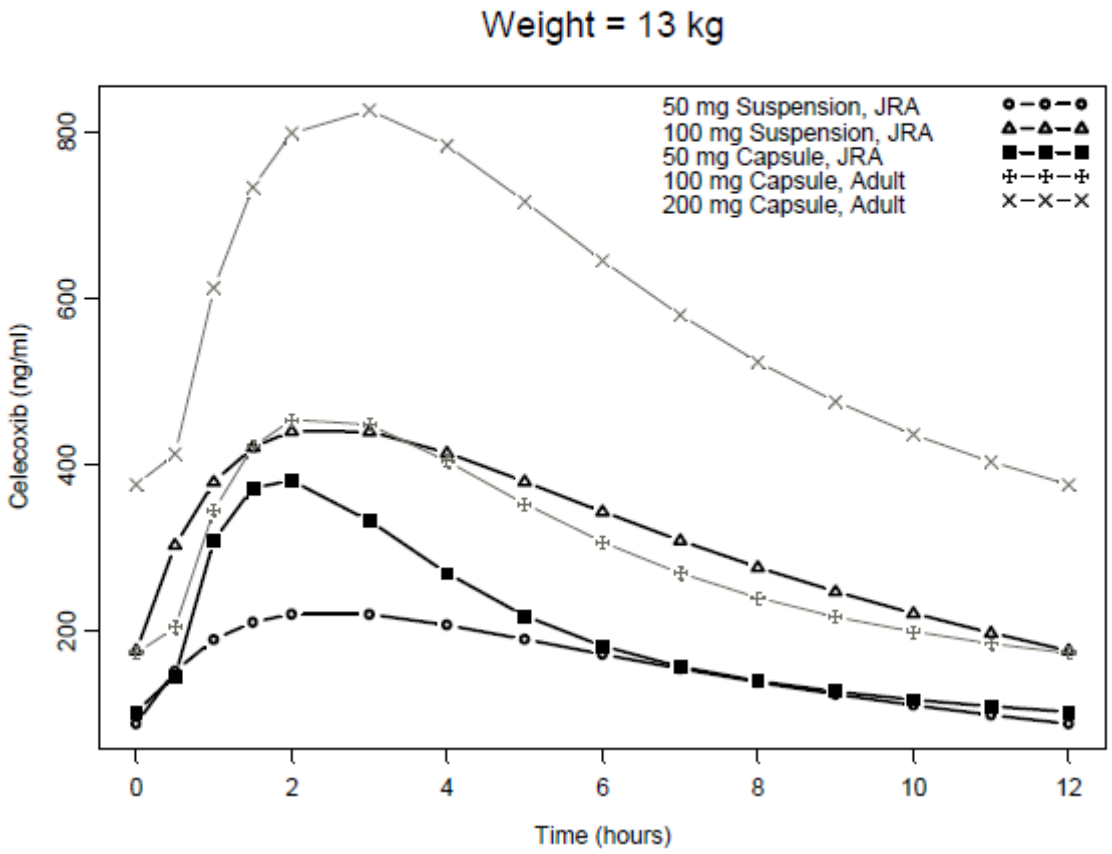
Figure 12. Steady-State Concentration-Time Profile in JRA (6 mg/kg BID) and Adult RA (200 mg BID) Subjects Using Historical Capsule Disposition Parameters

Figure 13. Predicted Mean Steady-State Concentration Profile for a 10-kg Subject Receiving a 50-mg BID Capsule Dose Relative to Typical JRA Suspension and Adult Capsule Profiles



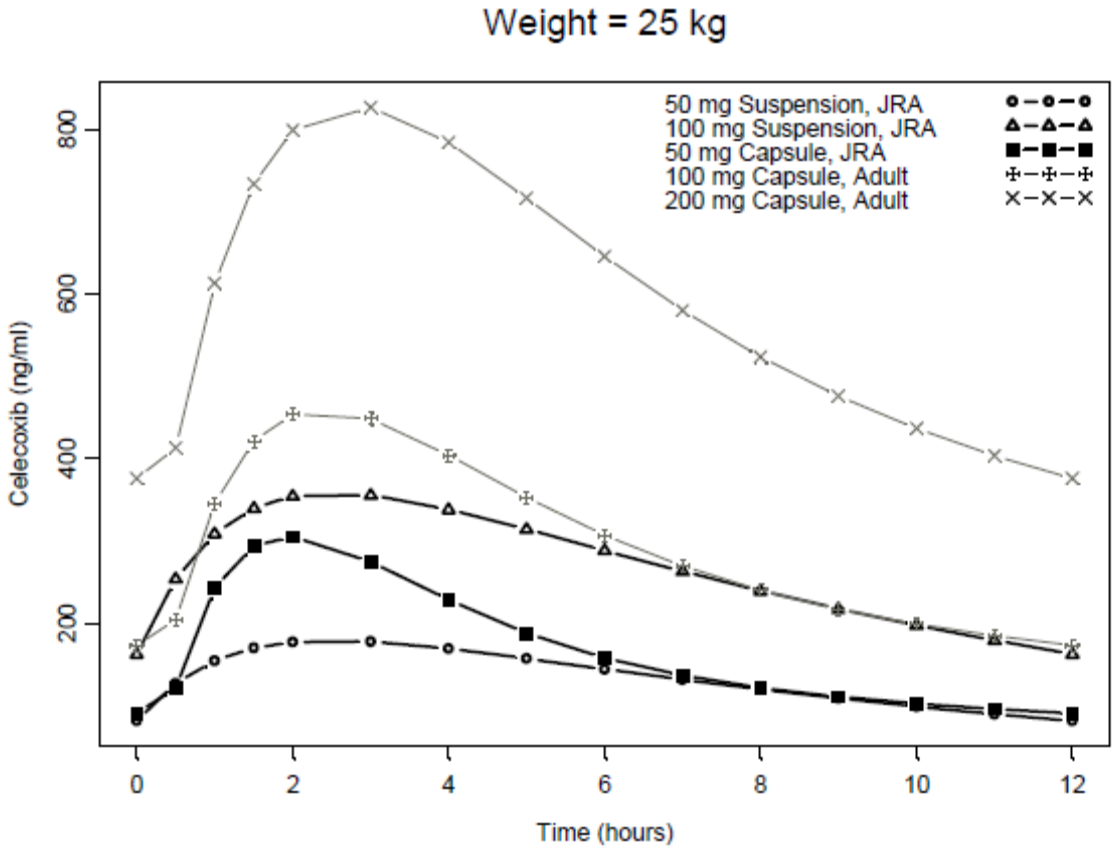
Weight = 10 kg (Figure 13): A small number of subjects (N= 5) weighing between 10 and <13 kg received 25- or 50-mg BID suspension doses. It is evident that the predicted suspension concentrations in the JRA trial for a 10-kg subject receiving 25- and 50-mg BID suspension doses are lower than those in 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.

Figure 14. Predicted Mean Steady-State Concentration Profile for a 13-kg Subject Receiving a 50-mg BID Capsule Dose Relative to Typical JRA Suspension and Adult Capsule Profiles



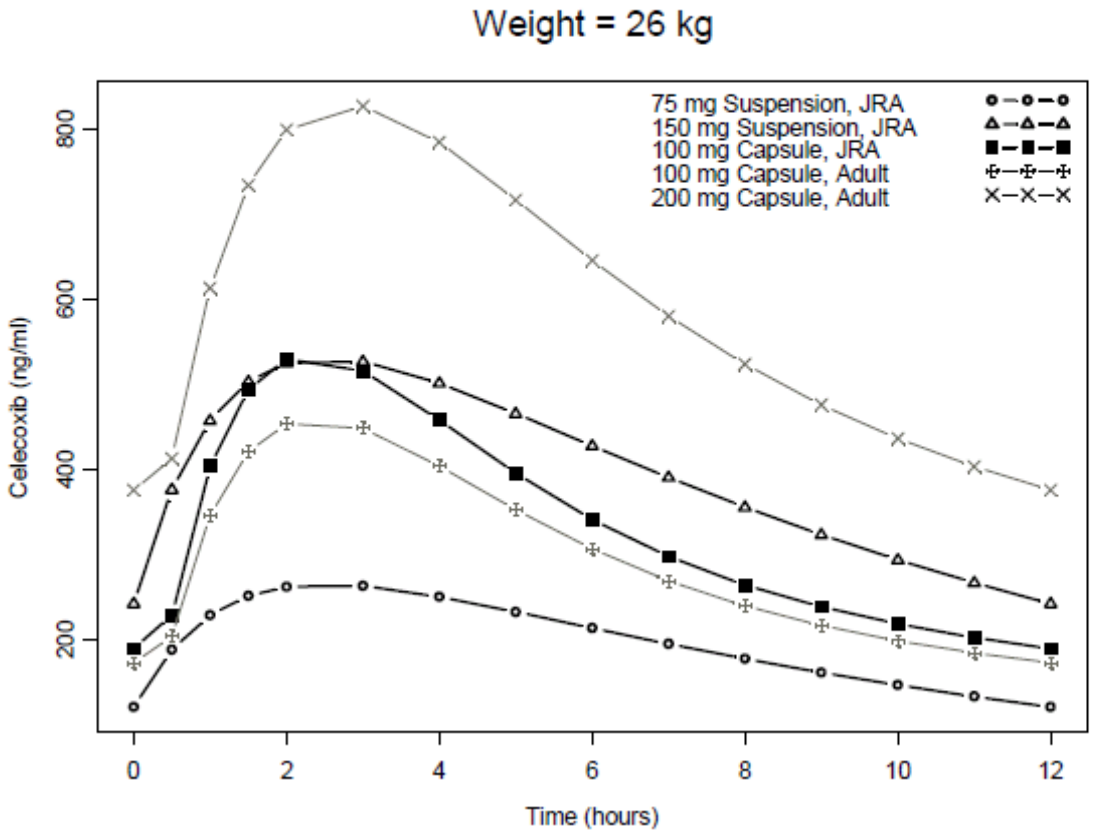
Weight = 13 kg (Figure 14): Predicted concentrations for a 50-mg BID capsule dose in a 13-kg subject are within the range of those predicted for 50- and 100-mg BID suspension doses in the JRA trial. Given that the capsule predictions are not very different between a 10-kg and a 13-kg subject, the adequacy 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.

Figure 15. Predicted Mean Steady-State Concentration Profile for a 25-kg Subject Receiving a 50-mg BID Capsule Dose Relative to Typical JRA Suspension and Adult Capsule Profiles



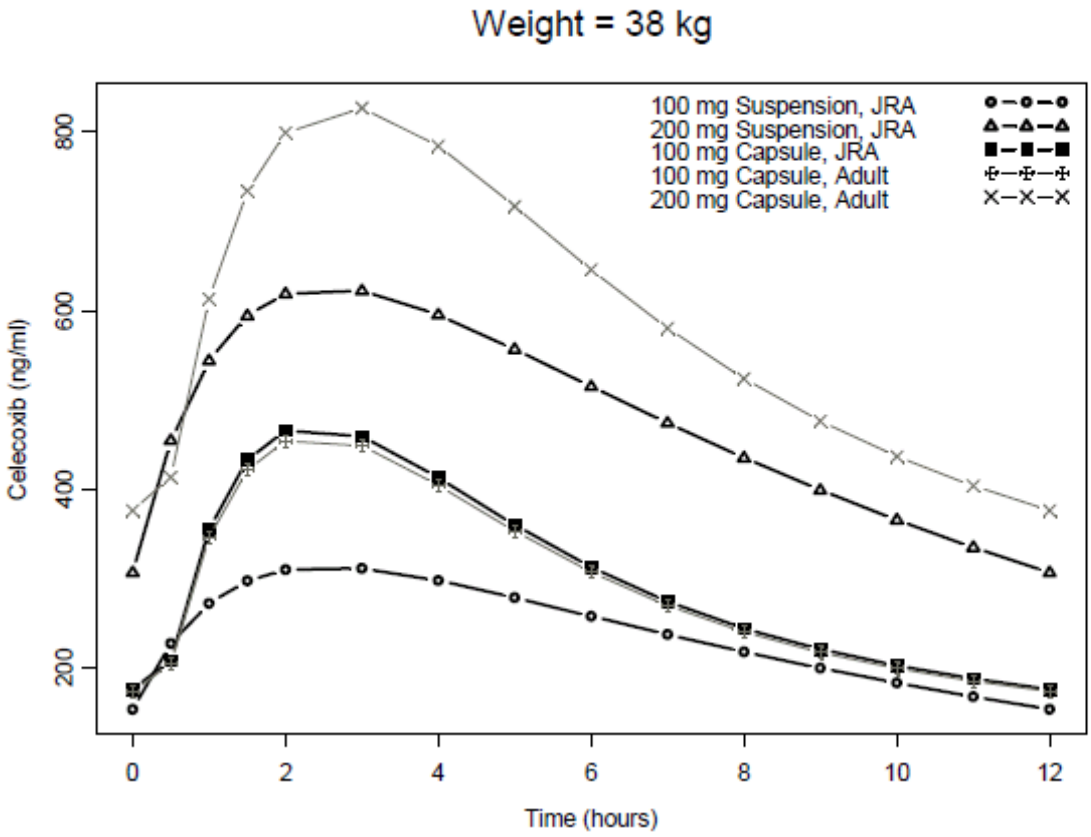
Weight = 25 kg (Figure 15): Predicted concentrations for a 50-mg BID capsule dose in a 25-kg subject are within the range of those predicted for 50- and 100-mg BID suspension doses in the JRA trial.

Figure 16. Predicted Mean Steady-State Concentration Profile for a 26-kg Subject Receiving a 100-mg BID Capsule Dose Relative to Typical JRA Suspension and Adult Capsule Profiles



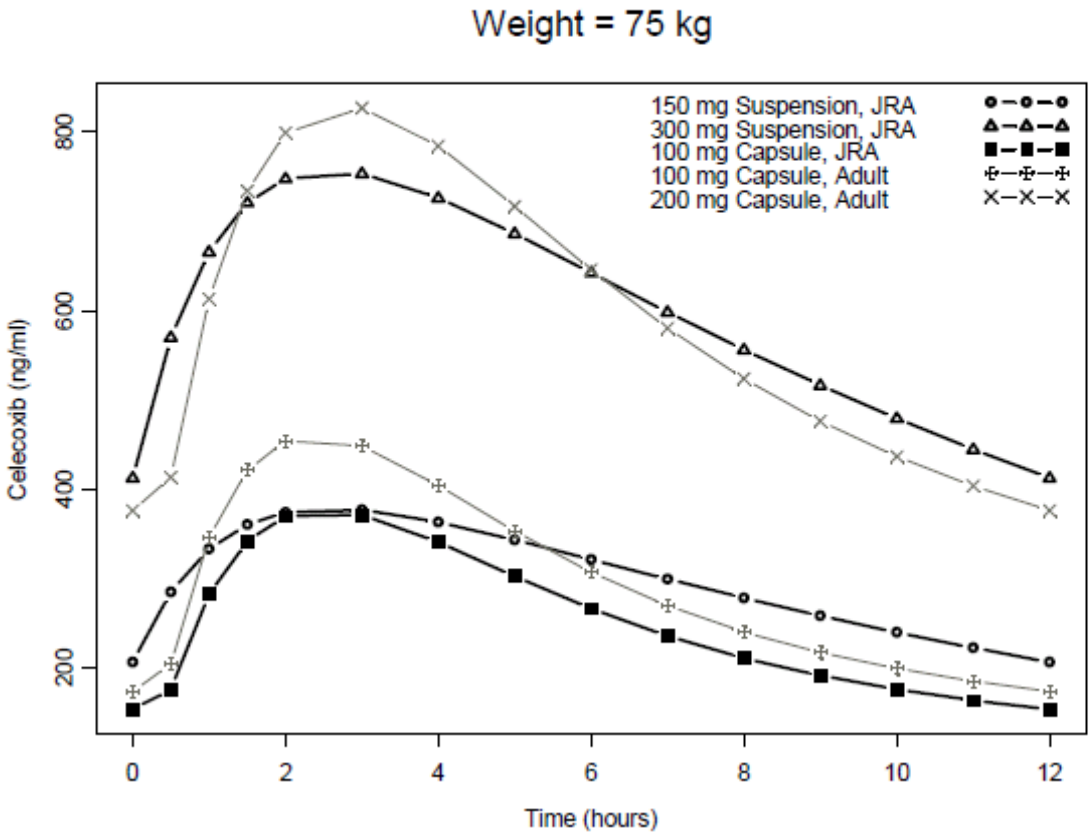
Weight = 26 kg (Figure 16): This weight represents the cut off point where a higher dose of the capsule may be administered. As shown in the figure, the predicted concentrations for a 100-mg BID capsule dose in a 26-kg subject are within the range of those predicted for 75- and 150-mg BID suspension 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.

Figure 17. Predicted Mean Steady-State Concentration Profile for a 38-kg Subject Receiving a 100-mg BID Capsule Dose Relative to Typical JRA Suspension and Adult Capsule Profiles



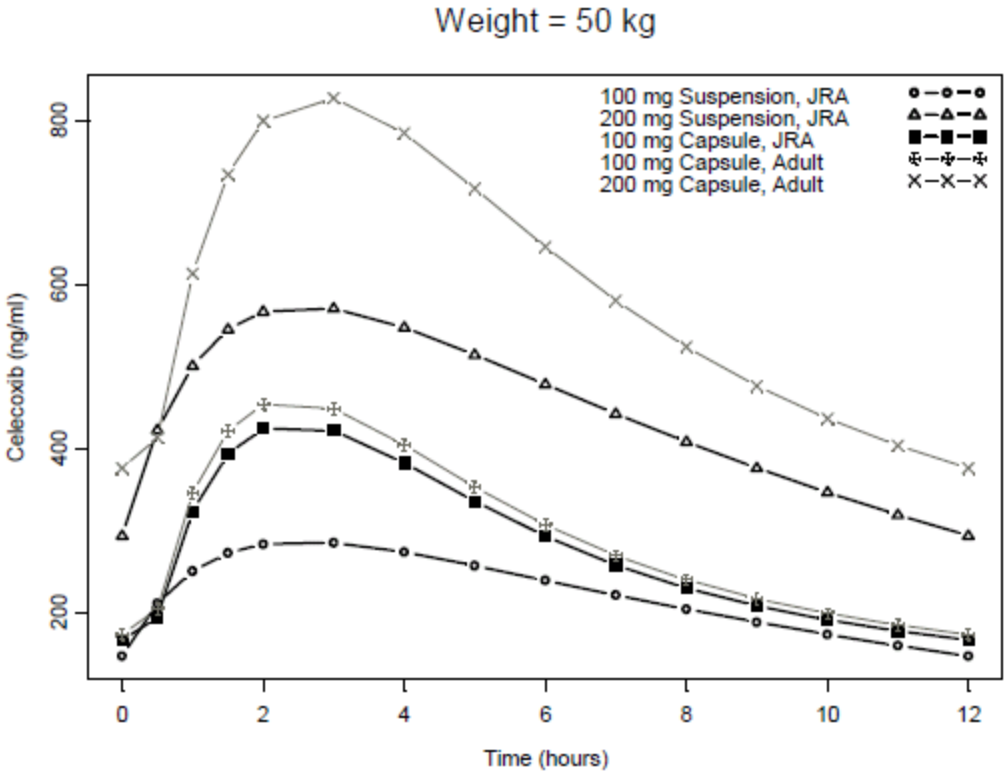
Weight = 38 kg (Figure 17): Administration of a 100-mg BID capsule dose to a 38-kg subject (lowest weight to receive 100- and 200-mg BID suspension doses) continues to predict concentrations within the range of those predicted for 100- and 200-mg BID suspension doses in the JRA trial.

Figure 18. Predicted Mean Steady-State Concentration Profile for a 75-kg Subject Receiving a 100-mg BID Capsule Dose Relative to Typical JRA Suspension and Adult Capsule Profiles

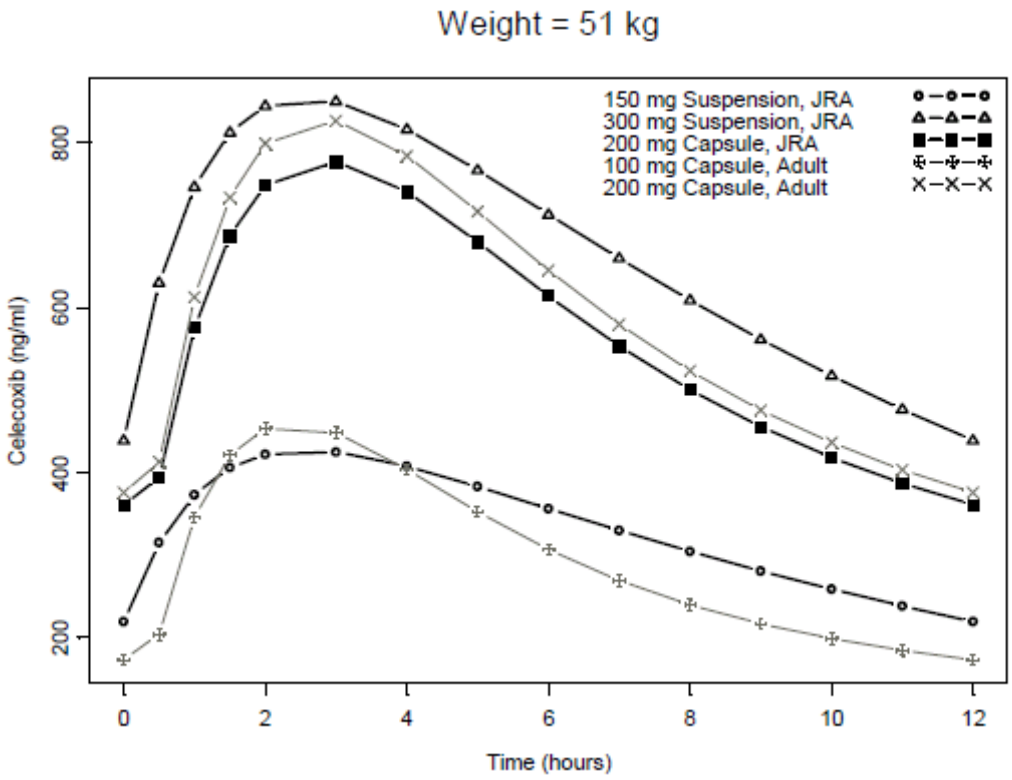


Weight = 75 kg (Figure 18): Predicted concentrations for a 100-mg BID capsule dose are slightly lower than those predicted for the 150-mg BID suspension dose in the JRA trial. However, the differences do not appear to be significant enough to increase capsule dose. Hence a 75-kg subject can essentially 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.

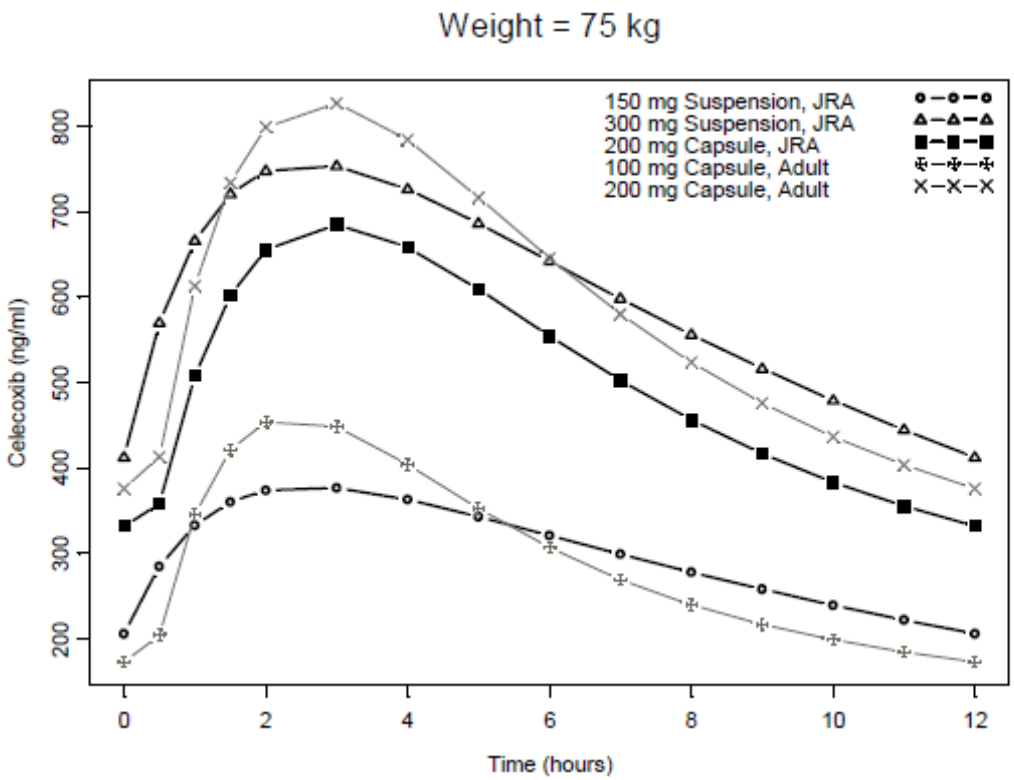
At a pre-sNDA meeting on January 10th 2006, the sponsor was asked to simulate mean concentration-time profile after administration of 200 mg capsules in patients who weigh greater than 50 kg. Sponsor conducted the simulations and provided graphs that show the mean concentration-time profile in patients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

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		

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.

4.3 Synopsis of Study # 1162

CLINICAL STUDY REPORT SYNOPSIS: PROTOCOL A3191162

Protocol Title: An Open-Label, Randomized, 4-Period, 4-Treatment, Relative Bioavailability Study of Celecoxib Commercial Capsule and Suspension Formulations in Healthy Volunteers (Protocol A3191162)

Investigators: SA Daniel

Study Center(s): 1 center; United States

Publications Based on the Study: None

Study Initiation and Completion Dates: 07 January 2004 to 19 February 2004

Phase of Development: Phase 1

Study Objective(s): The primary objective was to assess the bioavailability of celecoxib administered as oral single doses of 200- and 400-mg suspensions relative to 200- and 400-mg commercial capsules. A second objective was to investigate the safety and tolerability of single doses of celecoxib oral suspension versus capsule formulation.

Study Design: This was an open label, randomized, 4-sequence, 4-period, 4-treatment crossover study. Subjects received single 200- and 400-mg celecoxib capsule doses, and 200- and 400-mg celecoxib suspension doses at 20 mg/mL.

Number of Subjects: Twenty-one subjects entered the study and 17 subjects completed the study. All subjects were included in pharmacokinetic and safety evaluations.

Diagnosis and Main Criteria for Inclusion: Healthy subjects of any race and either gender; age 18 to 55 (inclusive), with a body weight of 50 to100 kg (inclusive) desirable, and a body mass index (BMI) <35 kg/m^2 (weight [kg]/height [meters]^2); females required to be not lactating and either of nonreproductive potential (postmenopausal ≥1 year, hysterectomy, or tubal ligation), or must have a negative pregnancy test result prior to randomization and using adequate contraception as evaluated by the investigator during the study.

Study Treatment: Subjects received single 200- and 400-mg celecoxib capsule doses, and 200- and 400-mg celecoxib suspension doses at 20 mg/mL with 240 mL water, according to a randomization schedule under fasting conditions on Days 1, 8, 15, and 22.

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Plasma samples collected over 72 hours following each dose were analyzed for celecoxib concentrations using a validated liquid chromatography/mass spectometry (LC/MS/MS) method. Pharmacokinetic parameters were calculated from plasma concentration-time data using standard noncompartmental methods.

Safety Evaluations: All subjects were evaluated for safety. Safety was assessed by clinical laboratory measurements, physical examinations, vital signs, and electrocardiograms (ECGs).

Statistical Methods: Pharmacokinetic parameters including log-transformed area under the plasma concentration-time profile (AUC) and maximum observed plasma concentration (Cmax) were analyzed with a crossover analysis of variance (ANOVA) model consisting of Subject, Subject within Sequence, Period, and Treatment effects. The Subject within Sequence effect was considered random. Model-based 90% confidence intervals for Test (200- or 400-mg suspension) as a percentage of Reference (200- or 400-mg capsule) were constructed as an aid in data interpretation.

Pharmacokinetic, Pharmacodynamic, and/or Other Results: Celecoxib pharmacokinetic parameters are summarized in the following table.

Table S1. Summary of Celecoxib Pharmacokinetic Parameter Values Following Administration of 200-mg and 400-mg Celecoxib Capsule (Reference) and Suspension (Test) Doses, Study A3291162

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	200-mg Suspension (Test)	200-mg Capsule (Reference)		
N	19	19		
Cmax, µg/mL	0.329	0.692	47.6	40.3 to 56.1
AUC(0-3), hr*µg/mL[a]	0.623	0.962	64.7	53.3 to 78.5
AUC(0-tlqc), hr*µg/mL	5.95	7.08	84.0	76.3 to 92.6
AUC(0-∞), hr*µg/mL	6.37	7.51	84.8	76.7 to 93.7
tmax, hr	3.38	3.34	Not Applicable	
t½, hr	11.7	10.5	Not Applicable	
	400-mg Suspension (Test)	400-mg Capsule (Reference)		
N	19	20		
Cmax, µg/mL	0.506	0.880	57.5	48.8 to 67.8
AUC(0-3.5), hr*µg/mL[a]	1.21	1.78	68.0	56.1 to 82.5
AUC(0-tlqc), hr*µg/mL	9.62	11.2	85.6	77.7 to 94.3
AUC(0-∞), hr*µg/mL	10.5	12.1	86.7	78.4 to 95.9
tmax, hr	2.48	3.00	Not Applicable	
t½, hr	12.5	12.2	Not Applicable	

[a] AUC to median tmax of reference treatment

Results were similar for the comparisons of 200-mg suspension to 200-mg capsule doses, and 400-mg suspension to 400-mg capsule doses. Based on mean Cmax values, peak celecoxib exposure following 200- and 400-mg suspension doses was roughly half of that observed following the 200- and 400-mg capsule doses. Total exposure based on mean area under the plasma concentration-time profile from time zero to least quantifiable concentration [AUC(0-tlqc)] and area under the plasma concentration-time profile from time zero extrapolated to infinite time [AUC(0-∞)] values ranged from 84-87% for the suspension doses relative to

Safety Results: There were no deaths, serious adverse events, or withdrawals due to adverse events during the study. Three of 19 subjects receiving the 200-mg celecoxib capsule dose, 3 of 19 subjects receiving the 400-mg celecoxib capsule dose, 2 of 19 subjects receiving the 200-mg celecoxib suspension dose, and 5 of 19 subjects receiving the 400-mg celecoxib suspension dose reported adverse events. No adverse events were considered treatment associated. All adverse events were mild or moderate in intensity. There were no clinically important physical examination, vital sign or ECG findings. Clinical laboratory abnormalities were sporadic and appeared to be unrelated to study drug administration.

Conclusion(s): Celecoxib bioavailability following single oral 200- and 400- mg suspension doses is approximately 85% relative to 200- and 400- mg commercial capsules, respectively. Maximum plasma concentrations following suspension doses were approximately half of those observed following the respective capsule doses.

Single 200- and 400-mg celecoxib capsule and suspension doses are safe and well-tolerated in healthy subjects.

4.4 Synopsis of Study # 1202

Clinical Study Report Synopsis: Protocol A3191202

Protocol Title: A Relative Bioavailability Study of Celecoxib Administered as Capsule Contents Sprinkled on Applesauce in Healthy Adult Volunteers

Investigators: Dr. Thomas E. Murtaugh

Study Center(s): Pfizer New Haven Clinical Research Unit

Publications Based on the Study: None

Study Initiation and Completion Dates: 11 February 2006 to 08 March 2006

Phase of Development: Phase 1

Study Objective(s): The objective of this study was to assess the bioavailability of celecoxib when administered as capsule contents sprinkled on applesauce relative to capsule administered intact.

METHODS

Study Design: This was an open-label, randomized, 2-period, 2-treatment, 2-sequence (AB and BA), single-dose trial in 24 healthy adult volunteers. The 2 treatments were A) a single dose of 100 mg celecoxib capsule administered intact (Reference); and B) a single dose of 100 mg celecoxib capsule administered as capsule contents sprinkled on applesauce (Test). Trial treatments were separated by a washout of at least 7 days.

Diagnosis and Main Criteria for Inclusion: Subjects were healthy men or women between the ages of 18 and 55 years, inclusive, with a body mass index (BMI) of approximately 18 to 30 kg/m^2 and a total body weight >50 kg (110 lbs).

Study Treatment: Pfizer supplied celecoxib as 100-mg commercial capsules intended for oral administration. The formulation number was A0400295, and the lot number was 06-034272. Pfizer also supplied Musselman's® applesauce for use in Treatment B.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Evaluations: Blood samples for pharmacokinetic (PK) analysis were collected predose, and 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 24, and 48 hours postdose on Days 1 (Period 1) and 8 (Period 2). Samples were analyzed for celecoxib plasma concentrations using a validated high-performance liquid chromatography (HPLC) method with mass spectrometry/mass spectrometry (MS/MS) detection. PK parameters were calculated from plasma concentrations using standard noncompartmental methods.

Safety Evaluations: All subjects were evaluated for safety, as assessed by clinical laboratory measurements, physical examinations, vital signs, and electrocardiograms (ECGs).

Statistical Methods: The bioavailability of capsule sprinkles (test) relative to intact capsule (reference) was assessed using 90% confidence intervals (CIs) for the ratios test/reference of adjusted geometric means for $AUC_{(0-\infty)}$, $AUC_{(0-tlqc)}$, and maximum observed plasma concentration (Cmax). Natural log-transformed $AUC_{(0-\infty)}$, $AUC_{(0-tlqc)}$, and Cmax were analyzed with a crossover analysis of variance (ANOVA) model. The model consisted of sequence, subject-within-sequence, period and treatment effects. The subject-within-sequence effect was considered random. Safety data were listed and inspected for clinically relevant trends. Treatment-emergent adverse events were summarized descriptively using preferred terms.

RESULTS

Subject Disposition and Demography: The 24 subjects in this study included 15 men and 9 women. Eleven subjects were black, 7 were white, 1 was Asian, and 5 were of other races. Their mean age was 31.7 years and mean BMI was 25.2 kg/m^2. All of the subjects were healthy volunteers. None had presenting medical conditions or history that the investigator considered sufficient to affect the conduct of the study or to represent a potential risk to the subject during study participation. All subjects received both doses of celecoxib and completed the study.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and/or Other Results: Administration of 100 mg celecoxib as capsule contents sprinkled on applesauce (test) or intact (reference) resulted in mean (90% CI) test/reference ratios of 90.3% (77.90-104.68) for Cmax and 97.3% (92.44-102.46) for $AUC_{(0-\infty)}$. The mean time of maximum observed plasma concentration (tmax) value for capsule contents on applesauce was within 15 minutes of that for the intact capsule. Celecoxib terminal half-life ($t_{½}$) values were similar for each treatment, averaging approximately 11 hours. These results indicate that celecoxib can be administered either as intact capsules or by emptying the contents onto applesauce without altering its bioavailability.

Safety Results: There were no deaths, other serious adverse events, or withdrawals due to adverse events during this study. A total of 9 treatment-emergent adverse events were reported by 7 subjects. These included 5 events in 4 subjects following treatment with 100 mg celecoxib as intact capsules and 4 events in 3 subjects after treatment with 100 mg celecoxib sprinkled on applesauce. Five of the 9 adverse events were considered treatment-related by the investigator. One event (headache) was moderate; all other events were mild. There were no clinically significant changes in vital signs, clinical laboratory values, ECGs or physical examinations.

Conclusion(s): Celecoxib administered as capsule contents sprinkled on applesauce is a suitable dosing alternative for patients who have difficulty swallowing an intact capsule. Single doses of 100 mg celecoxib are safe and well tolerated whether administered to healthy subjects as intact capsules or sprinkled on applesauce.

4.5 Synopsis of Study # 088

INTEGRATED CLINICAL AND STATISTICAL REPORT FOR AN OPEN LABEL, RANDOMIZED, SINGLE DOSE, FOUR-WAY CROSSOVER STUDY TO ASSESS THE DOSE PROPORTIONALITY AND THE EFFECT OF FOOD ON THE PHARMACOKINETIC PROFILE OF 50 MG AND 100 MG SC-58635 IN HEALTHY ADULT SUBJECTS

Protocol Number:	N49-98-02-088
Document Number:	N49-98-06-088
Document Date:	26 May 1998
Study Dates:	2 March 1998 - 30 March 1998
Investigator(s):	Stuart I. Harris, M.D., Ph.D. Seaview Research Miami, IL
Authors:	Jeanne Zemaitis, B.S. Dawn Bradford, B.S.
Monitors:	Dwain S. Tolbert, Ph.D. (847) 982-8579 Richard C. Hubbard, M.D. (847) 982-7467
Statistician:	Carl Wallemark, M.S. (847) 982-8639

ABSTRACT

The purpose of this study was to examine the pharmacokinetics and dose proportionality of 50 mg and 100 mg doses of the commercial formulation of SC-58635 administered with and without a high fat breakfast. This was an open label, randomized, single dose, four-way crossover study. Subjects received single doses of each of the study medications (50 mg SC-58635 under fasting conditions, 50 mg SC-58635 immediately following a high fat breakfast, 100 mg SC-58635 under fasting conditions, and 100 mg SC-58635 immediately following a high fat breakfast). Treatments were separated by seven days.

Under fasting conditions, the SC-58635 commercial formulation was readily absorbed and reached C_{max} within 2-3 hours of dosing. Following the administration of food, C_{max}, T_{max} and AUC values were increased in both the 50 mg and 100 mg dose groups compared to corresponding values under fasting conditions. Although peak plasma concentrations were delayed by approximately two hours, overall absorption (as assessed by mean AUC values) increased by 7-12% in the 50 mg dose group and by 7-20% in the 100 mg dose group.

Parameter	SC-58635 50 MG SD High Fat Breakfast/Fasting		SC-58635 100 MG SD High Fat Breakfast/Fasting	
	Ratio (a)	(95% CI)	Ratio (a)	(95% CI)
AUC(0-48) (ng/mL)*hr	1.12	(1.03 - 1.21)	1.20	(1.11 - 1.30)
AUC(0-lqc) (ng/mL)*hr	1.11	(1.02 - 1.21)	1.19	(1.09 - 1.29)
AUC(0-∞) (ng/mL)*hr	1.07	(0.99 - 1.16)	1.07	(0.99 - 1.15)
Cmax (ng/mL)	1.15	(0.92 - 1.43)	1.62	(1.30 - 2.02)

(a) Ratios based on least squares means

Dose proportionality between the 50 and 100 mg doses under fasting conditions was demonstrated for all of the AUC values, but not for C_{max} values. When administered with food, dose proportionality between the 50 and 100 mg SC-58635 doses was achieved for both AUC and C_{max} values.

	SC-58635 50 mg vs SC-58635 100 mg P-values (a)	
Parameter	Fasting	High Fat Breakfast
AUC(0-48) (ng/mL)*hr	0.226	0.566
AUC(0-lqc) (ng/mL)*hr	0.608	0.296
AUC(0-∞) (ng/mL)*hr	0.896	0.965
Cmax (ng/mL)	<0.001	0.751

(a) Based on dose-adjusted least squares means

Only one adverse event (mild toothache) was reported during SC-58635 100 mg treatment under fasting conditions. Neither the Investigator nor the Searle Medical Monitor considered this event to be attributable to the study medication.

This study demonstrated that the administration of food with SC-58635 delayed study drug absorption but also increased mean AUC values (by 7-12% in the 50 mg dose group and by 7-20% in the 100 mg dose group). Dose proportionality between the 50 mg and 100 mg doses was demonstrated for AUC under fasting conditions and for both AUC and C_{max} under non-fasting conditions. Administration of SC-58635 was well tolerated.

4.6 OCP filing memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-998**	**Brand Name**	**Celebrex**
OCP Division (I, II, III)		**Generic Name**	**Celecoxib**
Medical Division		**Drug Class**	**Cox-2 inhibitor**
OCP Reviewer	**Srikanth C. Nallani, Ph.D.**	**Indication(s)**	**Juvenile Rheumatoid Arthritis**
OCP Team Leader	**Suresh Doddapaneni, Ph.D.**	**Dosage Form**	**Capsule**
Pharmacometrics Reviewer **Pharmacometrics Team Leader**	**Atul Bhattaram, Ph.D.** **Joga Gobburu, Ph.D.**	**Dosing Regimen**	**≥10 – ≤25 kg body weight – 50 mg capsule** **> 25 kg body weight – 100 mg capsule**
Date of Submission	**6/20/2006**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**11/27/2006**	**Sponsor**	**Pfizer**
PDUFA Due Date	**12/20/2006**	**Priority Classification**	**Priority**
Division Due Date	**11/27/2006**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	**Study from Original NDA with food effect component**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1	1	PK/PD data was from clinical safety efficacy trial
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	2	2	**Oral suspension vs capsule Intact capsule vs capsule contents over applesauce**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**	**3**	

Filability and QBR comments		
	"X" if yes	4.6.1.1.1.1.1.1.1 Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**None**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	Is the dose/dosing regimen proposed by the sponsor reasonable?	
Other comments or information not included above	Pharmacometrics consulted for review of the POP PK analysis and the exposure-response relationship (AUC vs JRA-30 efficacy measure) in pediatric subjects.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Srikanth Nallani
11/22/2006 02:23:04 PM
BIOPHARMACEUTICS

Atul Bhattaram
11/22/2006 02:30:21 PM
BIOPHARMACEUTICS

Jogarao Gobburu
11/22/2006 02:37:24 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/22/2006 05:43:47 PM
BIOPHARMACEUTICS